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Salivary biomarkers related to potentially malignant disorders and oral carcinomas: Brief update

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ABSTRACT
Early diagnosis of oral cancer can improve the quality of life and increase the survival rate of patients. Saliva is a biological fluid of non-invasive access and easy collection, in which it is possible to detect proteins that play an important role in the discrimination of diseases. The presence of salivary protein biomarkers, such as cytokines (IL-6, IL-8, TNF-α)), may aid in the early diagnosis of malignant changes and may be an indicator of the presence of potentially malignant disorders and oral carcinoma. However, due to the variability of the methodologies of the different studies, the absence of standardization of saliva collection, the lack of consensus on the concentration of biomarkers, and also the absence of multicenter studies with larger samples, the reality of clinical use of these biomarkers for early diagnosis of oral cancer is still for the near future.

Keywords: Saliva, Oral Neoplasms, Tumor Biomarkers, Salivary Proteins, Peptides.

1 INTRODUCTION

1.1 ORAL CANCER

Cancer is the leading cause of death worldwide and was responsible for approximately 9.6 million deaths in the year 2018, with 1.2 million deaths in the Americas. This mortality in the Americas is predicted to increase to 2.1 million by the year 2030. A total of 70% of deaths occurred in low- and middle-income countries, such as Brazil (PAHO, 2020).

For the triennium 2023-2025, the National Cancer Institute (INCA) estimates that there will be 704,000 new cases of cancer in Brazil. Of these, a total of 15,100 new cases of oral cavity cancer are estimated, 10,900 in men and 4200 in women, with an estimated incidence of 10.30 cases per 100,000 men and 3.83 per 100,000 women. Disregarding non-melanoma skin tumors, oral cavity cancer ranks eighth among the most frequent types (INCA, 2022a). In 2020, in Brazil, there were 6,192 deaths from oral cavity cancer, corresponding to a risk of death of 2.92 per 100,000 inhabitants, with this risk being higher in men (4.60 per 100,000) than in women (1.32 per 100,000) (INCA, 2020; BRAZIL, 2022).

Cancer mortality can be reduced if cases are detected early through screening and early diagnosis (PAHO, 2020).

Concerning carcinoma of the oral cavity, most of the time, the patient presents for treatment late, with the disease in its advanced stage (SOARES et al., 2019), and a consequent decrease in the survival rate (HU et al, 2008; LEE et al, 2011). Between 2004-2015, more than 60% of malignant neoplasms of the mouth diagnosed and treated in Brazil were in the advanced stage (stage IV) (SOARES et al., 2019). In addition, the treatment of these patients can still be disfiguring and debilitating (GILLENWATER et al., 1998).

Despite improvements in therapeutic and diagnostic modalities, the prognosis of patients with oral carcinomas remains poor (KHALILI, 2008). This worse prognosis is related to late diagnosis, with a five-year survival rate of only 40% to 50% (SCHAAIJ-VISSER et al., 2010; PFAFFE et al., 2011).

In this context, it is important to make an early diagnosis of oral cancer to improve the quality of life and survival rate of patients. In clinical practice, early diagnosis, conventionally performed, requires the performance of accurate clinical examination and biopsy for histopathological evaluation of the suspected site to determine its malignant potential (GILLENWATER et al., 1998). However, several factors contribute to the difficulty of effective development of tools for early detection of oral cancer, such as inexperienced professionals who do not recognize changes indicative of dysplasia and neoplasia (BOUQUOT et al., 2010), the distinction between inflammatory changes, which are much more prevalent, of potentially malignant disorders (INCA, 2022b) and reluctance to perform biopsy.

Epithelial dysplasia is traditionally divided into three categories: mild, moderate, and severe. Mild dysplasia is restricted to architectural changes accompanied by cellular atypia located in the basal layer without extending beyond the lower third of the epithelium. Moderate dysplasia demonstrates the proliferation of atypical cells that extend to the middle third of the epithelium. Severe dysplasia comprises more than 2/3 of the epithelium and may have architectural and cytological changes throughout the epithelium, from the basal layer to the upper third of it. In this case, it can already be considered carcinoma *in situ*. The classification should be based on the area most severely involved, even if it represents only a small portion of the tissue (BOUQUOT et al., 2006). The evaluation of dysplasia can be an important indicator of the malignant potential of a lesion (BARNES et al., 2005).

Among the potentially malignant disorders, we can mention leukoplakia, erythroplasia and actinic cheilitis (NEVILLE, DAY, 2002; INCA, 2022b). Leukoplakia represents 80% of oral lesions with the potential for malignant transformation, affecting mainly white men over 40 years of age (PETTI, 2003). Leukoplastic lesions located on the tongue, oral floor and lip often present dysplastic or malignant changes (NEVILLE, DAY, 2002). Erythroplasia is an alteration of the mucosa with a reddish aspect, with great chances of having dysplastic alteration. Actinic cheilitis is a diffuse alteration located in the lower labial semi-mucosa, which results from excessive or long-term exposure to the

ultraviolet component of solar radiation. The lesions rarely occur in people under 45 years of age and have a strong predilection for the male gender. They initially present as atrophy of the border of the labial semi-mucosa and, as the lesions progress, rough and scaly areas develop on the more dry portions of the lip. With progression, chronic ulcers can develop and last for a few months or progress to squamous cell carcinoma (NEVILLE et al., 2016).

Early diagnosis is the key to decreasing morbidity and mortality associated with the early stages of squamous cell carcinoma and potentially malignant disorders. In Western countries, such as Brazil, leukoplakia, leukoplakia, erythroplakia and cheilitis/actinic keratosis are the most frequent entities and are classically associated with the risk of malignant transformation. (INCA, 2022b). The latter may remain clinically undetectable for years until they progress to the surface. If the change is detected early, the treatment is less aggressive and leaves the patient with a better quality of life after treatment.

Therefore, accurate, objective and non-invasive diagnostic methods are necessary as auxiliary means for detecting suspicious lesions, such as diagnosis through saliva.

2 SALIVARY DIAGNOSIS

Saliva is an important fluid for detecting physiological and pathological changes in the human body (SHAH et al., 2011). Due to the ease of access to the mouth, its obtainment is an easy, inexpensive and non-invasive procedure having been used as a diagnostic tool (CASTAGNOLA et al., 2011; KAKARADDI et al., 2012; MELGUIZO-RODRÍGUEZ, 2020) for oral cancer (WONG, 2006; Zimmermann et al., 2007; LEE; WONG, 2009). This oral fluid can be taken as the mirror of the body, being the perfect medium to be explored in the analysis of health and disease (LEE et al., 2009).

The molecular composition of saliva can reflect the physiological state of the body, including emotional, endocrine, immunological, metabolic, and nutritional variations, and provides a source for monitoring oral and systemic health (ZIMMERMANN et al., 2007; SPIELMANN, WONG, 2011), besides being a marker of infectious or neoplastic diseases (ZIMMERMANN et al., 2007).

Salivary diagnosis could enable clinicians to monitor diseases frequently and easily, which could impact medical research and future therapies. Saliva can help detect lung cancer, pancreatic cancer, breast cancer, and type II diabetes. However, for each disease, there is a need for scientific validation, as well as confirming its superiority over other fluids (LEE, WONG, 2009). Also, saliva can be used to detect the risk of caries, periodontitis, salivary gland diseases and systemic disorders such as hepatitis, HIV and HCV (LEE et al., 2009; CASTAGNOLA et al., 2011).

The direct contact between saliva and altered mucosa makes salivary biomarkers an attractive alternative to blood. The DNA, RNA, and protein molecules of the altered cells can then be conveniently obtained by this fluid, reflecting physiological and pathological stages (LEE, WONG, 2009; SHAH et al., 2011). Oral epithelial cells can routinely be detected in saliva and oral

mouthwashes, making cytological and molecular analyses such as oral cancer monitoring quite attractive. Saliva analysis could monitor the presence of genetically altered oral epithelial cells (GILLENWATER et al., 2006), and also function as a fluid for the detection of biomarkers.

The term biomarker refers to measurable and quantifiable biological parameters that can serve as indicators for physiological measures, as well as parameters of pathological processes, environmental exposures, disease diagnoses and prognosis, and pharmacological response to a therapeutic intervention. Saliva is the only biological fluid that contains components found in serum, offering advantages over the latter. The correlation between plasma and saliva precedes the fact of plasma extravasation through intra- and extracellular pathways, including gingival crevicular fluid, produced by the epithelial cells of the gingival sulcus. Saliva and plasma, therefore, share essential proteins necessary for the maintenance of their physiological functions as body fluids and proteins derived from cellular debris are in close contact with these fluids (SPIELMANN; WONG, 2011). Depending on the size and ionic charge, some molecules penetrate from the blood to saliva via passive diffusion, such as hormones, via filtration and/or active transport, such as IgA, turning saliva into a diagnostic medium (PFAFFE et al., 2011).

Saliva contains hundreds of smaller proteins or peptides that are present in low concentrations but play an important role in discriminating diseases. In addition to proteomes, salivary transcriptomic technology advances the diagnostic potential of saliva for medical applications (LEE, WONG, 2009; LEE et al., 2011; SPIELMANN; WONG, 2011).

The proteome is the analysis of the portion of the genome that is expressed, being the protein complement of the latter. Analysis of the salivary proteome in the course of an alteration can detect early-stage morbidity and monitor disease progression (LEE, WONG, 2009). The amino acid sequence of proteins provides a link between proteins and coding genes via genetic code, and mainly a link between cellular physiology and genetics (SPIELMANN; WONG, 2011). The salivary transcriptome is messenger RNA (mRNA) molecules that cells use to carry instructions provided by DNA for subsequent protein production (LEE, WONG, 2009).

Proteomic constituents are the first choice for salivary analysis (ZIMMERMANN et al., 2007, BARBOSA et al., 2012). The importance of analyzing proteins directly lies in the fact that they perform physiological and pathological functions in the cells. In addition, they are subject to post-transcriptional modifications. The transcription rate, measured through mRNA, does not always have a direct relationship with the biological activity of the protein, its function or quantity (BISCH, 2004).

The collection of unstimulated total saliva is often used for the diagnosis of systemic diseases because it can be readily collected and, more importantly, contains serum constituents (PFAFFE et al., 2011). When using saliva to detect biomarkers, the salivary method has sufficient specificity and

sensitivity, and the collection can be done without the need for prior training (BRINKMANN et al., 2010).

Although biomarkers are in lower concentrations in saliva compared to serum, there are currently sensitive methods capable of detecting them. Also, concerning serum, the possibility of contamination of the professional in the manipulation is greatly reduced. And as the collection is simple, it reduces anxiety, in addition to allowing more frequent monitoring without generating discomfort (LEE; WONG, 2009; SPIELMANN; WONG, 2011).

Although proteomic constituents are the first choice for saliva analysis, genomic targets have emerged as informative and discriminatory biomarkers. The future for salivary diagnosis consists of combining biomarker panels used as *screening* tools to improve diagnostic accuracy and specificity. A biomarker alone is not sufficient as a reliable source to aid in the investigation of the pathogenesis of a given disease. The combined use of biomarkers should provide additional and powerful diagnostic information (PFAFFE et al., 2011).

According to Shah et al. (2011), salivary screening may be the best choice as the primary test for oral cancer screening. The systematic analysis of genomic and proteomic biomarkers facilitates the identification of sensitive and specific parameters for oral cancer and should help identify high-risk patients, in addition to indicating better treatment modalities, improving the survival of these patients.

The use of saliva to monitor the patient's health and disease status is highly desirable for health promotion and health research. It is also possible to evaluate the concentration of drugs, hormones, antibodies and molecules in saliva (PUNYANI; Shatwane, 2012).

As a clinical tool, saliva has numerous advantages over serum, including ease of collection, storage and ease of obtaining in sufficient quantities for analysis at low cost (WONG, 2006). This is particularly relevant in developing countries, where many health and disease risks remain poorly defined and receive inappropriate treatment. In addition, little information about the disease is available to guide the population in health decisions (LEE et al., 2009).

The ease of saliva collection, as well as the fact that it offers less risk of contamination to the operator when handling it, represent important aspects to support the choice of saliva as a means of diagnosis. In addition, it is a reliable method when compared to other scientifically proven methods, such as blood and urine, with validated applicability (MOURA et al., 2007).

According to Loo et al. (2010), approximately 73% of salivary proteins are not present in plasma, providing unique opportunities to discover exclusively salivary proteomic markers. Regarding immunoglobulins, there is relative linearity in the distribution of these proteins between saliva and plasma, suggesting that antibodies can be found concomitantly in plasma and saliva, with salivary concentration being linear and reflecting serum concentration.

It was verified that high levels of Interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were found in saliva in patients with leukoplakia, concerning patients without oral alterations. IL-6 inactivates the tumor suppressor gene P53, hypermethylating its promoter region, resulting in suppression of apoptosis and uncontrolled cell proliferation. TNF-α activates the transcription factor NFκB, which stimulates cell proliferation and blocks apoptosis, in addition to increasing the secretion of pro-inflammatory cytokines (BRAILO et al., 2006).

Sato et al. (2010) verified an increase in the concentration of IL-6 in the saliva of patients with oral carcinoma, when compared to controls.

IL-8 is a pro-angiogenic and pro-inflammatory mediator, which is significantly increased in the saliva of patients with oral carcinoma when compared to control patients (PUNYANI; Shatwane, 2012).

Osman et al. (2012), in a literature review, reported the need for new large-scale studies for the validation of salivary cytokines (IL-6 and IL-8, mainly) as biomarkers for the diagnosis of oral carcinomas, taking into account that their expression was also altered in periodontal disease.

When assessing the salivary levels of pro-angiogenic and pro-inflammatory TNF-α, IL-1, IL-6 and IL-8 in patients with potentially malignant disorders and squamous cell carcinomas, Rhodus et al. (2005) observed significant differences between groups and patients without lesions. Such cytokines were significantly elevated in patients with potentially malignant disorders with patients without lesions and significantly increased in patients with oral carcinomas, when compared to patients without lesions.

Brailo et al. (2012) observed that IL-6 was significantly increased in the saliva of patients with oral cancer, when compared to patients with leukoplakia and control patients. However, the authors did not observe significant differences in IL-6 levels among patients with leukoplakia when compared to control patients. In addition, they observed that there were no differences in salivary levels of TNF-α when comparing the three groups. The authors noted that the increase in pro-inflammatory cytokines in saliva reflects the development of oral cancer from leukoplakia, but was reluctant to state whether the increase in IL-6 and IL1β occurred before the carcinoma became clinically evident or whether it could be used to monitor the transformation of leukoplakia into carcinoma.

Importantly, many salivary biomarkers are not specific to a particular disease and these can be used to aid the diagnosis of various pathologies. Because of this, it is important to consider the different biomarkers that are affected in each disease for a more specific diagnosis and prognosis (MELGUIZO-RODRÍGUEZ, 2020). According to a simple literature review by these authors, information on the usefulness of biomarkers in oral leukoplakia has not yet been conclusive, and more research is needed to explore new biomolecules that are candidates for this purpose.

Bugshan and Farooq (2020) reported in their review that, for the diagnosis of oral cancer, biopsy should be performed, but salivary biomarkers could also be used as aids in the early diagnosis of the same. According to Rusling et al. (2010), the diagnosis and detection of cancer using salivary protein biomarkers should require accurate detection of panels with approximately 4 to 10 biomarkers for each type of cancer.

Second Li et al. (2020), reliable proteomic biomarkers should be not only highly related to disease but also have stability and be collected from saliva in a standardized way. In addition, the sample should be processed immediately so that there are no changes, and protease inhibitors and refrigeration of the sample should also be used. In addition, protein biomarkers require extensive validation by cohort research before they can be used clinically so that, shortly, they present sufficient specificity to be applied in early-stage cancer screenings and thus greatly improve the quality of life of patients.

Chiamulera et al. (2021) conducted a systematic review and meta-analysis, evaluating 28 case-control studies that used cytokines as cancer biomarkers. The studies described 10 different cytokines, with interleukins (IL-6 and IL-8) being the most studied. According to the meta-analysis, the authors found that salivary levels of some cytokines were different between healthy patients and those with oral carcinoma and potentially malignant disorders. This fact would indicate that these cytokines could represent potential biomarkers for these alterations. However, the salivary levels of these cytokines varied greatly between studies, requiring better standardization in the evaluation by the ELISA technique (*Enzyme Linked Immunosorbent Assay*), to be able to transpose the results into clinical practice. According to the authors, IL-6, IL-8 and TNFα could be considered as biomarkers of oral carcinoma, since their concentration was significantly higher in patients with carcinoma when compared to healthy patients. But levels of IL-6, IL-8 were also shown to be increased in potentially malignant disorders. However, carcinomas were significantly increased than in potentially malignant conditions, and it is important to determine the level of this difference between these two conditions, although in both were more increased than in healthy patients. According to the authors, these two biomarkers are the most promising as reliable diagnostic tools, since none of the other biomarkers showed significant differences in their concentration in oral cancer and potentially malignant disorders. Meta-analysis with twenty-three studies showed that salivary levels of IL-8, IL-6, TNF-α, IL-1β and IL-1α were significantly higher in patients with oral carcinomas compared to healthy patients. Salivary IL-8 and IL-6 levels were statistically higher in patients with carcinoma compared to patients with potentially malignant lesions. In the comparison between healthy patients and patients with potentially malignant disorders, the authors observed an increase in salivary levels of IL-6 in the latter. To use these biomarkers in clinical practice, standardization of saliva collection and cytokine dosage is necessary, as well as further studies with larger samples and multicenter studies.

In the systematic review conducted by Ferrari et al. (2021), using 27 observational studies (cross-sectional and longitudinal), which used the ELIZA technique to identify cytokines, the authors identified that cytokines IL-6, IL-8, TNF-α were in higher concentrations in the saliva of patients with oral carcinoma, when compared to healthy controls, and can be considered biomarkers and serve as a basis for the development of rapid tests for early diagnosis of oral cancer. They also found that the levels of these cytokines were higher in patients with carcinoma when compared to those with potentially malignant disorders. For the authors, there should be an appropriate combination of biomarkers in longitudinal studies to avoid confounding factors, such as patients' behavioral habits and periodontitis. Further studies would also be needed to confirm the reliability of salivary screening tests, with an increase in the sample size and multicenter studies, with a combination of several cytokines, and standardized quantification of the same, using reliable and quality reagents, in addition to paired control patients, according to their periodontal health.

Shaw et al. (2022), in their systematic review and meta-analysis using 13 studies with a total of 1048 patients, found that most of the eight salivary biomarkers (mRNA, miRNA, DUSP100, s100P, IL-8, IL-1B, TNF-a and MMP-9) evaluated in the studies showed good diagnostic accuracy. The authors reported that the detection of mRNA and micro-RNA had a sensitivity of 91% and specificity of 90% when they were detected by the PCR (polymerase chain reaction) technique. IL-8 had 54% and 74% for ELIZA, and 89% and 90% for CRP, of sensitivity and specificity, respectively. According to the authors, the early detection of oral squamous cell carcinoma was best achieved by mRNA and micro-RNA screening by PCR, and these biomarkers can potentially be used for early diagnosis of oral squamous cell carcinoma.

3 FINAL CONSIDERATIONS

It is possible to detect malignant changes with the aid of salivary tests to verify protein biomarkers, such as IL-6, IL-8 and TNF-α. However, these saliva tests should be standardized, using reliable reagents, combination of several biomarkers and standardized quantification of them. In addition, multicenter studies are also necessary before the validation of these markers for their use in clinical practice.

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Analysis of the impacts of the COVID-19 pandemic on people living with HIV/AIDS in a reference unit in Maceió – Alagoas

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ABSTRACT

Introduction: Due to social distancing due to the COVID-19 pandemic, the habit of sexual practices may have been affected, which impacts the alteration of the exposure of individuals to HIV infection. However, data on sexual behavior among Alagoas are still unknown. Objective: To analyze the impacts of the COVID-19 Pandemic on people living with HIV/AIDS in a Reference Unit of Maceió-Alagoas. Methods: This is an exploratory and descriptive study with a quantitative approach of the documentary type. The sample comprises 183 questionnaires applied from August 2021 to March 2022 to individuals undergoing HIV testing at the Specialized Care Service (SAE) of PAM Salgadinho, in addition to the analysis and comparison with the specialized literature. Results: The major cause of the search for the rapid test resulted from unprotected sexual intercourse, representing 36.00% of the cases. When asked if the pandemic affected the usual number of sexual partners, 78 (42.60%) answered yes, and 61 (78.21%) of them claimed that there was a decrease. Asked about the practice of sexual activity, it was observed that 34.43% of the interviewees said they had interrupted it. However, for 52.46% of those who remained sexually active, there was an increase in the number of unprotected sexual relations. Conclusion: It can be observed that, with the measures of social isolation, there was a reduction in the number of sexual contacts with different people among the interviewees. In addition, a significant number of individuals reported having ceased their sexual activities during the period. This may have had a positive impact on reducing HIV exposure.

Keywords: Coronavirus, HIV infections, Serology, Sexual behavior.

1 INTRODUCTION

SARS-CoV-2, a virus of the Coronavirus family, is an agent with a high rate of infectivity and human mortality. Identified in China in 2019, it is the protagonist of the health and economic crisis experienced in current times (FERGUSON, 2020; Mirzaei et al, 2020).

This pathogen triggered a series of social isolation measures by public agents aimed at containing the disease, aiming to reduce the burden on the global health system. However, such measures may have hurt the care of continuous users of the health service, such as, for example People Living with HIV/AIDS (PLWHA) and on the screening of new HIV infections through rapid tests (ESPANHA, 2020).

Because of this, the use of rapid tests for the screening and diagnosis of new HIV-infected individuals is fundamental for the fulfillment of the UNAIDS 90-90-90 goal, which aims to achieve the diagnosis, treatment and undetectable viral load of 90% of PLWHA. However, policy measures aimed at resolving COVID-19 and social isolation may have affected access to rapid tests, making it difficult to diagnose early and meet the 90-90-90 target (JIANG et al, 2020; John et al, 2015; Saharia et al, 2013).

Another aspect that may have been affected due to social distancing is sexual practices, which impacts on the alteration of individuals' exposure to HIV infection. Interim studies have shown that the COVID-19 pandemic has had effects on sexual behavior among Spaniards. However, data on the sexual behaviors of Brazilians, especially Alagoas, are still unknown, which highlights the importance of adding new knowledge and, thus, promoting policy proposals to combat HIV (BALLESTER-ARNAL, 2020).

For this reason, it is valid to investigate the possible change in sexual behavior among Alagoas during the pandemic, as well as to analyze the presence of other sexual practices, such as online sex and masturbation. The aim is to investigate whether the confinement has made it possible to reduce the number of sexual partners or to act in the reduction of the number of different people with whom these contacts are made, directly implying in the reduction of the risk of HIV infection.

2 OBJECTIVE

2.1 GENERAL

To analyze the impacts of the COVID-19 Pandemic on people living with HIV/AIDS in a Reference Unit of Maceió-Alagoas.

2.2 SPECIFIC

Relate the pandemic with the possible change in sexual behavior among Alagoas, the number of sexual partners or the number of different people with whom contacts are made, determining the influence on the risk of HIV infection.

3 MATERIAL AND METHODS

Because it is a study with human beings, this research project was forwarded and approved by the Ethics and Research Committee (CEP) of the State University of Health Sciences of Alagoas (UNCISAL). In addition, it was necessary to recruit subjects and use the Free and Informed Consent Form (ICF).

Type of study: It is exploratory and descriptive, with a quantitative approach of the documentary type. Data are obtained through the application of questionnaires to individuals undergoing HIV testing, in addition to the analysis and comparison of specialized literature.

Research location: The research is linked to the State University of Health Sciences of Alagoas – UNCISAL, the researchers' link institution. Questionnaires were applied to individuals who underwent rapid HIV testing at the Specialized Care Service (SAE) in block I of PAM Salgadinho.

Sample: The sample consists of 183 questionnaires answered by people who sought the NCS between the periods of August 2021 and March 2022.

Inclusion and exclusion criteria: Questionnaires answered by individuals recruited from the NCS who underwent rapid HIV testing between August 2021 and March 2022 were included, and those who did not have an active sex life were excluded.

4 RESULTS AND DISCUSSION

A total of 183 questionnaires were applied to people who sought care for the rapid test at the Specialized Care Service (SAE) of PAM Salgadinho.

There was a greater search among people from 20 to 35 years old, totaling 108. Overall, there were 111 males and 72 females. Being 90 heterosexual, 63 homosexual, and 24 bisexual.

The major cause of the search for the rapid test resulted from unprotected sexual intercourse, representing 36.00% of the cases. While 26.00% claimed curiosity, being the second largest cause.

Table 1 – Reflection of the pandemic on the number of partners

Has the pandemic affected the number of partners you used to relate to? No. (%)		If so, what is the change in the number of partners? No. (%)	
Yes	78 (42,60)	Increased	14 (17,94)
No	36 (19,68)	Decreased	61 (78,21)
There was no change	46 (25,14)	NDR	03 (03,85)
NDR	23 (12,58)		
Total	183 (100,00)	Total	78 (100,00)

When asked if the pandemic affected the usual number of sexual partners, 78 (42.60%) answered yes, 61 (78.21%) of them claimed that there was a decrease. Similarly, BALLESTER-ARNAL and GIL-LLARIO (2020) showed that confinement reduced the number of sexual contacts or at least the number of different people with whom these contacts were made between Spaniards.

Table 2 – Means used to know possible sexual partners

Wherewithal	Before the pandemic No. (%)	During the pandemic No. (%)
Social networks, social networking sites and apps	69 (37,70)	105 (57,38)
Parties, bars and restaurants	35 (19,13)	00 (00,00)
Other	41 (22,40)	42 (22,95)
I don't want to answer	38 (20,77)	36 (19,67)
Total	183 (100,00)	183 (100,00)

According to BRODIE, WILSON and SCOTT (2019), technological progress has allowed a revolution in the media, providing the intimate approximation, emergence and maintenance of relationships between various individuals.

According to table 2, with the restrictive measures resulting from the pandemic, people stopped going to parties, bars and restaurants to meet and relate to others. In contrast, the 37.70% of respondents who used digital media (social networks, social networking sites and applications) in the search for partners increased to 57.38% during the pandemic period.

Table 3 – Sexual activity during the period of confinement

During the period of confinement No. (%)	
Stopped sexual activities	63 (34,43)
I didn't have relationships before the pandemic, I did during the pandemic	03 (01,64)
I maintained relationships only with people from the same household/house	66 (36,07)
I left home to have relationships with other people	36 (19,67)
I don't want to answer	15 (08,20)
Total	183 (100,00)

Asked about the practice of sexual activity during the period of confinement, it was observed that 34.43% of the interviewees said they had interrupted it. At the same time, 36.07% reported keeping it only with people from the same household.

Table 4 – Habits that have increased during the pandemic

	Has the habit of masturbating and there has been an increase during the pandemic No. (%)	Have practiced virtual sex and there has been an increase during the pandemic No. (%)	It has already had an unprotected relationship and there has been an increase during the pandemic No. (%)
Yes	87 (47,54)	48 (26,23)	96 (52,46)
No	78 (42,62)	120 (65,57)	72 (39,34)
I don't want to answer	18 (9,84)	15 (8,20)	15 (8,20)
Total	183 (100,00)	183 (100,00)	183 (100,00)

In contrast to the isolation in the pandemic period, there was an increase in masturbation for people who already had the habit of this practice, in addition to the growth of virtual sex. What TURBAM, KEUROGUILIAN and MAYER (2020) see as an important fact, given the fulfillment of human needs for intimacy necessary for the preservation of individual and collective mental health. For, sexuality is a fundamental piece of human development (PONTES, 2011).

However, for 52.46% of the interviewees, there was an increase in the number of unprotected sexual relations. A relevant fact, however, its motives were not explored in the questionnaire applied.

Table 5 – Protection methods used before and during the Pandemic

Methods	Before the pandemic No. (%)	During the pandemic No. (%)
Men's/women's condom	120 (65,57)	105 (57,38)
Coitus interruptus	09 (4,92)	10 (5,46)
Male / female condom – Coitus interruptus	06 (3,28)	05 (2,73)
Contraceptive	05 (2,73)	04 (2,19)
Male / female condom – Coitus interruptus – Contraceptive	05 (2,73)	03 (1,64)
SAYS	00 (00,00)	00 (00,00)
None	26 (14,21)	49 (26,78)
Other	00 (00,00)	00 (00,00)
I don't want to answer	12 (6,56)	07 (3,82)
Total	183 (100,00)	183 (100,00)

There was a reduction from 120 (65.57%) to 105 (57.38%) condom users, when compared to the current period before the pandemic. Another important data was the 12.57% increase in the number of people who said they used no protective method during the pandemic.

5 CONCLUSION

One can Note that with the social isolation measures resulting from the pandemic period, there was a reduction in the number of sexual contacts with different people among the interviewees. In addition, a significant number of individuals reported having ceased their sexual activities during the turbulent period. Thus, these findings may have had a positive impact on reducing exposure to the human immunodeficiency virus (HIV), given that the pathogen is more commonly transmitted through unprotected sexual intercourse and the exchange of body fluids. However, it was observed that among people who maintained an active sexual life, there was an increase in the number of unprotected sexual relations, largely among those from the same household. Other characteristics of sexual behavior observed by the study are the growth in the use of digital media in the search for partners, virtual sex, as well as increased masturbation.

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Epidemiological analysis of the clinical profile of patients with incarcerated hernia at the Ceilândia Regional Hospital in the Federal District

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ABSTRACT
The patient with the picture of incarcerated inguinal hernia is in an emergency stage, requiring an emergency surgical procedure. Seeking to evaluate this picture, to understand the clinical profile, to foster a clinical-epidemiological analysis, analyzing the important variables in this type of patient, define the risk factors and most commonly found conditions. It is also necessary to address the intraoperative findings, complications and postoperative time. Thus, changes could be made in relation to the conditions encountered, which may change the clinical outcome of many patients. In a descriptive qualitative observational study, with 40 patients with the clinical picture of incarcerated hernia, all patients underwent hernioplasty. Following the same surgical technique. The primary outcome was that only patients with comorbidities/risk factors had complications and the second outcome was that patients undergoing the surgical procedure did not die. After the follow-up of similar pictures for 12 months. The first outcome, it was possible to observe that the patients with previous comorbidities/risk factors, 35 (87.5%) of the 40 selected, had the following conditions: 14 (35%) patients with obesity, 7 (17.5%) were chronic smokers and 14 (35%) of the patients had previous tenesmus and 5 patients had no risk factors. Among the comorbidities, 1 patient had Down syndrome, 3 patients had liver cirrhosis, 8 had systemic arterial hypertension, 5 were defined as difficult to control, 4 with diabetes mellitus, 6 patients with anterior diverticulosis and 6 with chronic constipation. The secondary outcome occurred with 40 patients, since all of the group were operated on as a matter of urgency, in addition to patients who are not submitted to the surgical procedure die. It is concluded that the 5 patients who did not present comorbidities/risk factors, arrived at the hospital in a milder picture compared to the other (35) patients, having a better recovery and fewer days of hospitalization. Since preventive measures can be implemented for patients who have hernia, it is recommended to monitor the risk factors, in order to avoid severe conditions and long hospitalizations.

Keywords: Incarcerated hernia, Hernia, General surgery, Digestive system.

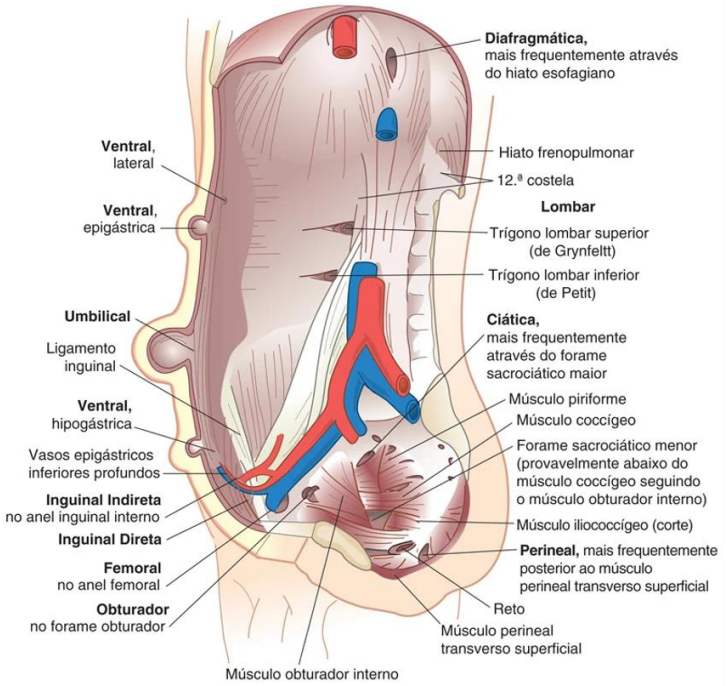
1 INTRODUCTION

Hernia is a word derived from Latin and means rupture. In medicine it is the definition of the protrusion of an organ or tissue through the walls that surrounds it and can occur in various parts of the human body and is associated with the lack of coverage of the fascia and aponeurosis by striated muscle. Anatomically the hernia originates from a neck or hole in the innermost musculoaponeurotic layer and the hernial sac is formed by peritoneum.

The causes for hernias can be congenital, such as the persistence of the peritoneum-vaginal conduit, some metabolic to even external syndromes can also be associated with smoking that decreases skin thickness, bone density and causes muscle toxicity. Hernias can be classified into internal when the protrusion occurs within a defect inside the peritoneal cavity, or external when it crosses all layers of the abdominal wall or even interparietal when it is limited to the musculoaponeurotic layer of the abdominal wall.

The most prone site to suffer herniations is the abdominal cavity, with the most affected areas being the inguinal, femoral and umbilical, the linea alba, the lower portion of the semilunar line and sites of anterior incisions any segment of the abdominal wall. In the groin, inguinal hernias are located, subdivided into indirect, direct is combined, and femoral; umbilical, epigastric and Spiegel's hernias occur in the anterior wall; in the posterior wall the lumbar hernia, in the superior triangle and inferior triangle and, finally, in the pelvic region the hernias of the obturator, sciatica, perineal. There is a higher prevalence of occurrence in the inguinal region.

Figure 01: Types of hernias of the abdominal wall. (From Dorland's illustrated medical dictionary, ed 31, Philadelphia, 2007, W.B. Saunders, Plate 21.



2 METHODS

2.1.1 TRIAL SUPERVISION

The epidemiological analysis of the clinical profile of patients with incarcerated hernia at the Hospital Regional da Ceilândia in the Federal District was a qualitative descriptive observational study that was conducted at the Hospital Regional da Ceilândia in the Federal District. The trial design and baseline characteristics of the patients have been preserved and not published. The study was designed

at the Hospital and supervised by the Regional Ethics and Research Committee, and was approved for production. The study has no funders. The authors take responsibility for the accuracy and completeness of the data and analyses, as well as the fidelity of the essay.

Patients:

During the period analyzed, a prevalence of males was observed among the patients treated at the Regional Hospital of Ceilândia (HRC) with incarcerated hernia. The distribution by sex is 67.5% (27) men and 32.5% (13) women, totaling 40 patients. Patients who had an incarcerated hernia during the study period were included. The inclusion and exclusion criteria are in the supplementary appendix. It was based on the collection of secondary data, available in the "Trakcare" system – a system used in the patient care services of secondary hospitals in the Federal District.

Findings:

The primary outcome was that only patients with comorbidities/risk factors had complications. Among them, the most significant that happened to 35% of the patients (14) was the length of hospitalization that lasted more than 4 days, due to a longer delay in presenting improvement. In addition, it was possible to observe that in 5 patients (12.5%), of those who had previous comorbidities/risk factors, they presented delay for diuresis to return to normal. The secondary outcome was that the patients submitted to the surgical procedure did not die, since this confirms the surgical protocol.

Statistical analysis:

TABLE 1 - RISK FACTORS AND COMBITIES IN INCARCERATED PATIENTS WITH HERNIA

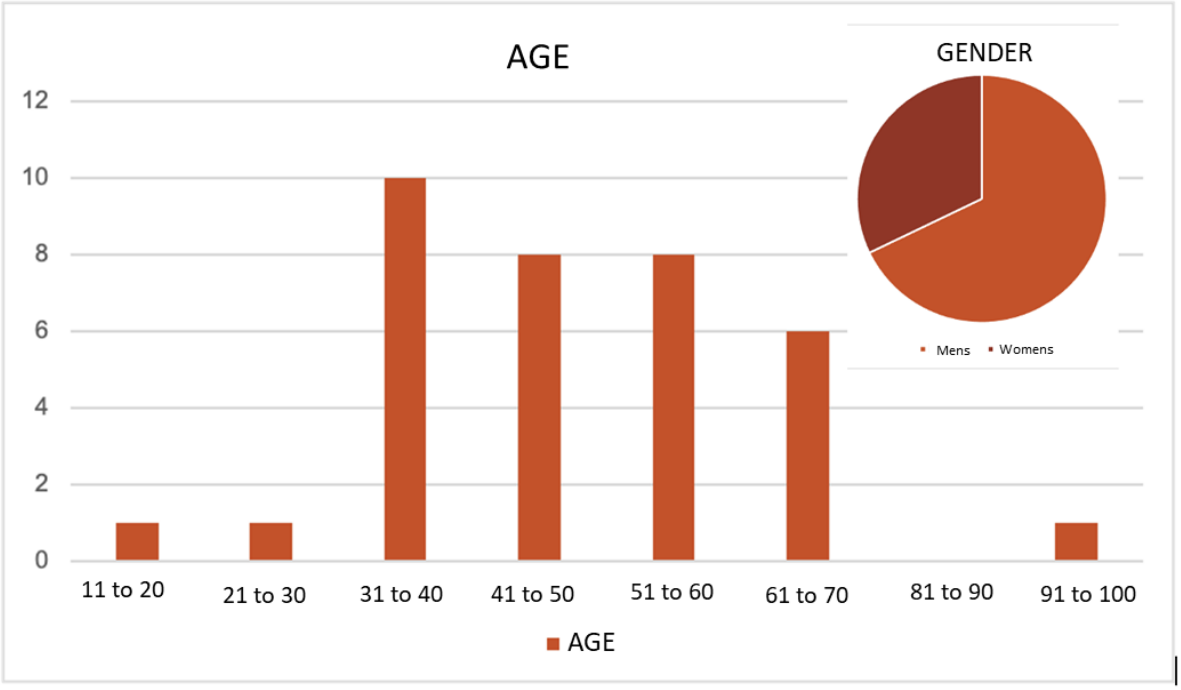
RISK FACTORS	COMBITIES
• Smoking • Chronic constipation • Tenesmus • Obesity • Chronic cough	• Hepatical cirrhosis • Diabetes Mellitus • Down's syndrome • Systemic Arterial Hypertension • Previous infarction

Among the patients analyzed, they had the risk factors and comorbidities mentioned in Table 1. We analyzed each medical record, looking for similar patients with specific characteristics.

3 FINDINGS

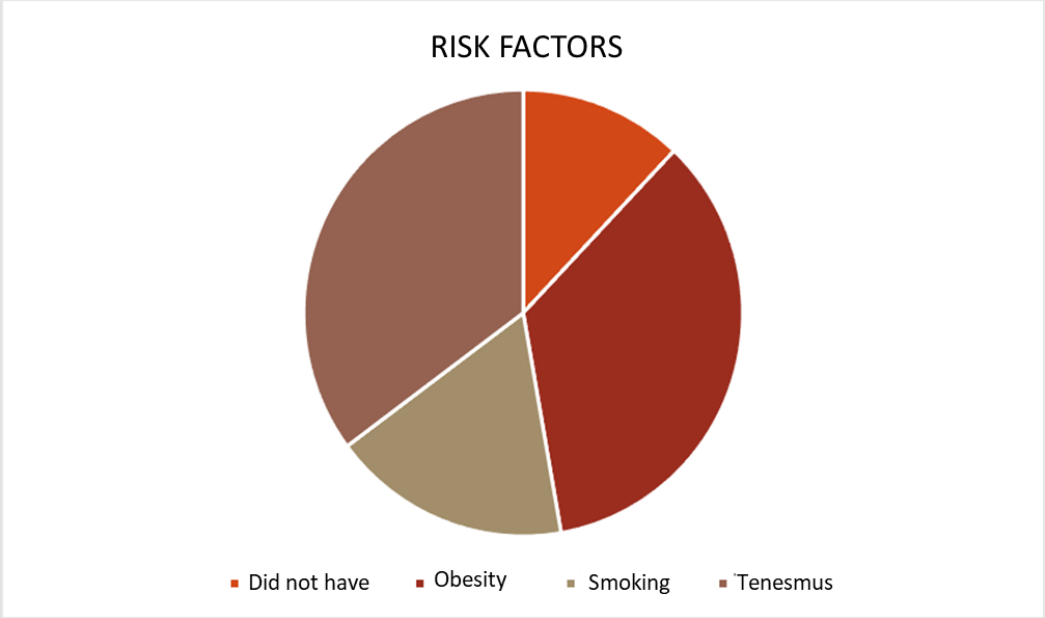
The study aimed to analyze the profile of patients with incarcerated hernia. When we analyzed the 40 cases and all patients were discharged, it was possible to conclude the study and proceed to the

analysis of the data we were able to identify. All analyses were aimed at the prognosis. The results were analyzed using time and event methods.



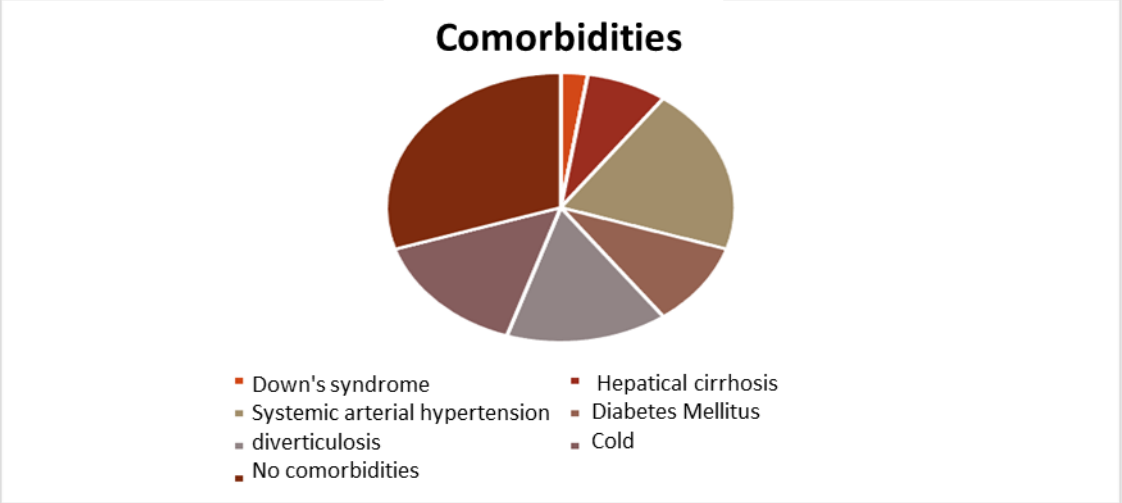
During the period analyzed, a prevalence of males was observed among the patients treated at the Regional Hospital of Ceilândia (HRC) with incarcerated hernia. The distribution by sex is 67.5% (27) men and 32.5% (13) women, totaling 40 patients, as can be seen in graph 01. Regarding the distribution by age group, it is observed that there were only 01 patient in the range of 11 to 20 years, 1 patient between 21 and 30 years, 10 between 31 and 40, 08 in the range of 41 to 50 and 51 to 60, respectively, 06 between 61 and 70 and 06 over 71 years. The concentration in adult patients is noted, with 38 patients older than 31 years.

Graph 02- Risk factors.



Among the risk factors analyzed in the patients: 35 had at least 1 risk factor and 5 no associated factors, among these factors 14 (35%) had obesity, 7 (17.5%) reported being chronic smokers and 14 (35%) had previous tenesmus.

Graph 03- Comorbidities.



Among the comorbidities, 1 patient had Down syndrome (2.5%), 3 patients had liver cirrhosis (7.5%), 8 with systemic arterial hypertension (20%), 5 of which were defined as difficult to control, 4 with diabetes mellitus (10%), 6 patients with anterior diverticulosis (15%) and 6 with chronic constipation (15%). The secondary outcome occurred with 40 patients, since all of the group were operated on as a matter of urgency, in addition to patients who are not submitted to the surgical procedure die.

3.1.1 ACCOMPANIMENT

After the follow-up of similar pictures for 12 months. The first outcome, it was possible to observe that the patients with previous comorbidities/risk factors, 35 (87.5%) of the 40 selected, had the following conditions: 14 (35%) patients with obesity, 7 (17.5%) were chronic smokers and 14 (35%) of the patients had previous tenesmus and 5 patients had no risk factors. Among the comorbidities, 1 patient had Down syndrome, 3 patients had liver cirrhosis, 8 had systemic arterial hypertension, 5 were defined as difficult to control, 4 with diabetes mellitus, 6 patients with anterior diverticulosis and 6 with chronic constipation. The secondary outcome occurred with 40 patients, since all of the group were operated on urgently, in addition to patients who are not submitted to the surgical procedure will die

4 DEBATE

Hernia is a disease with high prevalence worldwide and its development is multifactorial, since it is associated with age, lifestyle habits, genetics, comorbidities among other factors. Of which are part smoking, which can affect various pathogenic pathways of collagen formation and degradation.

According to the studies, hernia incarceration mainly affects adults of productive age. According to our research, there actually was a higher prevalence at the ages of 31 to 40 years.

Hernias represent a worldwide problem and although it does not have a known incidence the risk of developing inguinal hernias throughout life is estimated to be around 25% for men and less than 5% for women. Our study agrees with the references, evidencing a prevalence of males among the patients attended.

In addition, tobacco use is related to increased recurrence of hernias. A large prospective series of 4,855 patients undergoing different types of gastrointestinal surgery shows that smokers have a 64% higher risk of postoperative wound infections and an 80% higher risk of postoperative rupture of wounds or sutured tissue in the first 30 days after surgery.

The effort to evacuate is another factor that implies the development of hernias, as it causes increased pressure in the abdominal cavity, one of the main etiopathogenic mechanisms.

Cough in smokers or patients with chronic obstructive pulmonary disease (COPD), family history and constipation are the main risk factors for increasing the pressure in the abdominal cavity (Sperandio, 2008) and favor the passage of structures through places where the abdominal wall is fragile

5 CONCLUSION

In view of the above, it was observed that the cases of incarcerated hernia in the Regional Hospital of Ceilândia confirm the data of the studies on the subject regarding the epidemiological characteristics of the involvement of hernias.

It was noticed that the development of the hernia is multifactorial, but the need for a local predisposition for their formation must be considered. It was also verified the high prevalence in male adults, in addition, the most preponderant risk factor in the cases is tenesmus and smoking. Therefore, all the data corroborate with the information in the bibliography on the subject.

This work consists of alerting the health professional to prioritize the epidemiology of the patient for the diagnosis of the disease, since this diagnosis is relatively simple, when observing the clinical history and evaluating by computed tomography and ultrasonography.

Finally, the treatment of hernias is a challenge for surgeons, mainly due to the lack of consensus on the best techniques and also due to the large number of postoperative recurrences. Thus, it is necessary to create guidelines based on scientific evidence that guide the best techniques for treatment.

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Public policies in children's mental health: Ways to promote health

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ABSTRACT
The study aimed to reflect on the evolutionary process of public policies on mental health for children. This is a theoretical essay with a reflective nature. The proposed reflections were based on relevant international and national literature. Anxiety Disorders become increasingly common in children, causing negative impacts on various cognitive and learning functions. It is concluded that it is necessary to develop and strengthen public policies in mental health, which are capable of reorienting care practices regarding the prevention of mental disorders in childhood.

Keywords: Anxiety disorder, Infancy, Mental health, Public policy.

1 INTRODUCTION

The development and implementation of public policies directed to the population of children and adolescents were non-existent about mental health care for population groups. Thus, children and juveniles who presented psychological distress were absent from care, although there were special

schools, psychiatric hospitals and shelters, these acted in an authoritarian and oppressive way (FERNANDES et al., 2022).

Children and adolescents who presented some mental alteration were submitted to the power of the State, which established social protection through institutionalization, without interest in understanding the current psychological needs. These children began to be taxed in society as: abandoned, delinquent and/or incapable, thus removed from social life as a public strategy (SOARES et al., 2018).

In 1927, the Code of Minors or Mello Mattos Code emerged, helping to modify the institutionalization of minors with mental changes, however its focus was on "street" children, seen as a threat to society (SOARES et al., 2018). With the emergence of population movements in search of rights, some means provide mental health care to Brazilian children and adolescents, such as the psychiatric reform and the Child and Adolescent Statute (ECA) in 1990. In 2003, the Child and Youth Psychosocial Care Centers (CAPSij) were created, and in 2004 the Child and Youth Mental Health Forum was created through the Ministry of Health (FERNANDES et al., 2022).

According to the Ministry of Health (S.D.), aimed at children and adolescents, there is the Child and Youth Psychosocial Care Center (CAPSi) intended to care for children and adolescents with severe and persistent mental disorders, including the use of psychoactive substances that includes cities or regions with at least 70 thousand inhabitants.

The use of services such as CAPSi presents some obstacles in its functioning, since referral is the main form of contact between the family health strategy (FHS) team and the CAPSi, often carried out via telephone call, direct sending of the patient to the other unit, or through a regulation center, to verify if there is a vacancy available to perform the triage of the patient. However, some cases the referrals occur without contact between the teams, often without any reception for their need (Delfine and Reis, 2012)

Thus, it is understood that there is no sharing of the therapeutic plan, being notorious the occurrence of passage of cases and isolated evaluation of the case by each team, evidenced the disarticulation and fragmentation of actions, making integral and transdisciplinary care unfeasible (DELFINI; REIS, 2012).

In 2001 there is the publication of the Mental Health Law, Law 10,216, as well as the III National Conference on Mental Health (CNSM), thus favoring the constitution of mental health as a State policy. Care comes to be understood as a model of community care, with the development of the inclusion, in psychosocial care, of mental disorders in children and adolescents (COUTO; DELGADO, 2015).

The main records of the psychiatric reform were the gradual closure of existing asylums and hospices in the country, changing the treatment for hospitalization of patients in case of inefficiency

of extra-hospital treatment. In addition, in place of psychiatric hospitals, in 2002 the Psychosocial Care Centers (CAPs) were created, considered centers for the reception of patients with mental disorders, in non-hospital treatment, providing multiprofessional care, to promote reintegration into society (BRASIL, 2021)

The new conception of children and adolescents through the III National Conference on Mental Health in 2001 made it possible to visualize them as beings susceptible to suffering and mental illness, with the right to be assisted throughout life, to promote quality of life, support of social ties and/or adaptation of behaviors. Still, the State could take responsibility for the care and treatment of these individuals, aiming at recognizing their psychosocial need while maintaining ethics and respect for their rights as citizens (COUTO; DELGADO, 2015).

A study shows that the country has around 13% of the child and adolescent population have some mental health diagnosis, with a tendency to persist of symptoms in a chronic form. It is believed that among the severe and chronic cases registered, of these, only 37.5% have received some treatment in five years (FATORI, 2018).

The insertion of child mental health in public health late, especially after the year 2001, expanded health care and promotion. However, it is believed that there are significant barriers to the holistic view of the mental changes suffered by children and adolescents in Brazilian society.

In this context, it is evident the importance of understanding the trajectory of public policies in children's mental health, as well as promoting greater integration between existing services, aiming to establish strategies for the health promotion of this group of individuals to optimize the care and care of these patients who need individualized and humanitarian health care.

Given the above, the study aimed to reflect on the evolutionary process of public mental health policies for children.

2 METHOD

It is a theoretical essay of reflective nature, based on the discursive formulation of the theme, supported by the national and international scientific literature and critical analysis of the authors.

It is emphasized that the reflections woven result from the interpretations of the literature and also from the impressions of the authors. The presentation of the explanations will take the form of a guiding axis on the theme, arising from interpretations. As there was no interaction of direct/applied research, the need to submit the study to ethical procedures was excluded.

3 RESULTS AND DISCUSSION

3.1 PUBLIC POLICIES: NEW PRACTICES FOR CHILDREN'S MENTAL HEALTH

There is an urgent need for reflections on health needs, which should be understood as a broad field of care processes for each individual, to establish limits for health-promoting interventions. In this sense, it is necessary to consider, therefore, characteristics intrinsic to the way of life of the individual, whether or not related to their disease (FREITAS, 2022).

Thus, it is necessary to understand the definition of health, disease, understand the demands of the field and differentiate individual needs from those that are intrinsic to the collective context. Therefore, thinking about health transcends the issue of disease itself, highlighting the need to reproduce a vision that seeks to incorporate knowledge related to aspects related to the health-disease process. This understanding should focus on a horizontalized and systematic approach to health, seeking to identify the conditioning factors and determinants that interfere with health (LIMA, 2015).

The expansion of the concept of health introduces plurality over the understanding of the social context in which the subjects are inserted as a powerful determinant for the health condition. On this basis, it approaches the assumptions of health promotion, under the prism of investigating the health-disease process of the social determinants of health (BUSS, 2014).

In this context, the plurality of the health object expresses the need to understand it in the search to achieve a state of quality of life. Mental health is defined as a state of well-being in which the individual perceives his abilities, being able to deal with his normal tensions of his daily life, namely, life, work productively, and able to offer contributions to his community (WHO, 2005).

With the advent of the globalization process in the postmodern world, there was an increase in the prevalence of mental illness in the population, caused by the rhythm of life instilled by industrial societies, which are responsible for the different demands and pressures on individuals (BAILEY, 2022).

The Anxiety Disorder (ED), represents as one of the most recent conditions reported in the current population. ED is characterized by excessive fear and anxiety, and fear corresponding as the emotional response to threatening situations that prepares the subject for fight or flight. As for anxiety, this corresponds to an anticipated reaction of future threat, composed of muscle tension and a high level of vigilance, leading to behaviors of caution or avoidance (DSM-5; APA, 2014).

ED presents with persistent anxious symptoms that can affect a wide variety of behaviors. Such manifestations can vary over time and include symptoms of motor tension, for example, fears, inability to relax, fatigue, headache, symptoms of atomic hyperactivity, such as palpitations, sweating, dizziness, cold and hot flashes, shortness of breath, irritability and difficulty concentrating (LOPES, 2018).

Anxiety currently corresponds to the second leading cause of disability among the main mental disorders (GBD, 2016). A study reveals that the prevalence of anxiety in Brazil is comparable to data

from other countries. Latin America and Brazil have prevalence rates of anxiety higher than the global average, and Brazil is ranked 4th. position among the countries in which anxiety has the highest rates around the world (MANGOLINI, 2018).

Among population groups that showed a substantial increase in ED, children and adolescents point out. In Brazil, data show that the incidence of anxiety disorders in children and adolescents reaches 3.40% and 5.04% respectively (FUNDAÇÃO OSWALDO CRUZ, 2022).

Epidemiological data indicate that among the main anxiety disorders in children are: social anxiety disorders, panic, depression increase with age. Among the disorders presented we have the social phobia acting predominantly in children and adolescents, who present continuous fear in situations that present insecurity (ASBAHR, 2007).

In the year 2020, the World Health Organization (WHO) declared the Coronavirus Disease *(COVID-19) pandemic, constituting a Public Health Emergency of International Importance (PHEIC) (WHO, 2020*). Among the interventions to reduce the contagion, in mid-March 2020, social distancing began with school closures, keeping all children at home, as well as part of the general population that did not work with essential services (BRASIL, 2020).

Therefore, such measures evidenced important impacts on the daily activities of children, who had routine changes, such as attending schools, having their studies interrupted, facing a new one. The restriction of social contact has had negative consequences for the mental health of this specific group (PAIVA, 2021).

In this context, it is inferred the need for public health policies that can consolidate care that seeks new propositions regarding the health construct (BRAGA, 2019). Public policies in health are based on a perspective that considers the importance of understanding the conception of health constructed by movements of social struggles, historically marked by the curative model, centered on hospital-centered care (SARRETA, 2009).

The development of public policies starts from the assumption of the need for the way social policies are structured and, among them, health policies, fundamental for the development of horizontalized health practices. Therefore, it is important to recognize the articulations between economic, political and health practices as important elements for the development and implementation of health policies (TORRES, 2020).

The State assumes the role of creating and implementing alternatives to promote and direct economic and social development. Such actions make the State as an inducing agent of the movement of society as a whole, with actions that can reduce inequities between population groups (PESSOTO, 2015).

In the Brazilian context, the performance of the State presents itself as an organizer of the great production and social control of the collectivity. Thus, the recognition of the needs of different social

groups, operates as an instrument that allows to evaluate and understand the health-disease process in its plurality (CARMO, 2017).

It is known that mental health care in Brazil began in the late 1970s, with the process of psychiatric reform regarding struggles for the redemocratization of the country, and criticism of the conditions of psychiatric care and search for improvement in psychiatric care (AMARANTE, 2003).

In this sense, the Brazilian public policies for Mental Health - MH, Law 9.867/1999 provided for the creation and operation of Social Cooperatives, aiming at the social integration of citizens and people at a disadvantage, listed as follows: the physically and sensory disabled; the mentally and mentally handicapped, people dependent on permanent psychiatric monitoring, and those discharged from psychiatric hospitals; drug addicts and prison graduates. This law is a follow-up to the Caracas Declaration, a document generated at the Regional Conference for the Restructuring of Psychiatric Care held in 1990 (BIREME/PAHO/WHO, 1999; BRAZIL, 2005).

In 2001, a new law was enacted that introduced the National Mental Health Policy. Law 10.216 is considered as a sociopolitical movement resulting from it the so-called Brazilian Psychiatric Reform (BERLICK et al., 2008).

In the search for a new care model that would enable health services within the SUS domain, Decree No. 7,508 was created in 2011, which established the requirement of psychosocial care as one of the requirements for the establishment of Health Regions and organization of Health Care Networks, being considered as a historical landmark in Brazilian mental health care (BRASIL, 2016).

In the context, child and adolescent mental health care was included late in the public health agenda. However, although the introduction of this population in public health policies was late, positive results were observed in terms of progress in the field of care practices and knowledge production. Law No. 10,216/04, which deals with the mental health of children and adolescents, gave visibility to the main milestones from the understanding of the continuous need to expand the participation of children and adolescents in mental health services (BRAGA, 2019).

Another important milestone in the mental health care of children corresponded to the creation of the Child Psychosocial Care Center (CAPSi), which seeks to qualify the information of the practices of the Psychosocial Care Center (CAPS), which aims to qualify practices, affirming the articulation and integration of the different points of care, as well as defining strategies and actions in the daily practice of health services (BRASIL, 2011).

In this context, the need for health professionals who can offer mental health care to children with anxiety disorders emerged, with practices articulated with the care care networks, to identify protective factors and promote interdisciplinary care

A study points out that a professional assistance to children with ED, based on care practices through individual consultations and collective activities, where one can assume a social function, with

the inclusion of welcoming (FREITAS, 2020). Thus, listening is presented as a therapeutic instrument at the interface of recognizing the health needs of individuals

Thus, it is necessary to discuss the role of primary health care in the health care of children with ED. Primary Health Care (PHC) is presented as a proposal to reorient the health care model, with a commitment to seek comprehensive care with a focus on health promotion and disease prevention. Thus, it is a key element in ensuring integrality, universality and equity, thus reinforcing the principles of the Unified Health System (SUS) (OCCHIUZZO, 2021).

PHC is anchored in a longitudinal, comprehensive (integral) care oriented to the family and community, from the perspective of health promotion, which aims at preventive health actions to face the social determinants of health-disease and greater autonomy of the subjects regarding their health condition (MATTIONI, 2023).

However, it emphasizes that the development of care practices for children with ED presents itself as a challenge for health professionals, both due to the characteristics of this population group, the sociocultural aspects, and the forms of organization of health equipment (BATISTA, 2017). Therefore, it is necessary to reflect on the training of these professionals as a way to expand their dimensions of care

Thus, faced with the need to reorganize health practices that can meet the assumptions of health promotion, that in 2015 the United Nations (UN), presented ways to achieve dignity in the next 15 years, effective between 2015 and 2030, through the construction of the post-2015 development agenda with the 17 sustainable development goals (SDGs), reinforcing the multilateral commitment to eradicate problems that afflict population groups (UN, 2017; Smith, 2019).

Health is represented in Goal 3 in the 2030 Agenda, which aims to ensure a healthy life and well-being in all phases of the life cycle, but also emphasizes its interrelationship with the problems of poverty eradication (Goal 1), food security (Goal 2), basic sanitation (Goal 6) and inequality between countries (Goal 10). It highlights the need to understand that all the Sustainable Development Goals are products of the socio-geographical territory, whose achievement of goals depends on the integration of the local with the global with interrelation with health (UN, 2017; DJONÚ, 2018).

The health SDG presents nine goals, namely: reduction of maternal mortality; ending preventable infant deaths; in the fight against epidemics and diseases transmitted by water and other vehicles; reducing premature deaths from non-communicable diseases; prevention and treatment related to the use of alcohol, tobacco and narcotics; reducing deaths in traffic situations and from hazardous chemicals; necessary access to health systems; and reducing the number of deaths and diseases from chemical products (EMBRAPA, 2018).

In Brazil, an important step in structuring the 2030 Agenda was the promulgation of Decree No. 8,892/2016 that created the National Commission for the Sustainable Development Goals

(CNODS) to internalize, disseminate and giving transparency to the implementation process of the "2030 Agenda" of Sustainable Development. According to the Decree, the CNODS has a consultative nature and is part of the Secretariat of Government of the Presidency of the Republic, for articulation, mobilization and dialogue with the federative entities and civil society to fulfil the international commitments assumed by Brazil (BRASIL, 2016).

4 FINAL CONSIDERATIONS

Faced with the above reflections, it expresses the need for the health object to be understood in its polysemic sense, corresponding as a state of complete well-being. Thus, understanding the social determinants of health of a population group allows the identification of health needs.

Thus, the development of public health policies and modes of mental health care for children with anxiety disorders is shown as a process for qualification and implementation of qualified health care, which can produce advances in the production of mental health care for children.

Finally, it is expected that new care strategies will be implemented as a way to guide practices and conducts of health professionals caring for children with anxiety disorders. Thus, these health practices can subsidize a new broader conception of health, understanding the dynamism and influence on the mental health-disease process.

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Public policies for mental health of schoolchildren: Prevention of child anxiety

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ABSTRACT
The study aimed to discuss public policies in the prevention of childhood anxiety and impacts on the teaching-learning process. This is a theoretical essay with a reflective nature. The proposed reflections were based on relevant international and national literature. Currently, increases in Anxiety Disorders have been observed in school-aged children, impairing their health, social relationships and learning performance. In this context, it is believed that the development of public policies is presented as strategies for promoting mental health, especially in the school context.

Keywords: Anxiety Disorder, Infancy, Mental health, Public policy.

1 INTRODUCTION

The Brazilian psychiatric reform had its project presented in 1989, by Deputy Paulo Delgado. However, only after 12 years, President Fernando Henrique Cardoso sanctioned Law No. 10216/2001, known as the Psychiatric Reform Law, the Anti-Asylum Law and the Paulo Delgado Law. Thus, the attention dedicated to the mental health of children and adolescents is one of the main challenges

related to the Brazilian Psychiatric Reform, since the emergence of the Child and Adolescent Statute, it is the responsibility of the State to assist and establish public policies related to this population of children and adolescents (SENADO FEDERAL, 2021; DELFINI; REIS, 2012)

With regard to Mental Health, the World Health Organization (WHO) defines it as a state of well-being in which the individual can fully develop their skills, recover from everyday stresses, have productivity and contribute to the community in which they are inserted. Currently, it refers to competition situations as the main reason for stress, where data reveal that one person in five develop some mental health problem as a result of work (BRASIL, S.D).

In general, mental disorders present behavioral changes that impair routines, be it school, work, social life and any other area of life. Regarding the signs and symptoms in children and adolescents, the main warnings are changes in sleep routine, abrupt isolation from family and social life, negative comments related to life, self-mutilation in the arms, use of cold clothes even in hot weather to hide the scars and decrease in school performance (BRAZIL, 2022).

Data provided by the Pan American Health Organization (2022), infer that in the year 2019 around one billion people had some mental disorder (MD), worldwide, of which 14% are adolescents. MD is a factor of great disabling potential in society, patients with the disorder evolve to death on average 10 to 20 years earlier. Still, after the first year of the pandemic, depression and anxiety increase by 25%, it is noted that a cause of childhood depression consists of sexual abuse and bullying abuse.

Anxiety is understood as a normal manifestation of an affective state, being a symptom that is present in several mental disorders as an essential clinical feature. This manifestation enables the individual to be alert to dangers and have survival attitudes in the face of threats and unknown situations. Also known as a state of apprehension or anticipation of dangers or unfavorable events, associated with feelings of worry, discomfort and tension causing suffering or significant impairment of functions (FROTA, 2022).

That said, anxiety presents subjective symptoms related to the psychological, such as fear, emotional concerns, depersonalization, and objective or somatic symptoms, which present nausea, abdominal pain, vertigo, dry mouth and palpitations (FROTA et al., 2022).

The Unified Health System (SUS) offers care to people in psychological distress, through the services of the Psychosocial Care Network (RAPS). Primary Health Care (PHC) is the gateway to specialized care, providing care and playing a fundamental role in addressing Mental Disorders and making the appropriate referrals. Therefore, care is composed of different levels of complexity, and the strategic points of attention of RAPS are the CAPS - Psychosocial Care Center, which consists of open and community health services, consisting of a multiprofessional team that acts in an interdisciplinary way (BRASIL, 2022).

A cross-sectional study conducted with individuals between 18 and 35 years of age showed a prevalence of anxiety disorders of 27.4% in 1,953 people. Of the total cases of anxiety there is a prevalence of agoraphobia and generalized anxiety disorder, as for sex there were higher occurrences in women (COSTA, 2019). The prevalence of anxiety regarding the distribution in the Brazilian regions, where they infer a predominance of anxiety disorders in the Southeast and South regions, with a high rate (19.9%) in the metropolitan region of São Paulo (MANGOLINI, 2019)

Anxiety disorders are increasingly present in society, regardless of age, but it reveals evolution among children and adolescents. Therefore, there are concerns about the triggering of other diseases in the face of anxiety, often without an adequate treatment, and alternative treatment with medicinal plants can be cited as an allied alternative (LOPES; DOS SANTOS, 2018).

Faced with this, the school phase is one of the phases that requires more attention, since it is the phase in which the manifestation of childhood anxiety occurs the most. Given this, it is undoubtedly that there are health promotion actions aimed at children and adolescents in order to establish an early diagnosis and timely and appropriate treatment, promoting quality of life to these individuals without major harm to their mental health.

The study aimed to discuss public policies in the prevention of childhood anxiety and impacts on the teaching-learning process.

2 METHOD

It is a theoretical essay of reflective nature, based on the discursive formulation of the theme, supported by the national and international scientific literature and critical analysis of the authors. It is emphasized that the reflections woven result from the interpretations of the literature and also from the impressions of the authors. The presentation of the explanations will take the form of a guiding axis on the theme, arising from interpretations. As there was no interaction of direct/applied research, the need to submit the study to ethical procedures was excluded.

3 RESULTS AND DISCUSSION

3.1.1 ANXIETY DISORDER IMPACTS ON CHILDREN'S LEARNING

Currently, there is an increase in mental disorders in the world population. Therefore, the need arose to understand a new paradigm about the health object, which is characterized by considering the individual in its complexity by inserting social, psychological and physical aspects as a dimension of health (FARIA, 2020).

In this direction, mental health should be understood as the ability to achieve and maintain a good psychosocial functioning and a state of well-being in which the individual perceives his own abilities, and can cope with the normal tensions of life, work (WHO, 2014).

Tooth the population groups with mental disorders, deserve to be highlighted for children. Studies indicate that, on average, 8% of this school-age population has relevant symptoms or suffers from some Anxiety Disorder (ED) (FERNANDES, 2014). In Brazil, data show that the incidence of anxiety disorders in children and adolescents reaches 3.40% and 5.04% respectively (FUNDAÇÃO OSWALDO CRUZ, 2022).

The association of mental disorders in childhood are associated with greater losses in educational activities, lack of social cohesion and reduced ability to face future adversities (KESSELER, 1995). Also in Brazil, more than 80% of children aged 6 to 12 years with mental disorders do not receive adequate treatment, evidencing gaps in mental health care (FATORI, 2019).

In the case of this population, ED is shown to have a high incidence, causing damage that affects school performance, the relationship with family, friends and often prevents the social contact of these children (ASBAHR, 2004). Anxiety has as main characteristics self-protection and concern in relation to events that may bring danger to the child or to his acquaintances, and the intensity of manifestation and interference in the day to day is what makes it become pathological or not (ASBAHR, 2004; STALLARD, 2010).

The AT is characterized by excessive fear and anxiety, and fear corresponding as the emotional response to threatening situations that prepares the subject for fight or flight. As for anxiety, this corresponds to an anticipated reaction of future threat, composed of muscle tension and a high level of vigilance, leading to behaviors of caution or avoidance (DSM-5; APA, 2014).

Among the main symptoms are, stomach pain, excessive sweating and palpitation without clinical cause, too much worry and irritability, avoidance of events or circumstances, fear of public speaking or manifesting, among others (FRIEDBERG AND MCCLURE, 2004).

Some anxiety disorders with a higher incidence in children are pointed out, among them: Separation Anxiety Disorder, characterized by the excessive and abnormal fear that the child feels in separating from his attachment figures or from his home, so that this impairs his development; Social Phobia, which is the excessive fear of strangers or situations of social contact with many people in which there is the possibility of feeling evaluated; Panic, characterized by sudden attacks of fear or intense discomfort in which there is presence of very strong anxiety and fear of dying, being constant the fear that new episodes may occur; Agoraphobia, characterized by fear or avoidance of very small situations and environments, with many people or without nearby exits, in which the subject may feel humiliated or embarrassed; fear and anxiety are usually disproportionate to the danger presented; Generalized Anxiety Disorder, which manifests itself through the feeling of insecurity, anxiety and persistent worry that the child presents daily (ASBAHR, 2004; APA, 2014; STALLARD, 2002).

The factors related to the causes of anxiety in childhood may be associated with the complex interaction of biological, cognitive, behavioral and social influences. Notably, the weight of these

causal factors may vary between individuals. Therefore, the child's vulnerable temperament, the behavior of the parents (personality and stress factors) and environmental factors, such as low socioeconomic level, child abuse, criminality, alcohol and drug use by family members, among others (LIZUCA & BARRET, 2011).

It is worth mentioning the losses of anxiety in childhood in the school context, presenting impairments in the performance of various cognitive functions, such as memory, attention and executive functions. Factor that will directly impact the learning process, which depends on the relationship between synapses with other brain and neural instances (DAMASIO, 2010).

Neuropsychology, which is a science that studies behavior, emotions and thoughts and how they are linked to the brain, plays an important role, measuring children's cognitive abilities, by encompassing a set of procedures, such as observation, interview, task administration and the use of standardized performance assessment tools (MALLOY-DINIZ et al., 2018).

Therefore, children with anxiety disorder have limitations regarding activities that require specific focuses, and/or maintain sustained attention for a period of time, as well as concentrate, related to the disabling of focusing, causing significant losses in their teaching-learning process (SANTOS, 2022).

Given this context, the importance of public health policies as a fundamental pillar of social protection systems is highlighted. To observe in recent decades the reformulation of public policies, which could perceive, understand and select the pluralities of the social refractions of a collectivity, in order to offer answers to the existing demands (MADEIRA, 2020).

Therefore, the struggle to infer the broad attribution of States and types of interventions in society, whether in the economy, or in the provision of public services, is based. Thus, to allow the effectiveness of the principle of universality, focusing on subjects in a situation of vulnerability, such as people with mental disorders (CARMO, 2018).

In this context, the State assumes a role over actions related to the multiple dimensions of social life. Therefore, it is understood that the understanding of social refractions directed at the State makes it a legitimate agent to resolve disputes and understand collective demands, in order to reduce inequities between population groups (PESSOTO, 2015).

In the national scenario, public health policies in Brazil were the result of intense debate between different professional, academic, popular and political categories, the Brazilian constituent process, in the 1980s, driven by the national redemocratization movement, allowed them to enter the Federal Constitution of 1988, resulting in what is today the Unified Health System (SUS) (MENDES, 2022).

The SUS represents the consolidation of the intersectoriality of public policies, and it is up to the State to guarantee the universal right to health reaffirmed by Organic Health Laws No. 8,080/90

and No. 8,142. With the objective, of governmental actions distributed in different sectors, to ensure social rights, creating conditions to promote their autonomy, integration and effective participation in society, reaffirmed the right to health in the various levels of SUS care (TORRES, 2020).

In Brazil, mental health began to constitute as a health policy in Brazil in 2001 from the enactment of Law 10.2016, fruit of the Psychiatric Reform movement, seeking to consolidate an open field of psychosocial care, territorially based (BRASIL, 2001).

The Psychosocial Care Network (Raps), established in 2011, organizes the joint work of the various mental health care services into seven components; among them, Primary Health Care and Specialized Psychosocial Care stand out (BRASIL, 2011).

The Psychosocial Care Centers (Caps), considered strategic points of attention of Raps, make up the specialized care and are organized in modalities, among them the Caps i destined to the care of children and adolescents with psychic suffering (BRASIL, 2017).

The mental health of children and adolescents is on the agenda in debates in various fields of health. In addition, it is the target of Brazilian public policies, according to Ordinance No. 3,088 of 12/23/2011 of the Ministry of Health, which understands that this public needs specialized care, which takes into account the profile and needs of this age group. However, child mental health has gone through a long course of neglect and marginalization and, therefore, the construction of strategies aimed at this public is a recent challenge (RIBEIRO, 2006; CUNHA & BOARINI, 2011).

In this context, it reinforces the development of health practices aimed at prevention and health promotion, as a way of coping with the possible determinants that cause disease and disorders (BUSS, 2018). Therefore, the Primary Health Care (PHC), printed a new strategy of health practices, aimed at reorganization of services, and development of comprehensive care (BATISTA, 2017).

This new model of care assistance, through preventive and promotional strategies and actions, has imprinted a new dynamic regarding mental health in primary care, reaffirming the effectiveness of the principles of the SUS in the daily care routine, with emphasis on the Expanded Clinic. Is defined as a theoretical and practical tool whose purpose is to contribute to a clinical approach to illness and suffering, which considers the uniqueness of the subject and the complexity of the health/disease process (BRASIL, 2010).

In the field of mental health care for children in primary health care, I inferred the emphasis on the School Health Program (PSE), which aims, from the teaching units, not only to articulate basic health and education, but also to contribute to the construction of a social care system, focusing on the promotion of citizenship and human rights (BRASIL, 2010).

The PSE is based on the following axes of actions, grouped into five components: clinical and psychosocial evaluation of students; ER actions and prevention of diseases and injuries; continuing

education and training of education and health professionals and young people for the PSE; monitoring and evaluation of students' health; and monitoring and evaluation of the PSE (TELES, 2014).

In this scenario, the implementation of educational actions in the school propose the development of an intrinsic relationship between discussions on the theme of health in classroom health in a perspective of construction of citizenship, which denotes the understanding of health not only as a set of habits to be developed, but rather from the idea of the right to be continuously exercised and resignified (MONTEIRO, 2015).

However, there are gaps in teacher education and training regarding the effectiveness in the development of preventive practices and promoters of harm to children. Study reinforces the importance of teacher education and training to work in the PSE, being able to enhance the development of knowledge that can privilege the educational dimension of health care (MACHADO, 2015).

It signals the importance of the intersectoral approach between the school community and health professionals, as a way of recognizing the potentialities of the school and the territory of which it is inserted and in which the health-disease processes are carried out, becoming a challenge as the dialogue with different organizational cultures (BUENO, 2022).

The school context should be understood as a scenario for the implementation of health education practices that are capable of empowering children and adolescents regarding care actions related to their health condition and their peers, as well as strengthening the articulation between schools and teams of the Family Health Strategy (FHS) (MACHADO, 2015).

Thus, the implementation of educational practices consistent with the assumptions of health promotion aims to avoid the process of illness through actions aimed at reducing the incidence and prevalence of diseases in a population. Breaking with educational practices in a verticalized perspective that dictate behaviors to be adopted for health maintenance (SILVA, 2018).

Given the complexity of the new paradigm of the concept of health and reformulation of public health policies, which are consistent with the promotion of the health of individuals, that the Sustainable Development Goals (SDGs), were created as coping tools to ensure full human development (SILVEIRA, 2020).

Implemented in 2015, the 2030 Agenda for Sustainable Development is distributed among 17 Sustainable Development Goals, composed of 169 targets that must be met by the year 2030. Crossed by wide and diversified fields of action that transit through the eradication of poverty and hunger; health and well-being; education; gender equality; access to safe water and sanitation; clean energy; decent work; sustainable economic growth; reduction of social inequalities; sustainability of life; innovations in infrastructure; responsible consumption; healthy cities; climate responsibility; reduction of inequalities; effective institutions; and social peace (MOREIRA, 2019).

Health, Goal 3 reveals to ensure a healthy life and well-being in all phases of the life cycle. Therefore, it brings the recognition of the complex understanding of the main paradigms on the conception of the concept of health, which is understood as a social production between subjects about their interests and health needs (DJONÚ, 2018).

Mental health is represented in the goal that aims to reduce premature mortality from non-communicable diseases by a third via prevention and treatment, and to promote mental health and well-being (ORGANIZATION OF THE UNITED NATIONS, 2019). However, there are gaps in mental health care from a global health perspective. Thus, it is necessary to think of mental health as a multidimensional construct, which must be analyzed in a dialectical perspective, from individual and contextual aspects (LUND et al., 2018; Mills, 2018).

The construction of the mental health construct should be seen as a matter for everyone: from individuals to International Organizations, considering the need for a unified and multidimensional language for the application of theory in public policies, an integrative sense in the sharing of resources destined to actions, as well as full participation of all sectors of international society for greater effectiveness (SILVEIRA, 2020).

4 FINAL CONSIDERATIONS

In view of the above, it is considered necessary to train educators in understanding the development of actions to care for the mental health of children, in order to meet the needs and problems presented and neglected. Therefore, we highlight the school environment as a space that promotes educational practices in health, which yearns to strengthen the autonomy and empowerment of the subjects.

In the interim, the development and strengthening of public policies in mental health for children represent advances consistent with the new paradigm of the health construct, breaking with hegemonic practices still present in the current care model.

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Depression symptoms and quality of life in medicines students in Ribeirão Preto-SP

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ABSTRACT

Depression is a major public health problem, characterized by discouragement, loss of interest in daily activities, changes in sleep, mood swings, among other symptoms. On the other hand, quality of life is defined for some as the understanding that an individual has in relation to the environment in which he is inserted, his goals, expectations, concerns, values. Depression among medical students is increasingly evident due to the major changes experienced in their lives when entering higher education, a fact that directly affects the student's quality of life. In this scenario, the present study aims to evaluate the prevalence of depressive symptoms and quality of life among medical students in the city of Ribeirão Preto-SP. For the present study, the Sociodemographic Characterization tests, the Satisfaction With Life Scale (SWLS) and the Beck Depression Inventory-

II (BDI-II) were used. Through prediction of sample data, 319 university students, of both sexes, participated in the study. The participants answered virtually the questionnaires that characterize and stratify the sample, evaluated the concept of satisfaction with life and the components associated with depression. Descriptive statistics were presented as means and standard deviation for continuous variables and as absolute and relative frequency for categorical variables. Spearman's correlation and Person's chi-square tests were performed. There was an inversely proportional correlation between quality of life and depression. 54.8% of participants had some degree of depression. Findings in the literature show that about 50% of the university medical population may have some type of mental disorder, however, there was no statistically significant difference between the university cycles and the classification of depression. A study using the BDI-II shows a higher prevalence of severe symptoms of depression in pre-university students of the medical course when compared to students who taught other courses. Another factor cited by the authors as a trigger for mood swings is the development of medical activities and also separation from the family, having difficulty maintaining interpersonal relationships and socializing. Thus, it is concluded that the quality of life is closely linked with depression. In addition, students are already entering the university with some degree of depression and this depression persists throughout the course. It is necessary to develop strategies that favor a more welcoming environment for students who face problems of this nature.

Keywords: Depressive symptoms, Quality of life, Medicine student.

1 INTRODUCTION

Considered a major public health problem, depression is characterized by discouragement, loss of interest in daily activities, changes in sleep, mood swings, among other symptoms. Globally, 4.4% of the population suffers from depression, which is one of the biggest causes of disability. Its multifactorial origin can generate problems for the individual, with profound personal and professional impact, including low academic performance (DYRBYE, *et al.,* 2011; VOS *et al.,* 2016).

Depression among medical students is increasingly in evidence and has become a concern for health and education systems around the world (OLUM; NAKWAGALA; ODOKONYERO, 2020; ROTENSTEIN, *et al.,* 2016).

The changes that occur in the lives of students entering higher education are drastic. They undergo various stressors, in addition to being a period that coincides with important biopsychosocial changes (CERCHIARI; CAETANO; FACCENDA, 2005). Numerous challenges can be observed in this new phase, such as leaving the parents' home and deprivation of family life, overload of academic and extracurricular activities, few hours for leisure, greater exposure to alcohol and drugs and sleep alteration (PAIXÃO *et al*., 2021).

Students in the health area experience beyond the situations described above situations of constant stress, because they are intensely evaluated in practice, are afraid of making mistakes during the care provided, suffer a constant exposure to cases of anguish and death causing feelings of vulnerability or negative perception of reality (BAMPI *et al*., 2013; CONCEIÇÃO, *et al.,* 2019). Therefore, psychological and physical exhaustion have an impact on the quality of life of students, triggering depression and anxiety (CUNHA, *et al.,* 2017).

In studies conducted around the world, a higher prevalence of depression was denoted among future physicians, than in the general population and in peers of the same age group (ROTENSTEIN, *et al*., 2016; DYRBYE; THOMAS; SHANAFELT, 2006; INAM, 2007).

Ward and Outram (2016), evidence that the medical culture triggers a chronic stress in the exercise of the profession by demanding excellence in practices and an adoption of infallible knowledge. As a result, physicians and medical students have higher rates of psychological distress, *burnout*, diagnosed mental illness, suicidal ideation, and suicide attempts when compared to the general population.

The health assessment parameter is no longer centered on symptoms or morbidity and mortality, but on the well-being of people in various areas of life. Within this perspective, the construct "quality of life" emerges as an object of study in several areas of human knowledge (DOWARD; MKENNA, 1997).

Quality of life is defined for some as the understanding that an individual has in relation to the environment in which he is inserted, to his goals, expectations, concerns, values, that is, all the habits learned and adopted during life, which are related to his family reality, whether they have access to food, basic sanitation, housing, work, health, leisure and social. Each society establishes a standard of living based on its culture, directing the satisfaction levels of its individuals. This perception interferes with what is or is not a good quality of life. This all reflects on personal well-being, health care and social relationships (ALMEIDA; GUTIERREZ; MARQUES, 2012).

Medical students according to the graduation phase present different results regarding quality of life and depression. Students who are in the basic cycle, first and second year of graduation, are frustrated with the curricular structure, due to the little contact with medical practice and the course of the basic disciplines, generating a break in expectations of freshmen (ARDISSON, *et al*., 2021).

During the clinical cycle, between the second and fourth year of graduation, there is a greater practical clinical activity, initiating the first contact with patients, which can make students surrender to feelings of anxiety and insecurity, especially due to their initial inexperience, in the face of new demands (ARDISSON, *et al.,* 2021).

In the internship phase, between the fifth and sixth year of graduation, there is an accumulation of knowledge which is necessary to put into practice. The beginning of the charges by patients and teachers in relation to the previously acquired fundamentals, the confrontation of human pain and suffering and the conflicting relationships arising from the differences in ethical behaviors generate anxiety and can negatively interfere in the student's self-esteem (ARDISSON, *et al*., 2021).

At the same time that medical students turn their gaze to others, they usually do not recognize their fragilities and their illness in the psychic sphere. Not looking for professional help to solve problems (MACHADO *et al.*, 2015). There is also concern about cognitive, academic and functional

impairments regarding the mental health of these students, due to the low performance in the course and the mental condition of this population (COSTA *et al*., 2020). In this scenario, the present study sought to evaluate the impact that the medical course currently has on duality: quality of life and depression among students of Medical Schools in the city of Ribeirão Preto.

2 MATERIAL AND METHODS

2.1 PARTICIPANTS

Participants were university students, of both sexes, who were enrolled in medical courses in the city of Ribeirão Preto - SP. The following inclusion criteria were used: being enrolled in a medical course in the city of Ribeirão Preto and of Brazilian nationality. The following requirements were used as exclusion criteria: not answering one or more questionnaires and having other activities, other than the exclusive dedication to the course. The sample size calculation to determine the number of students who participated in the study was obtained by the Qualtrics $^{XM\ software}$ with a confidence level of 95%.

2.2 MATERIALS

Sociodemographic characterization questionnaire: It was developed by the researchers themselves for further characterization and stratification of the sample. Data such as age, ethnicity, educational level, socioeconomic status, university, course, period of graduation (APPENDIX A) will be requested.

Satisfaction with Life Scale (SWLS): The Life Satisfaction Scale (DIENER et al., 1985) is composed of five items that assess the concept of life satisfaction by measuring the overall judgment of individuals about their lives. It is a well-known and well-used measure of subjective well-being. The items are scored along a Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The final score corresponds to the sum of the items, with higher scores indicating high satisfaction. The sum of the scores of all items gives a maximum number of 35. In Brazil, the instrument was adapted by Gouveia *et al*. (2009), maintaining the characteristics of the original version (ANNEX A).

Beck Depression Inventory-II (BDI-II): The Beck Depression Inventory-II (BECK; STEER; BROWN, 1996) is composed of 21 items that assess the behaviors associated with depression in the Brazilian population. Items are scored on a 4-point Likert-like scale (0, 1, 2, and 3). The sum of the scores of all items provides a maximum number of 63, which is a measure of the intensity of depressive symptoms. Variations in this scale can be classified as minimal, mild, moderate or severe depression. To the score between 0 and 13: no depression; Score from 14 to 19: mild depression; Score from 20 to 28: moderate depression; Score from 29 to 63: severe depression. This scale was adapted for Brazil by Gomes-Oliveira *et al.* (2012) (ANNEX B).

2.3 PROCEDURES

The project was accepted by the Research Ethics Committee (CAAE: 70621517.0.0000.5581) and the study participants were recruited through personalized invitation, by e-mail (direct mail) and social networks. In this invitation, the objectives and importance of the research were presented; identification, institution, address and contact of the researchers; instructions and address (URL) to access the form. After sending the invitation, it was waited two weeks and then it was sent for another time.

The participant who accessed the form through the link provided was directed to the data collection platform, in which the Term of Free and Informed Consent (ICF) (ANNEX B) was presented. After the participant accepted the term, he was directed to the Sociodemographic questionnaire. If the participant answered yes to any alternative related to the exclusion criteria, he was redirected to the thank you page and his participation in the research was terminated. Participants who clicked no, for all alternatives related to the exclusion criteria were directed to the next questionnaires. The order of presentation of the instruments was: Sociodemographic Characterization Questionnaire, Beck Depression Inventory-II and Satisfaction with Life Scale.

2.4 DATA ANALYSIS

The scores of the participants in the tests were evaluated according to the recommendations of each technique, explained earlier in the item "materials" of this project.

2.4.1 Statistical Analysis

Descriptive statistics were presented as means and standard deviation for continuous variables and as absolute and relative frequency for categorical variables for the total sample.

Spermman correlation tests were performed following the type of sample distribution and chi-square person hypothesis test.

All analyses were performed with the aid of SPSS version 23.0, establishing the alpha criterion for significance greater than or equal to 0.05.

3 FINDINGS

In total, 322 individuals participated in the research, but the data of three participants were excluded because they did not fit the established inclusion criteria. The total sample consisted of 319 individuals between 17 and 60 years of age. The sociodemographic characterization data are presented in Table 1.

The mean age of the participants was 24.8 years (*SD* = 6.77) and the mean scores for the scale that assessed life satisfaction was 23.57 (SD=7.14) and for the questionnaire that assessed depression

was 17.53 (SD=12.88). Regarding categorical variables, it was observed that 48.6% of individuals were attending the basic cycle, 39.8% the clinical cycle and 11.6% the internship.

Regarding socioeconomic classification, it was observed that 32.6% of the people belonged to class A, followed by 30.7% of class B, 21.0% of class C, 10.3% of class D and 5.3% of class E. The most reported etiology in the sample was white (82.4%), followed by brown (11.0%), yellow (4.1%) and black (2.5%). Single individuals represented 79.9% of the total sample, followed by 10.0% married, 8.5% cohabiting and 1.6% divorced. Among the total participants of the research, 45.14% studied at University 1, 16.3% at University 2, 23.82% at University 3 and 14.73% at University 4.

Table 1- Distribution of the absolute and relative frequency of the Socioeconomic Classification, Ethnicity, Marital Status and University and mean, standard deviation, minimum and maximum for age and for the scores of the Life Satisfaction Scale and the Beck Depression Inventory-II, in the sample of Medical Students (n=319) from the city of Ribeirão Preto, obtained through the application of questionnaires. Ribeirão Preto, 2022.

	Average	***DP***	**Minimum**	**Maximum**
Age	24,8	6,77	17	60
Life Satisfaction	23,57	7,14	5	35
Depression	17,53	12,88	0	55
Cycle	**Absolute Frequency (n)**		**Relative frequency (%)**	
Basic	155		48,6	
Clinical	127		39,8	
Interned	37		11,6	
Socioeconomic Classification				
A	104		32,6	
B	98		30,7	
C	67		21,0	
D	33		10,3	
And	17		5,3	
Ethnic group				
White	263		82,4	
Black	8		2,5	
Brown	35		11,0	
Yellow	13		4,1	
Marital status				
Single	255		79,9	
Married	32		10	
Divorced	5		1,6	
Kneaded	27		8,5	
University				
1	144		45,14	
2	52		16,3	
3	76		23,82	
4	47		14,74	
Second Graduation				
Has	63		19,75	
Does not have	256		80,25	

Source: Own Author.

Analyzing the data described in Table 2, an inversely proportional association of the data is observed. The higher the depression, the lower the satisfaction with life, because correlation coefficients equal to or less than 1 indicate negative perfect correlations.

Table 2- Correlations between quality of life scores and depression in the sample of medical students (n=319) from the city of Ribeirão Preto, obtained through the application of questionnaires. Ribeirão Preto, 2022.

Variable	Life Satisfaction	Depression
Life Satisfaction	-	-0,49**
Depression	-0,49**	-

** p <0.001. Spearman correlation.
Source: Own author.

Regarding the classification of depression, 54.8% of the participants had some degree of depression, 21.6% had severe depression and 45.1% had no symptoms. The data are described in Table 3.

Table 3- Distribution of the absolute and relative frequency of the Depression Classification in the sample of Medical Students (n=319) from the city of Ribeirão Preto, obtained through the application of questionnaires. Ribeirão Preto, 2022.

Classification	Absolute Frequency (n)	Relative frequency (%)
No Symptoms	144	45,1
Mild Depression	51	16
Moderate Depression	55	17,2
Severe Depression	69	21,6

Source: Own author.

Through the chi-square test of *Person* $\chi 2$ (6) = 7.75, (p = 0.26) it was verified that there is no statistically significant association between the crossings of the cycles and the classification of depression, as illustrated in Table 4.

Table 4- Chi-square test of the cross-relationship between cycles and degrees of depression of the sample of medical students (n=319) from the city of Ribeirão Preto, obtained through the application of questionnaires. Ribeirão Preto, 2022.

	Value	Gl	Significance	Phi
Person's chi-square	7,75	6	0,26	0.16 (small effect)

Source: Own Author.

4 DISCUSSION

The present study was composed of 319 medical students from the city of Ribeirão Preto, who answered the socioeconomic characterization questionnaire, the Life Satisfaction Scale (SWLS) and the Beck Depression Inventory-II (BDI – II) in order to understand the impact of the medical course on the quality of life and depression of these university students.

When the presence of symptoms of depression was evaluated, it was possible to observe that about 54.8% of the participants had some degree of depression. The high prevalence of depressive symptoms in medical students in different countries has been pointed out by several authors as alarming and worrisome (TORRES, *et al.,* 2012; BALDASSIN, 2010; STOLEN; FALCONE; Clark, 2003; BRUCH; RAM; JOURNEY, 2009; KUNWAR; RISAL, 2016; MOUTINHO, *et al.,* 2017). Findings in the literature show that about 50% of the medical university population may present some type of mental disorder (GOEBERT *et al.,* 2009; REIMER; TRINKAUS, 2005).

Although some authors have found a relationship between the advancement of the medical course and the development of mental illness, signs of anxiety and depression, the present study did not identify a statistically significant association between depression and the cycles of the course. Authors such as Givens (2002) and Furtado, Falcone, Clark, (2003), refer that excessive academic activities in the initial period of the course are important triggers of the symptomatology found in the research.

The present study demonstrated that the students of the basic cycle presented some symptom of depression. For some authors, the drastic change in routine, with high workloads, increased volume of information and content and methods different from those that students were accustomed to before entering the undergraduate program are triggers for the development of depressive symptoms (MILLAN; ROSSI; DE MARCO, 1995; MILLAN; BARBEDO, 2020).

Regarding the course, 63 individuals (19.75%) reported having attended another college before entering the medical course. The decision to start medical school as a second degree requires great determination and resignations. Cavalcanti and Melo (2022) identified that the choice of the first and second graduation refers to self-realization and personal achievement, but the second graduation was determined with fewer external influences. In addition, frustrations with the first course, difficulty in getting a job in the chosen area and low salary remuneration were cited as decisive factors for this choice (CAVALCANTI; MELO, 2022).

Corrêa *et al.* (2016), conducted a study with students of the Medical School of the Federal University of Minas Gerais (UFMG) who had finished an undergraduate course at a higher level. The authors demonstrate that for these students, maturity was a positive point in relation to the development of social relations, better use, reasoning and learning capacity of the contents. On the other hand, the individuals reported greater concerns and financial insecurities, difficulties in reconciling the course workload with work and the extensive curriculum to be fulfilled. In addition to this fact, students with previous training report greater difficulty in dealing with the setback to dependence on third parties to finance the university, losing the autonomy gained with the first graduation.

The study data obtained from the Beck Depression Inventory – II (BDI-II) and the Life Satisfaction Scale (SWLS) indicate an inversely proportional relationship between depression and life satisfaction, that is, the higher the satisfaction with life, the lower the depressive symptoms, mutually.

Graduation with the previous presence of some mental disorder has been increasingly common. The study by Melo *et al.* (2021) using the BDI-II evidences the higher prevalence of severe symptoms of depression in pre-university students of the medical course when compared to the students who provided the other courses. In addition, the authors report that the greater competition for the course and the longer pre-vestibular period are decisive factors for these students to enter the university with more mood disorders.

The studies of Schonhofen *et al.* (2020) and Terra *et al*. (2013) reinforce the findings regarding the greater number of students with some type of previous mental disorder, resulting from stressful factors such as greater pressure from pre-vestibular courses, greater competition and charging for the medical course.

The students who composed the basic cycle in the present study were, for the most part, up to 22 years old. This is an important factor, since authors point out the entry of adolescents into university during the phase of great psychosocial changes, because at that moment they will have greater autonomy and decision-making power over their choices, building a new identity (DO CARMO RIBEIRO et *al*., 2018).

Authors show that most medical students need to change cities and even states to be able to attend graduation. This change generates a greater distance from family and friends, generating insecurity. In addition, family separation increases responsibility in personal attributions such as hygiene, domestic services, such as household organization and cooking one's own meals, financial organization, among others (DE MELO *et al.*, 2021).

The researchers cite that the responsibilities acquired during this process can cause anxiety and fear of performing procedures and clinical examinations in the wrong way. Another factor cited by authors as a trigger of mood changes is the development of medical activities, since the young person will experience experiences of suffering, loss and anguish related to death. Everyday situations that can increase the vulnerability of medical students to the manifestation of suffering (DE MELO *et al.*, 2021).

Studies show (AQUINO; CARDOSO; PINE, 2019; MOUTINHO, *et al.,* 2017), that not only the large volume of content, exhaustive workloads and charges are mitigating factors of depressive symptoms in medical school students. The difficulty in maintaining interpersonal relationships and socialization often occur in this population, since exacerbated self-criticism and negative thoughts cause greater insecurity in creating bonds and relationships. Rapport *et al.* (2009), in his study, described that the students reported great difficulties in maintaining a healthy social life, in addition to adversity in dealing with family members and children.

Most participants in the present study started the course or were already pursuing medical school during the COVID-19 pandemic. During the pandemic period, activities were carried out through distance learning (EAD), in a digital way. Foly and Bellemo (2023) and Sun *et al*. (2021) found in their study that about 67% of the students who took part in the course through distance education reported a lack of concentration and almost 40% reported not being able to learn the subject correctly. In addition, the authors found a negative influence of the COVID-19 pandemic on the emotional state of these college students. Among the influencing aspects were the fear of

contamination and, subsequently, of readaptation to the college routine, the difficulty of learning in distance learning and the deficits related to this teaching modality.

Thus, the pandemic period stands out as a strong stress factor and trigger of mental disorders in medical school students. These data indicate that this may be an important reason for the high rates of depressive symptoms in students of all periods who participated in the present study.

5 CONCLUSION

It is concluded that the fact that a student has some level of moderate or severe depression and attends a medical university, in which there is a whole history of external pressure, can aggravate the symptoms. Thus, it is important to evaluate the framework in which this student is entering college and develop interventions that favor a more welcoming environment for students who face problems of this nature.

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ANNEX A – Sociodemographic Characterization Questionnaire

1. Age (years): _____
2. Are you currently attending higher education (undergraduate)?

( ) No

( ) Yes, graduation in: _____

3. What semester of graduation are you in? _____
4. What is the name of the university you study at? _____
5. Do you already have a degree in another course? _____
6. You declare yourself:

( ) White

( ) Black

( ) Yellow

( ) Pardo (a)

( ) Indigenous

7. What is your marital status?

( ) Single

( ) Living together

( ) Married

( ) Divorced

( ) Widower

8. What is your socioeconomic level (consider the current minimum wage of R$1045.00):

( ) Class A (average gross family income above 20 minimum wages per month)

( ) Class B (average gross family income between 10 and 20 minimum wages per month)

( ) Class C (average gross family income between 4 and 10 minimum wages per month)

( ) Class D (average gross family income between 2 and 4 minimum wages per month)

( ) Class E (average gross family income in the month up to 2 minimum wages per month)

ANNEX B - Term of Free and Informed Consent

TERM OF FREE AND INFORMED CONSENT

You are being invited, as a volunteer, to participate in the survey: "Symptoms of Depression and Quality of Life in Medical Students' Courses of Ribeirão Preto-SP", this being the scientific initiation project of Maria Carolina F. da Cunha, Leticia R. Martinez, Marcela T. O. B. de Paiva, Larissa N. de Siqueira, Gabriel B. Carvalho and Marília de P Ferreira, students of the medical course of the University Center Estácio de Ribeirão Preto/IDOMED, under the guidance of Prof. Dr. Carla Duque Lopes.

The objective of this study is to investigate the prevalence of depressive symptoms and quality of life in medical students from the city of Ribeirão Preto.

The collection procedure will be as follows: you will answer questionnaires that investigate depressive symptoms and quality of life, and also a questionnaire with questions about your age, ethnicity and family income. You'll be able to take the surveys from anywhere, and filling out the questionnaires can take about 15 minutes.

There is no prediction of risks in the participation of the study as to its physical integrity, defamation, slander or any moral damage. You may refuse or withdraw from participation at any time, without this entailing any penalty or damage, or reprisals of any kind. Because it is an epidemiological research, which uses instruments that are not capable of making diagnoses, researchers will not be able to offer any form of psychological assistance, but may indicate health services, with no guarantee of care.

No direct or immediate benefit will be generated, however, your participation in the study will contribute to help understand psychological aspects in medical students.

We inform you that your privacy will be respected, that is, your name or any data or element that can, in any way, identify you will be kept confidential. We, the researchers, take responsibility for the custody and confidentiality of the data. Any and all clarification of doubts about the research may be clarified by the Researcher in charge: Prof. Dr. Carla Duque Lopes, by Phone (16) 3523-4202 or (16) 3523-4196.

Free access to all additional information and clarifications about the study and its consequences is ensured, everything you want to know before, during and after your participation. At the end of this research, you will receive a copy of this term in pdf format to the e-mail you leave registered. If you are aware of all the terms, agree to participate in the survey and want to get started, click "Yes". If you do not wish to continue and do not want to participate, click "No" and the survey will be automatically terminated, with no record of any damage or injury to you.

Possible clarifications on ethical aspects of the research can be answered by the Research Ethics Committee of the Estácio de Ribeirão Preto University Center located at Avenida Maurilio Biagi, 2103. Ribeirânia neighborhood. Ribeirão Preto, SP. Brazil. Zip Code: 14096-170. Opening hours: Mondays to Fridays from 14h00 to 18h00. Phone: (16) 3523-4187. Email: cep.ribeirao@estacio.br

APPENDIX A – Life Satisfaction Scale

Below you'll find five statements you may or may not agree with. Using the following response scale, which ranges from 1 to 7, indicate how much you agree or disagree with each. Please be as candid as possible in your responses.

	I totally disagree	Disagree	I slightly disagree	Neither agree nor disagree	I slightly agree	Agree	I totally agree
1- In most respects, my life is close to my ideal.							
2 – The conditions of my life are excellent.							
3 - I am satisfied with my life.							
4 – As much as possible, I have achieved the important things I want out of life.							
5 – If I could live a second time, I would change almost nothing in my life.							

APPENDIX B - Beck Depression Inventory-II

Instruções:

Este questionário consiste em 21 grupos de afirmações. Por favor, leia cada uma delas cuidadosamente. Depois, escolha uma frase de cada grupo, a que melhor descreva o modo como você tem se sentido nas **duas últimas semanas, incluindo o dia de hoje**. Faça um círculo em volta do número (0,1,2,ou 3), correspondente à afirmação escolhida em cada grupo. Se mais de uma afirmação em um grupo lhe parecer igualmente apropriada, escolha a de número mais alto neste grupo. Verifique se não marcou mais de uma afirmação por grupo, incluindo o item 16 (Alterações no padrão de sono) e o item 18 (Alterações de apetite).

1. Tristeza
- 0 Não me sinto triste.
- 1 Eu me sinto triste grande parte do tempo.
- 2 Estou triste o tempo todo.
- 3 Estou tão triste ou tão infeliz que não consigo suportar.

2. Pessimismo
- 0 Não estou desanimado(a) a respeito do meu futuro.
- 1 Eu me sinto mais desanimado(a) a respeito do meu futuro do que de costume.
- 2 Não espero que as coisas dêem certo para mim.
- 3 Sinto que não há esperança quanto ao meu futuro. Acho que só vai piorar.

3. Fracasso passado
- 0 Não me sinto um(a) fracassado(a).
- 1 Tenho fracassado mais do que deveria.
- 2 Quando penso no passado vejo muitos fracassos.
- 3 Sinto que como pessoa sou um fracasso total.

4. Perda de prazer
- 0 Continuo sentindo o mesmo prazer que sentia com as coisas de que eu gosto.
- 1 Não sinto tanto prazer com as coisas como costumava sentir.
- 2 Tenho muito pouco prazer nas coisas que eu costumava gostar.
- 3 Não tenho mais nenhum prazer nas coisas que costumava gostar.

5. Sentimentos de culpa
- 0 Não me sinto particularmente culpado(a).
- 1 Eu me sinto culpado(a) a respeito de várias coisas que fiz e/ou que deveria ter feito.
- 2 Eu me sinto culpado(a) a maior parte do tempo.
- 3 Eu me sinto culpado(a) o tempo todo.

6. Sentimentos de punição
- 0 Não sinto que estou sendo punido(a).
- 1 Sinto que posso ser punido(a).
- 2 Eu acho que serei punido(a).
- 3 Sinto que estou sendo punido(a).

7. Auto-estima
- 0 Eu me sinto como sempre me senti em relação a mim mesmo(a).
- 1 Perdi a confiança em mim mesmo(a).
- 2 Estou desapontado(a) comigo mesmo(a).
- 3 Não gosto de mim.

8. Autocrítica
- 0 Não me critico nem me culpo mais do que o habitual.
- 1 Estou sendo mais crítico(a) comigo mesmo(a) do que costumava ser.
- 2 Eu me critico por todos os meus erros.
- 3 Eu me culpo por tudo de ruim que acontece.

9. Pensamentos ou desejos suicidas
- 0 Não tenho nenhum pensamento de me matar.
- 1 Tenho pensamentos de me matar, mas não levaria isso adiante.
- 2 Gostaria de me matar.
- 3 Eu me mataria se tivesse oportunidade.

10. Choro
- 0 Não choro mais do que chorava antes.
- 1 Choro mais agora do que costumava chorar.
- 2 Choro por qualquer coisinha.
- 3 Sinto vontade de chorar, mas não consigo.

_____ Subtotal página 1 CONTINUA NO VERSO

11. Agitação

0 Não me sinto mais inquieto(a) ou agitado(a) do que me sentia antes.
1 Eu me sinto mais inquieto(a) ou agitado(a) do que me sentia antes.
2 Eu me sinto tão inquieto(a) ou agitado(a) que é difícil ficar parado(a).
3 Estou tão inquieto(a) ou agitado(a) que tenho que estar sempre me mexendo ou fazendo alguma coisa.

12. Perda de interesse

0 Não perdi o interesse por outras pessoas ou por minhas atividades.
1 Estou menos interessado pelas outras pessoas ou coisas do que costumava estar.
2 Perdi quase todo o interesse por outras pessoas ou coisas.
3 É difícil me interessar por alguma coisa.

13. Indecisão

0 Tomo minhas decisões tão bem quanto antes.
1 Acho mais difícil tomar decisões agora do que antes.
2 Tenho muito mais dificuldade em tomar decisões agora do que antes.
3 Tenho dificuldade para tomar qualquer decisão.

14. Desvalorização

0 Não me sinto sem valor.
1 Não me considero hoje tão útil ou não me valorizo como antes.
2 Eu me sinto com menos valor quando me comparo com outras pessoas.
3 Eu me sinto completamente sem valor.

15. Falta de energia

0 Tenho tanta energia hoje como sempre tive.
1 Tenho menos energia do que costumava ter.
2 Não tenho energia suficiente para fazer muita coisa.
3 Não tenho energia suficiente para nada.

16. Alterações no padrão de sono

0 Não percebi nenhuma mudança no meu sono.
1a Durmo um pouco mais do que o habitual.
1b Durmo um pouco menos do que o habitual.
2a Durmo muito mais do que o habitual.
2b Durmo muito menos do que o habitual.
3a Durmo a maior parte do dia.
3b Acordo 1 ou 2 horas mais cedo e não consigo voltar a dormir.

17. Irritabilidade

0 Não estou mais irritado(a) do que o habitual.
1 Estou mais irritado(a) do que o habitual.
2 Estou muito mais irritado(a) do que o habitual
3 Fico irritado(a) o tempo todo.

18. Alterações de apetite

0 Não percebi nenhuma mudança no meu apetite.
1a Meu apetite está um pouco menor do que o habitual.
1b Meu apetite está um pouco maior do que o habitual.
2a Meu apetite está muito menor do que antes.
2b Meu apetite está muito maior do que antes.
3a Não tenho nenhum apetite.
3b Quero comer o tempo todo.

19. Dificuldade de concentração

0 Posso me concentrar tão bem quanto antes.
1 Não posso me concentrar tão bem como habitualmente.
2 É muito difícil para mim manter a concentração em alguma coisa por muito tempo.
3 Eu acho que não consigo me concentrar em nada.

20. Cansaço ou fadiga

0 Não estou mais cansado(a) ou fadigado(a) do que o habitual.
1 Fico cansado(a) ou fadigado(a) mais facilmente do que o habitual.
2 Eu me sinto muito cansado(a) ou fadigado(a) para fazer muitas das coisas que costumava fazer.
3 Eu me sinto muito cansado(a) ou fadigado(a) para fazer a maioria das coisas que costumava fazer.

21. Perda de interesse por sexo

0 Não notei qualquer mudança recente no meu interesse por sexo.
1 Estou menos interessado(a) em sexo do que costumava estar.
2 Estou muito menos interessado(a) em sexo agora.
3 Perdi completamente o interesse por sexo.

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The (un)constitutionality of the COVID-19 health passport: An analysis under the medico-legal approach

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ABSTRACT
The work aims to analyze, from the perspective of Medicine and Law, the possibilities of relativizations - and even suppressions - of fundamental rights and guarantees in the face of the global health crisis imposed by the coronavirus (COVID-19). The pandemic, in general, has implemented numerous restrictions aimed at the gradual opening of the economy and the consequent return to normalcy. However, these limitations, however necessary they may be considered, have also led to violations of the constitutional rights of citizens, under the pretext of promoting the well-being of the social body. Thus, the justification of the thematic relevance is based on the consequences of the sophistry that the COVID-19 health passport, imposed by the public authorities, may cause for society, especially in the absence of previous and/or technical parameters capable of proving the effectiveness of the measure, which is extremely burdensome and flirts with the state of exception. The so-called COVID-19 health passport is problematic, that is, to examine the motivation of the State to relativize and even suppress the guarantees and individual freedoms of those who are deliberately affected by such a measure. The objective of this study is to demonstrate that the COVID-19 health passport, because it is an atypical measure, cannot be used haphazardly by the Government, under penalty of causing social segregation, since they privilege certain groups to the detriment of others, in addition to focusing on evident abuse of power. The methodology used was bibliographical, with a selection of books, articles, legal and jurisprudential texts and news extracted from official journals. The most important results of the study indicate that the health passport, at first, sought to implement the standardization of vaccination, however, in the background, it began to be used as a discriminatory measure. Finally, it is imperative to highlight that research cannot be equated with the anti-vaccine movement, much less be understood as a way of encouraging non-vaccination, on the contrary, the proposed approach aims to demonstrate that public policies should be based on humanization, and not on disrespect for rights, freedom and fundamental guarantees.

Keywords: Law and Medicine, Vaccination passport, Covid-19, Fundamental guarantees.

1 INTRODUCTION

Brazil falls into the category of Democratic State of Law, which presupposes a form of State based on popular sovereignty, that is, state power is conceived, subordinated and supervised by popular desires.

Because it is a free and democratic society, the fundamental guarantees are essential to protect the freedom to come and go of all those who are in the national territory, without any restrictions, reprisals or censures of the governmental powers (Executive, Legislative and Judiciary) or even of the citizens themselves.

The Federal Constitution of 1988 brought in its core inexorable rights, which provide ample and free movement in national territory, and any citizen can enter, remain or leave it with their goods. From these rights, the dignity of the human person stands out, enshrined as a constitutional principle provided for in article 1, item III, of the Magna Carta, being one of the pillars of the Federative Republic of Brazil and consists in the search for equity among citizens.

Based on these premises, it is easily perceived that individual freedoms, especially the right to come and go, are intrinsically related to the dignity of the human person, receiving protection not only from the constitution, but also from the United Nations Universal Declaration of Human Rights of 1948.

Faced with such magnitude, it is extracted that individual freedoms aim at the protection of the human being, subject of rights and obligations supported by the State, entity charged with protecting those who are under its guard against any and all acts of a degrading and inhuman nature, as well as promoting the minimum existential conditions for a healthy life.

Despite the salutary importance of the figure of the State in the protection of the guarantees provided for in the Constitutional Digest, currently, it is observed that the Public Administration has relativized - even suppressed - these rights, under the justification of the decree of the state of emergency resulting from the COVID-19 pandemic, in order to protect the interests of the collectivity.

Consequently, infra-constitutional legislation was enacted, which imposed very serious restrictions on the right to come, such as the requirement of proof of vaccination of COVID-19 for free access to public and private agencies. At first glance, the vaccination card was designed with the purpose of promoting the standardization of immunization in the face of the numerous laboratory brands available. However, over time, the document lost its purpose, so that even its nomenclature was modified, starting to be called "sanitary passport".

Then, the controversy arises about the constitutionality of the indispensability of proving COVID-19 vaccination, upon presentation of the health passport, for the wide and free access to public and private spaces, maximum for the conflict of individual freedoms with the interests of the social body (health and life).

That said, the paper intends, under a thorough analysis, to demonstrate in the light of the fundamental guarantees, that the imposition of the requirement of the sanitary passport for access to certain places can be considered unconstitutional.

2 THE DYSTOPIA OF SANITARY METHODS TO CONTAIN COVID-19

The first complaint about something different in terms of contagion was registered on December 19, 2019 in Wuhan City, Hubei Province, People's Republic of China, according to the World Health Organization (WHO). It is worth remembering that, at first, a "Strange Pneumonia" was detected and the ophthalmologist who made such an appointment was arrested and after some time died of the infectious viral disease. The first case was of a Wuhan market vendor, who fell ill on December 11, 2019 (Worobey *et al*., 2020).

Afterwards, speculation arose about the possibility of the disease having started in October 2019, due to contamination by seafood ingestion (Huang *et al*., 2020). The truth is that when the Chinese sanitary system could no longer cover up the gravity of the situation, the disease was then admitted around December 29, 2019 and the sanitary measure with restrictive imposition, such as the departure of the population from the region, was only taken on the date of January 19, 2020.

Despite the attempt to contain the contamination of the disease and taking into account the number of inhabitants of the city (11 million), of cosmopolitan character, with business in several countries of the world, mainly in the north of Italy, approximately 5 million people had already traveled to various regions of the world, a factor that helped in the spread of the virus. The dissemination was in geometric index with cyclopean manifestations of the disease throughout the world.

The World Health Organization, as of February 11, 2020, designates the new virus SARS-CoV-2 (*Severe Acute Respiratory Syndrome*), novel Coronavirus, and the diseases caused by the virus are named COVID-19 (*Coronavirus Disease of 2019*). On March 11, 2020, the WHO declared a state of pandemic, pointing out the geographical distribution, not the severity of the disease. Both in the national and international scenario, the term ESPII (Public Health Emergency of International Interest) is used, and in Brazil the terminology is ESPIN (Public Health Emergency of National Interest). These designations are based on the International Health Regulations (IHR 2005) which endorse the obligation of extreme sanitary measures such as quarantine, use of masks, vaccination and even compulsory isolation.

At the same time, it is stated that Brazil faced the Spanish Flu Pandemic in 1918 that even claimed the life of President Rodrigues Alves, at the age of 70, in 1919. The Brazilian population was around 29 million, while the world population did not exceed 2 billion. There are no precise statistics on the number of fatal cases of the H1N1 pandemic (Spanish flu), however, it is estimated that in Brazil, the number of deaths ranged from 35,000 to 300,000 deaths, while in the world it reached 100 million in the interim of two years (Neufeld, 2020).

In modern times, on January 30, 2020, the Presidency of the Republic issued Presidential Decree No. 10,212, in attention to the text revised and agreed at the 58th General Assembly of WHO

on May 23, 2005. That decree rescued the guidance on sanitary measures based on Brazilian laws proposed and approved by the National Congress to deal with the pandemic.

In fact, Law No. 13,979 of February 6, 2020, established actions to be taken in the face of the approaching pandemic, such as isolation, quarantine and even mandatory vaccination. President Jair Messias Bolsonaro, through the Ministry of Health, issued Ordinance No. 188 on February 3, 2020, seeking to prepare the country to face the virus.

In that scenario, the WHO had not yet established a pandemic condition, a circumstance that led to the denial of the possibility of viral spread by some public representatives, who claimed that the measure would cause gigantic economic damage to the states, already advertised with the carnival. Numerous governors, mayors, health professionals, including a doctor from a specific hegemonic television network - which analyzes diseases - denied the disease and stated that there was no reason to panic, because it was a "little flu", and then this same television network tried to preach the labeling to the President of the Republic as the author of the statement.

Unfortunately, there was no action in the state of emergency that would be triggered by the ordinance in question, and this occurred only because the minister of health at the time, in an orchestrated action with those who opted for the realization of the carnival, turned a deaf ear to the medical wisdom essential to adequate prevention against the virus. No case of the virus had been detected, which only occurred on February 26, 2020, in a 61-year-old male patient (Brasil, 2020). From the date of the Ministry of Health ordinance to the day of detection of the first case, 23 days were counted, in the interim sufficient for preventive measures to be taken, especially with regard to the suspension of carnival festivities.

This was not done because it was contrary to economic interests and, currently, it is conceded that there were also the interests of the big pharmaceutical companies, vaccine manufacturers. It was necessary to spread the virus to generate panic and pressure the federal government to acquire immunizers that, evidently, have not prevented the spread of the virus and have not even presented satisfactory immunization as advertised. Faced with the growing number of cases and with the carnival helping in the spread of the virus, another narrative was created, that is, it was necessary to close everything and condemn society to confinement.

Thus, the inconsequential absurdity of global closure of economic activities was established, even in desert territories and in the distant cities of the population agglomerations. This conduct, notably insane and without any technical-scientific basis, was ratified, directly and indirectly, by the Federal Supreme Court (STF) in the judgment of Direct Actions of Unconstitutionality (ADI's) No. 6341, 6362, 6586 and 6587.

The motivation of the Supreme Court granted safe conduct to governors and mayors for the imposition of notoriously serious and unconstitutional measures, such as the absolute blockade of

people or loads (*lockdown*). Obviously, this has caused real economic chaos with a 9.1% drop in Gross Domestic Product (GDP), without any repercussion on the reduction of COVID-19 cases and mortality. According to Herby, Jonung and Hanke (2022), in the United States of America and Europe, the imposition *of lockdown* has had very little or no effect on mortality, having reduced on average 0.2% of deaths caused by the coronavirus.

In addition, according to Roelfs, Shor, Davidson and Joseph Schwartz (2011), unemployment increases the risk of premature death by up to 63%, which justifies the fact that several scientists are against *lockdown, not least because lockdown concentrates and spreads the virus more easily (Henderson* et al., 2006). Based on this premise, the important thing is that in certain situations and circumstances vertical isolation is used for the elderly and debilitated, but still in a limited way.

SARS-CoV-2 is a virus of high infectivity and low virulence, as its ability to infect is measured by the Ro (basic reproductive rate) which is 1.4 to 2.5, common influenza 1.5 and Measles Ro of 18, highly contagious (CDC, 2021). The size of the virus is 0.065 mμ (milli micron) or 65 nanometer, that is, 1 million times smaller than the millimeter (Chen *et al.,* 2020). In this sense, the dust grain is 10 microns (1,000 times smaller than mm) and the coronavirus is 80 times smaller than dust. N95/PFF2 surgical masks have the obligation to filter between 90% and 98% of particles with 300 nanometers, that is, 4.5 times larger than the coronavirus (Artaxo *et al.*, 2021).

These data demonstrate that the virus is unbeatable in terms of mechanical barrier and the most effective way to contain it is through the immune barrier, but therapeutic contamination was not allowed when the *lockdown was determined*. Once the vaccine was applied, immunization was done over a long period and, at the time of vaccination, the principle that one does not get vaccinated during the pandemic was contradicted.

This is because the virus, a living being, seeks adaptability with change of its molecular characteristics, what happened and the antibody generated by the vaccines initially, were not effective for the viral mutations that determined other outbreaks, because the vaccine, with the exception of coronavac, of low efficacy, was of certain viral segments.

Public policies were implemented to encourage the population to submit numerous booster doses without, however, presenting convincing results regarding immunization and mitigation of new cases. There is a lack of research to detect the effectiveness of the immunizer compared to those who contracted the virus in terms of recrudescence. Faced with this instability, questions, lack of answers and seriousness in the scientific approach, the narrative was established that we have to wear a mask at all times, continue vaccinating and in some places undergo the RT-PCR test.

As for masks, there is, to date, no scientific research that reports the importance of their use, however, there are sparse statements to the effect that the equipment provides safety, does not compromise blood oxygenation and does not cause carbon dioxide poisoning. These opinions are based

on the worst level of scientific evidence that is the 'C', that is, consensus of experts with weak degree of recommendation IIb, and in some cases reaches III, which means loss. There is no randomized scientific study on the topic. What is available is a meta-analysis of 172 observational studies in 16 countries on 6 continents, for a total of 25,697 patients, with the conclusion that the best outcome is obtained with social distancing (Huang *et al*., 2020).

In view of the data, the question from a logical-rational perspective is pertinent: if masking, hand hygiene with alcohol-gel and immunization are effective, why the viral spread despite all the restrictive measures and even the enactment of *lockdown*? Everything was proposed, and extreme measures were taken in the fertile soil of ignorance and unpreparedness of most states and municipalities, armed with the vested interests of higher hierarchical leaders.

It is perceived that abuses were committed in the name of "science," but that in reality the larger purpose was to destabilize the federal government. What truly worked was scorned by the media on the grounds that there were no scientific studies. This statement is ignoble, behold, the first scientific study aimed at the treatment of the disease was carried out by the University Hospital of Marseille in France, with 36 patients, 20 of whom were treated with hydroxychloroquine (HCQ), with full recovery when added Azithromycin (Gautret *et al.*, 2020).

In another study, Italian physician Annalisa Chiusolo told *The JPost*[1] that the Italian Society of Rheumatology surveyed 1,200 rheumatologists who cared for 65,000 patients with Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). These patients were receiving hydroxychloroquine as an immune modulator and only 20 patients tested positive for COVID-19. The drug has long been safe and there have been no deaths among those using the drug for rheumatic morbidities.

Regarding immunization, that is, vaccination, the issue is also controversial and obscure. It is noted that the credibility of vaccines is not opposed, since they have been used safely for 226 years; Likewise, the problem does not compare to the anti-vaccine movement, nor can it be understood as a form of encouragement to non-vaccination. In fact, the strong position of the media against the treatment of the virus with the antimalarial drugs repositioned in the therapeutic arsenal, such as chloroquine and hydroxychloroquine, is questioned.

The initial argument was that there was no skillful scientific confirmation to justify the administration of the drugs. In fact, there was no scientific robustness, mainly because society had never experienced infection with SARS-CoV-2, however, it was found that several viruses are sensitive to these drugs, including Dengue and Chikungunya (Wang *et al*., 2020). As the disease spread, it was

[1] Available in: < https://www.jpost.com/health-science/italian-scientist-says-she-discovered-main-mechanism-behind-covid-19-626737>

proven that antimalarial drugs were effective when administered in the first 5 (five) days of the first clinical manifestations, so this measure was called "Early Treatment".

The vaccines were studied and tested with the application of 2 (two) doses and immediately began the process of evaluation of efficacy. Efficacy is the ability of the immunizer to determine the synthesis of antibodies specific to the inactivated virus with little or no adverse reaction. These reactions can range from mild allergic occurrence to life-threatening manifestations.

Despite the adverse events, society longed for the release of immunizers. Thus, in record time the vaccines were made available by the National Health Surveillance Agency (ANVISA) after the end of the 3rd phase. In this phase, the purpose and safety of the immunizer is analyzed. The first dose was administered on January 17, 2021, in the State of São Paulo, and one year later, 78.8% of the Brazilian population had received the first dose and 68% the second (Brasil, 2022).

The irony is that, with practically 70% of the population vaccinated with both doses, there should be no resurgence, and this, unfortunately, happened in Brazil and in the world, with the emergence of the *omicron variant*. Considering the failure of vaccination in containing the pandemic, the narrative shifted to the discourse that, despite not guaranteeing immunization, let alone preventing contagion, the contamination of the disease promoted only mild symptoms.

The statement is fallacious and, over time, the more severe the pandemic has become, showing us total ignorance of the behavior of viral variants. In reality, the virus humiliated everyone and, over time, more propositions were offered and the vaccine booster, like a panacea, began to be defended without any scientific basis or foundation based on unscientifically proven logic.

Therefore, the last "reason" to try to justify the threat of imposition of new absolutely restrictive measures by the Government, was to decree the requirement of proof of the "certificate of immunization", also known as the "health passport" of COVID-19, as a condition for the exercise of freedoms.

With this condition, those who did not undergo the doses of the immunizer, were and continue to be prevented from attending public and private places, such as courts of justice, notary offices, ministries, municipalities, educational institutions, restaurants, bars, malls, etc. Moreover, the limitations are not exhaustive, and may affect, depending on the case, restrictions on the exercise of professional activity, dismissal for just cause and, above all, the right to come and go.

A parenthesis is opened to state that the vaccination card was instituted by the Ministry of Health to promote the organization, standardization and control of immunization protocols. Despite the laudable intention, the document has become a method of repression, since the Federative Entities, in their majority, - by infraconstitutional legislative decrees - have misrepresented the primary purpose of the certificate by using it to suppress rights and, with this, generate clear social segregation.

It is inferred from this conjuncture that the last time society had to deal with such discretion was in times of war, precisely during the Second World War, when Nazi Germany, with the tolerance of the Axis countries, restricted people's freedom to work and access to places as a form of persecution of Jews.

Therefore, like the Nazis, the health passport affronts the dignity of the human person and induces stigmatization and segregation, since not everyone could have access to immunizers, in addition to scientific studies pointing out that vaccination does not produce immunization capable of preventing the contagion and proliferation of the virus. After all, the vaccinated both transmit and are contaminated by the disease (WHO, 2021). Therefore, it is ineffective and totalitarian measure.

On the other hand, and in the worst case, it could be argued that, in the name of the collectivity, the State could even impose the requirement of proof of the vaccination cycle for free movement with public agencies, provided that it made available to citizens other forms of access to services. Unfortunately, that didn't happen.

In view of the above, it appears that the sanitary methods recommended by the Government were not satisfactory to contain the COVID-19 pandemic, on the contrary, they were dystopian with serious economic and social consequences, in addition to denying the basic foundation of medicine, which is the diagnosis followed by treatment.

3 FINAL CONSIDERATIONS

The work aimed to investigate the constitutionality of the requirement of proof of the vaccination cycle, through sanitary certification, by citizens for free access to public and private agencies.

To answer the question, which guided the entire development of the research, a brief exposition was made on the sanitary methods for the containment of the disease, both nationally and worldwide, in addition to the analysis of legislation and judgments within the scope of the Federal Supreme Court.

Finally, based on medical and legal science, it is concluded that the requirement of the health passport is an unnecessary, disproportionate and discriminatory measure, especially because the State does not provide other means of access to public and private agencies, in addition to demonstrating that immunization is not absolute, much less prevents the spread of the disease, and there are no justifications to support such arbitrariness.

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Repercussion of the COVID-19 pandemic in the treatment of patients with autism spectrum disorder: A case report

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ABSTRACT
INTRODUCTION: Autism Spectrum Disorder (ASD) is a biologically based neurodevelopmental disorder characterized by interaction and communication deficits, as well as restricted and repetitive patterns of behaviors and interests. CASE REPORT: We describe the clinical history of a patient with a late diagnosis of Autism Spectrum Disorder and correlate the worsening of the clinical picture with the isolation associated with the onset of the COVID-19 pandemic. CONCLUSION: There is a relevant association between the COVID-19 pandemic and the worsening of the symptoms of the autism spectrum observed in the patient, mainly due to the inconsistency of the multidisciplinary treatment based on the disorder.

Keywords: Autism Spectrum Disorder, COVID-19, Multiprofessional team, Early diagnosis.

1 INTRODUCTION

Autism Spectrum Disorder (ASD) is a bio-based neurodevelopmental disorder characterized by persistent deficits in social interaction and communication observed in different environments, as well as restricted and repetitive patterns of behavior, interests, and activities. ASD can be classified to varying degrees depending on the level of impairment and associated functional impairment.

2 OBJECTIVE

To report the case of T. R. S., a patient with ASD diagnosed at the age of 32 years.

3 METHODOLOGY

3.1 CASE REPORT

3.1.1 Description of the Clinical Case

Female patient, T.R.S., 35 years old, white, deaf from birth due to the occurrence of rubella during pregnancy and molt. At the age of 10, he began psychiatric treatment for aggression and insomnia without, however, obtaining a diagnosis of autism. Other clinical signs associated at the time were repetitive movements, lack of social communication and interaction, restricted and specific interest in assembly toys, and total dependence on performing daily activities. From the psychiatric

follow-up, she is referred to the daily assistance of the APAE (Association of Parents and Friends of the Exceptional) in the municipality of Lagarto – Sergipe, an institution directed to the psycho-pedagogical and social development of patients with intellectual or multiple disabilities. As a result, she showed clinical improvement in social interaction and autonomy: decreased isolation and aggressiveness, learning eating behaviors (transporting some foods to the mouth), and personal hygiene (own toothbrushing, gestures indicative of the need to go to the bathroom). Only at the age of 32 years, he was diagnosed with ASD, initiating appropriate pharmacological treatment, but without significant results. After the onset of the COVID-19 pandemic, however, the trips to the APAE ceased, making the patient deprived of the multidisciplinary care offered by the institution. Currently, she has not been to the place for almost 3 years, presenting worsening behavioral patterns characteristic of ASD, especially aggressiveness (excessive self-mutilation and hostility to others), social isolation, and insomnia. Drugs in use: haloperidol 5 mg (2x/day), promethazine 25 mg (2x/day), chlorpromazine hydrochloride 25 mg (2x/day), sodium valproate 250 mg (2x/day), and levomepromazine 100 mg (2x/day).

4 CONCLUSION

The COVID-19 pandemic negatively affected the patient in question by depriving her of essential care for her psychosocial development, an aspect evidenced by the worsening of the clinical picture. Thus, it is reinforced that therapeutic management with a multidisciplinary team is fundamental for the treatment of patients with ASD. It is also noteworthy that an early diagnosis, by allowing the early institution of this type of follow-up, contributes to a better prognosis from the biopsychosocial point of view.

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Innovative formulation containing tocotrienol: A proposal for a food supplement

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ABSTRACT
The global population aging trend has been studied for more than 30 years. Data indicate that the Brazilian population of elderly will be larger than that of young people by the year 2050. In the United States this phenomenon has also been observed. The human biological system most affected with aging is the central nervous system, resulting in the decrease of neurons and loss of nerve conduction velocity, limitations in motor areas and incidence of pathological events related to advancing age. In this context, science has pointed out the effectiveness of the consumption of Vitamin E and its isoforms (tocotrienols) in neuroprotection, being effective in the prevention and treatment of senile diseases. Thus, the present work aims to propose an innovative formulation containing tocotrienol of annatto (Bixa orellana) to be consumed as a food supplement. Through a bibliographic survey and online market research, the supplements containing tocotrienol available to the consumer were evaluated. These supplements, for the most part, are presented for consumption in the form of soft gel. From this study, it was possible to define a proposal for a theoretical formulation in the form of an orodispersible tablet, which was tested in the pharmacotechnical laboratories of the Biopark, enabling the elaboration of a prototype of an innovative product. As a result, it was possible to obtain samples of the product with the possibility of being marketed in the American market, where dietary supplements are sold freely in supermarkets and pharmacies.

Keywords: Pharmaceutical Technology, Research, Pharmacy, Pharmaceutical Research.

1 INTRODUCTION

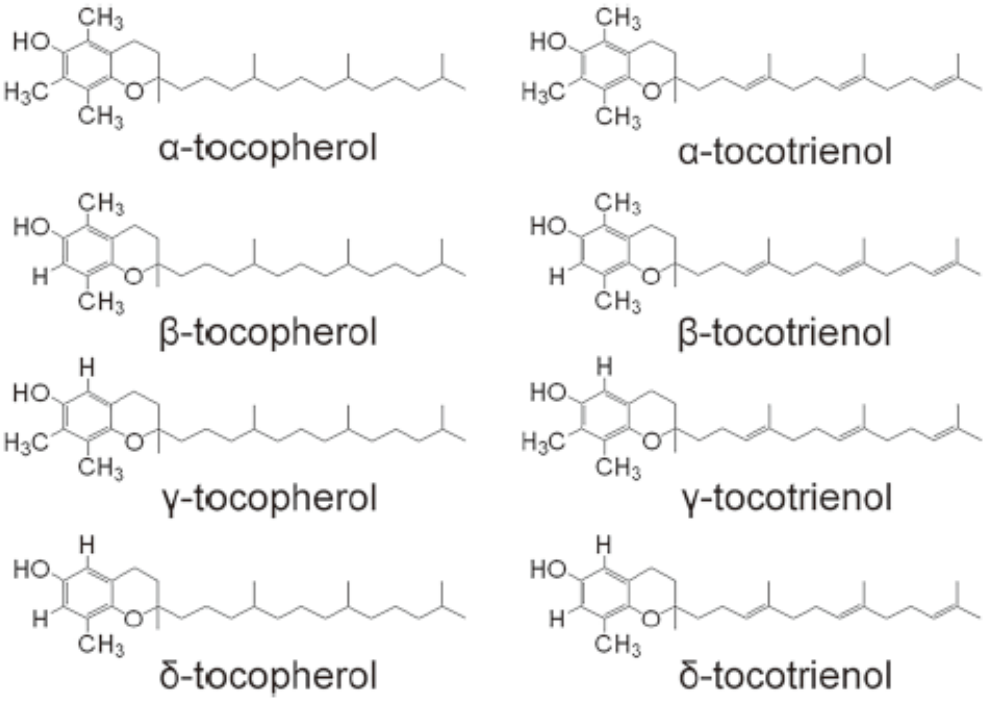
Scholars for nearly 30 years have been observing the aging population as a demographic revolution that has manifested itself at the global level. Especially in emerging countries, a reduction in fertility and mortality rates is perceived, resulting in older population groups and with very advanced individuals (KALACHE, VERAS, RAMOS, 1987). For example, the Brazilian Institute of Geography and Statistics (IBGE) (2018) conducted a study between 2012 and 2017 that demonstrates the population increase of the elderly group, which reached an approximate number of 30.2 million people. Estimates indicate that in 2050 the group of young people will be lower than that of the elderly in Brazil.

As a characteristic of the human species, the body begins the aging process naturally after reproductive age. The human body is affected gradually, presenting cumulative effects that vary in their severity according to biological factors and the influences of the individual's lifestyle. Thus, the elderly person becomes prone to present diseases of a physical and mental nature (CHAGAS, ROCHA, 2012). As the body ages, changes in the nervous system interfere with the individual, resulting in reduced brain function, changes in the activities of neurotransmitters and nerve cells, accumulation of toxins, manifestations arising from genetic changes, decreased blood supply and reduction of nerve cells (MAIESE, 2021).

Therefore, authorities and scientists have been concerned about the health of the elderly population, seeking an increase in life expectancy, and envisioning how this population will reach the end of life (IBGE, 2018). Thus, the scientific community has been studying the theme of aging to obtain treatments for the ills involving the central nervous system (CNS) and cognitive improvement (FUKUI, 2019). In this context, foods can contribute to the state of disposition, behavior and health of the population thanks to the functional properties they present. The neuroprotective activity of some substances has shown promising results in recent scientific research, demonstrating actions that directly impact on metabolic changes that are, or maybe, responsible for the onset of diseases of the central nervous system (GUEDES, MATIAS, 2021).

Scientifically highlighted, the medicinal substances discovered in the seed of annatto (*Bixa orellana*) can be mentioned, which have been studied and may contribute to the increase of the culture of this plant in Brazil. In the seeds of annatto are found high dosages of tocotrienols (CARVALHO, 2020). This group of compounds is part of the vitamin E family, as can be seen in Figure 1, and is relevant for its ability to prevent or treat several diseases associated with aging (MALAVOLTA et al., 2018; PLA, 2018). Thus, authors, such as Fukui (2019), Gopalan et al., (2014) and Mbachiantim (2021), studied tocotrienol and highlighted it as a potent neuroprotective agent, with chemical structures very similar to those of tocopherols.

FIGURE 1 - Chemical structure of tocopherols and tocotrienols



Source: Fukui, 2019.

Tocotrienols manifest themselves differently in the body, acting as a neuroprotector and inducer of the elimination of damaged cells of the nervous system, which represents advantages compared to tocopherols (FUKUI, 2019). In this same line of reasoning, Plá (2018) presents a relationship between the consumption of tocotrienols and the mechanisms described as neuroprotective in already published works.

The first studies proved the neuroprotective action of tocotrienol from cellular and animal models. However, Gopalan et al. (2014) published a study considering the experience conducted with 121 volunteers aged 35 years or older who had white matter lesions which were confirmed by magnetic resonance imaging. Those studied were randomly assigned to receive 200 mg of mixed tocotrienol twice a day, and the result of the study showed that patients who received the product showed attenuation in white matter lesions.

Following this aspect, it is possible to verify, through an online search, that there are already products being marketed in the North American market that contain tocotrienols as a bioactive substance. Most of the form presented is in soft gelatin capsules or *softgels*.

The supplement market is interesting if we consider that the consumption of these products increased by 48% in Brazil in 2021, covering 59% of the country's households (BAIMA, 2022). In addition, another study demonstrated that the consumption of plants and herbal medicines increased by 49% during the period of the COVID-19 pandemic in Brazil (BRAGA, DA SILVA, 2021). On the other hand, in the United States this consumption reaches 80% of the adult population habitually. Even

so, forecasts point to a 50% growth in consumption in five years. This trend is also reflected globally with estimated sales of 252 billion dollars in 2025 (BAIMA, 2022).

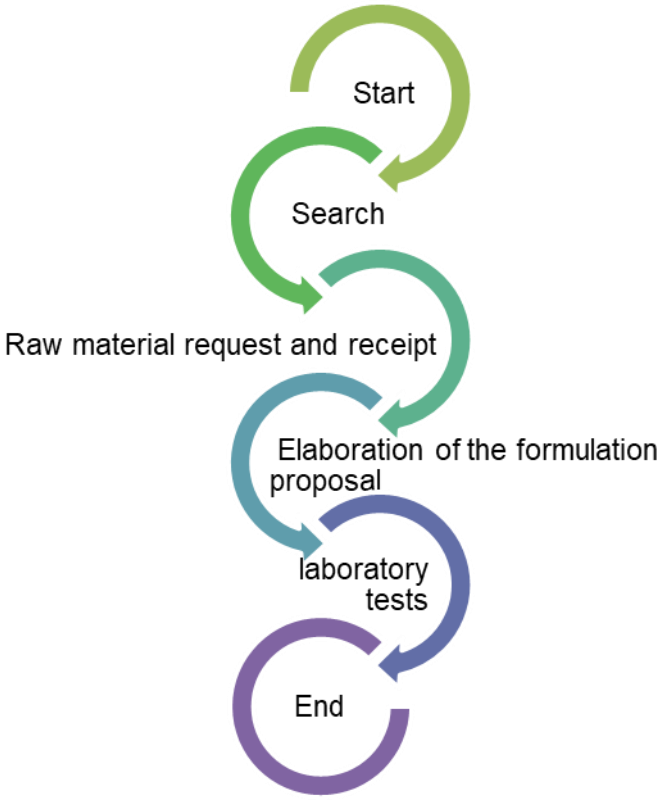
It is worth mentioning that dietary supplements follow specific regulations in each country. In Brazil, normative instruction 28 of July 27, 2018 presents the list of constituents and their respective limits of use, permitted claims and information on complementary labeling for dietary supplements (MINISTRY OF HEALTH, 2018). However, in this list of permitted bioactive substances, tocotrienol is not included. It is important to note that the company New Max Industrial LTDA has been working to insert this input in this list since 2021 (FERREIRA, CARVALHO, CARVALHO, 2021). When it comes to the U.S. market, which is regulated by the U.S. Food and Drug Administration (FDA), tocotrienol is already considered a foodstuff. The FDA considers safe the use of tocotrienol derived from annatto (*Bixa orellana*) by humans (FERREIRA, CARVALHO, CARVALHO, 2021). About the final product, according to the guidelines of this agency, the producer is responsible for the information described in the labeling, the ingredients of the formulation, safety and accuracy of the facts and does not require that chemical analyses be performed on the product, since the supplements do not have the purpose of diagnosing, treating, curing or preventing diseases. All product information must be on the label (BAIMA, 2022).

Thus, the present work aims to develop a proposal for an innovative formulation of a food supplement with tocotrienol from annatto (*Bixa orellana*) and is justified by the care to the elderly population that tends to increase, as cited by statistics. The tested form will be an orodispersive tablet aiming at the ease of swallowing the product and the use of tocotrienol whose studies have shown high benefits in the treatment and protection of the CNS.

2 MATERIALS AND METHODS

The activities planned for the elaboration of the proposal for the formulation of a food supplement containing tocotrienol are described in Figure 2.

Figure 2 - Flowchart of activities related to the proposed formulation of the food supplement



Source: Own elaboration, 2023.

The studies used to obtain data related to research on tocotrienol, concentration, studies on neuroprotective effects, toxicological data, safety and efficacy were selected from a bibliographic research with literature review, and the first stage of the methodological referral is shown in Figure 2. Books, scientific publications and technical materials available on the *web* pages Google Scholar, Scientific Electronic Library Online (SciELO), Pubmed and website of the company sponsoring tocotrienol, New Max Industrial LTDA., were searched. The descriptors used were "tocotrienol", "neuroprotective," and "*neuroprotective*," being performed between March 2022 and March 2023. The approximate results were 200 thousand articles and papers, which were submitted to the exclusion and inclusion criteria. As exclusion criteria, only studies published after 2010 that presented research containing tocotrienol as a neuroprotective agent were maintained. As inclusion criteria, the works that presented clinical research data and bibliographic reviews in Portuguese, English, and Spanish were maintained. The selection of articles was performed by evaluating the title and abstract and resulted in the full reading and use of eight works that were used in the theoretical basis for the theme of tocotrienol.

From this selection and research, we advanced to the next stage, as shown in Figure 2. A sample of the product Naturalmax Tocotrienol do Urucum (Powder) 30% and the additional inputs were requested to start the formulation tests at the level of academic bench in the laboratories of Biopark Education to obtain a prototype of the food supplement. The company New Max Industrial LTDA.,

headquartered in Americana – S.P. (Brazil) sponsored the bioactive compound Naturalmax. The other ingredients were provided by the university.

Regarding the regulatory basis, the research and reading of the norms established by the FDA, Anvisa and other bodies recognized by global regulatory agencies were carried out. Even so, the present study was carried out with a main focus on American regulations since, as already presented in the introduction chapter of the present study, the American standard allows the researcher to have the freedom to explore his technical knowledge, the consumption habits of dietary supplements by the North American population and the fact that the use of tocotrienol is already authorized as a food supplement by the regulations of that country. Therefore, it is possible to expect that the proposed formulation can be commercialized in the United States after its development and transposition of scale for industrial purposes.

3 RESULTS AND DISCUSSION

The theoretical research carried out served as an important source of information for the beginning of the development of this project, bringing truthful data on the amount of the bioactive compound to be used, determination of the limits of safety and efficacy of the consumption of tocotrienol as an option in the treatment of diseases related to brain degeneration. The main work reporting the study in humans, dated 2014 and written by Golapan et al, brings conclusions about the daily use of 200 mg of tocotrienols mix for two years, proving to be safe and effective in the treatment of brain injury. In addition, Plá (2018) contributes to these data by presenting his literature review highlighting data from five in *vitro and in* vivo *studies with tocotrienols demonstrating safety and efficacy in neuroprotection and considering testing at high concentrations*. Other authors such as Xia, Mo (2015) and Malavolta et al., (2018) have also studied the neuroprotective actions of tocotrienol, all of which concluded that the compound shows evidence of efficacy. Finally, it can be noted that dietary supplements containing tocotrienol are freely marketed in the North American market. The concentrations of these products vary between 50 and 125 mg of tocotrienol, being below the range tested by the authors. Thus, the present work presents the formulation test considering the use of 125 mg of Naturalmax Tocotrienol do Urucum (Powder) 30% as the concentration used in the tests performed in the laboratory.

From the definition of the amount of the bioactive compound to be used, a sample of the product Naturalmax Tocotrienol do Urucum (Powder) 30% was requested. The sponsoring company New Max Industrial Ltd. sent the sample in February 2023, which was subsequently used.

Since the objective of the present work was to develop a proposal for an innovative formulation, the excipients that make up dispersive tablets and that are marketed in Brazil were researched and analyzed. The study of these ingredients was carried out having as main guide the *Handbook of*

Pharmaceutical Excipients, 6th Edition *(2009), and the* parameters evaluated were the physical, chemical, and physicochemical properties, functional category, applications of the input in pharmaceutical and food formulations, description, incompatibility, safety, precautions and comments. Thus, the use of the inputs described in Table 1 was defined.

TABLE 1 - Inputs, their functions and recommended amounts for use in pharmaceutical or food formulations, according to the *Handbook of Pharmaceutical Excipients, 6th Edition,* 2009

INGREDIENT	FUNCTION	% RECOMMENDED FOR USE
Mannitol	Diluent	10 - 90
Crospovidone	Dismemberment	2 - 5
Microcrystalline cellulose	Diluent/disintegrating	5 - 90
Sorbitol	Diluent/sweetening agent	25 - 90
Sucralose	Sweetening agent	0,03 - 0,24
Magnesium stearate	Sliding/lubricant	0,25 - 5
Vanilla aroma	Flavoring	Not defined
Aroma of solid orange	Flavoring	Not Defined

Source: Own elaboration, 2023.

All ingredients were tested on the bench of the pharmaceutical technology laboratory of Biopark, considering that the formulation proposal should present reproducibility conditions on an industrial scale. Therefore, between November 2022 and March 2023, five cycles of bench tests were carried out, in which the parameters of mixture, humidity, average weight of the tablets, hardness, thickness, diameter, friability and disintegration were evaluated.

The parameters and the determination of specifications for the tablets were determined from the evaluation of guides and official compendia made available by the regulatory agencies whose application covers the areas of dietary supplements and medicines, also serving to meet the in-process control evaluations. The selected tests are presented in Chart 1.

TABLE 1 - List of parameters and specifications selected for laboratory bench tests using tocotrienol

TEST	SPECIFICATION	REFERENCE	PURPOSE
Appearance	Circular, non-grooved, light yellow tablet	NSF; DL	CQ
Middleweight	300 mg ±5%	FB	CP
Hardness	≥ 3 N	NSF; FB	CQ
Diameter	10 mm ± 5%	DL	CP
Thickness	4,10 mm ± 5%	DL	CP
Friabilidade	Loss ≤ 1.5% of your weight	NSF; FB	CQ
Disintegration	< 3 minutes	NSF; FB	CQ

Source: Own elaboration, 2023.
Note: DL - Local Development; F.B. - Brazilian Pharmacopoeia; C.P. - Control in Process; C.Q. - Quality Control.

Another guide consulted was the *Stability Testing Guideline for Dietary Supplements* (2011), which suggests a list of trials that differ according to each type of pharmaceutical form. From this guide, the appearance, hardness, friability and disintegration tests for tablets were selected. Other

parameters that define the specifications of the bench tests performed followed the Brazilian Pharmacopoeia, 6th edition, volume 1 (2012). On the other hand, the researchers were responsible for defining the specification for the appearance test, considering that this test should describe the characteristics of the product elaborated and tooling used. Thus, the specifications for the diameter and thickness evaluations were also defined, which are performed only as in-process control, since they are related to the tooling used in the powder compression equipment.

To know the characteristics of the inputs, the first three bench tests were performed. These tests also served to define the quantities of each of the inputs and understand the process of mixing and compressing the powders. The set of punctures chosen for these tests was the one that uses the 10mm matrix. The average weight of the tablets was defined at 300 mg, considering the use of the amount of 60 mg of Naturalmax Tocotrienol do Urucum (Powder) 30%. The mean of the results obtained in each test can be seen in Table 2.

TABLE 2 - Comparison of the mean of the results obtained in the formulation tests using the compression matrix of size 10mm

COMPARISON OF RESULTS						
TEST	**MIDDLEWEIGHT**	**HARDNESS**	**THICKNESS**	**DIAMETER**	**FRITABILITY**	**DISINTEGRATION**
Test 1	301 mg	1.60 N	4,16 mm	10,11 mm	0,01%	47”
Test 2	302 mg	3.10 N	4,20 mm	10,10 mm	0,01%	32’’
Test 3	312 mg	1.35 N	4,30 mm	10,13 mm	0,01%	1'10"

Source: Own elaboration, 2023.

To achieve the stipulated goal of producing a food supplement with 125 mg of the bioactive compound Naturalmax Tocotrienol do Urucum (Powder) 30% and improve the formulation, two more bench tests were performed. The compression matrix was modified to 12 mm size, increasing the size and weight of the tablets to 500 mg. In this context, the parameters defined for in-process control were reconsidered: average weight, thickness and diameter, as shown in Chart 2.

TABLE 2 – New parameters and specifications defined, due to the test of increase in the concentration of the bioactive compound

TEST	**SPECIFICATION**	**REFERENCE**	**PURPOSE**
Middleweight	500 mg ± 5%	FB	CP
Diameter	12 mm ± 5%	DL	CP
Thickness	4.50 mm ± 5%	DL	CP

Source: Own elaboration, 2023.
Note: DL - Local Development; F.B. - Brazilian Pharmacopoeia; C.P. - Control in Process.

The mean of the results obtained after evaluation of the tablets elaborated in tests 4 and 5 are presented in Table 3.

TABLE 3 - Comparison of the mean of the results obtained in the concentration increase tests, using the compression matrix of size 12mm

COMPARISON OF RESULTS						
TEST	**MIDDLEWEIGHT**	**HARDNESS**	**THICKNESS**	**DIAMETER**	**FRITABILITY**	**DISINTEGRATION**
Test 4	498 mg	1.60 N	4,76 mm	12,15 mm	0,17%	2’04”
Test 5	497 mg	3.9 N	4,88 mm	12,11 mm	0,01%	1'00"

Source: Own elaboration, 2023.

The tablets produced in test number 5 met the new specifications determined for the prototype of the proposed food supplement. After compiling the results of the process control and quality control tests, the tablets were approved and can be seen in Figure 3.

FIGURE 3 - Tablets obtained in test 5



Source: Own elaboration, 2023.

Thus, the tests were finalized and the composition of ingredients used in the bench test number 5 was defined as the best combination for the tablet composed of tocotrienol.

4 CONCLUSION

Health experts have shown great concern regarding the care to be taken with the elderly population in the face of global trends of population aging and consequent increase in senile diseases, which generates the need to develop proposals focused on health treatments in the chemical and natural spheres. Given this scenario, the present project met the objective of elaborating a proposal for the formulation of a food supplement with the compound tocotrienol of annatto (*Bixa orellana*). This study resulted in the development of a prototype of a pleasant-tasting orodispersive tablet that can be used as a form of neuroprotection. The product followed the guides and compendia available in the year 2023 and, therefore, can only be marketed in the North American market at this first moment. However, after being regularized by Anvisa it can be sold in Brazil.

It is important to highlight that, if there is interest of the industry in commercializing the product, the proposal described here will need to be retested and receive the necessary adjustments aimed at industrial production, including performing stability studies to meet the requirements of the regulatory agency of the country intended for commercialization, in addition to developing the analytical method to attest to the final quality of the finished product and the realization of the financial feasibility study for the composition of the selling price.

The inclusion of a product composed of annatto (*Bixa orellana*) in the form of an orodispersive tablet represents an innovative product, probably capable of generating an excellent financial return for the producing industry since market research has shown that the products currently marketed are presented in the soft gel pharmaceutical form.

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Water supply sources in the neighborhood city of Lobo in Porto Velho – Rondônia, Southern Amazon

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ABSTRACT
The objective of this work is to characterize the sources used to obtain water destined for residences in the Cidade do Lobo neighborhood in the city of Porto Velho, State of Rondônia - Southern Amazon. The methodology employed was descriptive, using the inductive method, and the procedures adopted consisted of bibliographical research, field verification, production and analysis of graphs and characterization of the water supply scenario in the neighborhood during the second half of 2018, through the application of a form with objective questions, in 58 residences, chosen by convenience sampling. It was possible to identify the predominance of two types of wells: the semi-artesian and the amazon, the latter as the main source of water supply for this population. The general network plays an important role in people's lives, but the supply of treated water is limited to some homes in this neighborhood, forcing residents, who do not use well water for direct consumption, to seek alternative solutions to have access to better water. quality, including the purchase of water using a water tank or mineral water available in shops, in addition to collecting water using jerrycans in places that have piped water, demonstrating that a large part of the neighborhood's population is excluded from policies offered by the government, regarding the supply of treated water through protected springs.

Keywords: Spring, Water supply, Wells, Cidade do Lobo.

1 INTRODUCTION

Water is an essential natural resource for the survival of human beings and is one of the problems faced by a part of the population of Portovelhense. There is also a lack of sufficient infrastructure to supply essential services, such as the supply of treated water through the general supply network to serve the homes of all neighborhoods of the city of Porto Velho, State of Rondônia, located in the southern Brazilian Amazon. Water is found in different physical states, they are: liquid, solid and gaseous. Temperature is the factor responsible for maintaining or transforming the physical state of the same.

The hydrological cycle is the movement of water on the planet, occurs in the oceans, continents and the atmosphere. The water is subject to evaporation, turning into clouds, where the process of condensation occurs and returns to Earth in the form of rain. This process and dynamics characterizes a constant cycle of compound movement between several stages, by precipitation, evaporation, surface

runoff, infiltration and groundwater (BRASIL, 2018). The water, to be consumed, is that destined to the ingestion, preparation and production of food and also for personal hygiene, must comply with the standards of potability in force, such as: microbiological standard, turbidity, organoleptic standard, among others.

Due to technological advances arising from scientific research and better knowledge of the reality of the country, this legislation undergoes frequent revisions and updates, such as Ordinance No. 2,914 of December 12, 2011 of the Ministry of Health (BRASIL, 2011) partially amended by Consolidation Ordinance No. 5, of September 28, 2017 (BRAZIL, 2017). The latter had its Annex XX modified more recently by Ordinance GM/MS No. 888, of May 4, 2021 (BRAZIL, 2021). It is worth noting that these documents present the competences attributed to the Union, the States and Municipalities.

The standard of potability established by these official documents also mentions the microbiological standard that has as its main objective:

> Provide support regarding its potability, that is, the absence of risk of ingestion of disease-causing microorganisms, usually from contamination by human feces and other warm-blooded animals. It is worth mentioning that the microorganisms present in natural waters are, for the most part, harmless to human health (BRASIL, 2013, p. 09).

When contamination by sewage percolation occurs, microorganisms present numerous health risks. The consumption of contaminated water manifests itself in different ways, from activities carried out daily such as food and beverage intake, or even amid exposure in environments of collective use, such as swimming pools, baths, among others. The implementation or improvements in the water supply is one of the important factors for the maintenance of the health of the population and reduces the number of diseases of transmission directly through water (OLIVEIRA, 1987).

The objective of this work is to characterize the springs used to obtain water for residential purposes in the Cidade do Lobo neighborhood, located in the South Zone of Porto Velho, capital of Rondonia, describing the situation found in the second half of 2018, the period that was carried out the research, through a survey in bibliographic materials, data related to the subject at the Brazilian Institute of Geography and Statistics - IBGE by the Automatic Recovery System - SIDRA (IBGE, 2018) and through the application of an interview form, "obtaining the answers of the residents surveyed to verify information obtained through the previous bibliographic survey" (LAKATOS; MARCONI, 1992, p. 107).

It is important to highlight that the definition presented by Oliveira (1987, p. 2) was adopted:

> By source is conceptualized the source of water supply, which can be, for example, a river, a lake, a spring or well, coming from the water table or the deep sheet" and as for the sanitary conditions, the same author classifies the springs in "protected and unprotected.

The form application was performed in 58 residences in the Cidade do Lobo neighborhood, chosen by convenience sampling. According to the data obtained, the line of methodological research developed is the descriptive, with the inductive method, which aim to "study particular situations, aiming not only at the identification of the problem, but the relationship that it has with factors that directly influence the current situation, then the comparison is made to discover the correlation between the factors presented" (GIL, 2008, p. 10).

2 HISTORICAL CONTEXT OF THE CIDADE DO LOBO NEIGHBORHOOD

The urban space is articulated, each of its parts always relates to the others, directly or indirectly, causing all to get in sync and develop in an egalitarian way, although they have different intensities. This articulation in a concrete way is defined:

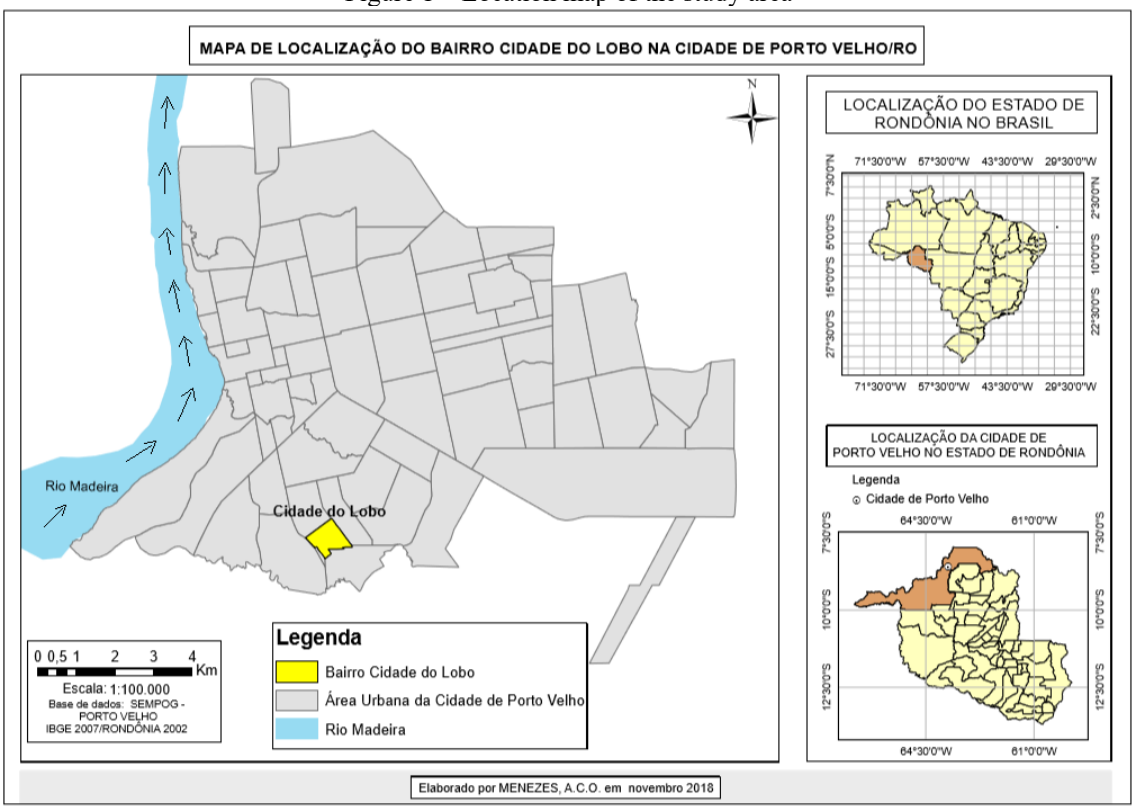
> [...] through flows of vehicles and people associated with the loading and unloading of goods, the daily commutes between residential areas and the various workplaces, less frequent trips for shopping in the city center or the shops of the neighborhood, visits to friends and relatives, and trips to the cinema, religious worship, beach, parks, squares (CORRÊA, 1989, p. 7).

It is also characterized according to its spatial organization, "distinguishing the different forms of land uses, whether they are intended for commercial, industrial, services, residential or leisure areas, always aiming to interact socially with the rest of society" (CORRÊA, 1989, p. 7).

Rondônia is a state that has been growing at a fast pace in recent years, mainly due to the coming of large enterprises such as the construction of the hydroelectric plants of the Madeira River. The expressive flow of migrants provided some socioeconomic growth in the city, these people came from various parts of the country in search of employment and better quality of life, so new neighborhoods were created and others regularized. The housing search has grown in a disorderly way, forcing the municipality to create public policies to assist essential services to serve the entire population.

Figure 1 shows the location map of the city of Porto Velho and identification of the study area that has its boundaries established between the following neighborhoods: to the north with the Conceição neighborhood, to the south with the New City, to the east with Caladinho and the west with the Novo Horizonte neighborhood. It is also part of zone 3 along with the neighborhoods Aeroclube, Areia Branca, Caladinho, Castanheira and Cohab (PORTO VELHO, 2018).

Figure 1 – Location map of the study area



Prepared by Menezes (2018).

According to the 2010 IBGE census (IBGE, 2012), the neighborhood had 1,179 households and about 4,433 people. It emerged in mid-1984, without planning, sanitation, urbanization or any other form of infrastructure. It had its name in allusion to the surname of the former owner "*João Leal Lobo*", who made in the place rice plantations and over time, had his property invaded by people in search of a land to establish housing.

In 2011 the residents were contemplated with the Usucapião Program, which is the right that a citizen acquires about the possession of a movable or immovable property as a result of the use of this for a certain time, "the program was conducted by the city and gave the right of possession to the resident who was on the land for at least 5 consecutive years and that the owner had not shown interest in the lot" (BORZACOV, 2016, p. 133).

Because its creation came from invasions, the Cidade do Lobo neighborhood was expanding outside the proper standards and without any form of planning, hindering the isonomic implementation of the treated water supply service.

The research was conducted by the importance that water plays in people's lives and how those who do not have access to the general network of treated water do to dispose of the service even in their way, as is the case of wells, and what diseases have water as a source of transmission and even diseases of water origin, that put public health at risk if there is direct contact with the contaminated

source. Soon after the definition of the theme, the search for official data such as the censuses released by the IBGE began.

In the stage of evaluation of the data obtained, it was identified that during the censuses of the years 2000 and 2010 the neighborhood was with a considerable number of residents who had wells, as a form of water supply in the residence, the remainder, about 193 houses in the year 2010, had the general network as the main maintainer of the water supply in the property, represented by Figure 2, as follows:

Figure 2 – Comparison between the water supply data obtained through the censuses of the years 2000 and 2010 in the Cidade do Lobo neighborhood



Source: Census 2000 and 2010 (IBGE, 2012). Organized by Menezes (2018).

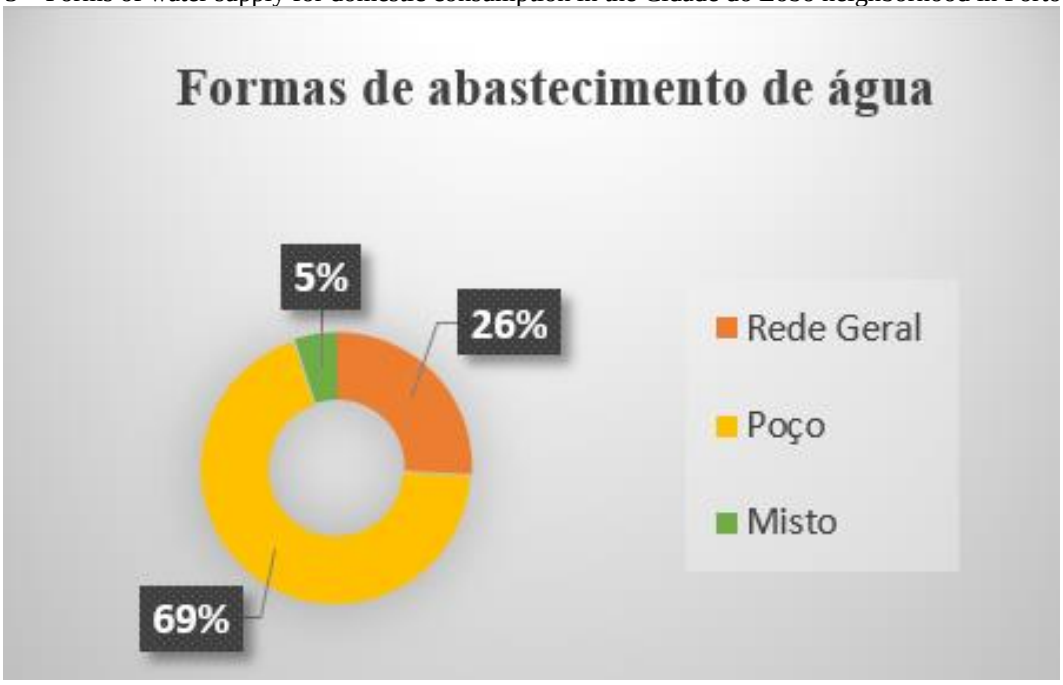
We went through the entire perimeter of the neighborhood's delimitation, between the main streets in search of residents who were willing to answer the form, composed of 15 questions that had objective alternative questions and justifying questions that required a better detailing of the situation. In all, 58 forms were answered with objective questions regarding the identification of the residence, the main source for the water supply in the house and the physical characteristics of the water and the quality of the service provided by the company responsible for the water supply in the capital, thus contributing to the achievement of the results achieved.

It was decided to keep the focus mainly on the characteristics of the springs, due to the resistance of people to talk about the subject of possible diseases caused by the use of inadequate water for consumption, when the questions were directed to the subject, the interviewees avoided passing on any type of information, especially the residents who have in their properties the characteristics of wells prone to contamination.

3 FORMS OF WATER SUPPLY IN THE CIDADE DO LOBO NEIGHBORHOOD

With the choice of the inductive method, when doing the case study and application of form in the neighborhood, it was possible to verify the situation that pointed out the census of 2010 (IBGE, 2012), which is the predominance of wells that are used as a form of water supply for domestic use in the Cidade do Lobo neighborhood in Porto Velho, indicated by Figure 3, which shows the percentage of respondents who make use of water in their homes having its origin through the general network, wells and mixed, which are those who have both forms of supply to meet the needs of their homes, the data represent the results through the field survey conducted in the neighborhood.

Figure 3 – Forms of water supply for domestic consumption in the Cidade do Lobo neighborhood in Porto Velho



Prepared by Menezes (2018).

At that moment, the confirmation of the data obtained through the SIDRA of the IBGE was clear, when of the 58 forms applied, the total of 40 were answered by people who have the residence only supplied by water from wells, 15 residents still stated that they have access to water provided by the general network not having a well in the residence and 03 interviewees have both forms of supply, where with the lack of one of the alternatives for an indeterminate reason, the other maintains the activities developed in the residence normally.

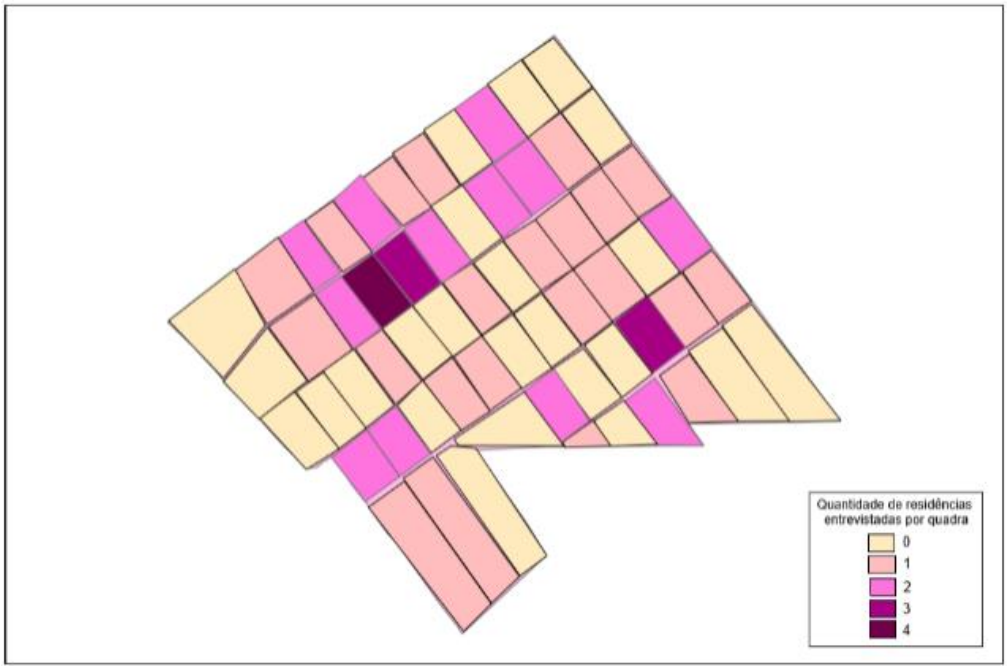
It was noticed during the fieldwork that people were afraid to answer the questions, because they thought that behind the form would be involved other intentions, of inspection for example, as said by some, who at first thought that the objective was to survey the houses that have wells, to request the future the closure and force them to use the water provided by the general network.

At this stage of the work it was necessary to describe in more detail about the objectives of the research and try to convince them of the importance of bringing the subject to be exposed in the future

before the community itself, since water is indispensable in all activities performed by the human being and requires great attention, because of the way it can bring numerous benefits to the body, It can also be harmful to health, and may even cause irreparable damage.

As people made themselves available to answer the questions, the results began to take shape. In some blocks, it was not possible to obtain results from the application of the form, since the sample type of convenience survey was followed and some residents chose to abstain. Figure 4 below represents the results obtained through the indicative classification of the number of properties in which the respective residents answered the form.

Figure 04 – Result of the application of the form by blocks of the Cidade do Lobo neighborhood



Prepared by Menezes (2018).

3.1 HOMES SUPPLIED THROUGH WELLS AND OTHER SOURCES

Drinking water is defined as water that meets the standard of potability established by the legislation in force and that does not pose health risks. Through the convenience sample survey, 40 people who own and make use only of the water from the well in the residence and 03 who also have access beyond the well to the general network as a form of supply to perform daily activities were interviewed.

It was found the predominance of residences that have wells supplying the houses in the Cidade do Lobo neighborhood in Porto Velho, starting from this point, the form brought a very important item to be observed that are the types of wells that perform this supply.

The number of households that have the well of the Amazonas/Cacimba type is equivalent to 36 interviewees, which is the type of well that has the cheapest cost about the construction, presenting

shallow depths, but it is the type of well that contains the greatest risks of contamination, because it is the water table.

The residences that use the semi-artesian well type are equivalent to 07 interviewees, and this is the type of well recommended for the capture of water from the underground table above 20 meters deep, using filters and pre filters to eliminate various types of impurities, such as dirt. Figure 5 shows the result obtained in the form of a graph, where it represents the percentage of the types of wells predominant in the study area.

Figure 5 – Types of wells predominant in the neighborhood Cidade do Lobo in Porto Velho – RO



Prepared by Menezes (2018).

After identifying the types of wells, it was possible to point out the average depth of the same, item of question No. 13 of the form, an important data to be verified, because most of the wells of the Amazon type in the neighborhood presented shallow depths for water capture, with results ranging from 06 to 20 meters deep. In this case it is important to guide the residents who have this type of well to observe their conditions, if there is the presence of insects and animals in the interior and the vicinity, if the fence is under the standards, carry out the cleaning and disinfection in an appropriate way, the construction of a box over the mouth of the well is fundamental, this can be made of concrete or bricks, with a height between 50 and 80 centimeters from the ground and mainly, close the mouth of the well with concrete or wood structure, leaving an opening for inspection and maintenance of the well, as represented in Figure 6.

Figure 06 - External view of an amazon-type well located in a residence in the Cidade do Lobo neighborhood in Porto Velho – RO



Photographed by Menezes (2018).

The biggest aggravating factor occurs with the arrival of the dry season in the middle of the year, popularly known in the Amazon as "summer", when the wells begin to have variation in their water level and some even dry up completely, forcing residents to look for various options to keep the house supplied, avoiding on average, the lack of water for three to four months in a row.

Figure 7 below identifies some of the main diseases related to inadequate water supply and consumption, such as wells with shallow depth that are more prone to various types of contamination, mainly by sewage percolation, this figure also specifies the forms of transmission and prevention.

Figure 7 – Diseases related to water supply

Grupo de doenças	Forma de transmissão	Principais doenças e agente etiológico	Formas de prevenção
Diarréicas e verminoses	Ingestão de água com contaminantes, má higiene dos alimentos e a forma de tratamento dos dejetos.	Cólera (*Vibrio cholerae*) Giardíase (*Giardia lamblia*) Criptosporidíase (*Cryptosporidium parvum*) Febre tifoide (*Salmonella typhi*) Febre paratifoide (*Salmonella paratyphi* dos tipos "A", "B"ou "C") Amebíase (*Entamoeba hystolitica*) Hepatite infecciosa Ascaridíase (*Ascaris lumbricoides*)	A educação sanitária, o saneamento e a melhoria do estado nutricional dos indivíduos. Implantar sistema de abastecimento e tratamento da água, com fornecimento em quantidade e qualidade para uso e consumo humano. Proteção de contaminação dos mananciais e fontes de água.
Pele	Relacionadas com os hábitos de higiene.	Impetigo (*Staphylococcus aureus*) Dermatofitose e micoses (fungos dos gêneros *Trichophyton, Microsporum e Epidermophyton*) Escabiose (*Sarcoptes scabiei*) Piodermite (*Sarcoptes scabiei*)	Não permitir banhos de banheira, piscina ou de mar. Lavar frequentemente as mãos com água e sabão.
Olhos	A falta de água e a higiene pessoal insuficiente criam condições favoráveis à sua disseminação.	Conjuntivites (vírus e bactérias)	Evitar aglomerações ou frequentar piscinas de academias ou clubes e praias. Lavar com frequência o rosto e as mãos, uma vez que estas são veículos importantes para a transmissão de micro-organismos patogênicos.
Transmitidas por vetores	As doenças são propagadas por insetos cujos ciclos possuem uma fase aquática.	Malária (*Plasmdium vivax, P. falciparum, P. malariae*) Dengue (DENV 1, 2, 3 e 4) Febre amarela (vírus do gênero *Flavivirus*) Filariose (*Wuchereria bancrofti*)	Eliminar os criadouros de vetores com inspeção sistemática e medidas de controle (drenagem, aterro e outros). Dar destinação final adequada aos resíduos sólidos.
Associada à Água	O agente etiológico penetra pela pele ou é ingerido.	Esquistossomose (*Schistosoma mansoni*) Leptospirose (Bactéria do gênero *Leptospira*)	Evitar o contato com águas infectadas. Proteger mananciais. Adotar medidas adequadas para disposição do esgoto. Combate do hospedeiro intermediário. Cuidados com a água para consumo humano. Cuidados com a higiene, remoção e destino, adequados de dejetos.

Source: Brazil (2015, p. 93).

The alternatives pointed out by the residents as a solution to keep water stored for use in the residence, were two: through the purchase, either by kite car or mineral water available in shops and through the solidarity of the neighbors, who make their wells available to supply the houses nearby.

Among the problems found by the residents, related to the arrival of "summer" is the remarkable change in the physical aspect of the water obtained through the well, it becomes muddy and sometimes even has a strong smell, when not used the water from the well in a rational way, this comes to dry completely, forcing the resident to perform the cleaning process of the same, claimed by most of the interviewees as the main factor for the execution of the well maintenance process; Among the answers, a large risk factor for contamination was verified, 10 interviewees reported that they do not clean their well.

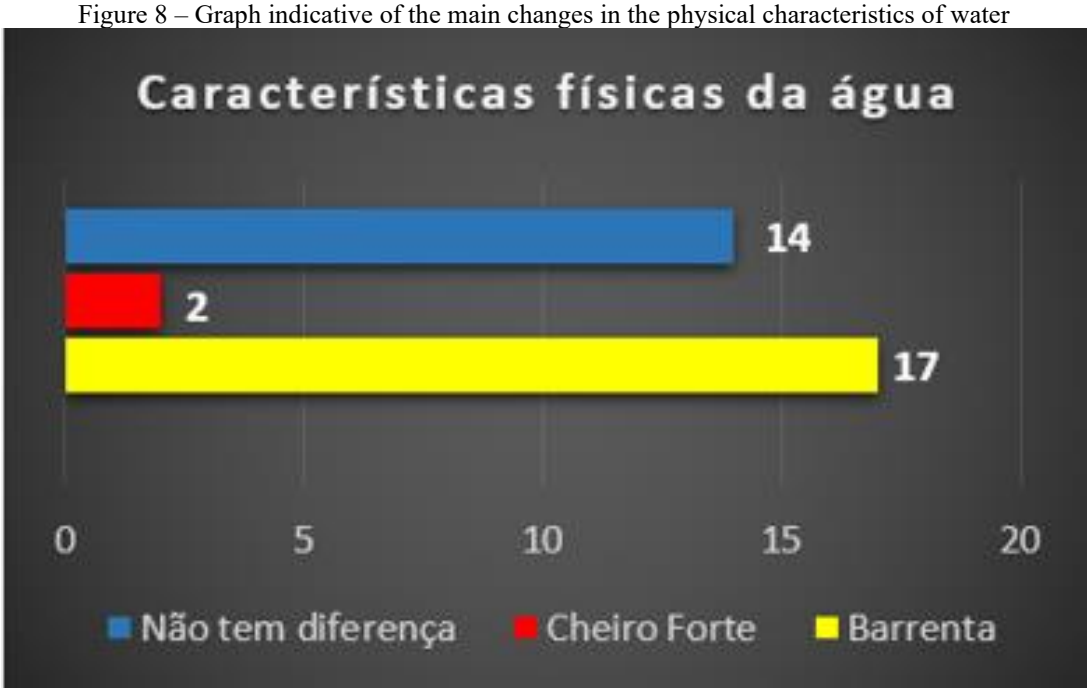
The disinfection process is done through some products derived from chlorine, mainly bleach and hypochlorite, this is made available by health units free of charge used by residents at home to disinfect the well, especially when significant changes in the color and smell of the water are perceived.

The change in the physical aspects of water can be indicative of the presence of metals such as iron and manganese, causing bad smell and also stains on tissues, fouling in pipes and if consumed in excess, over time can cause damage to the body, increasing the risk of heart, liver and pancreas diseases.

The presence of organic matter also contributes to color change and one of the most harmful factors to human health is contamination by sewage percolation, which can present changes in both color and smell.

This hypothesis by sewage contamination is considered by the fact that the city of Porto Velho is almost devoid of a general sewage network, thus forcing the population to resort to cesspools, which when built irregularly and without planning can contaminate the water table, making the water from nearby wells inappropriate for use. In Figure 8, the results obtained regarding the physical characteristics of the water are presented in the graph, indicating the quantity of responses obtained.

Figure 8 – Graph indicative of the main changes in the physical characteristics of water



Prepared by Menezes (2018).

The ideal before using the water that presents this type of characteristic is to look for the water treatment unit of the city and request the performance of examinations thus obtaining the certification that it has quality for residential use or not. The total of 06 interviewees verbally informed that they had already performed these tests with the treatment unit and obtained positive results, but these tests were performed a long time ago and allowed the use of this water in practically all daily activities, except for ingestion, where all claimed that they do not use the water for consumption itself, Because there is the fear in making food and drinking from it, since according to information passed on among

the neighbors themselves, some wells have already had problems with gases and had to be closed completely.

As stated by the Ministry of Health: "the wells of the Amazon type are built in free aquifers or groundwater, the static level of water in these wells coincides with the regional water table, once the water table is reached, it is recommended to deepen a little more to obtain its best use" (BRASIL, 2015, p. 93).

According to the answers obtained in the form, there is a variation concerning depth, the results found were between 06 and 20 meters for wells of the Amazon/cacimba type and between 18 and 25 meters for semiartesian wells, according to Figure 9, which depicts the variation of this depth in the form of a comparative line graph, identifying the greatest depths found.

Figure 9 – Graph identifying the declared depth of the wells used in the neighborhood

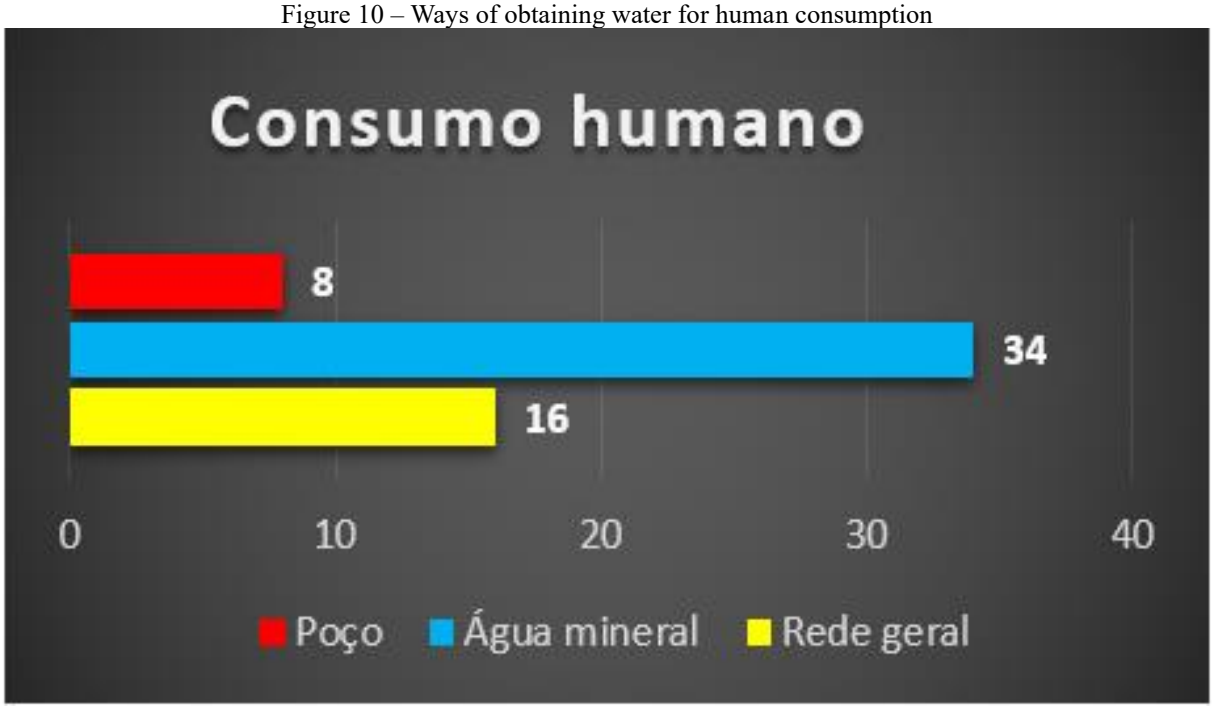


Prepared by Menezes (2018).

The representation of the Amazon type wells is made using the blue line that remains almost constant, obtaining few changes and oscillating mainly between 06 and 10 meters, very low depth, conducive to high levels of contamination. The semi-artesian wells represented by the orange line show results between 18 and 25 meters, maintaining the continuous traces between the points, a little greater depth, but can still receive contributions from the percolation of surface waters, subject to contamination.

Regarding the way water for human consumption is obtained, in the form, three alternatives were made available: 1) Through the purchase of mineral water, 2) Water provided by the general network, with complementary treatment to eliminate impurities and 3) the option Others, leaving residents free to express answers not contained in the form, having specific situations, as shown in Figure 10, where the identification of ways of obtaining water for consumption, used in essential activities such as food preparation and human consumption, is made.

Figure 10 – Ways of obtaining water for human consumption



Prepared by Menezes (2018).

The predominance of households that make the purchase of mineral water for consumption represents approximately 59% of respondents, because they believe that the waters of the residences, both from the well and the general network are ideal for other purposes and not for human consumption, about 27% reported that they use water from the general network, making complementary treatment to eliminate impurities and 14% of respondents confirmed that they use well water for all activities developed at home, including for direct consumption. Both residents who consume water from the general network and the well said they use filters, citing the clay filter as the most reliable and efficient.

As identified, some people claimed to use water from wells in the preparation of food and for their ingestion, a fact that brings concern, since the wells have low depths and capture water from the water table, increasing the risk of serious diseases.

Of the total of interviewees who claimed to make use of water from the general network for ingestion, some alternatives used by residents were identified as a temporary solution, such as the provision of joint action by neighbors, where households that have treated water provide others with access to it through 20-liter gallons. An alternative solution found by many residents and indicated by them for verification, was the existence of a water registry located on Aquiles Paraguassu street, near the entrance of a house, which receives treated water from the general network and that the community of the neighborhood and even people from the vicinity, move to the site, seeking access to treated water provided by the Water and Sewage Company of Rondônia – CAERD. As shown in Figure 11,

which portrays the reality of some people who have wells, but who make daily efforts in search of treated water in the so-called "CAERD Pipe".

Figure 11 – Record of people taking treated water for human consumption in the pipe supplied by the general network



Photographed by Menezes (2018).

It was not possible to make the most accurate identification of the time of existence of this point of collection of treated water, but according to the residents themselves, for a long time, this plumbing with sufficient force supplies dozens of houses.

According to data obtained from CAERD in 2018, the Cidade do Lobo neighborhood is not fully covered by the general supply network, so residents look for alternatives that meet the needs of water consumption in homes.

4 FINAL CONSIDERATIONS

The alternative and individual water supply system needs at least a standardization for distribution and access to water in an equal way to the residents. In the case of the place studied, according to the interviewees, the Cidade do Lobo neighborhood has all the necessary plumbing to supply treated water made available by the general network, however, in contact with CAERD, in search of information about which well performs the water supply in the neighborhood, no return was obtained from the company, to answer the question, thus generating the hypothesis of "insufficiency on the part of this well", which cannot meet the demand for water use, probably not having enough flow and/or pressure to reach the taps of many residents.

Thus, the general network plays an important role in people's lives, but has the supply of treated water limited to some residences, forcing the rest of the residents, who do not use well water for direct consumption, to seek alternative solutions to obtain access to better quality water, including the purchase of water through a kite car or mineral water available in shops, in addition to conducting water collections through gallons in places that have piped water service. By the field survey, it was possible to identify the predominance of two types of wells: the semi-artesian and the Amazonian type, the latter as the main form of water supply in the neighborhood.

Much of the neighborhood community ends up feeling violated and seeks to solve the situation in its way: the problem of water supply. Because it is a considerably old neighborhood, residents make use of wells that, in most cases, were not built according to current regulations, causing health risks.

The population understands that they need to consume good quality water, from the moment they make use of the spout in the pipe of CAERD. Improvements and expansions are needed in the distribution network of treated water to the neighborhood, which can be the subject of further research. The poor construction of wells, the low flow in the dry season, the inadequate conditioning and transport of water, are facts that show that the population of the neighborhood is excluded from the policies offered by the government, concerning the supply of water treated by protected source.

Finally, it is suggested to those responsible for the supply and sanitary inspection to carry out examinations in the wells, to verify the quality of the water and that the residents can be guided in the best possible way, how to proceed in situations that interfere with the well-being of the people, giving due importance to the diseases caused through the origin or transmission of water.

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The stigmatization of colorectal cancer in society

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ABSTRACT
Introduction: Although CRC is the main malignant neoplasm of the gastrointestinal tract and the third most typical type of cancer in the world, little is discussed about its morbidity and mortality. Because the lack of visibility does not provide an adequate budget for preventive health policies, most diagnoses do not occur in the early stages of the disease, which not only makes it more expensive but also makes the therapeutic process difficult for the patient for the health team. To analyze the insufficient prevention of colorectal cancer. Objectives: to identify CRC mortality and relate it to the lack of prevention and information about the disease. Methodology: a literature review that will be carried out through already published material made at the University of Ribeirão Preto. It will be an observational study that will establish correlations between the social and scientific aspects of colorectal cancer.

Keywords: Colorectal cancer, Mortality, Prevention.

1 INTRODUCTION

Colorectal cancer is one of the main types of neoplasms that kill around the world. There are numerous diagnosed cases that, in Brazil, tend to increase. It turns out that most of the time that this disease is diagnosed, it is in advanced stages. The prognosis of RCC is good only in early stages, which are diagnosed by prevention methods such as colonoscopy or detection of fecal occult blood. Such methods are indicated, above all, for the senile portion of the population, but there are few public incentives directed to health to better inform and encourage the search for means to diagnose and treat the carriers of the disease when it is still in the process of emergence. Although there are references that investigate all determinations of RCC, they are still insufficient to have a good understanding of how to predict possible carriers and treatment for those in advanced stages. Given the scarcity of data and information, the indicators do not bring real parameters of the proportion of the effect of the disease in Brazil. This means that it is necessary to deepen epidemiological studies in the country, with the effect of elucidating the gaps in public health management regarding the high incidence and mortality of the neoplasm in question. Thus, the little information known by people increases a stigma created by common sense that hinders access to existing knowledge that has contributed to increase a network of prevention-treatment of RCC.

2 THEORETICAL FRAMEWORK

RCC (colorectal cancer) is the main malignant neoplasm of GIT and the third most typical type of cancer in the world. Given this, little is addressed about its aggressiveness and how ordinary and routine it can be (MACHADO et al., 2016). Many of the deaths could be prevented.

Studies on molecular biology hold the greatest promise for new ways of knowing and remedying the problem of colorectal cancer. Such studies ensured a cluster of materials capable of identifying and manipulating biomolecules through biotechnology (PINHO, 2008). Even though more than 90% of RCC carriers are sporadic, some inherit the mutation (KATSAOUNOU, et al. 2023). To improve the diagnosis, prognosis and clinical treatment of patients with RCC, molecular research studies the disease by markers. Colorectal cancer was the pioneer in molecular biology studies in the field of carcinogenesis by sequential gene expression of adenocarcinoma, which demonstrated that cancer formation occurs by altering proteins that act on the cell cycle. This reveals that a healthy set of cells generates cancer from a sum of gene mutations. Following the proliferative disorder, angiogenesis, tissue invasion, and metastases occur as subsequent stages of carcinogenesis. To better determine the histological basis of the pathology, there are tools for identification such as the "Microarrays" method, which discriminates through the messenger RNA molecules which genes are activated in the tumor tissues, the "immunohistochemistry," which discriminates through the labeling and addition of monoclonal antibodies in proteins of the affected tissue, or the "SELDI" and "MALDI" methods, which are based on the condition that tumors will release fragments of proteins that will be compatible in a similar way to the proteins of individuals with the same diseases, thus emerging patterns that suggest a diagnosis (PINHO, 2008). MicroRNAs as molecular markers demonstrated that miR-125b and miR-137 make up the majority of the tumors in question since the former is crucial for the cell cycle and the latter is associated with advanced stages of RCC. (ANDREOLI et al., 2014) Such studies guide the direction of the singular treatment of the patient's tumor. In addition to molecular markers, most cancers of this type arise from pre-existing adenomatous or serrated polyps, which makes it easier to screen for the disease.

Based on epidemiological studies, in Brazil, the number of deaths due to colorectal cancer has increased, especially for males. Inappropriate lifestyle habits are relevant in the prevalence of RCC since they indicate a higher incidence. In addition, another factor that stands out is social inequality since disparities between Brazilian states is a predominant factor in CRC mortality. In 2012 the RCC was in fourth place among the cancers that killed the most men and third among those that killed the most women in the country, and third and second, respectively, about the world. The socioeconomic condition is closely linked to the lifestyle of the individual and conditions such as obesity, smoking, alcoholism, sedentary lifestyle, inadequate diet increase the risk of emergence and evidence the increase in cases of RCC related to the places that have reduced social disparity (OLIVEIRA, et al.

2018). What fundamentally reduces mortality rates is early diagnosis, but prevention can reduce by 60%. In addition to prevention, increasing the supply of tests, endoscopic resection of adenomatous polyps and better treatments are essential. Better epidemiological indicators regarding CRC cases will raise more capital for the area that, despite having many cases and deaths, is so little discussed collectively. Becoming, then, the increase in CRC mortality in Brazil is evidence of discrepancies in the Brazilian health infrastructure, which shows the link between better results of prevention, diagnosis, and treatment in more developed areas (OLIVEIRA, et al. 2018).

One should, from the age of 50, annually look for occult blood in the feces, every 5 years by rectosigmoidoscopy to screen for any tissue modification and from the age of 60, colonoscopy every decade. Colonoscopy is the best way to reduce mortality, as those who underwent the test showed less incidence. The identification of irregularities by direct visualization exams allows them to be repaired during the procedure before they progress. Although early diagnosis of RCC has a favorable prognosis, for the most part the tumor has already invaded neighboring tissues or metastasized. The incidence of RCC increases along with age, mainly above 50 years; however, encouraged by the westernized lifestyle that increases the risks for the disease, there has been an alarming increase in cases among younger people (KATSAOUNOU, et al. 2023). Among the risks, diabetes mellitus is a comorbidity that increases the risks of neoplasia by 20 to 30%. The screening of adults of medium risk is centered between 50 and 75 years of age, above this range, the demand is singularized by the patient's health condition. There is also evidence that aspirin, NSAIDs, COX-2 inhibitors, hormone, calcium supplementation and increased metabolic activity as elements that decrease the risk of the onset of the disease. Aspirin, for example, decreases new cases of RCC by 40%, especially in the proximal colon (WILKINS, McMECHAN, TALUKDER, 2018). The incidence of RCC has decreased in developed countries due to greater attention to prevention and diagnosis, in contrast, half of the origin of new cases in 25 years are from less developed areas. Due to the lack of visibility and not providing an adequate budget for preventive health policies, most diagnoses do not occur in the early stages of the disease, which not only makes it more expensive but also hinders the therapeutic process for the patient for the health team.

3 OBJECTIVES

3.1 GENERAL (PRIMARY)

Analyze the insufficient prevention of colorectal cancer.

3.2 SPECIFIC (SECONDARY)

Identify the high mortality rate of RCC;

Relate the lack of prevention with the incidence of cases;

Analyze the need to address the RCC with the lack of public policies;

4 HYPOTHESIS AND JUSTIFICATION

The level of information about colonoscopy as a method of prevention of RCC is still scarce; colorectal cancer is the main malignant neoplasm of the gastrointestinal tract; 1.4 million new cases were estimated around the world in 2012 and accounted for 50,000 deaths annually.

5 MAIN SCIENTIFIC CONTRIBUTIONS

The project highlights the importance of producing knowledge about colorectal cancer to bring to light greater discussions about the mortality and incidence of RCC in the social body and generate greater investments for public policies that prioritize discovering and treating patients with the disease still in its initial stage in a more simplified way. Bring visibility to the importance of preventive methods and the population at higher risk with the effect of ending stigmatization related to the disease.

Exploratory research is a way to encourage debate on RCC, a way to know and reflect on the way the disease affects the population and increase the scientific accumulation of the theme.

6 MATERIALS AND METHODS (METHODOLOGY)

The project is a bibliographic review that will be executed through material already published at the University of Ribeirão Preto. It will be an observational study that will establish correlations between the social and scientific aspects of colorectal cancer.

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The leptin receptor gene, its action mechanism, polymorphisms and obesogenic clinical associations

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ABSTRACT
With the significant increase in obesity cases worldwide, there is also an increase in research to understand its causes. Known that the predisposing factors may be environmental and / or genetic, the study focused on the Leptin Receptor (LEPR) gene, its action on satiety and the pathophysiology when the presence of polymorphisms, as well as their interaction with comorbidities that are directly related to obesity and increased adipose tissue. In addition, the motivators that influence a greater or lesser production and action of leptin, its pathway through the central nervous system and how this mechanism sends information on the body's lipid stock, thus regulating the body's energy metabolism, were highlighted. The main result of the LEPR gene mutation is leptin resistance, which consequently leads the individual to not have an adequate perception of satiety and body fat stores, the main effect of which is hyperphagia.

Keywords: Obesity, Genetics, Comorbidities, LEPR gene, Polymorphisms.

1 INTRODUCTION

In terms of biostatistics, the number of obese individuals is gradually rising, reaching epidemic levels, a basis validated by the NCD *Risk Factor Collaboration (NCD-RisC*, 2017), an organization responsible for a network of global scientists dedicated to providing rigorous and timely data on risk factors for NCDs in 200 different countries and territories. Of these, between 1975 and 2016 the prevalence of obesity increased from 69 million to 390 million in females and from 31 million to 281 million in males. Still, the WHO (2020) adds the subject versing that since the year 2000 there has been a 1.5-fold increase in the number of cases of the disease.

The etiology of obesity is multifactorial, and two main factors are listed: genetic and environmental conditions. The literature contextualizes genes as pillars of intervention and balance of body fat, and their action occurs through control of efferent and afferent pathways, as well as central mechanisms. That said, it is worth mentioning that the energy balance is regulated approximately 40% through genetic inheritance, mainly through genes of the Central Nervous System (SNC) (MARQUES-LOPES, *et al*., 2004).

Regarding genetics as a factor notably intervening in the regulation of body weight, Machado, Monteiro and Pinto (2015) review that one of the highlighted genes is leptin (LEP) and leptin receptor (LEPR), whose scope is to regulate food intake, in addition to body temperature, energy expenditure and cardiac function. The relationship of leptin - etymology from the Greek "*leptos*", which means lean - with obesity was discovered in 1974, thus being described as the "satiety hormone", since it is a peptide (similar to cytokines, being composed of 167 amino acids) that signals the energy balance and is the most important peripheral signal for energy homeostasis.

In this context, the parallelism between obesity and the LEP/LEPR genes also spreads in other spheres of the health area, fostering discussions tangent to the burdens caused by this interaction. These clinical associations raised by obesogenic polymorphisms are due to their strong risk factor implicated in other pathologies, are comorbidities, as well summarized Lima, Glaner and Taylor (2010).

In view of the above, the study aims to clarify the system that makes up the mechanism of action of the LEPR gene, establishing a link between its polymorphisms and the obese pathophysiology, in addition to exposing the links that may have repercussions of this obesity-LEPR relationship. In addition, the study intends to indicate potential treatments used for the obesogenic case.

2 DEVELOPMENT

According to Fernandes, Fujiwara and Melo (2011), although the substantial cause of obesity is associated with environmental aspects, the manifestation will occur mainly in those genetically predisposed. It is pertinent to clarify that phenotypic heredity is presented through a certain amount of genes and their variation. In fact, Serrasqueiro (2018) reveals that among the most known and studied genes are FTO, LEP and LEPR, BDNF, MC4R, MC3R, PCSK1, SH2B1, POMC and ADRB3.

Because the topic is broad and there is an extensive variety of genes, research and identification of genetic variants related to obesity have been carried out, aiming basically to identify the mechanisms of action and single nucleotide *polymorphisms (*SNPs) associated with the pathology in question.

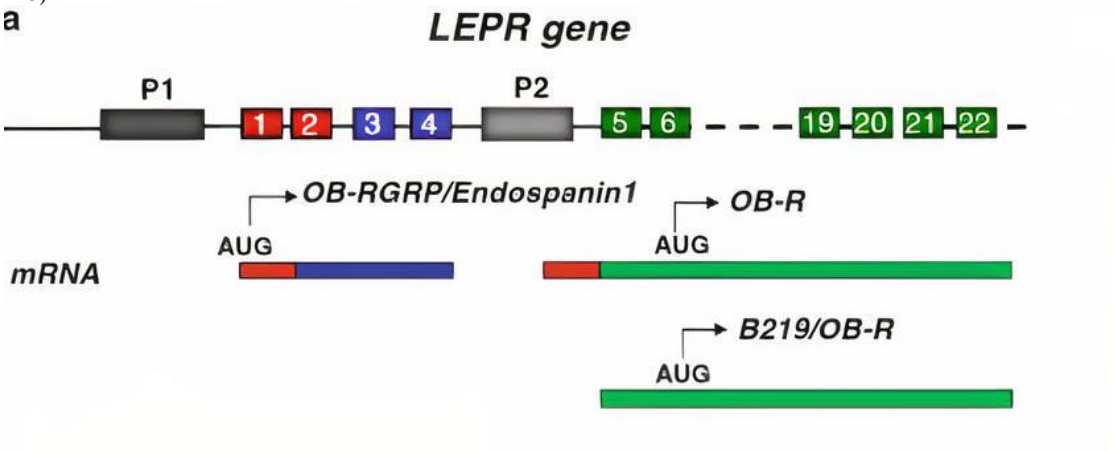
In general, Dagogo-Jack (2015) recommends that the history of obesogenic research began to deserve attention in 1949, in the United States, in studies implemented by the Jackson laboratory (independent and non-profit organization of biomedical research), when observing rats already overweight early in life, but with later obese development. Experiments in reproduction revealed that the syndrome was caused by a single autosomal recessive gene (represented by the gene symbol "*ob*"), located on chromosome 6. Years later, in 1965, in the same experiment, another gene was identified in the laboratory: it was a mutation inherited as an autosomal recessive gene, located on chromosome 4. This was called the diabetes genes, represented by the symbol "*db*". In both gene cases, the mice manifested infertility, hyperphagia, and early-onset obesity.

Meanwhile, Dagogo-Jack (2015) undertakes to point out that after the discovery of the *ob* gene, a long scientific journey was trodden and its climax was reached with the discovery of leptin by Douglas L. Coleman, a researcher at the Jackson laboratory. In this tuning fork, Coleman proposed that while *db* genes produced excessive satiety but could not respond to *it, ob genes* recognized and responded to satiety but could not produce it. Years passed and with the advancement of molecular biology, the scholar proved correct when there was the possibility of cloning leptin and the perception of its receptor, LEPR, which also presented mutations in the evaluated rats. Despite the vast array of information concerning the structure and functioning of LEPR, its molecular mechanisms of leptin resistance are still somewhat uncertain.

Regarding the basic architecture of the leptin receptor, Machado, Monteiro and Pinto (2015), certify that the gene is composed of three functional parts: 1. Extracellular: which performs the interactions; 2. Intracellular: if activated, stimulates cellular events, determining the action of leptin on target cells and; 3. Transmembrane: binds receptor to cell membrane. As for its location, Dias, *et. al.* (2012), define that the LEPR is installed in the short arm of chromosome 1, in position 1p31, and is composed of 18 exons and 17 introns.

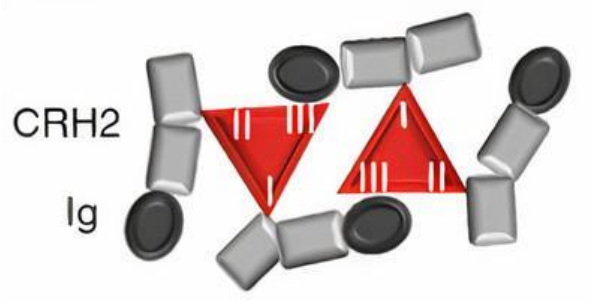
Following the teachings of Dagogo-Jack (2015), it is essential to address the genomic organization of the leptin receptor, which is structured when the activity of a promoter (region of DNA that initiates the transcription of the gene) begins, which produces two different transcriptions through an *alternative splicing* (process in which exons of a first transcript are cleaved at different locations in the newly synthesized RNA), giving rise to distinct proteins without homology in the sequence of amino acids. Important to the discussion of the study is the isoform OB-R (also called Ob-Rb), which is now named LEPR. It should be noted that in addition to this, five other isoforms are originated during *splicing,* all of which are identical in the extracellular medium, differing, however, in size and sequence. However, as well guided by Negrão and Licínio (2000), only the OB-R variant dominates the ability to transmit the signal to introduce leptin into the cell. The formulation of this gene can be presented as shown in Figure 1.

Figure 1: Representative scheme of the LEPR gene. LEPR expression is controlled by two promoters: P1 and P2. The first of these gives rise to two divergent transcriptions through an alternative splicing: LEPROT and LEPR. This generates two distinct proteins without homology in the amino acid sequence: OB-RGRP/endospanin-1 and LEPR in their short and long isoforms. In turn, the second promoter (P2) allows the expression of B219 OBR in its short isoform. (DAGOGO-JACK, 2015, p. 16)



The mechanism by which the leptin receptor is activated occurs at the moment it binds to LEP on the cell surface. In this perspective, Dagogo-Jack (2015) argues that the binding of LEPR to LEP is mediated by two domains: 1. One of the cytokine receptors allocated at the end of the polypeptide chain (called n-terminal), which is called CRH2.; 2. An immunoglobulin known as Ig, whose function is to separate the cytokine receptors CRH2 and CRH1. Thus, CRH2 and Ig bind to LEP, being also required in its activation. The consequence of this interaction is perceived after binding of two leptin molecules to LEPR, when a conformational change is triggered in the extracellular medium, causing dimers to be grouped and a hexameric complex to be formed. The composition of this complex therefore results in two leptin molecules and four LEPR promoters. Each leptin molecule binds to LEPR molecules through the binding sites, with whom they have affinity, whether high or low. For further clarification, Figure 2 is presented, which represents this succession of events:

Figure 2: Hexameric complex formed by the LEP-LEPR bond. It deals with a compound with two LEP molecules and four LEPR promoters. Each LEP binds to LEPR through the binding site: the binding site II connects to CHR2, with whom it has high affinity; binding site I is also related to CRH2, but has low affinity; finally, the link site III is associated with the IG domain, and interaction is also of low affinity (DAGOGO-JACK, 2015, p. 18)



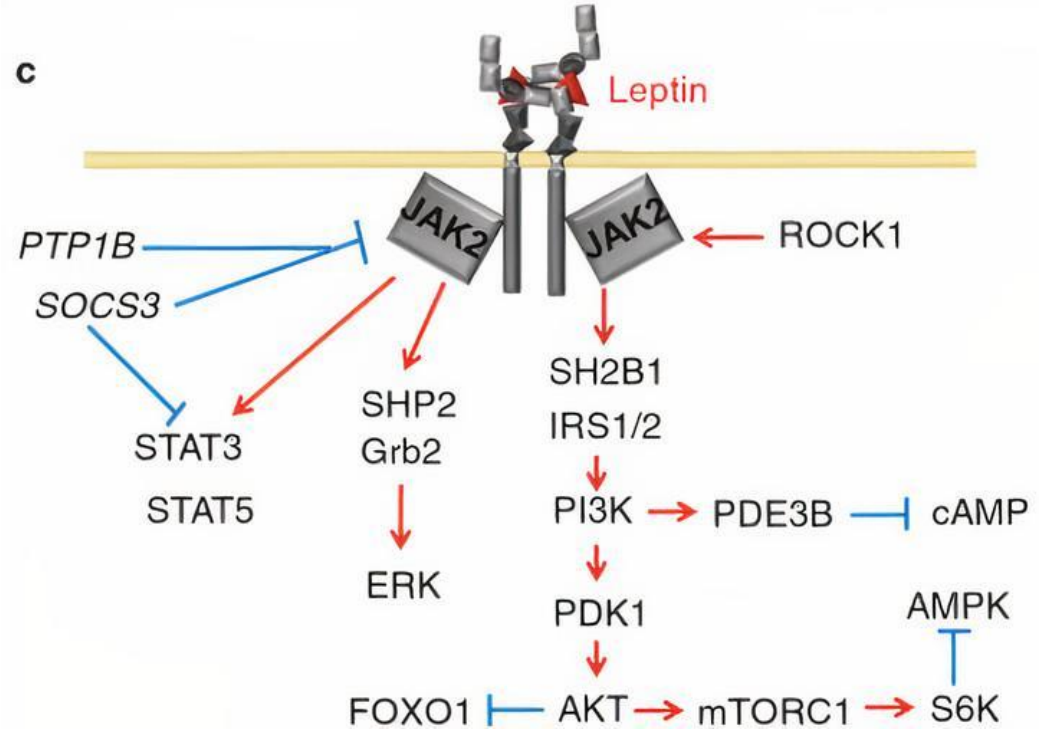
With respect to leptin activation, its activation results when one of the binding sites (designated as site II) of LEP interacts with the cytokine receptor CRH2. An interesting point to note is that there are two other LEP connection sites: I and III.

Another item to be pointed out regarding the mechanism of action of LEPR is its signaling system, which occurs after its activation with leptin. Since LEPR lacks intrinsic enzyme activity, its signaling depends on a tyrosine kinase titled JAK2. This compound, activated by RhoA-associated protein kinase 1 (ROCK1), is responsible for phosphorylating tyrosine residues in the cytoplasm, which results in a recruitment of signaling and transcription-activating proteins, called STATs.

Essential attention is given to the signaling pathway performed by STAT3, since it directly influences the effects of leptin on satiety and body weight. In view of this, as soon as STAT3 is recruited, it undergoes phosphorylation by JAK2, which causes dimerization and translocation of the nucleus to mediate gene transcription. Additionally, other signaling pathways detached by LEPR include, in the intracellular medium, the protein tyrosine phosphatase 2 (SHP2)/extracellular regulated kinase (ERK) pathway and the insulin receptor substrate (IRS)/phosphoinositide 3-kinase (PI3K) pathway. This entire process is certified in Figure 3.

When the intention is to interrupt signaling, the responsibility lies with the cytokine signaling suppressor 3 (SOCS3), which inhibits this activity through a negative *feedback loop*. Other inhibitory compounds are protein tyrosine phosphatase-1B (PTP1B) and T-cell protein tyrosine phosphatase (TCPTP).

Figure 3: LEPR signaling pathways. Leptin binds to the LEPR-b isoform and activates ROCK1 and JAK2. This phosphorylates LEPR-b, resulting in an interaction with signaling molecules, activating several pathways. The inhibition of this signaling is effected by the negative feedback of SOCS3 and PTP1B (DAGOGO-JACK, 2015, p. 18)



Continuing the course of this chain, Dagogo-Jack (2015) prints that the subsequent stage is consummated through neural pathway, which encompasses peripheral sensory and autonomic stimuli, acting on the CNS, which cross the blood-brain barrier. It deals with an important process of body regulation, since obesity, by way of example, can result from this homeostatic poor regulation in the circuits of the central nervous system.

The largest hypothesis pertinent to the regulation of body weight by the CNS is based on the idea of adiposity signaling, which sends constant information to the brain about its relative amount. The most significant signs of adiposity for the brain, if glimpsed over a long period of time, are leptin and insulin. In this same tone, Machado, Monteiro and Pinto (2015), complement indicating that the primary function of leptin is to take to the central nervous system a signal of the energy stores in the body (adipose tissue) so that the brain makes necessary adjustments to balance the expenditure and energy consumption.

The aforementioned authors also review that although leptin physiologically is in dispersed concentrations in the brain, some factors that influence its increase are insulin, glucocorticoids and pro-inflammatory cytokines, in turn, the factors that influence its decrease are testosterone, exposure to cold and catecholamines.

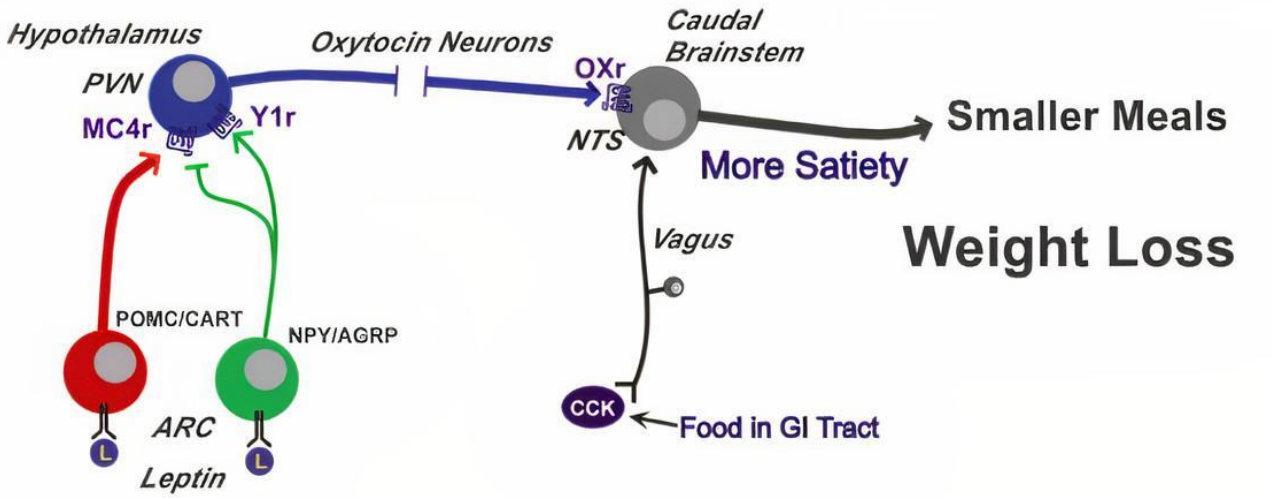
Moreover, regarding the general characteristics of LEP, important to the context, it is elucidated that its manufacture is effective through white adipose tissue cells, in addition to placenta, bone

marrow, stomach, muscle and brain. Moreover, it is noteworthy that its peak release occurs at night and its plasma half-life is approximately thirty minutes (Machado, Monteiro, Pinto, 2015)

Given this conjuncture of facts, Negrão and Licínio (2000) observe that subsequently the production of leptin by adipose tissue, the hormone is directed to the bloodstream, crossing the blood-brain barrier, and in the brain binds to specific receptors. Dagogo-Jack (2015) reasoning continues by adding that the effects of leptin on neural cells are mediated by transmembrane leptin receptors, encoded by the LEPR gene. In this same perspective, it is worth noting that the Ob-Rb isoform, widely distributed in the brain region, is the only functional variant responsible for the anorectic effect. In turn, the receptors of this isoform can be captured in the hypothalamus, especially in the arcuate nucleus, in addition to the ventromedial nucleus, dorsomedial nucleus, paraventricular nucleus and perifornical areas. Negrão and Licínio (2000) record that the region of the arcuate nucleus is the one with the highest uptake, given that leptin acts on four peptides produced by neurons in this region, they are: neuropeptide Y (NPY), peptide related to the agouti strain (AGRP), pro-opiomelanocorticotropin (POMC) and cocaine-amphetamine-dependent transcription factor (CART).

Thus, Dagogo-Jack (2015) finds that the anorectic effect in the brain opens when LEP acts on LEPR in neuropeptides named ARC / AGPR and NPY / CART, which causes the stimulation of POMC / CART neurons (which are anorexigenic) and a discouragement of NPY / AGPR neurons (which are orexigenic, that is, have the function of inciting hunger). That said, a substance symbolized by aMSH is released by POMC/CART neurons, activating the MC4r melanocortin receptors, which aims to elevate the oxytocin signal in NTS neurons, responsible for satiety signals. This course can be contemplated as shown in Figure 4:

Figure 4: Diagram on the leptin pathway in the brain, modeling the level of satiety. (DAGOGO-JACK, 2015, p. 30)

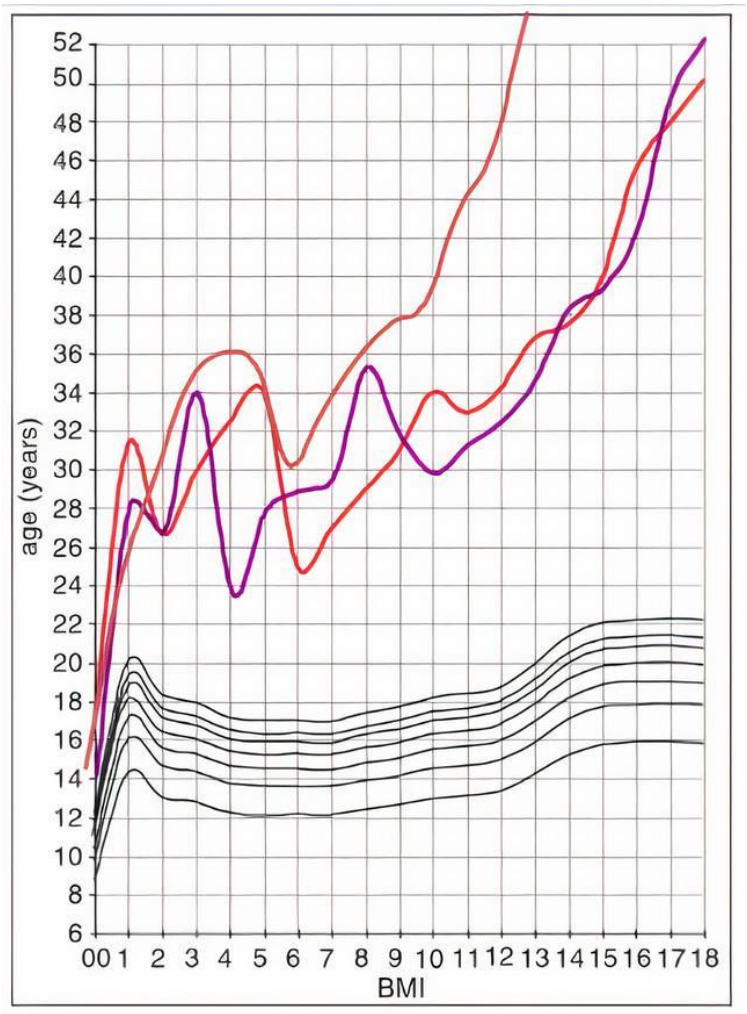


Pertinent to the anorectic effect, Negrão and Licinium (200) add that their result is fundamentally justified by the fact that leptin promotes the oxidation of fatty acids and triglycerides,

possibly through an inhibitory effect on the activity of acetyl-CoA carboxylase, one of the enzymes that regulate the synthesis of fatty acids.

The pathophysiological history of LEPR correlated with obesity is ascertained by Dagogo-Jack (2015), when he stated that the first mutation of this gene was described in 1998, announcing that the affected individuals were homozygous for the mutation resulting from an *abnormal "splicing*" in the transcription of LEPR, which generated a receptor without domains (CRH1, CRH2 and Ig) and, consequently, the obese phenotype. It is pertinent to repair the graph of the research, corresponding to Figure 5, which presents a relationship between BMI and age in people with the mutated gene.

Figure 5: Graph referring to the first research describing the association between LEPR mutation and obesity. Illustrates severe weight gain as age advances. The subjects with the mutation are demonstrated by the traces in color (DAGOGO-JACK, 2015, p. 20)



Since then, several LEPR mutations have been detected in extremely obese people, and in 2007 the gene was sequenced in 300 patients with hyperphagia and obesity, accounting for a high prevalence of pathological mutation.

In this direction Dagogo-Jack (2015) clarifies that, mostly, the main obesogenic pathophysiological mechanism involved in the LEP/LEPR gene is the so-called leptin resistance.

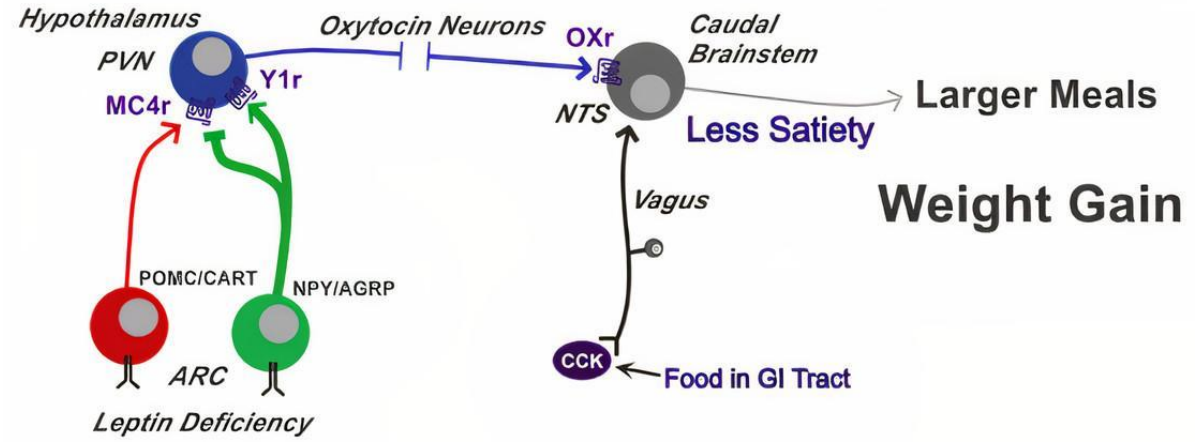
When this mechanism is ruled out, other less common mechanisms are insufficient leptin production or a partial or total sensitivity of leptin at its binding sites. Whatever the situation, the motivation derives either from a polymorphism and / or from some embarrassment in the neural pathway, causing a deficit in leptin signaling and, therefore, the ability to regulate appetite is reduced.

This clarified, Machado, Monteiro and Pinto (2015) see that leptin resistance occurs when high plasma concentrations of LEPR are unable to act effectively in the control of energy balance. The main motivator that triggers this mechanism comes from the increase in the serum concentration of triglycerides, which can act by binding directly to leptin in the bloodstream or in the leptin receptor located at the blood-brain barrier. This prevents the connection between leptin and its receptor. Other drivers of this dysfunction may be hyperleptinemia, which decreases receptor expression in skeletal muscle, deficiency in leptin transport to the brain, disturbances in the signaling mechanism in specific receptors and cytokines, as well as failure in the hypothalamic circuit that regulates energy homeostasis

The partial or total sensitivity of leptin at its binding sites arises in the activation of the LEP gene through LEPR. Therefore, if there is a mutation in binding sites II and III, but the I is intact, the leptin and its receptor will still bind, but activation of the compound will not be possible.

Another adversity, which is predominant in comparison to the previous case, can be identified in the neural pathway, when there is a mutation in leptin, causing its functional production to be insufficient. In this case, POMC/CART signals are minute and NPY/AGPR signals are stimulated. Thus, the orexigenic effects are activated and the anorectic effects are blocked, since aMSH does not receive activation incentive and, therefore, MC4r receptors are not incited to signal to oxytocin. Below, the succession of events is printed in Figure 6:

Figure 6: Diagram on the mutated leptin pathway in the brain, modeling the level of satiety. (DAGOGO-JACK, 2015, p. 30)



Machado, Monteiro and Pinto (2015) review that, once the mutation is identified, attention should be paid to the possibility of the most predicted polymorphisms in obesogenic syndrome by LEP

/ LEPR. In this sense, the most expected SNPs are: Gln223Arg (rs1137101), Lys109Arg (rs1137100) and Lys656sn (rs8179183). The first of these is the most commonly found, and its provenance comes from the replacement of adenine by guanine, resulting in the exchange of the amino acid glutamine (Gln) for arginine (Arg) at position 223. It deals with a mutation intrinsically associated with increased BMI, hyperleptinemia, increased fasting glucose, and predispositions to metabolic syndrome. The Lys109Arg SNP is strongly related to increased cholesterol and triglyceride concentrations, changes in weight; BMI and waist and hip circumference. Finally, the Lys656sn SNP has interaction with phenotypic obesity and low-fat dietary habits.

Alusive to the obesogenic clinical associations by LEP/LEPR, the first valuable mention concerns its relationship with the sleep period. As well supported by Negrão and Licínio (2000), leptin is secreted in pulses throughout the day, and its peak secretion is during the night. It is recommended by ABESO (2016) that sleep deprivation causes decreased secretion of leptin and TSH, increased levels of ghrelin ("hunger hormone") and decreased glucose tolerance. This is concatenated to that prescribed by Carneiro, *et. al.* (2007), when clarifying that patients with Obstructive Sleep Apnea Syndrome (OSAS) have increased leptin levels, considering that the pathology causes resistance to LEP and its concentration in the environment rises, without, however, making connections.

Another clinical association of genetic obesity intrinsically associated with the genes of the case in question is breast cancer. Cleveland, *et. al.* (2010) elucidate that, although there is no direct relationship with mortality, there is a modest increase in the risk of developing this pathology when the LEP gene is mutated (2548AA and 2548GG), especially in obese postmenopausal women.

Psychopathologies are added to the list of obesogenic comorbidities linked to LEP/LEPR. Pereira and Brandão (2014, p. 152) argue that "changes in inflammatory cascades, appetite-regulating hormones (leptin, adiponectin and resistin) and the hypothalamic-pituitary-adrenal axis may constitute correlation mechanisms between psychiatric pathologies and obesity." The authors note that, due to the insufficiency of the hormone and/or its resistance, there is a strong possibility that leptin has a role in the pathophysiology of depression. This occurs because depression, being considered a pro-inflammatory state, LEP tends to alter the immune system, increasing the response mediated by lymphocytes and Th1 and suppressing the Th2 response, which increases the production of pro-inflammatory drugs such as TNFα and IL-6.

An intrinsic relationship is also seen between leptin and Polycystic Ovary Syndrome (PCOS). In this step, Lecke (2010) leads reasoning when declaring that the gene expression of leptin in the subcutaneous adipose tissue in obese women with PCOS presents levels higher than those of normal weight. Melo (2001) adds that commonly these women are also insulin-resistant, hyperinsulinemic and/or infertile.

Regarding intervention resources, it is important to clarify that, as stated by ABESO (2016), treatment with recombinant leptin is effective in rare cases of leptin deficiency. In cases of polygenic obesity, most of the clinical pictures, the treatment has no effect. Its indication is pertinent only in children and adolescents with monogenic obesity in cases of production deficiency. Negrão and Licínio (2000) add this understanding when they discuss the inefficiency of recombinant leptin in cases of leptin resistance, since the level of the hormone is already high. In addition, these highlights complement Dias, *et. al.* (2012), when adducing that there is an importance in identifying cases of obesogenic mutations in younger age groups, having that this provides the possibility of changing the course of treatment, choosing the most appropriate therapy and allowing genetic counseling for affected families.

Another intervention model indicated by Negrão and Licínio (2000) was leptin injected directly into the cerebral ventricles, which led to the expression of the transcription factor STAT3 and neuronal activation in hypothalamus nuclei. However, more studies are needed to complete appropriate treatment.

3 CONCLUSION

The effects of genetic mutations on obesity can be reflected from the loss of the perception of satiety, reduction of the ability to control the balance of energy expenditure, as well as a greater tendency to comorbidities, which, in turn, can also influence even more weight gain and its consequences. It is also worth mentioning that the alteration in the leptin genes or its receptor can hinder the loss of weight and fat, requiring a more detailed and individual intervention so that there is an adequate response to treatment.

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Use of metoprolol as a relevant therapeutic agent in patients with cardiovascular disorders: A review

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ABSTRACT

This chapter has gathered scientific evidence on metoprolol as a pharmacological tool in various cardiovascular diseases. METHODOLOGY: This is a systematic review in which scientific articles published in Pubmed databases between 2021 and 2022 were selected. The following descriptors were used: metoprolol or pharmacokinetic, pharmacodynamics, efficacy, adverse effect, combined by means of the AND operator. A total of 46 articles were found, of which 17 met the selection criteria and, therefore, are included in this study. RESULTS: Regarding the clinical use of metoprolol, it was beneficial in the treatment of arrhythmias after resection of hepatocarcinoma, in cardiac improvement in patients with permanent pacemaker, in individuals with obstructive hypertrophic cardiomyopathy, and in addition to having been cited in the increase in survival in patients with type B aortic dissection. has been shown to be beneficial in both heart failure and carotid atherosclerosis, as well as hypothalamic obesity. With regard to adverse events, patients on metoprolol were more prone to nightmares than those exposed to another beta-adrenergic antagonist drug, such as carvedilol or labetalol. In addition, when compared with another drug, it did not have an advantage over esmolol for performing CT angiography and was less effective in antihypertensive therapy of men with erectile dysfunction. Finally, with regard to new methods of detection or therapeutic intervention of the use of metoprolol, one study was successful in discovering a new way to quantify metoprolol in rat plasma, while another recent study addressed relevant considerations in personalized therapy of the drug, based on the genetic polymorphism of CYP2D6.

CONCLUSION: The present systematic review corroborates updates on the use of Metoprolol found in the current literature, contributing to the institution of personalized therapy for patients with cardiovascular disease.

Keywords: Clinical pharmacology, Metoprolol, Cardiovascular diseases, Therapeutic Advancement.

1 INTRODUCTION

Metoprolol is a drug approved by the FDA in the treatment of diseases such as: angina, heart failure, myocardial infarction, arrhythmias and hypertension; in addition to being also recommended for thyroid crisis and circumscribed choroid hemangioma (ZAMIR *et al.*, 2022). It is also a cardioselective antagonist of adrenergic receptors (as well as atenolol), which competitively blocks β-1 adrenergic receptors with minimal or no effects on β-2 adrenergic receptors (MORRIS; DUNHAM, 2022).

According to Brunton *et al.* (2018), metoprolol has low bioavailability (approximately 40%), due to its first-pass biotransformation. It is a substance metabolized in the liver, in which CYP2D6 is the main enzyme involved, and only 10% of the administered drug is recovered in the urine unchanged.

As for therapeutic use, this drug reduces myocardial oxygen consumption, improves cardiac function and reduces the burden of atrial fibrillation, while improving QT interval dispersion (YE *et al.*, 2022). In continuity, it is also an antiarrhythmic for ventricular arrhythmias after AMI, in the prevention of paroxysmal crises of atrial fibrillation when these occur in a situation of sympathetic activation, in heart failure, where it is indicated for all patients (even asymptomatic), as it is associated with improved survival. (RITTER *et al.*, 2020). In hypertension, its use is no longer 1st line and is indicated in specific cases in which there is an association with another disease for which this drug is indispensable, or in specific cases of hypertensive crisis (such as acute aortic dissection) (BRUNTON *et al.*, 2018).

In addition to these classic applications, several studies have been developed in order to analyze the functionality of metoprolol in other cardiovascular diseases, a fact that reaffirms its relevance before the current pharmacology.

2 METHODOLOGY

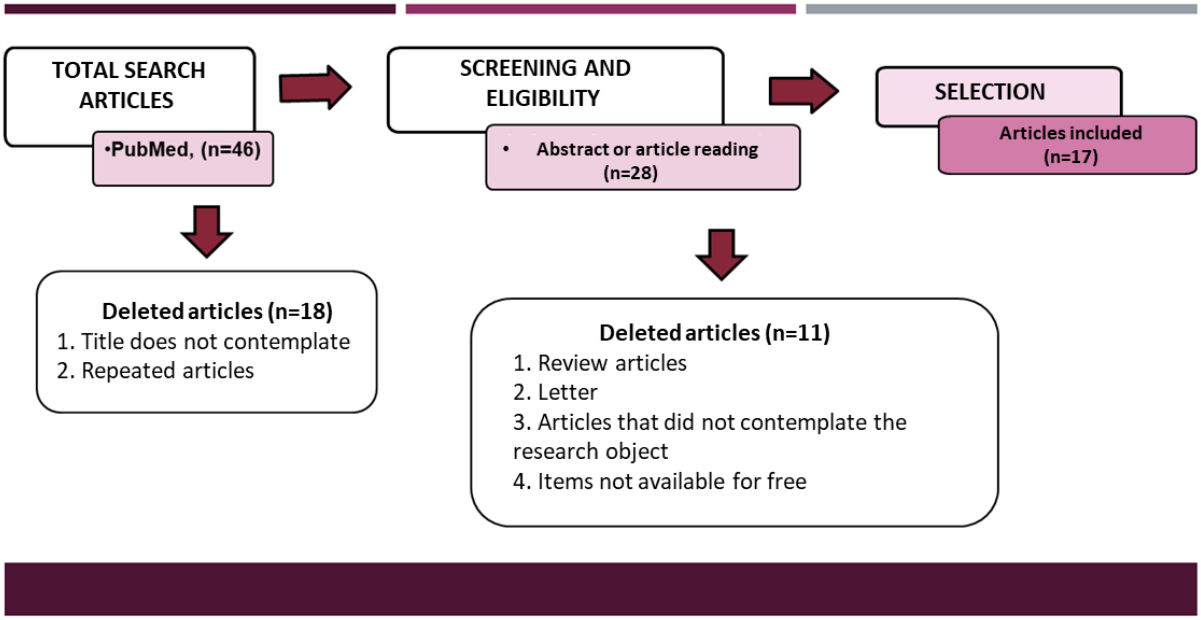
For the development of the work, a careful search of original scientific articles published in the PubMed databases was carried out, using the descriptors metoprolol or pharmacokinetic, pharmacodynamic, efficacy, adverse effect combined by means of the Boolean operator AND, according to the guidelines recommended by PRISMA.

The inclusion criteria were the original studies, which presented the descriptors in the title or abstract and written in English. Articles written in languages other than English were excluded, in

addition to those whose title or abstract/abstract did not fit the proposed theme. Comments, books, literature reviews and articles not available for free access were also excluded.

The collection of bibliographic data between 2021 and 2022 resulted in a total of 46 scientific articles. After extensive analyses, only 17 studies met all the selection criteria and were included in this study, as shown in Figure 1.

Figure 1: Diagram of recovery and selection of evidence of bibliographic research according to the guidelines of PRISMA.



Source: Own elaboration.

3 RESULTS

After using the inclusion and exclusion criteria, it was verified that PubMed presents 17 manuscripts that address pharmacological aspects of Metoprolol. Tables 1 and 2 show a brief description of the studies included in this study, highlighting the type of study, place of execution and the main findings. The 17 studies included in this review deal with biological assays (n=05) and clinical trials (n=12).

Thematically, the following division was found: 07 clinical studies address the clinical use of Metoprolol, and 03 of these evaluate the effects of when another drug is added to the therapeutic regimen with Metoprolol; one (01) clinical study addresses therapeutic equivalence; one (01) clinical study evaluated an adverse event of β-blockers, including Metoprolol; 02 clinical studies have shown therapeutic advantages of another β-blocker over Metoprolol; 01 clinical study and 03 biological studies analyzed pharmacological interactions of Metoprolol; and 02 biological studies presented the development of new pharmacokinetic methods of detection or therapeutic intervention of the use of Metoprolol.

Table 1 – Scientific studies of biological assays that address the pharmacokinetic aspects for metoprolol.

Title	Country	Sample/Study Method	Findings	Reference
Development and validation of a LC-MS/MS method for simultaneous quantification of Ivabradine and Metoprolol in rat plasma	India	*In vitro. Validation of a* bioanalytical method LC-MS/MS that can quickly and accurately estimate the values of Ivabradine and Metoprolol, simultaneously, in the plasma of 06 Albino Wistar rats.	The accuracy was between 99.71 to 100.3% for ivabradine and 99.9 to 100.31% for metoprolol. The intra- and inter-day accuracy ranged from 0.048 to 12.68% CV for ivabradine and 0.1 and 2.66% CV for Metoprolol. The established method was accurate and adequate to determine Ivabradine and Metoprolol simultaneously in plasma samples from rats.	Eswarudu *et al*. (2022)
Gut microbiota and host Cyp450s co-contribute to pharmacokinetic variability in mice with non-alcoholic steatohepatitis: Effects vary from drug to drug	China	*In vivo.* 32 rats. This study aimed to analyze the effects of gut microbiota and host CYP450 on the pharmacokinetic variability of omeprazole, metoprolol, midazolam, tolbutamide, phenacetin and chlorzoxazone in rats submitted to nonalcoholic steatohepatitis (NASH).	As for Metoprolol, it was observed that: there was no significant increase in its plasma exposure when administered intragastric or intravenously in the study group; analysis of pharmacokinetic parameters showed that the gut microbiota and host CYP450 exerted minimal effects on the pharmacokinetic variability of metoprolol.	Guo *et al*. (2022)
Inhibitory effects of fluoxetine and duloxetine on the pharmacokinetics of metoprolol in vivo and in vitro	China	*In vivo* and *in vitro* with 18 Sprague-Dawley rats. This study aimed to compare the effects of duloxetine and fluoxetine on the metabolism of metoprolol.	*In vitro*, duloxetine showed more significant inhibitory potential when compared to fluoxetine, but major pharmacokinetic parameters revealed differences in inhibition of metoprolol metabolism, showing to be more susceptible to fluoxetine in *vivo*.	Xu *et al*. (2022)
Physiologically Based Pharmacokinetic Modeling to Assess the Impact of CYP2D6-Mediated Drug-Drug Interactions on Tramadol and O-Desmethyltramadol Exposures via Allosteric and Competitive Inhibition	United States	*In silico* with PBPK model developed by PK-Sim® 8.0 Software. This study aimed to compare the impact of reversible allosteric/competitive inhibition on CYP2D6 when Quinidine/Metoprolol was co-administered with Tramadol and O-desmethyltramadol.	Tramadol increases the plasma exposure of Metoprolol by 50% when co-administered. If doses are separated by 2 hours, an increase of less than 20% in the plasma exposure of Metoprolol has been predicted.	Long *et al*. (2022)
Physiologically based pharmacokinetic modelling to predict the pharmacokinetics of metoprolol in different CYP2D6 genotypes	South Korea	*In vitro* and *in silico* with PBPK model developed by PK-Sim® 7.4 Software. The objective of this study was to develop a model of Metoprolol related to the genetic polymorphism of CYP2D6 for use in personalized therapy.	The developed PBPK model predicts AUC, C max, Tmax and T1/2 of the different CYP2D6 genotypes for Metoprolol in individuals of various races and ages.	Lee *et al*. (2022)

Source: Own elaboration.

Table 2: Clinical trials addressing pharmacological advances for metoprolol.

Title	Country	Sample/Study Method	Findings	Reference
β-adrenoceptor antagonists and nightmares: A pharmacoepidemiologic al- pharmacodynamic study	France	Cross-sectional observational study of pharmacovigilance in VigiBase®, analyzing 1138 cases of nightmares reported as an adverse effect of the use of β-adrenergic antagonists.	Pindolol, Metoprolol and Alprenolol were associated with increased risk of nightmares as an adverse effect.	Garcia *et al.* (2021)
A randomized, cross-over trial of metoprolol succinate formulations to evaluate PK and PD end points for therapeutic equivalence	United States	This is a prospective, randomized, crossover clinical experimental analytical study with adult patients with primary hypertension to compare the therapeutic equivalence of brand-name and two generic Sustained Release Metoprolol Succinate. The final study sample was 36 patients.	The pharmacokinetic parameters AUC and Cmax, as well as the hemodynamic parameters ambulatory BP, 24-hour HR and HRV were similar between the products. Tmax of branded Metoprolol was significantly higher than that of generic 01 and significantly lower than that of generic 02.	Mosley *et al.* (2022)
Co-prescription of metoprolol and CYP2D6-inhibiting antidepressants before and after implementation of an optimized drug interaction database in Norway	Norway	Cross-sectional retrospective observational study of drug dispensing data retrieved from the Norwegian Prescription Database during a 1-year period prior (2007) and two 1-year periods after (2012 and 2017) the implementation of a drug interaction database, which analyzed the co-prescribing rate of metoprolol and CYP2D6 inhibitor antidepressants.	The co-prescribing rate of metoprolol with CYP2D6 inhibitors decreased by 21% 5 years after database implementation and by 40% after 10 years. Compared with atenolol/bisoprolol users, patients treated with metoprolol were significantly less likely to be prescribed a CYP2D6 inhibitor antidepressant in the two post-implementation periods.	Gedde-Dahl *et al.* (2022)
Dynamic Electrocardiogram under P Wave Detection Algorithm Combined with Low-Dose Betaloc in Diagnosis and Treatment of Patients with Arrhythmia after Hepatocarcinoma Resection	China	Clinical experimental analytical study to evaluate the diagnostic value of the Dynamic ECG based on the P-wave detection algorithm for arrhythmia after hepatectomy in 60 patients with primary liver cancer, and to compare the therapeutic effect of different doses of Betaloc.	The study group that used the lowest dosage of Betaloc (≤ 47.5 mg) reached the lowest values of systolic and diastolic BP, levels of pre -pro-BNP and incidence of adverse effects, as well as the highest effective rate of improvement of cardiac function.	Jiang *et al.* (2021)
Effects of Metoprolol Succinate Combined with Entresto on Cardiac Function Indexes and Coagulation Function in Patients with Congestive Heart Failure	China	Clinical experimental analytical study to analyze the combination of Metoprolol with Entresto (Sacubitril-Valsartan) in 120 patients with Congestive Heart Failure.	There was improvement in cardiac, hemodynamic, vascular, endothelial, oxidative and coagulation parameters. The study group obtained more significant rates of improvement, with 3.33% of side effects.	Ding *et al.* (2022)
Efficacy of metoprolol plus atorvastatin for carotid atherosclerosis and its influence on carotid intima-media	China	Retrospective clinical experimental analytical study to analyze the effects of combining Metoprolol with Atorvastatin in 90	The analysis showed that the study group presented: significant reduction in carotid intima-media thickness indices,	Chen *et al.* (2022)

thickness and homocysteine level		patients with carotid atherosclerosis.	atherosclerotic plaque score, homocysteine levels, cytokines CRP and MMP-9, and coagulation factors. Lipid levels showed significant improvement only in the study group.	
Metoprolol Improves Myocardial Remodeling and Cardiac Function in Patients with Permanent Pacemaker Implantation	China	This is a randomized, clinical experimental analytical study with 90 patients submitted to permanent double-chamber pacemaker implantation. This study aimed to compare the effect of metoprolol on myocardial remodeling as well as on cardiac function in patients with permanent pacemakers.	Until the first week after pacemaker implantation, there was no significant difference in cardiac function between the control and study groups. 12 months after surgery, serum levels of IL-6 and TNF-α were lower in the study group, suggesting the myocardial protective properties of metoprolol.	Ye *et al.* (2022)
Nebivolol protects erectile functions compared to Metoprolol in hypertensive men with atherogenic, venogenic, psychogenic erectile dysfunction: A prospective, randomized, cross-over, clinical trial	Turkey	This is a clinical, prospective, randomized, crossover trial analytical study with 73 married men who maintained blood pressure above 140/90 mmHg and met the SEP and IIEF-5 tests for Erectile Dysfunction. This study aimed to compare the effects of Nebivolol and Metoprolol on cardiac and sexual functions and plasma NO levels. Of the total number of participants, 61 completed the study.	There was no difference in antihypertensive efficacy between the two drugs. Unlike Nebivolol, Metoprolol caused a significant decrease in the IIEF-5 score. After 4 weeks of treatment, baseline plasma NO levels did not change with the use of Metoprolol, but increased with Nebivolol. There was a positive correlation between plasma NO values and the IIEF-5 score used to assess sexual functions.	Gungor *et al.* (2022)
Prospective Clinical Trial Comparing IV Esmolol to IV Metoprolol in CT Coronary Angiography: Effect on Hemodynamic, Technical Parameters and Cost	Canada	This is a clinical, prospective and randomized experimental analytical study with 28 patients who underwent Coronary Computed Tomography Angiography. The objective of this study was to compare the use of IV Esmolol with IV Metoprolol to achieve HR of 60 bpm during the examination, analyzing hemodynamic response, image quality, radiation dose and cost.	Both Esmolol IV and Metoprolol IV reached the CF target. Esmolol IV resulted in a significantly less profound and shorter reduction in systolic BP than IV Metoprolol after the examination. There was no significant difference in HR, image acquisition, exposure window, radiation dose and image quality. The total cost of care for Esmolol IV was comparable with Metoprolol IV.	Vimala *et al.* (2022)
Randomized controlled trial of Tesomet for weight loss in hypothalamic obesity	Denmark	Phase 02, randomized, double-blind, placebo-controlled, clinical experimental analytical study with 21 adults with hypopituitarism and consequent hypothalamic obesity. The objective of this study was to analyze the safety and efficacy of Tesomet (0.5 mg Tesofenin	Adverse events related to the use of Tesomet were mild. There was no significant difference observed in HR and BP between the groups. Compared to placebo, Tesomet resulted in significant weight loss, an increase in the number of patients who were able to lose equal to or more than	Huynh *et al.* (2022)

		/ 50 mg Metoprolol). Of the total number of participants, only 18 completed the study.	5% of weight, and a tendency to increase abdominal waist reduction.	
Randomized Trial of Metoprolol in Patients With Obstructive Hypertrophic Cardiomyopathy	Denmark	Clinical experimental analytical study, monocentric, randomized, double-blind, placebo-controlled, with 29 patients with Hypertrophic Obstructive Cardiomyopathy. The objective of this study was to analyze the left ventricular outflow blood flow gradient, symptoms and exercise capacity.	The treatment with Metoprolol presented: significantly lower left ventricular outflow blood flow pressure gradient at rest, at peak exercise and post-exercise; improvement of symptomatology; no difference in exercise duration or load capacity achieved; oxygen uptake at peak exercise was comparable with placebo, with no difference observed in the METS achieved.	Dybro *et al.* (2022)
The Effect of Intravenous and Oral Beta-Blocker Use in Patients with Type B Thoracic Aortic Dissection	United States	Retrospective cross-sectional observational study with data extracted from Premier Healthcare between June/2009 and March/2015. The objective is to analyze the use of beta-blockers (oral or IV) in patients with type B thoracic aortic dissection.	In patients with non-traumatic thoracic aortic dissection, oral beta-blocker use was associated with significant protection against in-hospital mortality and stroke after repair. Metoprolol was the only type of intravenous beta-blocker associated with improved survival.	Nejim *et al.* (2022)

Source: Own elaboration.

Jiang *et al*. (2021) aimed to study the diagnostic value of the Dynamic Electrocardiogram (ECG) based on the P-wave detection algorithm for arrhythmia after hepatectomy in patients with primary liver cancer, and to compare the therapeutic effect of different doses of Betaloc (Sustained Release Metoprolol Succinate). For this, the authors selected 60 patients with arrhythmia after hepatectomy for primary liver cancer, being equally divided into 04 groups: control group (no Betaloc was used), DS group (with dose equal to or less than 47.5 mg), MD group (with dose between 47.5 and 95 mg) and HD group (with dose between 142.5 and 190 mg). As results related to the use of Betoloc after diagnosis of arrhythmia by the proposed algorithm, the authors found that: systolic (SBP) and diastolic (DBP) blood pressures in the DS, MD and HD groups were significantly lower than in the control group after 02 weeks of treatment, especially for the DS group; the heart rate (HR) of the DS group after 02 weeks of treatment was significantly lower than that of the control and HD groups; the pre-pro-BNP of the DS group was notably lower than that of the other groups; the effective rate of improvement in cardiac function in the DS group was significantly higher than in the other groups; the incidence of complications in the control, DS, MD and HD groups were 34.6%, 12.4%, 20.5% and 32.5%, respectively. Therefore, it is concluded that a small dose of Betaloc is safe and effective for the treatment of arrhythmia after resection of primary hepatocarcinoma.

In addition, Metoprolol has been shown to be effective in improving myocardial remodeling and cardiac function in patients who have had a permanent pacemaker implantation. Ye *et al*. (2022) enrolled 90 patients undergoing double-chamber pacemaker implantation surgery, which were divided into two equal groups of 45 people, one of these being the control group and the other, exposed to metoprolol more previously, where in the 12-month postoperative evaluation, the cardiac function index and heart rate variability (HRV) of patients treated with metoprolol were better, and the incidence of adverse events at 12 months postoperatively also lower, which indicates an effective use of metoprolol after definitive pacemaker implantation in improving the function of the cardiac pump of patients, regulating the function of the sympathetic and vagus nerves, and reducing the risk of adverse events (including postoperative hypotension, ventricular tachycardia, and dyspnea), in addition to acting in the prevention of ventricular arrhythmias.

In addition, metoprolol has been shown to be beneficial in patients with Obstructive Hypertrophic Cardiomyopathy. Dybro *et al*. (2022) aimed to analyze the effect of Metoprolol Succinate on reducing the left ventricular outflow blood flow gradient, symptoms and exercise capacity in patients with this CVD. For this, the authors conducted a monocenter, randomized, double-blind, placebo-controlled study with 29 cases of Obstructive Hypertrophic Cardiomyopathy.

Moreover, some studies have pointed out that the best therapeutic option is the use of Metoprolol combined with another drug. For Congestive Heart Failure (CHF), Ding *et al*. (2022) aimed to analyze the combination of Metoprolol Succinate with Entresto (Sacubitril-Valsartan) in cardiac function, endothelial vascular function, oxidative stress and coagulation function. After the 14-day treatment, the authors found as results that: the efficacy rate of the study group was higher than that of the control group; left ventricular ejection fraction (EF) increased; left ventricular diameters at the end of systole and diastole decreased; levels of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) increased; endothelin (ET) level decreased; levels of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) increased; malondialdehyde levels decreased; levels of partially activated prothrombin time (aPTT), prothrombin time (PT), and fibrinogen (FIB) decreased.

Also, Chen *et al*. (2022) aimed to analyze the effects of combining Metoprolol with Atorvastatin in the treatment of Carotid Atherosclerosis, more specifically Sustained Release Metoprolol Succinate at the maximum tolerated dose of 95 mg/day after gradual increase and Metoprolol and Atorvastatin, this at a dosage of 20 mg/day. The authors found that, after 24 weeks of treatment: there was a significant reduction in carotid intima-media thickness indices, atherosclerotic plaque score, homocysteine levels, and the two inflammatory cytokines detected (high-sensitivity C-Reactive Protein, or CRP; and Matrix Metalloproteinase 9, or MMP-9), for both groups, but with a reduction to lower values for the group that used Metoprolol with Atorvastatin; there was a significant improvement in blood lipid levels in the study group, with no statistically significant differences in the

control group; there was a significant improvement in coagulation factors - TT, PT, aPTT and FIB - in both groups, however, with significant differences in the post-treatment period. Of the 90 patients, 12 did not have any improvement in carotid atherosclerotic plaque and, according to the authors, the factors that affected efficacy were: advanced age (greater than or equal to 65 years), established coronary disease, established cerebral infarction, and high atherosclerotic plaque score (4 points).

3.1 THERAPEUTIC ADVANTAGES OVER METOPROLOL

The use of IV Esmolol was comparable with IV Metoprolol for coronary computed tomography angiography. Vimala *et al*. (2022) aimed to compare the two drugs, which are used to achieve HR of 60 beats per minute (bpm) during the examination, analyzing the hemodynamic response, image quality, radiation dose and cost. For this, they conducted β a prospective and randomized clinical study with 28 patients, of which 14 underwent the examination with Metoprolol IV and the others with Esmolol IV. The authors obtained as results that: both groups reached the HR target; Esmolol IV resulted in a significantly less profound and shorter reduction in SBP than Metoprolol IV; there was no significant difference in HR, image acquisition, exposure window, radiation dose and image quality. Although IV Esmolol is more expensive, the total cost of care was comparable with Metoprolol IV, as the post-examination observation period was reduced due to the rapid restoration of hemodynamic status.

In addition, Metoprolol has been shown to be less effective in antihypertensive therapy in men complaining of erectile dysfunction. Gungor *et al*. (2022) aimed to investigate the effects of Nebivolol and Metoprolol on the erectile functions of men with hypertension. For this, they conducted a prospective, randomized, crossover clinical study with 73 married men who maintained blood pressure above 140/90 mmHg. Those who answered negatively to the questions of the SEP (Sexual Encounter Profile) test and/or scored below 21 in the IIEF-5 (International Index of Erectile Function) score were considered to have Erectile Dysfunction (ED). Two groups of patients were made, which followed the regimen: in the 1st month, one group used Nebivolol Hydrochloride, 5 mg; and the other, Metoprolol Succinate, 50 mg, once a day; in the 2nd month, the participants did not use any β-blocker; In the 3rd month, the groups changed the β-blockers used in the 1st month of the study. Of the total, 61 patients completed the study, of which: 13 did not have ED; 27 had psychogenic ED; 10 had arteriogenic ED; and 11 had venogenic ED. The main results were: there is no difference in antihypertensive efficacy between the two drugs; unlike nebivolol, metoprolol caused a significant decrease in the IIEF-5 score of the 61 patients; in the group that did not have ED, both drugs significantly decreased the IIEF-5 score, but the decrease caused by Metoprolol was greater; after 4 weeks of treatment, baseline plasma NO levels did not change with the use of Metoprolol, but increased with Nebivolol; there is a positive

correlation between plasma NO values and the IIEF-5 score. The authors concluded that Nebivolol may be advantageous in terms of preserving sexual functions due to the increase in NO.

3.2 PHARMACOLOGICAL INTERACTIONS

The combination of the use of antidepressants and cardiovascular drugs is common, increasing the possibility of drug interaction. Thinking about it, Xu *et al*. (2022) aimed to compare the effects of Duloxetine and Fluoxetine on the metabolism of Metoprolol. For this, 18 Sprague-Dawley rats were randomized and equally divided into three groups: group A (received Metoprolol orally), group B (received Metoprolol and Fluoxetine orally) and group C (received Metoprolol and Duloxetine orally). Blood samples were collected and analyzed. In addition, *an in vitro* study was performed by incubating liver microsomes and CYP2D6.1 with Metoprolol and submitting them to Fluoxetine and Duloxetine. The authors obtained as results of the *in vivo* study: the administration of Fluoxetine and Duloxetine significantly increased the area on the plasma concentration-time curve and from 0 to infinity (AUC(0-infinity)) of Metoprolol; there are significant pharmacokinetic differences between Fluoxetine and Duloxetine in plasma concentration. The authors obtained as results of the *in vitro* study: Fluoxetine and Duloxetine inhibited the metabolism of Metoprolol via mixed competitive mechanism of cytochrome P450; the values of the semi-maximum inhibitory concentration (CI 50) of Fluoxetine and Duloxetine were 12.86 and 2.51 μM, respectively; the metabolism rate of Metoprolol was inhibited in 19.62% and 17.14% in CYP2D6.1 by Fluoxetine and Duloxetine, respectively. *In vitro*, duloxetine showed more significant inhibitory potential when compared to fluoxetine, but the main pharmacokinetic parameters revealed differences in the inhibition of metoprolol metabolism, showing that it is more susceptible to fluoxetine in *vivo*.

Knowing the interaction of Metoprolol with CYP2D6 inhibitor antidepressants, the frequency of its prescription also changes. Of this, Gedde-Dahl *et al*. (2022) analyzed this co-prescribing before and over a 10-year period after the implementation of an optimized drug interaction database in clinical decision support systems in Norway. Data from all individuals who received beta-blockers and antidepressants were retrospectively analyzed in the years 2007 (pre-implementation period), 2012 (post-implementation with database in the pharmacy computer system) and 2017 (post-implementation with database in pharmacies and physicians' electronic health record systems). A total of 23,341, 23,848, and 22,328 individuals received co-prescribed beta-blockers and antidepressants in 2007, 2012, and 2017, respectively, which constituted 8 to 9 percent of all persistent beta-blocker users each year. Metoprolol was the most frequently prescribed β-blocker, received by 67%, 72%, and 74% of the study population in 2007, 2012, and 2017, respectively. The proportion of metoprolol users prescribed CYP2D6 inhibitor antidepressants gradually decreased from 9.4% in 2007 to 7.4% in 2012 and 5.6% in 2017. Therefore, this study showed that the co-prescribing rate of metoprolol and potent CYP2D6-

inhibiting antidepressants was significantly reduced after the implementation of an optimized drug interaction database that provides recommendations on alternative drugs without interaction. After this implementation, the co-prescribing rate of metoprolol and potent CYP2D6 inhibitor antidepressants decreased by 21% and 40% after 5 and 10 years, respectively.

Another common combination is medications for cardiovascular disease and chronic pain, specifically opioids. Long *et al*. (2022), using a physiologically-based pharmacokinetic model (PBPK), compared the impact of allosteric inhibition caused by quinidine and reversible competitive inhibition caused by metoprolol on CYP2D6 with Tramadol and its active metabolite, O-desmethyltramadol. The authors found in this in *silico study* with simulation using PK-Sim® 8.0 software that Tramadol increases the plasma exposure of metoprolol by almost 50% when administered together. This can be significantly mitigated by separating the doses – and they cite as an example that if the doses are separated by 02 hours, an increase in the plasma exposure of Metoprolol by less than 20% has been predicted. Finally, the authors consider it necessary future studies to understand the clinical outcomes of this interaction, resulting from β2 adrenergic blockade – such as bronchoconstriction, bronchospasm and vasoconstriction.

4 CONCLUSION

In addition to the well-established clinical use of Metoprolol for various cardiovascular pathologies, such as heart failure and hypertension, new studies have pointed to its beneficial effects in the personalized treatment of patients, such as in the development of arrhythmias after resection of hepatocarcinoma, in the implantation of a permanent pacemaker, in patients with obstructive hypertrophic cardiomyopathy or with type B aortic dissection. it was possible to observe when the combination therapy of Metoprolol brings more benefits to patients with heart failure, carotid atherosclerosis, or hypothalamic obesity, for example. Other studies have pointed out interchangeability, adverse events, therapeutic disadvantages and pharmacological interactions that Metoprolol may present during its clinical use.

Thus, the present systematic review corroborates updates of the use of Metoprolol found in the current literature, contributing to the institution of personalized therapy for patients with cardiovascular disease.

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The importance of the nursing team in front of the early diagnosis of breast cancer

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ABSTRACT
Introduction: in the world, breast cancer is the type that most affects women, even considering developing countries as well as developed countries. Early diagnosis is the main ally for obtaining a positive response to treatment. Objective: to identify the importance of the nursing team in the face of early diagnosis of breast cancer. Methodology: this is an integrative literature review that aims to survey, analyze and describe scientific publications. The survey was carried out between January and March 2023 and covers the period of the last 5 years. The main databases used were: LILACS, BDENF and PUBMED, using the Boolean operator "AND" with the descriptors: "Mammary Neoplasia"; "Early Diagnosis"; "Nursing care". Results: the search for articles found 36 articles and, in the end, 10 articles were eligible for the search that will be part of the construction process. Conclusion: the nursing team masterfully fulfills its role according to its reality, but this does not mean that it cannot reach other means to actually improve its patient care. More studies are needed in this area and that public policies must be designed to solve the present and the future. Nurses must dedicate themselves to updating diseases and especially breast cancer in women so that they are actually prepared to deal with the stages of the disease in a way that their role is not just mechanized but humanized.

Keywords: Breast Neoplasm, Early Diagnosis, Nursing care.

1 INTRODUCTION

BRASIL (2021), in the world breast cancer is the type that most affects women, considering developing countries as developed countries. In the year 2020 about 2.3 million new cases were recorded worldwide. This significant number represents about 24.5% of all types of neoplasms diagnosed in women. Incidence rates vary according to different regions and have a higher incidence in developed countries.

In Brazil, 66,280 new cases of breast cancer were recorded in 2021. For every 100,000 women, the estimated risk is 61.61% of cases. Breast cancer ranks No. 1 in mortality among women in Brazil. The highest incidence and mortality rates were recorded in the South and Southeast regions of Brazil (BRASIL, 2021).

Early diagnosis contributes to the reduction of the stage of presentation of cancer. The nurse's role is to highlight the importance of early diagnosis for the recognition of signs and symptoms, as

well as to expedite rapid access to health services both in primary care and in reference services for diagnostic investigation (GONÇALVES et. al. 2018).

The following are considered suspicious signs and symptoms of breast cancer and of urgent reference for diagnostic confirmation: any breast lump in women over 50 years of age; Breast lump in women over 30 years old that persist for more than one menstrual cycle; Breast lump of hardened and fixed consistency or that has been increasing in size, in adult women of any age; Unilateral bloody papillary discharge; Eczematous lesion of the skin that does not respond to topical treatments; Men over 50 years of age with unilateral palpable tumor; Presence of axillary lymphadenopathy; Progressive increase in breast size with the presence of signs of edema, such as orange-peel-like skin; Retraction in the skin of the breast; Change in the shape of the nipple (GONÇALVES et. al. 2018).

The nursing team should encourage the woman to seek the doctor, whenever she notices an alteration in her breasts. It is necessary that the health system is able to welcome, inform and perform the examinations for the diagnosis in time favourable. The priore for scheduling examinations has to be given to these women who present symptoms, that the lesion in the breast is palpable or presents other warning signs (BRAZIL, 2022).

The objective of this study was: "To report, through research in databases, the importance of the nursing team in the face of the early diagnosis of breast cancer".

2 METHODOLOGY

It is an integrative literature review that aims to survey, analyze and describe scientific publications in a predetermined area (COELHO, 2021).

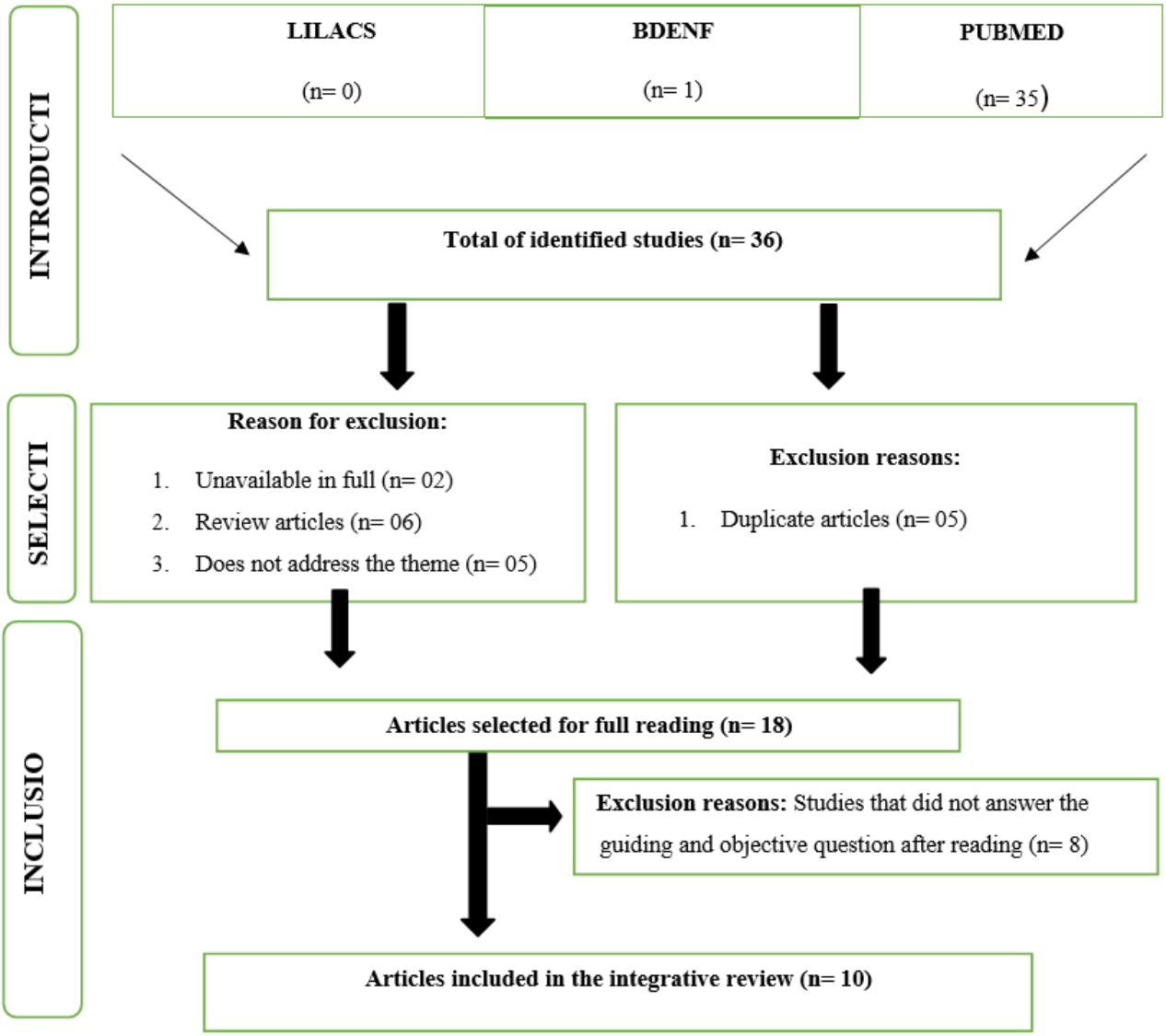
The survey was conducted between the months of January to March 2023 and covers the period of the last 5 years. The guiding question was: "What is the importance of the nursing team in the face of the early diagnosis of breast cancer?". The databases used were: LILACS (Latin American and Caribbean Health Sciences Literature), BDENF (Nursing Database) and MEDLINE (Medical Literature Analyses and Retrieval System Online (MEDLINE/PUBMED), using the Boolean operator "AND" with the descriptors: "Breast Neoplasm"; " Early Diagnosis"; "Nursing Care".

As inclusion criteria, we considered original articles in English and Portuguese, published between 2018 and 2022, that involved the importance for the success of breast cancer treatment when diagnosed early. Reports, case series, letters to the editor, abstracts, dissertations or academic theses, and articles that did not understand the proposed theme were excluded.

3 FINDINGS

After searching the databases where 36 articles were found and after the inclusion and exclusion criteria, 10 articles eligible to compose the research were obtained.

Figure 01- Result of the searches in the databases inserted in the PRISMA flow diagram.



Source: prepared by the authors, 2023.

The following table shows the 10 eligible articles during the search and the main findings of these articles.

Table 01. Description of the articles selected for the construction of this article.

Author / year of publication	Goal	Type of study	Findings
BARBOSA Y. C.; RABÊLO P. P.; AGUIAR M. I.; AZEVEDO P. R.; CORTÊS L. S. 2018. São Paulo.	To investigate the actions for the control of breast cancer developed by Nurses of the Family Health Strategy in a capital city of the Brazilian Northeast.	Transverse	There was a lack of familiarity with the high-risk factors and the indications for early detection tests. Most of the actions are not planned systematically and are restricted to the moment of the Pap smear.
PEREIRA A. C.; OLIVEIRA D. V.; ANDRADE S. S. 2018. Rio de Janeiro.	To evaluate the effect of educational intervention on breast cancer through the Systematization of Assistance of Nursing (NCS).	Descriptive	The stages of the International Classification of Nursing Practice (ICNP) ® were followed, through the seven axes. Considering the importance of health promotion, dissemination of means of prevention and early detection of breast cancer, this proposal strengthened professional autonomy in educational activities through the use of NCS.
BELFORT L.R.M.; LIMA K.M.; DUTRA L.P.F.; DELLACUQUA M.N.; MARTINS V.H.S.; MACEDO L.J.A. 2019. Paraíba.	To understand the role of nurses in the early diagnosis of breast cancer, to describe the actions and strategies used for this objective and to know their perceptions about their role.	Descriptive	The professionals present knowledge about breast cancer and its screening, however, they are still deficient and confused. There is a need for public policies that prioritize the training of professionals so that they can reflect on the improvement of health indicators.
FERREIRA D. S.; SANTOS F. M.; COSTA E. C.; MACIEL N. S.; COSTA R.L.; CARVALHOC. M. L. 2020. São Paulo.	Analyzes knowledge, practices and attitudes about the detection of breast cancer by nurses in primary care.	Descriptive	Regarding the nurses' knowledge, 6.4% presented adequate knowledge with the need to improve it. Regarding attitude, 85.4% obtained adequate results and in practice, 50% obtained adequate results.
SILVA J.; MARINHO V.R.; IMBIRIMBA T.C.O. 2021. São Paulo.	Identify the role of the nurse in the care of cancer patients.	Qualitative description	It is understood that the Nurse is indispensable in the care of cancer patients through the realization of nursing consultations, elaboration of therapeutic planning as a preventive method, application of chemotherapy, treatment of side effects, monitoring of vital signs, in addition to referrals to other sectors and multiprofessional team.
MOURA T. S.; MAGALHÃES P. A. P. 2021.	To identify the nurse's perception of knowledge about the Systematization of Assistance fr om Nursing in the early detection and prevention of breast cancer in women in Primary Care Health.	Descriptive	The nurses who participated in the study demonstrated knowledge about their role and prevention strategies for early detection of breast cancer, but with the overload of work and the time factor, they present difficulties regarding these actions in practice.

Minas Gerais.	Unveil the behavioral changes of the different social supports from the diagnosis of breast cancer.	Descriptive	There were behavioral changes in social support networks after the diagnosis of breast cancer, the greatest behavioral changes occurred in the family (43.5%), followed by the intimate partner (30.4%) and among friends (26.1%).
AMBROSIM M. Z.; BARBOSA	Report the experience Acquired To sensitize w omen about the self-knowledge of the breasts as a way of prevention an d early diagnosis of breast cancer.	Descriptive	The strategy involved about 16 women, all over the age of 40, since the focus was on prevention. It was observed that prevention is a way to sensitize women about the risk of developing breast cancer, in addition, it was perceived that nursing intervention was extremely important. The experience of the individual approach provided a broad view on each preventive report, making professional contact and customer.
B. L.; OLIVEIRA A. G.; AMBROSIO M. M.; LIMA E. F.; LEITE F. M.	To investigate the actions of nurses working in Primary Health Care in the prevention of MC in Campina Grande (PB).	Descriptive and explorative	In their results, five categories emerged: General knowledge about MC; Professional training and health education of the population; Nurse's clinical approach in the prevention of MC; Difficulties in prevention; Self-analysis of professional practice.
2021. Minas Gerais.	Understand t he development of women's autonomy to prevent breast cancer.	Qualitative	From the analysis emerged the theme, development of women's autonomy for the prevention of breast cancer.

Source: prepared by the authors, 2023.

4 DISCUSSION

4.1 PATIENT AUTONOMY ALLIED TO THE NURSING TEAM

It is known that the female public in numbers of breast cancer cases holds the highest percentage. It is worth mentioning the importance of women's autonomy in relation to the search for health services, since this autonomy is one of the main reasons that makes women undergo periodic examinations for the early detection of breast cancer (MARTINS et. al. 2022).

Following this line of thought in relation to autonomy, regardless of health status, autonomy becomes important when, within breast cancer, it is fundamental and is related to the positive effects on the change, for example, of lifestyle, and thus has been contributing to the improvement of health (VIEGAS et. al., 2022).

The nursing team during the detection of breast cancer becomes indispensable when related to adherence to treatment, the influence that nursing awakens in the patient is the starting point in the adherence of the actions proposed by the nursing team (AMBROSIM et. al., 2021).

The union of women's autonomy in relation to the care of their health allied with the actions proposed by the nursing team has within its cases a greater positive number in relation to adherence to the early discovery of the disease and to treatment, since this union makes the number of recovered is increasingly increasing (VIEGAS et. al. 2022).

When we mention women's autonomy, this means that it favors them to know their own health, so that cancer prevention measures are an ally, aiming at the opportunity to make decisions about their health, and this positively impacts the early discovery of cancer, where it becomes even more feasible to obtain a cure (VIEGAS et. al., 2022).

Nursing is the main ally in health promotion so that women's autonomy is respected and in this perspective it is understood that the nursing team provides development in health actions when it understands that women should be respected in decision-making during their treatment. The nursing staff, in addition to providing their services, has, in their first conversations with patients, that treatment actions combined with patient commitment have a greater chance of obtaining a positive result for their treatment (VIEGAS et. al., 2022).

4.2 NURSING PRACTICE IN BREAST CANCER DETECTION

The search for the improvement of their practices as nurses has grown in recent years. It is known that to become a professional of excellence it is necessary to have a reflective and critical view about their practices. Knowledge is the main ally that ensures the techniques of promotion, maintenance of health and prevention of diseases, thus aiming to provide that the care offered by the nursing team is safe, humanized and that in fact helps, for example, in the early discovery of breast cancer (MACIEL et. al. 2020).

Nurses face difficulties during the process of discovering breast cancer due to the lack of deep knowledge on the subject and adding the long waiting lines, scheduling exams and appointments, these last three factors that do not depend on the nurses, but directly impact on the delay in the discovery of the disease and with this the delay in diagnosis has had a negative effect and thus has increased the number of cases that have no cure (MARTINS et. al. 2022).

For these factors to be solved, it is necessary that there are public policies that encourage these professionals to always be improving in the new techniques that have been emerging. Knowing the conduct to be adopted in the detection of breast cancer is a practice of nurses who should be allied to their actions within the ideal treatment for each specificity. The knowledge of the various forms of cancer detection and screening is essential for the clinical practice of the nursing team, this is directly

linked to means that accelerate the scheduling of examinations, consultations and so that, in fact, the queues are reduced, and with this, the early diagnosis actually happens (MACIEL, et. al., 2020).

There are several means of improvement to consolidate the good practice of the nursing team in order to ensure humanized care for this type of patient. Improvement courses aim to contribute to the good care of this team in a responsible, humanized way that through their safe actions the best type of treatment is established. It is known that the knowledge of these professionals is vulnerable and this improvement is important when the improvement reaches not only the professionals but also the main stakeholders, which in this case are the patients (MOURA; MAGALHÃES, 2021).

It is impossible to have a good nursing practice without combining education. Education is the main means responsible for the training and maintenance of excellent professionals. Education stimulates, makes us reflect on the care offered, and it is through it that the public policy of incentive aims to demonstrate that a good professional never stops improving. The improvement aims to stimulate the individual while to his treatment offered to the patients so that he identifies where he needs to improve and that seeks to remedy the deficiencies existing in his profession (SILVA; MARINE; IMBIRIMBA, 2021).

4.3 EARLY DIAGNOSIS

The incidence of breast cancer is higher in women and early diagnosis is the main ally that increases the chances of treatment and its cure. Prevention is allied to healthy lifestyle habits such as ideal nutrition, without smoking and alcoholism and sedentary lifestyle are some factors that are linked to cancer prevention. It is known that self-examination, clinical examination of the breasts and imaging exams are indispensable means in the search for the early detection of breast cancer (BELFORT et al.; 2019).

The nursing team has in its role to be a health educator who aims to promote and guide women regarding the symptoms and their risk factors, the importance of their autonomy in relation to self-knowledge as well as in the identification of nodules, thus the performance of self-examination and search for care are roles of development by the nursing team with the in order to alert women about the importance of self-care and early diagnosis (SILVA, et. al., 2022).

Silva et. al. (2022) says that breast nodules are mostly detected by women during self-examination, so he reaffirms the importance that the nursing team develops during their consultations, for example, gynecological, the encouragement of self-care in relation to breast cancer in women. He says that during these consultations the team clarifies several doubts of the woman and with this opens an alert for the care of her health. Thus, these consultations become an important link of information about the importance of caring.

The strategies developed by the nursing team are humanized practices of disease prevention and coping with the disease. These strategies help during the treatment process, which is often painful and lonely, but this support network demonstrates to the patient that she is not alone, that she has professional and family support (SILVA, et. al., 2022).

The nurse knows that taking care of the cancer area is challenging, the lack of structure, excess demand, long lines, lack of training of professionals and sometimes in its great majority unaware of the control of the disease, are factors that make access to early treatment delayed. In general, it is necessary to create public policies that solve, for example, the lack of structure and long lines, encouraging the training of professionals so that the tracking of this public is met quickly (FERREIRA et. al. 2020).

The lack of organization allows for flaws in the early diagnosis process. The performance of nursing in patient care needs to be agile and thus prevents women from having sequelae or even the loss of their lives due to the late discovery of the disease (BARBOSA, et. al., 2018).

5 FINAL CONSIDERATIONS

This study was done in order to identify the importance of prevention when referring to breast cancer in women. Factors such as the improvement of the nursing team, the creation of public policies to encourage women's health care need to be intensified so that the number of successful treatment is increasingly increasing.

It is worth mentioning the importance of creating policies to encourage women's health care so that they do not seek help only when they feel something different, but that care should be at all stages of their lives. The nurse must dedicate himself to updating the diseases and especially here to breast cancer in women so that he is in fact prepared to deal with the phases of the disease in a way that his role is not only mechanized but humanized.

The nursing team fulfills its role with mastery according to its reality, but this does not mean that it cannot achieve other means to actually improve its patient care. Seeking new learning, updates on breast cancer are effective means in the search for as many cured as possible in the face of this disease.

It is also his role to respect the specificities of each one he serves, but his goal is to offer a better quality of life for these patients who with early diagnosis leaves no doubt that the number of cured is much higher in the face of this reality that should be a public policy to encourage these women.

During the construction of this article it was identified that more studies are needed in this area and the creation of public policies aimed at women's health is essential for early diagnosis. It is the duty of the state and of everyone, and especially of the health class, to fight for these policies that will

give hope for a better future, not only for those who fall ill, but also for those who follow the whole process, be it a professional or a family member.

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Nodal flow and *Situs inversus*: A literature review

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ABSTRACT

Variations of situs solitus totalis, the normal organ disposition pattern, involve dextrocardia, situs inversus, situs inversus totalis and situs ambiguous. These laterality defects have been documented for more than 400 years, and a connection to ciliary abnormalities has been elucidated by observing cilia from the primitive node, which can promote "nodal flow", possibly necessary for the development of left-right asymmetry. The aim of this work was to perform a literature review, showing variations in the usual anatomy and the connection between nodal flow and normal asymmetric pattern. A narrative review was carried out with articles from the MEDLINE/PubMed, SciELO and LILACS databases and with books relevant to the theme. The initial embryonic development comprises the formation of the organizing structure, a primitive node, and its cilia are responsible for the nodal flow, determinant in many vertebrates in the breaking of the embryonic bilateral symmetry. The formation of asymmetry is associated with morphogenic gradients to the left of the node, the model of two cilia and the mechanism of nodal vesicular plots, until it results in organogenesis. Ciliary abnormalities configure clinical manifestations in disorders such as Primary Ciliary Dyskinesia and Kartagener syndrome. The nodal flow, in fact, is important in normal anatomical standardization, and the cilia are necessary for the configuration of situs solitus totalis.

Keywords: Nodal flow, Situs Inversus, Laterality defects, Primary Ciliary Dyskinesia, Kartagener syndrome.

LIST OF ABBREVIATIONS AND ACRONYMS

Cerl2 - Cerberus-like 2
FGF8 - Fibroblast Growth Factor 8
LPM - Mesoderm of the lateral plate
NVP - Nodal vesicular portion
PCP - Planar cell polarity
SHH - Sonic Hedgehog
RA - Retinoic Acid
TGF-β - Transforming Growth Factor Beta
TIF - Intraflagellar transport

1 INTRODUCTION

The normal anatomical pattern, with all structures in their usual position, is termed *situs solitus totalis*. There are variations of this standardization, which may or may not be associated with important functional changes: *situs solitus* with dextrocardia, in which the abnormality is the presence of the cardiac apex on the right side; *situs inversus*, with the organs located in an inverted position, but

without dextrocardia; *situs inversus totalis*, with all organs inverted, and *Situs ambiguous*, or heterotaxy, in which the thoracoabdominal organs do not follow a normal pattern of disposition, may be partially inverted, arranged in the midline, or symmetrical bilaterally. Heterotaxy, which often causes serious health problems, is divided into two categories: *situs ambiguous* with polysplenia, or left isomerism, with a variable number of bilaterally bilobated spleens and lungs, and *Situs ambiguous* .com asplenia, or right isomerism, with absence of spleen and bilaterally trilobed lungs. Patients with these changes are likely to have other malformations, especially heart defects [1-3].

In the general anatomical context, considering in addition to the variations in cardiac morphology, known laterality defects, characterized by the abnormal disposition of structures and organs, have been documented for more than 400 years, having in many reports, however, unknown underlying causes. Girolamo Fabrizio was the first to describe such abnormalities, around 1600, followed by Marco Aurelio Severino, who in 1643 documented a case of human dextrocardia, and Matthew Baillie, responsible for describing a complete reversal of the thoracoabdominal organs in 1788 [4, 5].

In 1995, the published Afzelius study demonstrated a connection between changes in ciliary structures and the *situs inversus*, one of the existing defects of laterality of the general anatomy [6]. This correlation can be elucidated with the evidence of studies on the gastrulation of mouse embryos, which demonstrated that the primitive node, characterized as an organizing structure, consists of single-cilium presenting cells, that is, each cell has a monocilium [7].

In the fully developed primitive node, there are a total of 200 to 300 lashes, each of these measuring 7 to 10 micrometers in length and being spaced by intervals of 5 to 10 micrometers. Central nodal cells contain monocilia that exhibit motility, while peripheral nodal cells (crown cells) have immobile monocilia. The central cilia are thus able to produce a rotation and generate a directed flow of extra-embryonic fluid to the left through the node. This fact supports the existence of a "nodal flow" model, which would be necessary for the development of the left-right asymmetry of the embryo and, therefore, for a normal arrangement of the anatomical structures [7, 8].

Knowledge about the mechanisms involved in the determination of physiological left-right asymmetry is fundamental for understanding the causality of several laterality defects. The study of these abnormal anatomical states in characteristic disorders or in isolation allows to elucidate not only the triggering factor of the problem, but to establish the correlation between the embryonic abnormality involved and the clinical one presented. From this perspective, the work aims to present a review of the existing literature in this sphere, evidencing the variations of the habitual *situs* in a general anatomical context – without being limited to the nomeclatures of the cardiac context – and the link between the known nodal flow and the standardization of normal asymmetry.

2 METHODOLOGY

The present work consists of a narrative review of the literature, based on scientific articles selected from the databases MEDLINE/PubMed, SciELO (Scientific Electronic Library Online) and LILACS (Latin American and Caribbean Literature in Health Sciences), as well as important books for the explanation of the theme. Data and pertinent information were collected, with the search for studies using descriptors related to the subjects treated and without a pre-established publication period.

3 DEVELOPMENT

3.1 EARLY EMBRYONIC DEVELOPMENT

During the first week of human development, at the stage of blastogenesis, the conceptus – formed by the embryo and its membranes – gives rise to the blastocyst. In this, the separation of the blastomeres by liquid in the blastocystic cavity configures the trophoblast and the embryoblast, which constitute, respectively, the formation of its wall and a projection into the blastocystic cavity. With the gradual degeneration of the zona pellucida, the blastocyst grows rapidly and is adhered to the endometrial epithelium. From this moment, the trophoblast proliferates and differentiates into two layers: the cytotrophoblast (inner layer) and the syncytiotrophoblast (outer layer) which, with its enzymatic synthesis, enables the effective implantation of the blastocyst in the endometrium [9, 10].

With the continuation of the progress of implantation of the blastocyst, in the second week of development, morphological changes in the embryoblast, responsible for the formation of the embryo, lead to the generation of the bilaminar embryonic disc, consisting of the epiblast and the hypoblast. The epiblast contributes to the formation of the amniotic cavity, and the hypoblast to that of the exocoelomic cavity. The formation of the bilaminar disc thus defines the primitive dorsoventral axis of the embryo. In the third week of development, the bilaminar embryonic disc finally becomes a trilaminar embryonic disc, characterizing the gastrulation event. The three germ layers (ectoderm, embryonic endoderm and mesoderm) formed during the stage give rise to specific organs and tissues, constituting the principle of morphogenesis [7, 9, 11].

Gastrulation begins with the formation of a longitudinal structure in the midline of the epiblast surface: the primitive line, close to the caudal region of the embryonic disc, resulting from an induction of epiblastic cells by the extraembryonic region. This formation defines the main body axes: craniocaudal, mediolateral, dorsoventral and left-right axes. The cephalic end of the primitive line forms the primitive node, considered an organizing structure; This contains a circular depression called the primitive pit, which is caudally continuous with the primitive groove, a depression developed in the line. The pit and groove are the result of an invagination of cells of the primitive line. Some of these cells, which migrate to the interior of the embryonic disc, invade the hypoblast, forming a

definitive endoderm layer. Others migrate bilaterally, between the endoderm and epiblast, to form the intra-embryonic mesoderm. The remaining epiblastic cells form the embryonic ectoderm [10, 12].

3.2 CILIARY STRUCTURE

Cilia can be defined as slender extensions that protrude from the surface of different cells. They consist of a cytosolic axis – the ciliary matrix – surrounded by a prolongation of the plasma membrane; Inside, this matrix comprises the axoneme, a filamentous scaffold that follows the longitudinal axis of the ciliary structure and is formed by microtubules. These microtubules consist of protofilaments and sprout from the basal corpuscle (or basal body), which is located inside the cell, under the plasma membrane, and anchors the cilia. In addition, they have a positive end and a negative end, the latter facing the corpuscle. The axoneme and basal body have doubles (doublets) and trios of microtubules, respectively, and are connected by a transition zone. The microtubules A and B of the axoneme doubles are continuous with the microtubules A and B of the cracks of the basal corpuscle [13, 14].

The processes of formation and maintenance of cilia and their counterparts, the flagella, occur through the intraflagellar transport system (TIF), with motor proteins associated with the microtubules - kinesin and cytoplasmic dynein - involved. Under a different system, the fundamental process for moving structures requires a motor protein of the distinct dynein class: axonemal dynein [15], whose driving activity, as well as that of TIF proteins, also requires the hydrolysis of ATP as an energy source [16]. The axonemal dynein contains internal and external arms that protrude from the microtubule A of the axoneme doublets and interact with the microtubule B of the adjacent doublets, forming dynein bridges; through its ATPase activity, then, the portions of the protein associated with microtubule B slide along it toward the negative end. As an effect, motor proteins promote the sliding of one doublet in relation to the other and induce a ciliary curvature, thus characterizing the dynamics of the beating of cilia and flagella [13, 17].

There are three basic categories of eyelashes: mobile, primal, and nodal. The motile cilia, commonly found in epithelia responsible for the transport of secretions, and the flagella, considerably longer and unique by cells, have an axonemal organization 9 + 2, that is, they have 9 doublets of microtubules surrounding 2 central microtubules; Microtubules are associated with motor proteins necessary for ciliary motility. Primary cilia are immobile cellular projections in an arrangement of 9+0 microtubules (9 microtubule doublets, without a central pair), with no associated motor proteins. They are found in cells such as those of the renal ducts and in the epithelium of the bile ducts, and bend passively due to the flow of fluids; thus, they are able to act as sensory antennas and to generate and transmit signals to the intracellular environment in response to extracellular events. In addition, primary cilia are also involved in the transduction of the Hedgehog signal active in the early development of vertebrates. Finally, the nodal cilia, found in the embryo, have an axonemal

organization similar to that of the primary cilia; however, they are holders of associated motor proteins, having the ability to perform active movement. The absence of the central pairs of microtubules is possibly responsible for their rotational movement in full cone trajectory, contrasting with the movable cilia 9 + 2, whose trajectory is in half cone [18, 19].

The nodal cilia with axonemal architecture 9 + 0, then, are responsible for the dynamics of the nodal flow, which occurs at a speed of 15 to 20 μm/s, specifically between the stages of one to two somites and that of six somites [20]. Still, the rotational movement is established clockwise, unlike the commonly found eyelashes [21]. Studies in vertebrates also demonstrate a posterior positioning of these cilia at a time coinciding with the onset of flow specifically to the left. Initially, they are projected into the center of cells, but apparently become posterior by movement from the basal body to the posterior cell pole [22]. This positioning of monocilia is determined by signaling of the PCP (Planar Cell Polarity) pathway in some vertebrates [23].

In addition, the dominant unidirectional character of the flow to the left becomes feasible by the also posterior inclination of these cilia from a vertical angle, with the trajectory of its tip displaced posteriorly when compared to its root; With this configuration, the cilia perform a swing to the left, away from the surface of the cell, and a movement to the right, towards the surface of the cell. Thus, a movement of fluid directed specifically to the left occurs, since, according to hydrodynamics, the surface of the cell is stationary and slows the movement of fluid by the resistance to shear and, as an effect, the sweep to the right is less effective than the movement to the left [22, 24].

3.3 DETERMINATION OF THE LEFT-RIGHT PLANE

In all vertebrates, despite the noticeable external symmetry between the right and left sides, there are processes that trigger an asymmetrical pattern of organization of internal structures and organs, as well as the vascular network [25]. The fundamental processes for generating asymmetry require distinct mechanisms. Initially, a mechanism is needed for the breaking of bilateral symmetry of the embryo, such as a molecular asymmetry. Subsequently, the signaling of this asymmetry generated on a small scale must be established in larger regions of the embryo and ultimately result in an asymmetric organogenesis. Thus, the normal development of the left-right configuration results in the so-called *Solitus site* [8]. The left-right axis is possibly determined in relation to the anteroposterior and dorsoventral axes, these being the axes along which embryonic morphogenesis occurs [26].

The initiation of the asymmetric left-right configuration in vertebrates is a controversial process. In mice, however, experiments suggest that symmetry breaking begins with the generation of leftward extra-embryonic fluid flow: the so-called nodal flow, which occurs through the primitive node [20]. The node is described as a transient structure of the midline, holding a "ciliated well" on the ventral surface, which carries important activity for the determination of left-right asymmetry. This activity

can be proven by the role of the monocilia of the nodal cells, which with their rotational movements, are responsible for generating this nodal flow. Analyses of experiments with fluorescent spheres added to the liquid in the node region demonstrated the activity of the cilia in the nodal flow: in normal wild embryos, these spheres moved unidirectionally to the left, but in mutant embryos with absence of the motor proteins KIF3A and KIF3B, belonging to the kinesin superfamily, they showed Brownian (random) motion [24].

The application of artificial flow in embryos of cultured mice also evidenced the relationship between nodal flow and the beginning of the asymmetry process. It was observed that a rapid flow directed to the right resulted in a reversal of the normal flow to the left and in a reverse left-right development. On the other hand, the application of a flow directed to the left in embryos with mutations affecting inversin – a protein with ankyrin repeats –, which had slow nodal flow, and the left-right axonemal dynein, which had monociliary paralysis, was sufficient to rescue the normal asymmetric pattern. Several mutations are related to the impairment of left-right development, and some of the genes involved are responsible for the formation of the embryonic node itself [8].

Hirokawa *et al* [24] consider an absence of asymmetric event prior to nodal flow in mice. Thus, they discuss the possibility that flow has become the main mechanism of asymmetry with the emergence of viviparous and that it is sufficient for the determination of laterality in mammals. Dasgupta and Amack [22] report that many vertebrate embryos have ciliated structures analogous to the primitive mouse knot that are responsible for an asymmetrical flow, such as the Kupffer vesicle in certain fish, the gastrocele roof plate in the frog, and the posterior notochordal plate in the rabbit, characterizing left-right organizers. However, they point out that cilia would not be necessary to generate asymmetry in all vertebrates. The Hensen node, as they exemplify, holds the first asymmetrical gene expression in the chick, however, this structure may not present mobile cilia, since mutants with defective eyelashes present normal development of asymmetry. They also report that the node of the pig embryo does not have cilia, nor is it exposed to an extra-embryonic liquid – a factor also present in the cow embryo – unlike what occurs in the mouse embryo. Thus, they demonstrate that some vertebrates, and among them mammals, can use mechanisms independent of cilia in the development of asymmetry, unlike the idea that nodal flow, *for itself*, be sufficient.

Considering an asymmetric information generation based on the nodal flow mechanism, this can be elucidated, in principle, from two proposed models. The first concerns the formation of a gradient of morphogens on the left side of the node – equivalent to the left-right organizer of the mouse; The chemical morphogens would be secreted into the node and transported to the left through the nodal flow. The second proposes the existence of a physical stimulation generated by the flow, which would be mechanically detected by the immobile cilia of the peripheral region of the node, being called "two-

lash model", since there are distinct cilia responsible for both the generation of the flow and the perception of it [24].

McGrath e Brueckner [8] clarify that, in fact, the flow may be responsible for generating a morphogenic gradient on the left side of the node; The morphogenic molecule would then be able to set up an asymmetric gene expression cascade on the left. Many molecules found in the structure, such as the Nodal, perform an activity in left-right development, thus being candidates for the role of morphogen. Genes expressed on a single side of the embryonic midline employ mechanisms to propagate signals between cell subpopulations, and this occasionally results in the asymmetric morphogenesis of specific structures. In general, the gene products responsible for the asymmetry are not involved solely in this process, and some of them are not even present in an asymmetric way [26].

Nodal is a signaling molecule belonging to the transforming growth factor beta (TGF-β) family of proteins, initially expressed bilaterally in the crown cells of the mouse organizer. The protein produced in the node can migrate to the mesoderm of the left side plate (LPM) and thus activate the expression of the gene itself *Nodal*; the asymmetric manifestation in the LPM begins at the two-somite stage and ends at the six-somite stage, leading to the conclusion that nodal flow can occur specifically to initiate expression *Nodal* on the left side. The cells of the left LPM that received the Nodal signaling then contribute to the specific morphological characteristics of the left side, while those of the right side, which did not receive them, contribute to the characteristics of the right side [20, 27].

The fibroblast growth factor 8 (FGF8) transported by nodal flow also seems necessary for left-right determination by some mechanism, since mice deficient in *Fgf8* have no expression *Nodal* in the LPM. In mammals, Nodal signaling also induces the expression of Lefty genes: *Lefty1*, predominantly in the midline of the embryo, and *Lefty2*, predominantly in the left LPM. The absence of any of these – *Lefty1*, which acts as a barrier on the midline, or *Lefty2*, which acts as a Nodal feedback inhibitor – leads to a "leakage" of the mesoderm nodal signal from the left side plate to the right side, resulting in expression *Nodal* bilateral and alteration of normal morphology [20, 26].

Beyond genes *Nodal* and *Lefty2*, *Pitx2* it is also expressed in the left LPM, and its asymmetric expression is induced by Nodal signaling. The transcription factor Pitx2 is considered the main regulator of asymmetric organogenesis at the molecular level, but there are mechanisms independent of the factor also operative. Nodal activity, necessary for the cascade of asymmetric expressions, can also be controlled by a protein belonging to the TGF-β family of antagonists, Cerl2 (Cerberus-like 2). At first, the protein is found in the crown cells on both sides of the node, at the early stage of mouse development. Cerl2 then accumulates on the right side and prevents the Nodal from acting on the right LPM. Subsequently, the protein is translocated by the nodal flow to the left, terminating the nodal activity on the left side of the node and on the left LPM in a precise time [20, 28].

In the "two-cilia model", the distinct characteristics of the monocilia of the mouse organizer may provide support for the hypothesis. Monocilia that are mobile, centrally located, contain the motor protein Lrd (left-right dynein) and the protein polycystin-2, a cation-permeable channel; the immobile cilia, located peripherally, lack the Lrd protein, but have polycystin-2. This protein is a calcium-activated channel, which in the primary cilia of the renal epithelium functions as a mechanotransducer, increasing the concentration of intracellular calcium in response to fluid flow. In the nodal structure, it is evident that, while the Lrd-holding monocilia generate the nodal flow, the immobile monocilia, which do not have the Lrd protein, can function as mechanosensory cilia. Thus, they detect the nodal flow to the left, and the existing polycystin-2 leads to an increase in intracellular calcium on the left side of the node, generating asymmetric signaling. The calcium signal resulting from mechanosensitivity, then, can trigger the expression of a specific growth factor to the left of the node [25, 29].

A third mechanism proposed for the generation of asymmetric information by nodal flow – analogous to the first model – concerns nodal vesicular parcels (NVPs). NVPs are materials secreted from the surface of the mouse node that are transported to the left through the flow. These vesicles are made up of lipoprotein particles coated by a membrane; they may also comprise a content of signaling molecules such as Sonic Hedgehog (SHH), Retinoic Acid (RA) and other morphogens. The NVPs apparently fragment on the left side of the node, with the aid of the peripheral cilia, through the interaction of the SHH of the vesicles with its receptor called Smoothened in the cilia, and are absorbed by the nodal surface. Thus, they may be responsible for producing a concentration gradient to the left of the node, and the released molecules may play a role in the left-right determination. In addition, they may also be responsible for an asymmetrical elevation of intracellular calcium through Hedgehog signaling [21, 24].

Shiratori and Hamada [20], however, expose the fact that SHH plays an important role in left-right determination in avian species, but in distinct vertebrates, such as the mouse, it does not appear to be directly involved in asymmetric determination, but rather in the formation of a functional midline. Similarly, AR would be related to the maintenance of bilateral symmetry during the formation of somites, but not to the left-right determination itself. Thus, the authors refute the potential role of the content of NVPs in the establishment, in fact, of the asymmetric configuration in other vertebrates.

Macroscopically, at least three distinct mechanisms are involved in the formation of anatomically asymmetric structures: the first concerns the directional "looping" of initially tubular organs, such as the heart, which go through a series of steps (looping, flexion and rotation) and reach their correct final positioning; the second corresponds to differential branching, in which a pair of symmetrically formed organs, on both sides, acquires differences in their size or branching pattern, as occurs with the lungs and; The third – unilateral regression – is related to the disappearance of one side

of a symmetrical structure, such as a blood vessel [20]. The failure in the processes of establishing adequate left-right asymmetry results in a range of laterality defects, such as absence of bilateral symmetry breaking, independent localization of structures in relation to the *Site* normal and partially or totally abnormal asymmetric orientation [26, 29].

3.4 CILIARY ABNORMALITY

Changes in genes associated with cilia can lead to changes in their structure and affect their signaling mechanisms in various anatomical localities. The gene *PKHD1* (Polycystic Kidney and Hepatic Disease 1), for example, encodes the protein fibrocystin, or polyductin, expressed in the axoneme and basal body of primary cilia. Mutations in the gene lead to autosomal recessive polycystic kidney disease, a severe form of pediatric cystic kidney disease [30]. Genes *PKD1* (Polycystic Kidney Disease 1) e *PKD2* (Polycystic Kidney Disease 2) encode polycystin proteins, which are also located in the primary cilia and which play a necessary role for kidney function. Mutations involving these genes are responsible for the ciliopathy of autosomal dominant polycystic kidney disease, or adult polycystic kidney disease [31, 32].

Ciliary genes *BBS* (Bardet-Biedl Syndrome) mutants cause Bardet-Biedl syndrome, a rare autosomal recessive disorder that leads to varied manifestations such as obesity, renal abnormalities, hypogonadism, and retinopathy [33]. It is also characterized by involvement of the primary cilia, since the normally encoded BBS proteins are located in the basal body and ciliary axoneme and contribute to the formation of a complex active in the intraflagellar transport system [34].

Other mutations that lead to the absence or immotility of the cilia can cause abnormalities in the left-right organization, confirming their essential role in generating the directed nodal flow and, consequently, the initial process of symmetry breaking. Mice with the gene *Dvl* mutant – gene responsible for coding Dishevelled, cytoplasmic protein of the PCP pathway – present interruption of the posterior positioning of the basal bodies and randomization of the flow, which also determines a defective left-right standardization [35].

3.4.1 Changes in the laterality of the heart

Cardiac anatomy also involves the characterization of *Situs* and its complexities. Or *situs solitus* atrial corresponds to the usual arrangement of the atrium morphologically right to the right and left to the left, while the mirror image of this situation corresponds to the *situs inversus*. The presence of atrial isomerism, with the two atria presenting the right or left morphology, constitutes the *Situs ambiguous*. Also, the atrioventricular connection is characterized as concordant, when the right atrium is connected to the right ventricle and the left atrium to the left ventricle, and discordant, when the right atrium connects to the left ventricle and the left atrium to the right ventricle; When the atria are connected to

a single ventricular chamber, the univentricular connection is configured. The venoatrial connection is also analyzed, observing how the systemic and pulmonary veins are connected to the atrial chambers. The ventriculoarterial connection, finally, is classified as: concordant, when the aorta emerges from the left ventricle and the pulmonary trunk from the right ventricle; discordant, when the opposite occurs; double outflow tract, when the two vessels emerge from the same ventricle; and single outflow tract, when only one arterial vessel emerges from the heart or there is aortic or pulmonary atresia [36, 37].

3.5 IN THE MEDICAL CLINIC

3.5.1 Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a classically autosomal recessive disorder, rarely linked to the X chromosome, caused by mutations in more than 40 genes responsible for coding proteins necessary for the proper assembly and functioning of mobile cilia. Distinct mutant genes determine different severities of symptomatology, which is dependent on the extent of ciliary structural and functional changes. Mutations in the gene *DNAH5* (Dynein Axonemal Heavy Chain 5), for example, which encodes the heavy chain of the outer arm of the dynein of the proximal and distal zones of the cilium, lead to ciliary imotility, while mutations in the gene *DNAH9* (Dynein Axonemal Heavy Chain 9), which encodes the heavy chain of the outer arm of the dynein of the distal zone, lead only to a reduced curvature of the distal ciliary portion and do not alter the beating frequency [38, 39].

The disorder is characterized by a generalized ciliary dysfunction and, therefore, there are ciliary involvements in distinct anatomical regions, such as in the epithelium of the respiratory tract, in the epithelium of the vas deferens, in the fallopian tubes and in the ependyma, as well as there is involvement of the spermatozoa. Thus, the disease predisposes to dysfunctional mucociliary clearance and recurrent respiratory infections, and it is important to consider it as a differential diagnosis in cases of chronic infections of the respiratory system, and is also often associated with infertility and hydrocephalus, in addition to other clinical manifestations (TAB 1). The presence of other clinical indicators also raises the suspicion of PCD, including a family or personal history of ciliopathies and the existence of laterality disorders, since the cilia that present motility play an essential role in the left-right pattern [40, 41].

TABLE 1 - Clinical manifestations of primary ciliary dyskinesia

Lung	Respiratory distress syndrome, pneumonia, atelectasis (neonatal period)
	Chronic productive cough
	Bronchrhea
	Recurrent episodes of pneumonia
	Severe and/or atypical "bronchial asthma" with no response to conventional therapy
	Bronchiectasis
	Digital hypocratism
Middle ear	Chronic serous otitis media
	Transmission hypoacusis
	Persistent otorrhea after tympanostomy
Paranasal sinuses and nasal cavities	Chronic rhinosinusitis
	Nasal polyposis
	Continuous mucopurulent rhinorrhea (early neonatal period)
Lateralization of organs	*Situs inversus* total
	Heterotaxy - left isomerism (polysplenia) - Right isomerism (asplenia)
Fertility	Male infertility
	Decreased female fertility and ectopic pregnancy
Associated diseases	Complex congenital heart disease
	Polycystic renal and/or hepatic disease
	Biliary atresia
	Esophageal atresia
	Severe gastroesophageal reflux
	Hydrocephalus
	Retinitis pigmentosa

Source: Adapted from Fermeiro *et al* [42]

The definitive diagnosis is established when at least three of the following phenotypic manifestations coexist: difficulty breathing in term infants, chronic nasal congestion and chronic productive cough throughout the year, chronic otitis media with effusion for more than 6 months, chronic pansinusitis, bronchiectasis and other recurrent lower respiratory tract infections and, finally, male infertility, laterality defects and family history of the disease. When there is a simultaneous presence of bronchiectasis, pansinusitis and *situs inversus totalis*, one of the existing laterality disorders, the diagnosis is Kartagener syndrome [41, 42].

3.5.2 Kartagener syndrome

Kartagener syndrome is a subgroup of primary ciliary dyskinesia, being the most severe clinical form of the disorder and being present in 50% of cases. It is related to the deficiency of ciliary dynein, protein responsible for the generation of mechanical force in the movement of the eyelashes. It is also known as Immobile Cilia syndrome, associated with the absence of frontal sinuses, chronic rhinosinusitis and bronchiectasis, with recurrent respiratory infections and airway damage. The spermatozoa are immobile, being the male carrier, infertile [40, 43].

The main picture of a child born with the disorder is based on pulmonary symptoms, which become evident within 24 hours after birth and which, in a significant number of cases, cause neonatal respiratory distress syndrome. Other typical symptoms associated with seeking medical help refer to recurrent ear infections, persistent wet cough, nasal congestion, and chronic wheezing. In accordance with the abnormalities that accompany PCD, Kartagener syndrome also presents conditions justified by ciliary changes, which lead to abnormal positioning of certain organs and changes in the function of other structures. Approximately 20% of patients with *situs inversus* belong to the group with Kartagener syndrome [44, 45].

3.5.3 *Situs Inversus*

Or *situs inversus* It is characterized as a mirror image arrangement of the abdominal organs, but with a *Situs* normal cardiac, that is, the apex is located in the left hemithorax, and therefore there is a levocardia. Already the *situs inversus totalis* It is characterized by the mirror image of the *situs solitus totalis*, including abdominal viscera in reverse location, bilobate right lung and trilobed left lung and dextrocardia. Thus, the individual exhibits completely inverted left-right asymmetry, with transposition of the viscera in the chest and abdomen [46, 47]. The abnormality is typically asymptomatic and is not considered a premalignant condition, however, a small number of cancer cases have been reported, as well as cardiovascular malformations, intestinal anomalies, and respiratory comorbidities [48].

This abnormality is inherited as an autosomal recessive genetic trait and may occur in combination with primary ciliary dyskinesia. However, some genes are responsible for the occurrence of *situs inversus* and are not associated with the occurrence of PCD, and the mechanisms involved in this alteration of isolated laterality are based on the role of some of these genes in the coding of ciliary proteins. Mutations in the gene *CFAP52* (Cilia and Flagella Associated Protein 52), for example, which encodes a protein active in the processes of ciliary signal transduction, establish causality with the occurrence of *situs inversus* and heterotaxy in patients without dyskinesia [49, 50].

In the United States, an average distribution of 1 per 10,000 individuals was observed, however, the discovery of such a morphological alteration does not depend on symptoms resulting from the

inversion of the organs themselves, often being discovered in the research of unrelated health alterations, or even at the time of necropsy. This fact can be observed with the American patient Rose Marie Bentley, who died of natural causes, but as soon as her body was donated for research to a university in Portland, Oregon, the students of an anatomy class realized that many of her organs were mirrored [51].

4 FINAL CONSIDERATIONS

The scientific evidence based on the analyzed studies denotes the role that, in fact, the nodal flow can play in the establishment of normal left-right asymmetry in certain vertebrates and, therefore, in the usual anatomical pattern. Additionally, the clinic presented by patients with ciliary disorders reaffirms the conception that cilia are involved in the definition of a pattern of *situs solitus totalis*. As an effect, the laterality defects that initially had an undefined causality can be progressively understood and, thus, the need for a constant acquisition of knowledge in the scope of embryology is remarkable, aiming to elucidate the various abnormalities that involve human development and the mechanisms involved in their occurrence.

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The impact of multicomponent training on postural balance, cardiorespiratory capacity, and quality of life in individuals with Post-COVID-19 Syndrome: A randomized clinical trial

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ABSTRACT

Introduction: individuals with Post-COVID-19 Syndrome have symptoms such as chronic fatigue, myalgia, cough and mental health problems, which can compromise postural balance, cardiorespiratory capacity and quality of life. Multicomponent training is an association of different types of therapeutic exercises that can promote a better physical-functional recovery from illnesses such as severe respiratory disease that can be generalized for people with COVID-19. Objective: to investigate the relationship between multicomponent training and its effects on postural balance, cardiorespiratory capacity and quality of life of individuals with Post-COVID-19 Syndrome. Methodology: randomized clinical trial, in a sample of 59 individuals, of both sexes and aged between 18 and 70 years. In the initial and final evaluation, a form with sociodemographic and clinical questions was used. Postural balance was assessed using the Berg balance scale; cardiorespiratory capacity by the 6MWT walking test and quality of life by the quality of life questionnaire - SF 36. The sample was divided into: intervention group (IG: n=31) and control group (GC: n=28). The IG received 24 training sessions, 60 minutes each, for 12 consecutive weeks, while the CG received educational guidance during the same training period. Significance level $p \leq 0.05$. Results: the sample consisted of 59 individuals, with a mean age of 52.3+11.9, 57.6% female. On the Berg scale, the GI obtained a change from 48.8+4 points (Pre) to 51.9+4.26 points (Post) and GC, 47.8+3.96 points (Pre) to 47.9+ 4.96 points (Post). As for the distance covered in the 6MWT, GI ranged from 464.4 +81.3

meters (Pre) to 518.6 +82.7 meters (Post), and GC from 441.2 + 118.7 meters (Pre) to 433.9 + 111.7 meters (Post). And as for quality of life, GI presented a raw score of 96.3+ 10.1 (Pre) to 102.6 + 5.5 (Post), and GC, 96.4+8.0 (Pre) to 97, 7+7.7 (Post). All variables studied did not show statistically significant difference in intragroup and intergroup analysis ($p \geq 0.05$). Conclusion: multicomponent training had a positive impact on the analyzed variables; however, it was not more effective than the educational guidelines given to individuals with Post-COVID 19 Syndrome.

Keywords: Post-COVID-19 Syndrome, Quality of Life, Walk Test, Physical Therapy.

1 INTRODUCTION

Post-COVID-19 Syndrome is defined as persistent signs or symptoms for more than 12 weeks, developed during or after COVID-19 infection (MAHASE, 2020). These persistent symptoms include chronic fatigue, dyspnea, anosmia, difficulty sleeping, chest pain, headache, cough, and mental health problems (GARRIGUES et al., 2020; Bellan et al., 2021). The persistence of these dysfunctions can occur in both individuals with severe and mild symptoms, and may cause limitation in quality of life, as well as post-traumatic stress disorder (ARAB-ZOZANI et al., 2020; BELLAN et al., 2021 MANDAL et al., 2021).

One way to measure the aerobic capacity and endurance of patients who have had COVID-19 is with testing of a six-minute walk (6MWT). The 6MWT measures the distance covered during 6 minutes of walking and this measure can be used to compare performance capacity, having been used as a predictor of mortality in patients with idiopathic pulmonary fibrosis (IPF) (DU BOIS et al., 2013; MANCUZO et al., 2018).

Effective rehabilitation of individuals with Post-COVID-19 Syndrome, according to the guideline of the *National Institute for Health and Care Excellence* (NICE), requires integrated multidisciplinary rehabilitation services to better treat fatigue and respiratory symptoms (NICE, 2022).

Exercise, early mobilization and multicomponent programs may improve recovery after ICU admission for severe respiratory illness that can be generalized to people with COVID-19 (GOODWIN et al., 2021). Multicomponent exercises combine muscle strength training, cardiovascular endurance, postural balance and gait, producing significant improvements in physical and functional deficit, and in hospitalized elderly patients the results were also favorable in improving frailty, cognitive status, gait and postural balance (CASAS-HERRERO et al., 2019; COUREL-IBÁÑEZ et al., 2022).

In view of the above, this study investigated the relationship between multicomponent training and its effects on postural balance, cardiorespiratory capacity and quality of life of individuals with Post-COVID-19 Syndrome.

2 METHODOLOGY

This is a randomized, randomized clinical trial and simple blind, developed at the Laboratory of Kinesiotherapy and Manual Therapeutic Resources (LACIRTEM), of the Federal University of Pernambuco (UFPE). This study is in accordance with Resolution 510/2016 of the National Health Council, approved by the Ethics Committee Opinion N0. 5,236,588 and registered with ReBEC n^0 RBR-7yh559g. The guidelines established by CONSORT 2010 (*Consolidated Standards of Reporting Trials*) were followed in the construction of this study.

Data collection took place from March to October 2022. We recruited individuals with Post-COVID-19 Syndrome, with ages ranging from ≥18 years to ≤ 70 years, of both sexes, residents in Recife-PE and metropolitan region.

Individuals were included.uos: affected by COVID-19 proven by laboratory examination, RT-PCR or serology; Sedentary; absence of neurological or vascular diseases, blindness, foot and/or spinal deformity; absence of uses of gait aids. Individuals with hypertension were excluded systemic arterial and uncontrolled arrhythmia; active myocarditis; signs of respiratory distress at rest; acute systemic disease or fever; nausea; dizziness; shortness of breath and/or severe dyspnea; excessive sweating; anxiety crisis; Palpitations; pain or tightness in the chest; presented muscle pain during training. The participants read and signed the free and informed consent form (ICF).

2.1 RANDOMIZATION

The randomization of thea was performed by a blind researcher, using a website *www.randomization.com*. In the masking of the research, two researchers were responsible: one responsible for the evaluation/reevaluation and the other for the application of the intervention protocol. The participants were randomly distributed into 2 groups: Intervention Group (IG) and Control Group (CG). The IG performed two weekly intervention sessions for 12 consecutive weeks, lasting 60 minutes each. The CG did not undergo training, however it received only educational guidance in the same training period and at the end of the IG training was reassessed (Post-intervention).

2.2 PHYSICAL-FUNCTIONAL ASSESSMENT

In the initial evaluation, all participants answered a form with questions of a sociodemographic, anthropometric and clinical nature. Next, the equipostural libido (Berg balance scale), cardiorespiratory capacity (6MWT) and quality of life (SF-36 questionnaire). At the end of the 12 weeks of training, Both groups were reassessed with the instruments mentioned above.

IronEvaluation Scale: Berg's balance scale, which is composed of 14 items, containing activities such as transfers, reach, turning and unloading weight in a single leg graded on a scale

ranging from 0 (incapable/insecure) to 4 (independent/efficient/safe) (BERG, 1992). The scale was adapted for application in Brazil by Miyamoto (2004) presenting in each item scores of 0-4 and a determined time for each task; The 6-minute Walk Test (6MWT) is a test that reflects the level of physical activity, cardiopulmonary capacity, as well as provides valuable information about blood pressure (BP), heart rate (RR) and oxygen saturation (SpO2) (HAMILTON & HAENNEL, 2000; Solway et al., 2001; MOALLA et al., 2005); The Brazilian version of the SF-36 quality of life questionnaire was applied, with 36 items that measure: physical functioning (10 items), social functioning (two items), function limitations due to physical (four items) and emotional (three items) problems, mental health (five items), energy and vitality (four items), pain (two items), general perception of health (five items) and a question about health a year ago (BRAZIER et al., 1992).

2.3 INTERVENTION

The therapeutic intervention was based on the protocol adapted from Marques et al. (2015) whose intervention covered multicomponent exercises, and was applied twice a week, for 60 minutes each, for a period of 12 consecutive weeks, totaling 24 training sessions.

The multicomponent exercises were subdivided into: (I) Warm-up (10 minutes): joint mobility, global stretching, breathing techniques, such as breathing with pursed lips, body positions, diaphragmatic breathing; (II) Resistance (20 minutes): walking; (III) Strength (15 minutes): 7 exercises, with 2 sets of 10 repetitions for muscle groups of the upper and lower limbs, using elastic bands, free and ankle weights, the weight was progressively increased according to the participant's capacity; (IV) Balance (5 minutes): postures with gradual reduction of the support base; dynamic movements that disturb the center of gravity; post – stress of muscle groups; dynamic movements when performing secondary tasks individually; (V) Relaxation (10 minutes) (MARQUES et al., 2015).

2.4 STATISTICAL ANALYSIS

Data analysis for categorical variables was expressed as absolute and relative frequencies, while continuous frequencies were expressed as mean and standard deviation. For verificationthe normality of quantitative data was applied to the test *Kolmogorov-Sminorv;* In the comparison of the groups, in categorical variables, the chi-square test was used. Descriptive analysis for sociodemographic, anthropometric and clinical characterization. In the comparison of the Berg, the 6MWT and the SF-36, an intention-to-treat analysis approach was used, considering all participants and groups until the end, regardless of what happened to each of them (AMATUZZI et al., 2006). The mean comparison analysis corresponded to the moment before the intervention and ANOVA was performed *one-way*, to confirm starting homogeneity for the three groups. Statistical analysis was

performed using SPSS software *(Statistical Package for Social Science)* version 20.0 for Windows *(SPSS Inc, Chicago IL, USA)* and significance level p<0.05 for all analyses.

3 RESULTS AND DISCUSSION

We selected 59 individuals with Post-COVID-19 Syndrome with an average age of 52.3+11.9 (Table 1). The participants in this study had a mean BMI of +28.9 kg/m2, not corroborating the study by Eksombatchai et al. (2021) that found, in 87 individuals with COVID-19, BMI of +23.8 kg/m2.

Table 1 - Characterization of the sample regarding sociodemographic, anthropometric and clinical data.

Variables	Total (n= 59)	Intervention group (n= 31)	Control group (n= 28)	p*
Age (years), M(DP)	52,3 (11,9)	53,7(11,2)	50,7(10,1)	p≥0,05
Height (m), M(DP)	1,6 (0,1)	1,66(0,1)	1,64(0,1)	p≥0,05
IMC (kg/m²), M(DP)	28,9 (7,9)	27,5(4,5)	30,7(7,2)	p≥0,05
Female, n (%)	34 (57,6)	17 (54,8)	17(60,7)	p≥0,05
Comorbidade, n (%)				
Hypertension	26 (44,1)	12(38,7)	14(50)	p≥0,05
Cardiopathy	8(13,6)	2(6,5)	6(21,4)	p≤0,05
Diabetes mellitus	6 (10,6)	3(9,7)	3(10,7)	p≤0,05
Other	19(31,7)	14(54,9)	5(17,9)	p≥0,05

* Mean (M); Standard deviation (SD); Body Mass Index (BMI); Metro(m2); Kilogram (kg); Significance value=p*. Source: Authors (2022).

According to Klanidhi et al. (2022), who conducted a prospective observational study in patients with COVID-19, the mean age (SD) of the population studied was 68.76 (7.4) and 41% was female, partially corroborating our study, as the mean (SD) age was 52.32 (11.9) and 57.6% was female (Table 1), however, not corroborating a study by Yanamandra et al. (2022), because the mean age of 54.54 ± 14.35 years, with a predominance of males 60.38%.

As for the comorbidities, according to Klanidhi et al. (2022), Hypertension (58%) and diabetes (46%) were the two most prominent, partially corroborating our study, since hypertension was present in 44.1% of the cases, followed by heart disease (13.6%) and diabetes (10.6%) (Table 1).

The IG showed improvements in the variables examined. Table 2 shows the comparison of intra- and intergroup performance after 12 weeks of follow-up.

Table 2 – Inter- and intra-group comparison of the variables 6MWT, Berg and SF-36 after 12 weeks of follow-up.

	GI (n=31)		Difference	CG (n=28)		Difference	p-value*		p-value**
	Pre	Post	Average (Post-Pre)	Pre Post	T	Average (Post-Pre)	GIVE	GC	
TC6m (m), M(DP)	464,5 (81,3)	518,6 (82,7)	54,1	441,2 (118,7)	33,9 (111,7)	-7,3	0,5523	0,6123	0,1294
Berg, M(DP)	48,8(4)	51,9 (4,26)	3,1	47,8 (3,96)	47,9 (4,96)	0,1	0.6799	0.5630	0.8694
SF-36, M(DP)	96,3 (10,1)	102,6 (5,5)	6,3	96,4 (8,05)	97,7 (7,74)	1,3	0.0553	0.9005	0.8078

* Intervention Group = GI; Control Group= CG; Pre-intervention=Pre; Post-intervention = Post; Meters= m; Mean=M; Standard deviation (SD); 6-minute Walk Test=6MWT; Berg Balance Scale (Berg); Quality of Life Questionnaire (SF-36); p-values obtained from the Kolmogorov-Smirnov normality test= p-value*; p-values obtained from the Levene test for homogeneity of variance= p-value**. Source: Authors (2022).

The p-value obtained with one-factor ANOVA for the variables Berg, 6MWT and SF36 shows that there is no statistically significant differenceicative ($p \geq 0.05$), between the groups, with normality between the data and homogeneity of variances (Table 2).

Regarding postural balance, this study observed that after the 12-week intervention, the mean score on the Berg scale between the pre-intervention (Pre-intervention) and post-intervention (Post) period increased from 48 to 51.9, respectively, although it was not statistically significant with $p \geq 0.05$, not corroborating the study by Giardini et al. (2022), who observed dynamic balance deficit and increased oscillation during static posture in critically ill patients in the acute phase of COVID-19, which may be related to the length of hospitalization. According to Miyamoto (2004) score below 45 can represent high risk of falling.

With regard to the 6MWT, it was found that, initially, the participants covered an average of 464.5 $\pm$ 81.3 meters, after 12 weeks of intervention, they went on to walk an average of 518.6 $\pm$ 82.7 meters, demonstrating a mean difference (Pre - Post) of 54.1 meters.

When analyzing the results of the 6MWT, we confirmed the findings of Ferioli et al. (2021), demonstrating that the 6MWT is a useful test in the post-COVID-19 follow-up, correlating with the severity of the acute phase and losses in the chronic phase, offering the possibility of evaluating improvements in exercise capacity, corroborating the performance of our IG, because through the 6MWT it was possible to perceive an increase in the average distance covered from 464.4 (Pre) to 518.6 (Post) meters. In the study by Eksombatchai et al. (2021), in the COVID-19 groups with mild symptoms and non-severe pneumonia, there was a decrease from 538±56.8 to 527.5±53.5 meters, corroborating our CG, which showed a decrease in the average distance traveled between the Pre- and Post-intervention decreasing from 441.2 to 433.9 meters, respectively.

With regard to quality of life, the IG showed an increase in the mean raw score from 96.3 (Pre) to 102.6 (Post), although it was not statistically significant with $p \geq 0.05$ (Table 2). According to Brazier et al. (1992), a score of 100 points in the SF-36 represents a better state of health. However, in the

study by Sousa et al. (2022), participants with Post-COVID-19 Syndrome had worse results in the SF-36, not corroborating our study.

4 CONCLUSION

O tReigning with multicomponents provided a positive impact on the variables studied, although it was not statistically significant. However, due to the small sample used in this study, it is not yet possible to affirm that the protocol applied may provide greater benefits to the population observed, making it necessary to continue in order to expand the results. Given the challenge of studying this population, it is important to have new studies to make a greater contribution to the clinic and science of this disease.

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Perception of medical students about the extension activity "super powerful vaccines": Experience report

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ABSTRACT
Vaccination should be understood as the most effective measure to prevent diseases, contributing directly to the decrease in morbidity and mortality caused by infectious pathologies preventable by vaccination, including in children. Brazil has been a world reference in vaccination for years, but in the last ten years there has been a sharp drop in the number of users benefiting from immunizations, demonstrating a greater vulnerability, specifically to children. The present work is an experience report that seeks to describe
the experiences of medical students of the AFYA School of Medical Sciences. The extension action was entitled "Super Powerful Vaccines", held at the Family Health Unit (USF) São Rafael, João Pessoa-PB. Playful, dynamic and human approaches were carried out to welcome users, in order to expand vaccination coverage in the community. The extension action allowed an increase in the number of vaccines applied, revealing positive results in view of the strategies used. The experience provided an enriching moment for the students, expanding the sense of citizenship and represented a tool for achieving humanized medical training, providing a reflection on the importance of teamwork in this scenario and raising awareness about the health needs of the population.

Keywords: Vaccination of the child, Primary care, Community medicine.

1 INTRODUCTION

The National Immunization Program (PNI) is responsible for organizing the entire national vaccination policy of the Brazilian population, with the mission of controlling, eradicating and eliminating vaccine-preventable diseases (BRASIL, 2013).

It is considered one of the main and most relevant public health interventions in the country, due to the impact obtained in the reduction of diseases in recent decades (BRASIL, 2020). Currently, the SUS offers all the vaccines recommended by the World Health Organization (WHO) in the National Calendar, which are made available by the public health network. There are approximately 300 million doses of immunobiologics per year, to combat more than 19 diseases, in various age groups.

In this context, the PNI has become a world reference, not least because Brazil was a pioneer in the incorporation of several vaccines in the SUS calendar, and because it offers a comprehensive number of immunobiologicals in a universal way. However, the high coverage rate, which has always been its main characteristic, has been falling in recent years (CRUZ, 2017).

In 2007, a substantial reduction in vaccination coverage was identified in the country. As of 2016, the decline was approximately 10 to 20 percentage points (FREITAS, 2022). In a recent publication, the Butantan Institute (2022), revealed a sharp drop in the last ten years, demonstrating a greater vulnerability, specifically to children. In addition, anti-vaccine movements have emerged, and as a consequence, there has been an increase in the number of people who refuse to vaccinate their

children, fostering this dangerous movement that can bring back diseases such as measles and polio (CRUZ, 2017).

According to the Brazilian Society of Pediatrics (SBP) (2019), vaccination is the most effective measure to prevent vaccine-preventable diseases and reduce infant mortality. Failure to update the vaccine can leave children susceptible to preventable diseases, as well as endangering the health of others around them.

When considering the Family Health Unit of the São Rafael Community, located in the city of João Pessoa-PB and the internship field for medical students, it was noticed that the FHU provides all the necessary vaccines to its 1,287 registered users, however, it experiences difficulties in relation to the adherence of vaccines and their constant updating.

Based on this reality, the students, teachers and health team identified the need to carry out educational actions at the USF São Rafael with those responsible for children from 0 to 10 years old and the children themselves, in order to stimulate adherence to vaccination. Then, educational strategies were designed to enlighten the population about the importance of vaccines and the adequate follow-up of the vaccination schedule for the prevention/eradication of diseases, thus contributing to increase vaccination coverage and benefit the community as a whole, as well as the Brazilian population and health services.

2 OBJECTIVE

To describe an experience report on the extension activity "Super Powerful Vaccines" carried out by the medical students of the Medical Science School of Paraíba, AFYA.

3 EXPERIENCE REPORT

The present study is an experience report conducted on April 15, 2023, at the São Rafael Family Health Unit (FHU), located in the São Rafael Community, João Pessoa-PB. Initially, visits were made to the USF São Rafael in order to agree with the health team on the activities to be developed in the extension action on vaccination. After this moment, the students gathered to prepare material to publicize the event on social media and an educational pamphlet on vaccines, in addition to defining the schedule of activities to be held on the day of the action, entitled "Super Powerful Vaccines".

On the day of the event, firstly, a group of students toured the main streets of the community to hold a call to the residents that included the distribution of pamphlets and the dissemination of warnings, about the immunizers available for immediate vaccination in the USF and the recreational activities that would be carried out that morning, as well as the reproduction of children's songs, with the aid of a speaker and microphone.

Given that the target audience of the extension action was defined as children aged between 0 and 10 years, some students dressed up as characters such as Zé Gotinha, the princesses (Belle, Snow White, Fiona, Aurora) and the heroes (Thor and Captain America), in order to attract children and their families to go to the USF, with their vaccination card, to update their immunizers and participate in the action that would be developed in the unit.

Immediately, we noticed the curiosity, enchantment and joy of children and adults, who left their homes to observe the movement made. With the departure of people to the street, one can make a more personal, dynamic and human approach to welcoming children, who surprised, wanted to take pictures and embrace the children's characters. The adults also got involved, taking their children to the backyard and also taking pictures with the characters.

We took advantage of the approach of the local population to pass on information about the relevance of vaccines to avoid diseases, the importance of keeping the children's vaccination booklet updated and to make a direct invitation to go at that time to the Health Unit to get vaccinated.

The presence of the character Zé Gotinha was remarkable and a true rescue of the successful vaccination campaigns in Brazil, for being a historical symbol of the PNI, being able to dialogue with different audiences to motivate and inform about the importance of vaccination and prevention of various diseases (BRASIL, 2013).

Therefore, a prosperous approach was achieved, because, at the same time, in which the technical information of the importance of vaccination arrived, the language of the children and youth audience was also attended to with the presence of the characters.

In this context, it is possible to infer that the call of the community for vaccination in a playful way and the use of educational materials were assertive strategies, since health education is one of the pillars of health promotion, along with the creation of healthy environments and the strengthening of community action (BRASIL, 2018).

Therefore, health professionals should go beyond technical knowledge, developing a more sensitive look at the community in which they are inserted, in order to obtain greater adherence to preventive and health promotion proposals (NASCIMENTO, 2021). At the same time that the community was summoned and informed, another group of students remained at the USF São Rafael welcoming the users who arrived. During the reception, the students and professionals of the health team observed the vaccination booklets, regarding the presence of any vaccine delayed or within the period to be applied. At that time, too, it was explained to the individuals as to the programming to be carried out during the action.

The reception was ornate, becoming a playful space, with toys, face painting, princesses and heroes, to make the environment more cheerful, welcoming and special for children. The whole apparatus used aimed to make the moment of vaccination of children more relaxed and welcoming,

showing that the drill is the best protection against diseases (PROENÇA, 2015). Well, play is one of the most important activities in the life of a child for their motor, emotional, social and intellectual development (TAVARES, 2011).

Thus, one of the ways to inhibit the child from showing fear and insecurity, especially when exposed to an unknown and hospital environment, is to offer a light and pleasant environment, being essential and primordial the use of games, aiming to provide safety, comfort, mental, emotional and social well-being of the child (HOCKENBERRY; WILSON, 2014).

For Schreiber and Dreher (2021), "It is not enough just to request that the population get vaccinated, but rather to provide the necessary knowledge so that it has the security of choosing to perform immunization." In this sense, an educational action was held at the reception of the FHU in the form of a conversation circle about the importance of vaccination in the prevention of diseases, with explanations of how immunization works in the human body, about the main diseases prevented with vaccines and that, still, affect the health of the Brazilian population, and, therefore, deserve greater attention.

This educational initiative aimed to inform users, through the use of an appropriate language and with media support of pamphlets, which also brought the essential information, so that they would stimulate the maintenance of the booklet following the national immunization calendar.

Corroborating with Carvalho (2022), when stating that in addition to the concern with performing the technique of administering the immunizer correctly, it is necessary the common communication between health professionals and people who wanted to get vaccinated and their companions, to explain the information correctly.

In the vaccination room, the medical students were able to collaborate as the completion of the card and proof of vaccination, containing information about the vaccine, the lot, the laboratory and the expiration date.

Immunization was preceded by the registration of the user and presentation of their documents, the data collected such as name, date of birth, gender, address, date of application and signature of the professional, were filled in the respective vaccination mirrors, held by the FHU, for registration purposes by the nurse. After the verification and completion of the vaccination cards, the corresponding vaccination was carried out.

When considering children, immunization is especially crucial, since they may be more vulnerable to complications and infections. WHO (2022) highlights the importance of influenza and COVID-19 vaccination to reduce morbidity and mortality in children and control the spread of these viruses in the community. In this sense, updating the vaccine in children is crucial to ensure continued protection against various infectious diseases.

In the action carried out, all vaccines that were part of the children's vaccination schedule were covered and had good adherence, as reported by the USF management. 87 doses of vaccines were administered, 87% being Influenza and COVID, since the national campaign focused on these immunizers was taking place and covered children, the elderly, pregnant women, adults with comorbidities and health workers, and the remainder, 13% of the doses applied were for the other routine vaccines.

It should be noted that the presence of the children's characters also at the time of vaccination, allowed the children to be more tranquil and collaborative, because the existence of a playful element in the vaccination room brought lightness and relaxation to the moment. The children were encouraged to get vaccinated by the characters themselves, under the argument of becoming as strong and powerful as those.

In fact, Princess Belle, Thor and Captain America welcomed the children inside the room where they were applying the vaccines, hugging them at the time of the "powerful hole" and later rewarding them with a "magical princess hug", with a bravery medal and toys as a prize. Legitimizing the importance of the presence of children's characters in the vaccination room.

For Teles (2019), health care in childhood, demands a humanized and integral care, capable of recognizing feelings, wants and needs, aiming to minimize adversities at the time of the medical procedure and help the child to accept the procedures with more tranquility, because depending on the environment and the way to which the child is exposed, In this situation, the experience can stop being negative and traumatic. In this way, the focus on humanized attention enables a positive reinforcement, through the playful and fun experience, which can reflect on the vision of the child until adulthood.

Bridges et. al. (2015) informs that in child care, the suffering faced by children is not limited to the performance of procedures, but also to health professionals, of whom they are very afraid, especially those responsible for vaccination. Such fear is already an old construction of society, which has always stimulated this feeling regarding the vaccine in children, contributing to a greater rejection of them to health professionals, especially those in the vaccine room.

Since fear and anxiety are very common during this procedure, the use of the playful contributes to a better acceptance and collaboration with the procedure, in addition to contributing to a positive experience of these children during care. However, it is worth mentioning that, still, there is a difficulty for its routine use, due to the high demand of functions and short time that professionals have (SANTOS et al., 2019).

In addition, another strategy was used to increase the adherence of the population of the São Rafael Community to the event, through a bingo with fourteen rounds, which assured the winners of basic baskets. In addition, the characters conducted at the reception, games and circle dances for the children waiting for vaccination.

4 FINAL CONSIDERATIONS

The activities proposed by the medical students were well received, happening effectively and effectively. It is possible to observe the interaction of all participants in a dynamic and participatory way, both children and their families. In addition, the activity was important to sensitize parents and guardians about the importance of vaccination in the prevention of diseases, as well as to show the need to keep vaccination cards up to date.

The event also allowed the student to know the reality and functioning of the SUS. In order to experience important aspects of primary health care, such as: universality and integrality, understanding health as an element of citizenship and right of all people, teamwork, humanization of care, welcoming, promotion, prevention and health education.

Finally, the experience enabled the training of medical students to develop skills to work in Primary Health Care in a critical and reflective way, allowing them to confront theory and practice. The students inserted themselves as agents of social transformation, expanding the sense of citizenship and verifying the importance of the performance of the professional in training within the health services of the SUS.

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Prevalence and evolution of cases of sexually transmitted infections in adolescents in Brazil

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ABSTRACT
In Brazil, more and more, adolescents are affected by STIs. Therefore, the objective of this research is to present the prevalence and evolution of cases of sexually transmitted infections in adolescents in Brazil. This is an observational epidemiological study with a quantitative approach and descriptive analysis on data related to the prevalence of STI in adolescents aged 10 to 19 years between 2010 and 2021 in Brazil. Data were extracted from DATASUS electronic databases. In this period, there were 86,601 cases of syphilis, mainly between 15 and 19 years old, with a higher prevalence in incomplete high school and brown race, and 56.17% were female, with the most affected region being the southeast (50.53%). Regarding hepatitis B, there was a prevalence in females with 56.17%, with the most affected region in the north with 39.58%, especially between 15 and 19 years with 92.17%, and higher prevalence in incomplete high school (19.53%) and in the race ver parda (51.26%). There were 10,129 cases of AIDS, mainly in the age group of 15 to 19 years with 89.81% and in the brown race with 31.53%, 59.98% were male, with the most affected region being the southeast with 36.2%, among them 25.52% with incomplete elementary education. The study concluded that measures are needed that tend to decrease the prevalence of STIs in adolescents in Brazil. Therefore, it is important to carry out campaigns, especially in schools, in order to spread this information to reach our target audience, which are adolescents from 10 to 19 years old.

Keywords: Sexually transmitted infection, Adolescent, Prevalence, Sexual education, Evolution.

1 INTRODUCTION

The incidence of sexually transmitted infections (STIs) among adolescents has been increasing over time. It is known that adolescence is a period of physical and organic transformations, associated with the perception of sexual and occupational identity and comprises the age group of 10 to 19 years (MINISTÉRIO DA SAÚDE, 2018). This phase involves intense biopsychosocial changes, especially those linked to sexual maturation, the search for adult identity and autonomy from parents. In this same perspective, according to Foucault, 2010, **the disciplinary restraint** on sexuality would occur through the stimulus to the discourse about it, which would lead to a construction of knowledge about sexuality and not exclusively through negative mechanisms of sex. This knowledge was formed through the mechanism of confession, developing a categorical and normative order, initially in

religious institutions and followed by scientific institutions such as medicine (CHEQUER, et al., 1998).

In relation to the main STIs, AIDS stands out, whose epidemiological character presents a propensity to juvenilization (CHEQUER et al., 1998). Of the total number of AIDS cases reported to the Ministry of Health (MH) until February 1998, 43% were between 20 and 34 years old. As the latency time of the infection is long and can remain up to 11 years, probably many of these patients became infected in adolescence. And, based on supremacy data from 2009 to 2016, the World Health Organization (WHO, 2016) hasterminated a total of 376.4 million incident cases of STIs, considered remediable. Of this total, 127.2 million were estimated cases of chlamydia, 86.9 million of gonorrhea, 156.0 million of trichomoniasis and 6.3 million of syphilis. The estimated overall prevalence of syphilis in men and women was 0.5%, with regional values ranging from 0.1 to 1.6%.

In 2012, the global incidence was estimated at 357.4 million new cases of curable STI worldwide, in the age group of 15 to 49 years, most of them in developing countries. In these countries, STIs are among the 10 most frequent causes of demand for health services, with health, social and economic consequences. Thus, the STIs that are part of the national list of compulsory notification include cases of acquired immunodeficiency syndrome (AIDS), HIV, HIV in pregnant women, viral hepatitis, syphilis in pregnant women, acquired syphilis and male urethral discharge syndrome, Human Papillomavirus (HPV) infection, genital herpes, gonorrhea, trichomoniasis (PINTO et al., 2012).

It is known that the risk behavior of adolescents is a notorious fact, but it is necessary to better understand the causes that lead to the practice of such behaviors that result in increased incidence rates of STIs. In this same conception, the main factors that affect this target population are: resistance to condom use, early initiation of sexual life and the use of licit or illicit drugs (MOREIRA, et al, 2021).

Based on a study conducted by Costa et al., in 2013 the rate of adolescents who stated that the most effective way to avoid infection is the use of condoms in all sexual relations was 81.3%, but 18.6% highlighted sexual abstinence as a way to avoid STIs. On the other hand, several studies show the inconstancy in relation to the use of condoms in the same population due to thoughts such as "trivialization, belief in invulnerability to infections, minor pleasurable sensations, discomfort, difficulty in ejaculation during the use of condoms and non-agreement of the partner to use such a barrier method".

STIs can present through anogenital wounds, discharges and warts, among other possible symptoms, such as pelvic pain, burning when urinating, skin lesions and enlarged tongues. In addition, these signs and symptoms appear mainly in the genital organ, but can also manifest in other parts of the body, such as the palms of the hands, eyes and tongue. And, some STIs can be asymptomatic, which can lead to serious complications such as infertility and cancer if not diagnosed and treated (MINISTRY OF HEALTH, 2020).

Since there has been an increase in the incidence of STI cases in young people due to resistance to condom use, early initiation of sexual life, use of licit or illicit drugs and misinformation about ways of prevention, there is a need to conduct a research that presents the evolution of STI cases in adolescents in the regions of Brazil, In this way it will be possible to adopt health promotion and prevention measures specific to each location, in order to minimize these occurrences.

The objective of this research is to present the prevalence and evolution of cases of sexually transmitted infections in adolescents in Brazil.

2 METHODOLOGY

This is an epidemiological, cross-sectional and observational study related to cases of STIs in adolescents aged 10 to 19 years, both female and male, in Brazil. As a guiding question, the following question was used: What is the context of STI in the adolescent public?

The pathologies documented were the following: In this research we aimed to deepen the knowledge about the following STIs according to the International Classification of Diseases (ICD-10): A50 acquired syphilis, B16 Hepatitis B and B24 unspecified HIV. The variables included were: gender, age group, schooling, race and region of Brazil. The tables were formatted as follows: rows for the variables (gender, age group, education and race) and the columns as region of residence, all in the criteria from 2010 to 2021 and age group from 10 to 19 years.

The data collected covered the period from 2010 to 2021 and were extracted from the electronic databases of the Department of Health (DATASUS) of the Brazilian public health network (Sistema Único de Saúde - SUS). Afterwards, they were compiled in an Excel spreadsheet and later discussed descriptively.

The results were synthesized in a comprehensive way, seeking the compilation of scientific knowledge that guides this research model. As the use of data from the electronic department is public, they did not need to undergo evaluation by the Ethics and Research Committee (CEP).

3 FINDINGS

In Brazil, 86,601 adolescents contracted syphilis from 2010 to 2021. Among them, 56.17% were female, and the most affected region was the Southeast, with 50.53% of the cases. The age group with the highest prevalence was 15 to 19 years. The majority (19.71%) of the adolescents affected by this pathology had incomplete high school, and the ethnicity with the highest prevalence was mulatto (39.39%) (Table 1).

Table 1. Prevalence of Syphilis in adolescents aged 10 to 19 years by Brazilian regions from 2010 to 2021. Brazil, 2023.

	North		Northeast		Southeast		South		Midwest		Brazil	
GENDER	n	%	n	%	n	%	n	%	n	%	n	%
Ignored	2	3,64	8	14,55	29	52,73	4	7,27	12	21,82	55	0,06
Male	2.705	8,22	5.173	15,72	19.424	59,04	7.666	23,30	2.930	8,91	32.898	37,99
Female	2.752	5,66	6.756	13,89	24.308	49,97	11.872	24,40	2.960	6,08	48.648	56,17
AGE GROUP												
10 a 14	296	7,12	663	15,95	2.058	49,52	843	20,28	296	7,12	4.156	4,80
15 a 19	5.163	6,26	11.274	13,67	41.703	50,58	18.699	22,68	5.606	6,80	82.445	95,20
SCHOOLING												
Ign/Branco	1.496	5,02	4.395	14,75	14.830	49,77	6955	23,34	2120	7,12	29.796	34,41
Illiterate	32	12,85	42	16,87	69	27,71	91	36,55	15	6,02	249	0,29
1st to 4th incomplete grade of EF	146	7,87	444	23,95	700	37,76	451	24,33	113	6,09	1.854	2,14
Full EF 4th grade	174	9,46	351	19,09	828	45,02	368	20,01	118	6,42	1.839	2,12
Incomplete 5th to 8th grade of EF	1.002	6,98	2.547	17,73	6.429	44,75	3506	24,41	881	6,13	14.365	16,59
Completed elementary school	460	5,99	939	12,22	3.977	51,76	1735	22,58	573	7,46	7.684	8,87
Incomplete high school	1.130	6,62	1.839	10,77	9.440	55,31	3460	20,27	1199	7,02	17.068	19,71
Completed high school	853	7,32	1.178	10,11	6.479	55,58	2476	21,24	671	5,76	11.657	13,46
Incomplete higher education	133	7,59	178	10,15	829	47,29	431	24,59	182	10,38	1.753	2,02
Complete higher education	32	10,42	21	6,84	163	53,09	63	20,52	28	9,12	307	0,35
Not applicable	1	3,45	3	10,34	17	58,62	6	20,69	2	6,90	29	0,03
RACE												
Ign/White	389	3,12	2.081	16,67	6.254	50,10	2.907	23,29	851	6,82	12.482	14,41
White	541	1,81	1.218	4,08	14.019	47,00	12.572	42,15	1.480	4,96	29.830	34,45
Black	331	3,72	1.333	14,97	5.573	62,57	1.251	14,05	419	4,70	8.907	10,29
Yellow	58	8,53	105	15,44	303	44,56	125	18,38	89	13,09	680	0,79
Pardon	3.952	11,59	7.127	20,89	17.501	51,30	2.545	7,46	2.987	8,76	34.112	39,39
Indigenous	188	31,86	73	12,37	111	18,81	142	24,07	76	12,88	590	0,68
Total	5.459	0,01	11.937	13,78	43.761	50,53	19.542	22,57	5.902	6,82	86.601	100,00

During the study period, 1147 adolescents between 14 and 19 years of age contracted hepatitis B in Brazil. Among them, 72.54% were female, and the most affected region was the North, with 39.58% of the cases. The age group with the highest prevalence was 15 to 19 years with 92.07%. The majority (19.53%) of the adolescents affected by this pathology were from the 5th to 8th incomplete grade of PE, and the ethnicity with the highest prevalence was mulatto (51.26%) (Table 2).

Table 2. Prevalence of Hepatitis B in adolescents aged 10 to 19 years by Brazilian regions from 2010 to 2021. Brazil, 2023.

VARIABLE	North		Northeast		Southeast		On		C. West		Brazil	
GENDER	n	%	n	%	n	%	n	%	n	%	n	%
Male	134	42,54	30	9,52	76	24,13	55	17,46	20	6,35	315	27,46
Female	320	38,46	130	15,63	147	17,67	130	15,63	105	12,62	832	72,54
AGE GROUP												
10 a 14	49	53,85	14	15,38	14	15,38	10	10,99	4	4,40	91	7,93
15 a 19	405	38,35	146	13,83	209	19,79	175	16,57	121	11,46	1.056	92,07
SCHOOLING												
Ign/White	142	49,48	46	16,03	51	17,77	25	8,71	23	8,01	287	25,02
Illiterate	6	85,71	-		-		1	14,29	-		7	0,61
1st to 4th incomplete grade of EF	42	57,53	8	10,96	11	15,07	8	10,96	4	5,48	73	6,36
Full EF 4th grade	22	47,83	6	13,04	8	17,39	6	13,04	4	8,70	46	4,01
Incomplete 5th to 8th grade of EF	81	36,16	36	16,07	40	17,86	42	18,75	25	11,16	224	19,53
Completed elementary school	34	36,56	12	12,90	21	22,58	15	16,13	11	11,83	93	8,11
Incomplete high school	70	34,48	24	11,82	42	20,69	35	17,24	32	15,76	203	17,70
Completed high school	50	28,25	23	12,99	42	23,73	41	23,16	21	11,86	177	15,43
Incomplete higher education	4	16,67	4	16,67	6	25,00	9	37,50	1	4,17	24	2,09
Complete higher education	3	23,08	1	7,69	2	15,38	3	23,08	4	30,77	13	1,13
RACE												
Ign/White	42	50,00	17	20,24	17	20,24	3	3,57	5	5,95	84	7,32
White	36	12,12	15	5,05	80	26,94	141	47,47	25	8,42	297	25,89
Black	28	24,56	27	23,68	33	28,95	13	11,40	13	11,40	114	9,94
Yellow	10	52,63	2	10,53	3	15,79	1	5,26	3	15,79	19	1,66
Pardon	297	50,51	98	16,67	90	15,31	27	4,59	76	12,93	588	51,26
Indigenous	41	91,11	1	2,22	-		-		3	6,67	45	3,92
Total	454	39,58	160	13,95	223	19,44	185	16,13	125	10,90	1147	100,00

Regarding HIV/AIDS, 10,129 adolescents between 14 and 19 years old contracted the pathology in the country. Among them, 59.98% were male, and the most affected region was the Southeast, with 36.2% of the cases. The age group with the highest prevalence was 15 to 19 years, with 89.81%. The majority (25.52%) of the affected adolescents had incomplete schooling from 5th to 8th grade, and the ethnicity with the highest prevalence was mulatto (31.53%) (Table 3).

Table 3. Prevalence of HIV/AIDS in adolescents aged 10 to 19 years by Brazilian regions from 2010 to 2021. Brazil, 2023.

VARIABLE	North		Northeast		Southeast		On		Central-West		Brazil	
GENDER	n	%	n	%	n	%	n	%	n	%	n	%
Ignored												
male	913	15,04	1.344	22,13	2.328	38,34	973	16,02	514	8,47	6.072	59,98
female	550	13,58	958	23,65	1.337	33,00	957	23,62	249	6,15	4.051	40,02
AGE GROUP												
10 a 14	123	11,92	239	23,16	348	33,72	286	27,71	36	3,49	1.032	10,19
15 a 19	1.342	14,75	2.063	22,68	3.320	36,50	1.645	18,08	727	7,99	9.097	89,81
SCHOOLING												
illiterate	2	5,00	18	45,00	11	27,50	8	20,00	1	2,50	40	0,74
1st to 4th grade incomplete	25	10,08	96	38,71	70	28,23	47	18,95	10	4,03	248	4,59
4th full series	25	10,73	61	26,18	70	30,04	65	27,90	12	5,15	233	4,32
Incomplete 5th to 8th grade	205	14,88	326	23,66	367	26,63	393	28,52	87	6,31	1.378	25,52
Complete fundamental	52	8,20	155	24,45	252	39,75	131	20,66	44	6,94	634	11,74
incomplete medium	194	16,74	228	19,67	396	34,17	232	20,02	109	9,40	1.159	21,47
complete medium	140	11,41	220	17,93	547	44,58	218	17,77	102	8,31	1.227	22,73
Incomplete top	52	12,97	71	17,71	142	35,41	94	23,44	42	10,47	401	7,43
Complete Superior	6	7,79	13	16,88	38	49,35	9	11,69	11	14,29	77	1,43
does not apply	0	0,00	0	0,00	1	50,00	1	50,00	0	0,00	2	0,04
RACE												
Ignored	595	16,40	840	23,16	1397	38,52	528	14,56	267	7,36	3.627	35,81
white	110	4,37	214	8,50	1025	40,72	1004	39,89	164	6,52	2.517	24,85
Black	34	4,76	145	20,28	330	46,15	171	23,92	35	4,90	715	7,06
yellow	3	8,11	4	10,81	16	43,24	9	24,32	5	13,51	37	0,37
Parda	713	22,32	1095	34,28	892	27,93	211	6,61	283	8,86	3.194	31,53
indigenous	10	25,64	4	10,26	8	20,51	8	20,51	9	23,08	39	0,39
Total	1465	14,46	2302	22,73	3668	36,21	1931	19,06	793	7,83	10.129	100,00

Regarding the evolution of cases, 2 cases of death related to Syphilis were registered in the country between 2011-2021, 1 in the Southeast and another in the South, in the age group of 15 to 19 years. About hepatitis B, 17 cases, among them, 10 adolescents between 15 and 19 years. The North region had the highest prevalence (52.94%). As for the cases related to HIV/AIDS, 873 were registered. Among them, 741 cases were in the age group of 15 to 19 years. It had a higher prevalence in the Southeast region (43.76%) (Table 4).

Table 4. Evolution of cases related to the prevalence of syphilis, hepatitis B and HIV/AIDS in adolescents aged 10 to 19 years by Brazilian regions in the period from 2010 to 2021. Brazil, 2023.

HEPATITIS												
VARIABLE	North		Northeast		Southeast		South		Midwest		BRAZIL	
	n	%	n	%	n	%	n	%	n	%	n	%
Deaths	9	52,94	7	41,18	1	5,88	0	0,00	0	0,00	17	100
Age group												
10 to 14	3	42,86	3	42,86	1	14,29		0,00	0	0,00	7	41,18
15 to 19	6	60,00	4	40,00	0	0,00		0,00	0	0	10	58,82
SYPHILIS												
Deaths	0	0,00	0	0,00	1	50,00	1	50,00	0	0,00	2	100
Age group												
10 to 14	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0	0
15 to 19	0	0,00	0	0,00	1	50,00	1	50,00	0	0,00	2	100
AIDS												
Deaths	99	11,34	215	24,63	382	43,76	135	15,46	42	4,81	873	100
Age group												
10 to 14	18	13,64	40	30,30	45	34,09	23	17,42	6	4,55	132	15,12
15 to 19	81	10,93	175	23,62	337	45,48	112	15,11	36	4,86	741	84,88

4 DISCUSSION

The incidence of sexually transmitted infections (STIs) among adolescents has been increasing over time. It is known that adolescence is a period of physical and organic transformations, associated with the perception of sexual and occupational identity (CHEQUER, et al., 1998). Thus, the objective of this research was to present the prevalence and evolution of cases of sexually transmitted infections in adolescents in Brazil.

Among the STIs analyzed, syphilis is the one that most affects adolescents in Brazil, and the most reported region in this study was the Southeast, which may be related to the fact that it is the most populous region of Brazil and also due to the greater number of notifications in relation to more precarious regions (LAFETÁ, et al., 2016; MARINHO DE SOUZA, et al., 2019; SARACENI, Valéria and FERNANDO MENDES PEREIRA, et al., 2017). In addition, during the COVID-19 pandemic, there was a deficiency in the supply of penicillin in the Unified Health System due to the lack of raw material, which may explain the inadequate or not performed treatment for syphilis (CASTRO, et al., 2020). Even though the Southeast region has a better socioeconomic condition compared to other regions of the country, the situation may have been aggravated by the higher demand for the drug.

Still in relation to the Southeast region, this research identified that it represents the second highest illiteracy rate in the country, with 27.71%. And in relation to schooling, it indicated a higher prevalence in individuals with incomplete high school education, with 19.71%. However, population studies also show that some factors (sociodemographic, incomplete schooling, low income, stable

marital status or not) are higher among Brazilian women, and the average number of sexual partners decreases with increasing schooling (MACÊDO, et al., 2017).

This research also identified that women are the most affected. A study also states that, in Brazil, the number of cases of acquired syphilis in women is higher compared to men (MACÊDO, et al., 2017). This is due to biological issues, such as the extensive exposure of the vaginal mucosa to semen, added to sociocultural and gender issues that establish conditions of inferiority in relation to the opposite sex, also depriving them of the power to decide on sexual activity in a protected way (MOURA, et al., 2022). In addition, females are considered vulnerable to this pathology due to their behaviors in relation to the early onset of sexual life, high number of sexual partners and non-adherence to safe sex practices, by their own choice or that of their partner (MACÊDO, et al., 2017).

This study showed that there was a higher prevalence of cases in the brown race, with 39.39%. This can be explained by the fact that, in Brazil, health indicators based on the race/color variable revealed persistent social inequalities in the country, especially the most vulnerable groups (ARAÚJO, 2009). In addition, the difficulty of access to laboratories and health units, lack of social support, especially from the partner, and unsafe sexual practices may contribute to the increase in the incidence rates of the disease in this portion of the population (LIMA, et al., 2011).

This research revealed that, in Brazil, there is a higher incidence of reported cases of Hepatitis B in females, with 72.54%. Another study conducted in the Amazon region noted that cases were also more frequent in the group of women with positive markers for the B virus (HBsAg and or anti-HBc) (SILVA FILHO, 2010). This is all due to the multiplicity of partners, the non-use of condoms and the commercial practice of sexual activity, which are known factors of association with sexually transmitted diseases. In this same perspective, low family income was also positively correlated with the presence of anti-HBC (SILVA FILHO, 2010).

This study indicated a higher prevalence of hepatitis B cases in the northern region, with 39.58%. This may be related to the fact that this region has a profile with a high incidence of the disease, and that over the years the actions taken to try to control did not reflect in positive results regarding the control of the disease with regard to vaccination and the use of condoms, making its eradication unfeasible (ALMEIDA CE, et al., 2019; ADRIANE CBS, et al., 2015). In addition, another study conducted in the Amazon region showed a high prevalence of HBV, since data point to a rapid circulation of the virus in this region, reaching young individuals in the first years of life, and due to this high prevalence and rapid circulation some areas need more studies (SILVA FILHO, 2010).

Still on hepatitis B, the greatest involvement was in the brown race, with 51.26%, which converges with other studies that also point to the predominance of the brown race, throughout the period, drawing attention to the high percentages of ignored or blank information, which may impair the analysis of this item (MINISTRY OF HEALTH, 2019). This may be related to the ethnic formation

of Brazil, because in the Amazon the presence of pardos is due to miscegenation between whites, blacks and Indians (GONÇALVES, et al., 2019).

Regarding schooling, a greater predominance was identified among the 5th to 8th incomplete grades of PE, with 19.53%. This can be explained by the conditions of socioeconomic vulnerability of the populations, which can propitiate the transmission of the disease (GONÇALVES, et al., 2019). The gender variable showed a higher predominance in males, with 59.98%. This may be related to the context that there was greater notoriety of prevention campaigns for the most relevant groups in the AIDS epidemic: homosexuals, sex workers, women and injecting drug users. Thus, because they are not perceived as a group at risk for HIV infection, heterosexual men end up not receiving prominence in policies or prevention actions. Although the National Policy of Integral Attention to Men's Health, of 2009, encompasses the prevention of HIV, this ends up being a broader theme and that ends up being neglected in practice (SILVA, et al., 2022).

In addition, our study showed that the incidence rate of HIV/AIDS prevails in the Southeast region (36.21%). Other studies confirm these data, giving a highlight to the states of Rio de Janeiro and São Paulo, having an increase between 2010 and 2014 and a decrease between 2015 and 2019, with a peak in 2017 (MARTINS RODRIGUES, et al., 2022). The greater predominance in the Southeast region can be explained by the history of the dispersion of the epidemic in Brazil, by the spread of AIDS from the river-São Paulo axis, which began in large cities and over time spread to small metropolises (BRITO, 2001). The predominance of cases in relation to schooling was in students between the 5th and 8th incomplete grade of PE, with 25.52%. However, studies indicate that a process of inversion of pauperization is occurring, with an increased incidence among people with complete high school education or even higher education. Therefore, according to data from the Ministry of Health (MINISTRY OF HEALTH, 2019), the trend is for the predominance of AIDS in individuals with higher education.

Regarding race, there was a higher number of cases in the brown race, with 31.53%. Studies indicate a higher prevalence in the white race (46.67% in the last 10 years), but this incidence has been decreasing, giving room to the brown race. (MARTINS RODRIGUES et al., 2022). This change is due to the process of increasing cases among the most socioeconomically vulnerable populations, with a consequent increase in the brown race and a reduction in the white race, in both sexes (FRY PH, et al., 2007).

With regard to the weaknesses of the research, we may have underestimated data, since the research does not take into account the fact of having underreporting or unreported cases, both due to socioeconomic factors, which may end up leading to lack of information, and even in relation to the difficulty of access to health.

However, a research related to STI in adolescents in a country with a comprehensive territorial extension is difficult to be carried out in the field, and the data collected in DATASUS allows us to have an overview of the main variables of STIs. In relation to DATASUS, its focus is to bring statistical data from the country's indicators, from the collection, process and even dissemination of information. In addition, it aims to assist the SUS organs, provide support in informatics and in relation to systems necessary for their planning, operation and controls. Therefore, despite the great territoriality of Brazil, this mode of research allows us a better analysis of the health situation in certain territories, as well as the most appropriate action to be taken, making it possible to carry out specific projects in the health area.

To reduce the prevalence of STI in adolescents in Brazil, it is suggested the dissemination of knowledge of the form of transmission and understanding that the use of condoms is indispensable. It is important that the population is aware of what the general clinical manifestations of STIs are like so that they can identify and seek medical help for diagnosis and treatment, for early detection and prevention of complications.

Therefore, it is important to carry out campaigns, especially in schools, in order to spread this information to reach our target audience, which are adolescents from 10 to 19 years old.

In addition, the identification with regard to sex, education, race and age group helps us to identify the most affected groups, and in this way we can promote specific actions for each STI.

It was possible to observe that there is involvement of STIs and the socioeconomic part in the country, so we suggest further research for a better understanding of these variables. Thus, in the context of variables that relate STI with schooling, a field study between state and private schools, comparing them could serve as a parameter for activities to promote and prevent these diseases. In addition, differences can also be better detected between the variables sex and race versus per capita income and type of housing.

In terms of behavioral bias, we suggest further research that relates the prevalence of STI to the behavior of adolescents with an active sex life. For example, sexual orientation, contraceptive methods, condom use, number of partners, knowledge about STIs and their clinical manifestations, and drug use.

Since there has been an increase in the incidence of STI cases in the young public due to resistance to condom use, early initiation of sexual life, use of licit or illicit drugs and misinformation about forms of prevention, there is a need to conduct research related to understanding the sexual behavior of the adolescent public.

5 CONCLUSION

This research identified greater involvement of females in syphilis and hepatitis B, while in HIV there was greater involvement of males. In relation to the region, in the Southeast there was a prevalence of syphilis and HIV and in the North region hepatitis B prevailed. In the context of schooling, incomplete 5th to 8th grade represented the history of STIs hepatitis B and HIV, compared with syphilis that predominated in individuals with incomplete high school. In the scope of race, mulatto prevailed in the three STIs of the study, syphilis, hepatitis B and HIV.

Therefore, it appears that the diseases have an epidemiological profile characterized in relation to sex, in which women are more vulnerable due to the extensive exposure of the vaginal mucosa to semen, sociocultural and gender issues.

Thus, as there is a different epidemiological profile in each region, there is a need to act based on the particularities of each one. For example, in the North and Northeast regions there is a greater lack of access to health due to the high prevalence of cases. While the Southeast region has a greater gap in terms of schooling, with a high illiteracy rate in the country. In the South region, the greatest involvement in relation to STIs was in the white race.

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Influenza A virus: Origin and its subtypes

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ABSTRACT
INTRODUCTION: It is known that flu epidemics arise quite frequently, but there are no regular intervals between these events. Epidemics may differ in their consequences, but they often cause an increase in mortality in elderly people. The great flu epidemic of the last century claimed millions of human lives. Scientist Richard E. Shope, who investigated swine flu in 1920, suspected that the cause of the illness was a virus. As early as 1933, scientists at the National Institute for Medical Research in London isolated the virus for the first time. Thus, the present study seeks to understand how the influenza A virus emerged and was identified. METHOD: Approach used this is a literature review, where research was conducted through scientific articles, published in the MEDLINE and SciELO database, where 4 were selected because they fit the inclusion method. RESULTS and DISCUSSION: The viral etiology of influenza was proven in 1933, and the three serotypes that infect humans were only identified in 1950. In that same year, it became clear that the strain responsible for the 1918-1919 episode belonged to the variety particular antigen of subtype A. In 1957, with the emergence of subtype A, influenza reached China and, in 1968, in Hong Kong, subtype A appeared, causing a moderately severe pandemic. Even after almost a century after the recognition of this strain, the flu virus remains one of the greatest health control challenges due to its easy antigenic variability and contagiousness. FINAL CONSIDERATIONS: For the formation of new subtypes, there is recombination, which corresponds to a mixture of, for example, genes from a virus that infects human beings with genes from viruses that infect other animals, such as birds, thus explaining how the retrovirus Influenza type A can become more aggressive due to mutations derived from the mixture of genes from animal viruses, especially birds and swine.

Keywords: Virus, Influenza, The flu.

1 INTRODUCTION

The first description of influenza, also known as Influenza, the Italian word for "influence", in the context of medicine and epidemiology, before the microbial theory, was made by Hippocrates, in the fifth century, year 412 BC who described the disease among the inhabitants of the island of Crete, in Greece; and, attributed the disease to environmental causes and climatic variations, Within the miasmatic theory, influence of the stars and the air.

However, the first medical description with interesting observations is attributed to the physician Molineux in Ireland and England between 1688 and 1693. References to seventeenth-century influenza epidemics are found in North America and Europe. From the beginning of the eighteenth century, data on the disease increased in quantity and quality, as chroniclers and doctors

recorded information and comments on the number of people infected, whether epidemic or pandemic, the countries involved and the possible origins of viral strains.

From the genus Mixovirus influenzae, it belongs to the family Orthomixoviridae, which contains a segmented RNA genome and single strand. It is classified into 03 types: A, B, and C and its isolations occurred in the years 1933, 1940 and 1947, respectively. The type A virus, the most important, can infect both humans and animals and is implicated in episodes epidemic and pandemic; the type B virus, which infects only humans, is linked to moderate outbreaks; and the C virus, more stable, affects humans and pigs, causes subclinical disease, without epidemic potential. According to FORLEO NETO et al (2003), pandemics occur irregularly, usually 30 to 40 years apart. Since the century. At least 30 pandemic episodes have been described.

Due to its ability to penetrate the body through the mucous membranes of the respiratory tract and eyes performing its dissemination through the bloodstream and reach the cells, subtype A presents mutations and rearrangements with higher frequencies in relation to subtypes B and C. That subtype has two surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA) that enable the transport of the virus in the host cells. The function of HA is the fixation and fusion of the virus in the host cell, and is divided into 18 different subtypes, of which 16 circulate in waterfowl and two were isolated from bats. NA subtypes play an important role in the release of viral particles after virus replication, as well as the spread of the virus from one host to another. These proteins are responsible for the viral classification and its morbidity, mortality, lethality and pathogenicity.

The present work aims to carry out a historical approach to the origin and knowledge of the influenza A virus as well as its subtypes, in order to highlight its main occurrences in the world.

2 METHOD

The study is characterized as a bibliographic study of systematic review of the specialized literature, carried out through scientific research available in the database of MEDLINE (Medical Literature Analysis and Retrieval System Online) and SciELO (Scientific Electronic Library Online) using the keywords: Virus, influenza and influenza. Articles or theses published between 2000 and 2016 were used as inclusion methods, since these were the most recent containing relevant information for the study, with texts available in full in the aforementioned databases.

3 RESULTS AND DISCUSSION

In 2009, the world faced its first influenza pandemic of the twenty-first century, caused by the influenza A/H1N1/California/2009 strain that contains swine, poultry and human genes. Popularly known as "swine flu", swine influenza A had its first cases in Mexico in March 2009 and due to its high contagiousness and virulence spread rapidly to Europe, Canada, Southeast Asia, Africa and Latin

America. In June 2009, the World Health Organization officially declared a flu pandemic. In the post-pandemic period that lasted until August 2010, it had reached 214 infected countries, causing death of 18,500 people and infection of 575,400. (The Lancet Infectious Diseases, 2012).

In March 2013, a new strain of the influenza A virus was described in Asian countries. This strain has the proteins hemagglutinin serotype 7 and neuraminidase serotype 9, and is therefore called influenza A (H7N9). This new variant is a recombination of strains circulating among birds that has been shown to infect humans and, as cases outside the Asian continent have not yet been described, classifying the epidemic as geographically restricted.

Among the communities, influenza epidemics and pandemics begin abruptly and peak in two or three weeks, with a total duration of 5 to 8 weeks. The impact of influenza epidemics is a reflection of the interaction between viral antigenic variation, the level of protection of the population for circulating strains, and the degree of virulence of viruses. Minor antigenic variations occur every two or three years for subtypes of virus A and every 5 or 6 years for viruses of type B. Such variations are due to point mutations in segments of the viral genome that result in changes in the amino acids that make up surface glycoproteins, particularly in hemagglutinin. The largest antigenic variations are those associated with the complete replacement of one or both segments of the viral genome, which control the production of surface glycoproteins.

> The challenge is, for WHO screening, to correctly predict or detect emerging strains at an early stage, because due to the 6 or more months required to prepare a vaccine, there is a possibility that to date a vaccine is manufactured to support a global campaign, it is no longer compatible with circulating viruses. Any vaccination approach that targets the classic neutralizing responses to HA and/or NA must deal with antigenic drift effectively. (KIM et al., 2018)

The worst epidemic of the influenza virus occurred in the early twentieth century, between the years 1918 and 1920, still with dubious origin, began in Asia or in the military camps in the interior of the United States of America, due to the intense movement of troop transport of allied nations and, had as a biological agent causing the disease was identified as the virus of type A (H1-N1). The Spanish designation is given by the fact that Spain, neutral in World War 1, made official notification to the World Health Organization about the disease that devastated lives in the country with great power of contagion, morbidity and lethality. In Brazil, for example, although the number of infected and dead are variable, it is estimated that 35,240 people were fatal victims of the virus, among them the 5th president of Brazil, the lawyer and Counselor of the Empire, Mr. Francisco de Paula Rodrigues Alves. This disease was introduced into the country by crew members of the English ship "Demerara" that left Liverpool, England, docked and disembarked passengers in the ports of Recife, Salvador and Rio de Janeiro.

> This pandemic was marked by extreme scope, aggressiveness and contagiousness, believed to have killed 38 million people in Europe and America. Although in many parts of the world there is no data, it is estimated that it has infected 50% of the world's population, 25% have suffered a clinical infection and the total mortality has been between 40 and 50 million. The number of 20 million deaths, often cited, is noticeably very low (Costa, L et al., Influenza Pandemics).

Again on the Asian continent, this time originating in China during the 50s, the Influenza A/Singapore/1/57 (H2N2) virus, with the glycoproteins HA and NA different from all the previous types, led to the death of 4 million people affecting about 25% to 50% of the world's population. The virus was first isolated in Japan in 1957, followed by the United States and England in the same year. Years later, during 1968 and 1969, a genetic variation of H2N2, H3N2 gave rise to the Hong Kong Flu, whose virus was identified and isolated in this Chinese city in 1968, with a higher incidence of 40% in the population aged 10 to 14 years, and hospitalization and mortality among the elderly, young people and individuals at defined risk for chronic and cardiopulmonary diseases.

In 1930, researchers began the development of the flu vaccine in order to find a solution containing the damage caused by the influenza virus. After 10 years, in 1940, the first influenza vaccine was approved in the northern hemisphere, while in Brazil, the applications began 40 years later, in 1980, being composed of different strains of the Myxovirus influenza virus and inactivated, fragmented and purified and, usually containing elements of the surface of the virus, such as hemagglutinin and neuraminidase, being an inactivated vaccine, that does not cause the disease and provides protection based on the induction of the production of neutralizing antibodies of the virus, mainly against the viral hemagglutinin contained in the vaccine. The immunity conferred by the vaccine develops after 15 days of vaccination and its duration is about 6 months to 1 year. As the maximum titers of antibodies, obtained within 1 to 2 months after vaccination. Currently, there are four brands of the tetravalent influenza vaccine available: Fluarix Tetra (GSK), Fluquadri (Sanofi-Pasteur), Influvac Tetra (Abbott) and Vaxitetra (Sanofi-Pasteur).

4 CONCLUSIONS

The retrovirus Influenza type A may acquire greater aggressiveness due to mutations derived from the mixture of genes of viruses of animals, especially poultry and pigs. In order for new subtypes to form, recombination occurs, which corresponds to the mixing of, for example, genes from a virus that infects humans with genes from viruses that infect other animals, such as birds. The severity of the infection is attenuating as the population is immunized, either by vaccines or by the flu clinic itself.

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Dysplastic barrett's esophagus: Surveillance, treatment and follow-up – A systematic horizontal review

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ABSTRACT

INTRODUCTION: Gastroesophageal reflux disease (GERD) is important due to its recurrence, being the main reason for consultations and with prevalence higher than 25% in Asia and Southeast Europe. The most feared complication of GERD is esophageal adenocarcinoma (ECA), preceded by Barrett's esophagus (EB), defined as the replacement of the stratified squamous epithelium with an abnormal columnar epithelium with intestinal characteristics. The epidemiology still remains unknown due to the low specificity of the symptoms and the lack of consensus on the endoscopic characteristics for its diagnosis. In the dysplastic forms of EB with more chance of progression to ACE, there are few studies and better conducts in relation to dysplastic EB. OBJECTIVE: to clarify controversies about the conduct of dysplastic EB. METHOD: horizontal review, PRISMA method through electronic search in PubMed, between 2018 and 2022, with descriptors: "Barrett's Esophagus" and "Surveillance AND dysplasia AND esophagus" for all age groups. Inclusion: articles in English, with compatible titles and abstracts. We obtained 620 results and after selection 17 articles were included. RESULTS: 13 articles indicate the Seattle Protocol for diagnosis and surveillance; 5, anti-reflux therapy before endoscopy and 12, confirmation of dysplasia by a specialized pathologist. Follow-up low-grade dysplasia (GBD): radiofrequency ablation therapy (ART) and surveillance are feasible in 13 articles, with ART preferred in 8 and surveillance in 4. High-grade dysplasia (DAG) follow-up: endoscopic therapies recommended in 12 articles. Follow-up after dysplastic eradication: periodic and continuous endoscopic surveillance indicated in 9 articles and treatment with proton pump inhibitors in 2 articles. DISCUSSION: Although the Seattle Protocol is recommended for surveillance, it covers a small part of the esophageal mucosa, besides being time-consuming and having low adherence. Controversies persist about the management of BPD, but, in general, ablation is recommended to the detriment of surveillance. There is consensus on endoscopic ablation therapy until complete eradication of DAG. Esophagectomy is not recommended. After eradication, continuous surveillance and proton pump inhibitors. CONCLUSION: Disagreements persist due to discrepancies between studies, especially in low-grade dysplastic EB.

Keywords: Barrett's Esophagus, Gastrointestinal Endoscopy, Follow-up Care.

LIST OF ABBREVIATIONS AND ACRONYMS

GERD: gastroesophageal reflux disease
ACE: esophageal adenocarcinoma
EB: Barrett's esophagus
DBG: low-grade dysplasia
DAG: high-grade dysplasia
ART: radiofrequency ablation therapy
TEE: endoscopic eradication therapy
AGA: American Gastroenterological Association
ACG: American College of Gastroenterology

ESGE: European Society of Gastrointestinal Endoscopy
BSG: British Society of Gastroenterology
ASGE: American Society of Gastrointestinal Endoscopy

1 INTRODUCTION

Gastroesophageal reflux is a physiological mechanism, in which gastric contents move spontaneously toward the esophagus.[1] However, this condition becomes pathological when it manifests itself with uncomfortable symptoms or complications in order to configure gastroesophageal reflux disease (GERD).[2]

In large part, the importance of this pathology is due to its recurrence. In the United States, it is the main reason for outpatient visits, accounting for about 4% of visits in primary care3, while globally, it is estimated that the prevalence is higher than 25% in South Asia, Southeast Europe and less than 10% in Southeast Asia, Canada and France.[1]

The pathogenesis of GERD is complex and multifactorial, but in general, it involves the imbalance between aggressor and defensive factors to the esophagus. Defensive factors involve gastric acidity, the volume of gastric acid secreted and the elimination of duodenal contents, since constipation can lead to gastric stasis. Defensive factors involve the anti-reflux barrier, acid clearance in the esophagus and mucosal resistance to recurrent chemical aggressions4.

The anti-reflux barrier depends on the proper functioning of the lower esophageal sphincter (LES) and the crural diaphragm4 in order to prevent the passage of gastric contents to the esophagus. However, relaxations of the LES, therefore, openings of this barrier, may occur routinely associated or not with swallowing. When they are not associated with swallowing, they are considered as transient relaxations that last longer periods than those induced by swallowing, causing up to 90% of reflux events in healthy individuals or those with GERD.[5] In addition, after these events, it is known that acid clearance begins with peristalsis, which assists in the mechanical return of the refluxed structures to their physiological direction. Together, the additional tamponade from saliva swallowing also helps in this clearance, neutralizing the esophageal pH 4,3 ·

Likewise, factors that lead to increased intragastric pressure such as obesity, pregnancy and relaxation of the stomach after increased gastric volume have a clear relationship with the pathophysiology of the disease. This is true because the reflux of gastric contents from the stomach to the esophagus is determined by the pressure gradient between the abdomen and the chest, so the increase in intra-abdominal pressure increases the tension in the anti-reflux barrier, impairing one of the main protective factors of the esophagus.[5.6]

As for the clinic, GERD classically manifests itself with symptoms of heartburn and regurgitation, which are usually referred to by patients as a burning sensation in the retrosternal region, which radiates to the neck, throat and occasionally to the back. These symptoms occur in the

postprandial period and are usually more pronounced after fatty or spicy meals and after alcohol intake. [2.7.] Other symptoms may include nausea, dyspepsia, sore throat, epigastric pain, and a feeling of bloating.[7]

In addition, it is possible that GERD manifests with atypical symptoms, so it should be considered as a differential diagnosis in cases where other diagnoses have already been excluded by a specialist.[8] Thus, even if symptomatic, this disease presents a difficult diagnosis, since it is made through the combination of clinical symptoms, response to acid suppression, esophageal pH monitoring and upper digestive endoscopy, although the latter is not essential for the diagnosis.[8.2]

On the other hand, studies with the European population showed that about 46% of the patients were asymptomatic, a fact that poses a problem, since the diagnosis can be made only when the complications of GERD are already installed, since the course of the disease had minimal or absent symptoms.[2]

It is known that the most feared of these complications, adenocarcinoma of the esophagus (ACE), is preceded by an intestinal metaplasia of the esophagus called Barrett's esophagus (EB).[9] By definition, metaplasia is a reversible alteration, in which a differentiated cell type is replaced by another differentiated cell type of the same lineage and which is often better able to withstand the adverse environment to which the epithelium is being exposed.[10] Thus, EB occurs when the stratified squamous epithelium, which normally lines the distal esophagus, is replaced by an abnormal columnar epithelium, which has intestinal characteristics.[11.12]

This substitution makes the affected site more predisposed to malignancy with such intensity that patients with EB have 55 times more risk of developing ACE.[11] In this situation, the prognosis tends to be poor with 5 years of survival estimated in 10 to 15% of cases.[13th]

Thus, EB is a serious public health problem, especially when considering current epidemiological data. Globally, its prevalence has increased dramatically in recent decades with an estimated range of 0.7 to 5.6%, whereas currently the estimated annual incidence in the general population is 1 to 2%.[13] Corroborating this worldwide increase, the prevalence of this disease has also increased among the Asian population, even though EB predominantly affects white men between 40 and 60 years of age.[14.15]

Despite these data, the epidemiology remains largely unknown mainly because many individuals with EB are asymptomatic or manifest insensitive and non-specific symptoms generally similar to those related to GERD. However, not every individual who develops EB necessarily needs to have had GERD beforehand.[16] Consequently, for this reason, these patients are not correctly diagnosed.[17th]

Considering the low specificity and low sensitivity of the symptoms, for the diagnosis it is important to consider the risk factors to which this patient was exposed during his life. Thus, because

it is a multifactorial disease related to GERD, we should consider similar risk factors. Therefore, obesity, alcohol consumption and smoking are characteristics that should be alerted to the health professional as possible triggers for the progression of the disease.[11th]

However, to be confirmed, the diagnosis of EB requires complementary tests. Among them, the main one is endoscopy with confirmation by biopsy.[18.19]

However, in addition to the clinical factor, the lack of a consensus on the endoscopic characteristics for the definition of the diagnosis poses another challenge for the accurate diagnosis of patients. Although the Prague classification of 2006 has improved the assertiveness of the diagnosis, renowned societies around the world continue to follow their own criteria. For example, the American Gastroenterological Association (AGA) defines EB as any extension of intestinal metaplasia, while the British Society (BSG) defines it as any columnar metaplasia lining the distal esophagus with a minimum length of 1 cm. On the other hand, the American College of Gastroenterology (ACG) defines EB as an intestinal metaplasia that lines the distal esophagus with a minimum length of 1 cm.[19,20] Thus, to elucidate such controversies, the criteria recommended by each guideline for the definition of the diagnosis of EB are shown in Table 1.

Table 1 - Criteria accepted by each guideline for the definition of the diagnosis of Barrett's Esophagus.

GUIDELINE	EXTENSION CRITERIA	HISTOLOGICAL CRITERIA
AGA	Any extension	Intestinal metaplasia
Australian Society	Any extension	Intestinal metaplasia
Japanese Society	Any extension	Columnar metaplasia with or without intestinal metaplasia
ACG	Minimum 1cm extension	Intestinal metaplasia
ESGE	Minimum 1cm extension	Intestinal metaplasia
BSG	Minimum 1cm extension	Columnar metaplasia
Asia-Pacific Consensus	Minimum 1cm extension	Columnar metaplasia
ASGE	Does not define extension criteria	Intestinal metaplasia

Source: Marquis of Sá et. al,202019; Koike et. al., 202220

Likewise, regarding treatment and follow-up, there is no agreement between the recommendations of world-renowned societies. Therefore, more studies are needed to validate the best approaches for these patients until a consensus is reached.[18th]

It is also important to note that Barrett's Esophagus can present itself in multiple ways according to its evolution and severity. Therefore, it can manifest itself in a non-dysplastic form or in

a dysplastic form. Among these presentations, dysplasias are the most serious, because before the neoplastic cells become malignant, some of the same genetic and epigenetic changes that confer malignancy can cause the dysplasias.[15th]

As a rule, a dysplasia can be seen as the expression of a disordered growth, and according to the degree of histological abnormalities can be classified as low-grade or high-grade dysplasia.[15.21.] Also, there may be cases in which dysplasia is classified as undefined, and approximately 4.3 to 8.4% of EB biopsies are diagnosed as undefined.[22nd]

The study of dysplastic forms of EB is important, since it is estimated that the progression of these forms to esophageal adenocarcinoma is greater than in non-dysplastic forms. While the risk of progression from non-dysplastic EB to ACE is estimated at 0.3%, the risk of progression from low-grade dysplasia (DBG) to ACE is estimated to be 0.5% per year and 6.6% per year in the case of high-grade dysplasia.[22nd]

In view of this, it is essential that guidelines are established for early detection, treatment and follow-up of these dysplasias in order to improve patient survival and prevent deaths from esophageal cancer.[12] However, just as there is no consensus on these guidelines for EB in general, there are also no well-defined guidelines when it comes to dysplastic EB.[19th]

Considering this panorama, research that deepens the clarification of the best conducts in the face of dysplastic EB becomes important in order to direct medical practice according to the most recent evidence.

2 OBJECTIVE

The objective of this research is to elucidate the controversies related to the management of dysplastic EB through the analysis of the consensus and divergences of the guidelines recommended by the most influential world organizations in this subject to direct medical conduct according to the most current scientific evidence.

3 METHOD

This systematic review was carried out according to the *Checklist* PRISM.

3.1 RESEARCH IN THE LITERATURE

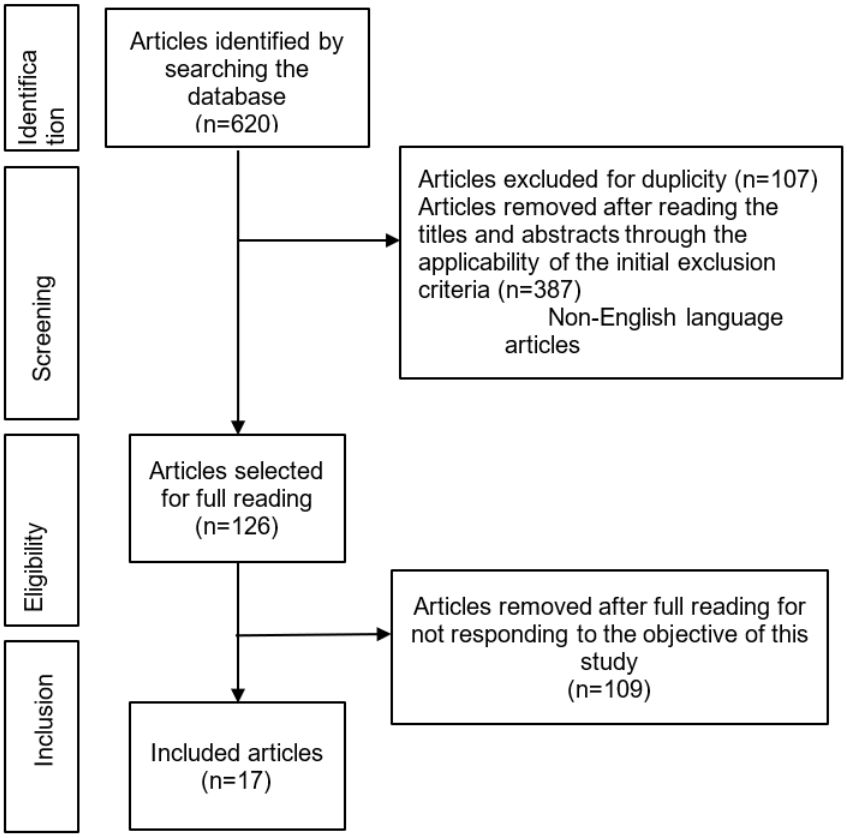
An advanced electronic search was conducted in the PubMed database for systematic reviews published between 2018 and 2022 using initially the descriptors "Barrett's Esophagus" and later using the descriptors "Surveillance AND dysplasia AND esophagus" in all age groups. This search was conducted between September and November 2022; articles eligible up to this period were considered for inclusion.

3.2 DATA SELECTION AND EXTRACTION

Two independent reviewers identified studies for inclusion and analyzed the selected articles and discrepancies were resolved by discussion. The selection process of this study is illustrated in Figure 1.

First, the titles and abstracts were revised to include only articles published in the last 5 years and to exclude manuscripts that were published in non-English journals, any study model that did not stand as a review and that did not address the surveillance of dysplastic lesions. The remaining full articles were evaluated for eligibility and excluded if they did not fit the questions to be answered by this research.

Figure 1 - Selection process according to the *PRISMA* checklist.



4 RESULT

The results found in the studies included in this systematic review are shown in Table 2.

Table 2 - Studies included in this systematic review.

1st AUTHOR (YEAR)	DIAGNOSIS OF DYSPLASTIC LESIONS	LOW-GRADE DYSPLASIA	HIGH-GRADE DYSPLASIA	SURVEILLANCE AFTER ERADICATION
Nabeeha Mohy-ud-din, MD (2019)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - Surveillance biopsies should only be obtained after resolution of active esophageal inflammation or in cases of esophagitis previously treated with anti-reflux therapy. - There is a direct relationship between the time interval between endoscopic examinations for surveillance and the detection of dysplasia.	- 1st line: ablation therapy - 2nd line: annual surveillance from 4-quadrant biopsies with 1 cm intervals. If two consecutive tests are negative for dysplasia, surveillance should be performed from 4-quadrant biopsies with 2 cm intervals at intervals of 3 to 5 years.	- 1st line: TAR every 2-3 months	- Complete eradication of intestinal metaplasia and dysplasia is confirmed after two negative biopsies. - Typically, ART sessions are repeated every 2-3 months until complete eradication. - After eradication, patients should follow a regular surveillance schedule. - There is no evidence to support stopping surveillance.
Michelle Clermont (2018)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - Recommended use of a high-quality endoscopic technique with white light.	- 1st line: TAR - 2nd line: surveillance from 4-quadrant biopsies with 1 cm intervals.	- 1st line: endoscopic ablative therapy.	- does not address surveillance after eradication.
Prateek Sharma (2019)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology.	- Endoscopic therapy and continuous surveillance are reasonable options for management. - 1st line: periodic surveillance in the range of 6 to 12 months. - Patients with confirmed DBG should repeat endoscopic examination with high-definition white light in 3 to 6 months to rule out visible lesion that should	- 1st line: endoscopic therapy.	- After DBG eradication, the ACG recommends surveillance in 1 and 3 years. - After the eradication of DAG, the ACG recommends surveillance every 3 months during the first year, every 6 months during the second year, and annually from the third year. - Evaluations should be made from high-definition white-light endoscopy and should

		receive immediate resection. - Esophagectomy not recommended.		include careful inspection of the neosquamous mucosa and retroflex inspection of the gastric cardia.
Vedha Sanghi (2019)	- Use of the Seattle Protocol recommended. - Confirmation of dysplasia by a pathologist who specializes in gastrointestinal pathology is recommended.	- This study does not draw its own conclusions about DBG.	- This study does not draw its own conclusions about DAG	- Discontinuing the investigation is not recommended even after multiple negative tests.
M Harrison (2018)	- The use of the Seattle Protocol is recommended.	- Radiofrequency ablation therapy and surveillance are possible treatment alternatives for DBG.	- doesn't address DAG.	- does not address surveillance after eradication.
John J. McGoran (2020)	- The use of the Seattle protocol is recommended. - At least one minute should be used for inspection of each centimeter of Barrett's mucosa, focusing on the right wall and proximal segment.	- Endoscopic eradication therapy and surveillance are viable treatment options. - In the face of any abnormality seen on surveillance examination, endoscopic mucosal resection should be performed. - On occasions when GBD is detected without the presence of injury, a careful multidisciplinary discussion on the merits and risks of the intervention is recommended.	- Endoscopic eradication therapy (TEE) is more cost-effective and eliminates the need for esophagectomy. - TEE is recommended at 3-month intervals until complete eradication of intestinal metaplasia.	- ART is effective for treating residual intestinal metaplasia and should begin 2 to 3 months after focal mucosal resection and performed every 3 months until no areas of EB are identified. - After eradication, endoscopic surveillance should be done. - Endoscopic surveillance should be done 1 to 3 years after endoscopic eradication therapy for DBG. - Endoscopic surveillance should be done 3.6 and 12 months later after endoscopic eradication therapy for DAG. - New lesions should be submitted to endoscopic resection and ablation of the columnar mucosa.
Kevin Kyung Ho Choi (2022)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - In the West, endoscopic surveillance every 2 to 5 years is recommended for EB patients for early detection of	- Surveillance program in a health center specialized in EB. - Endoscopic eradication therapy may be offered as a treatment. - The benefit of ART is related to aggressive protocols - In patients under	- Refer patient to a referral center in EB to repeat endoscopy in 4 weeks. - All visible lesions should be treated with endoscopic mucosal eradication, followed by sequential sessions	- does not address surveillance after eradication.

	adenocarcinoma.	surveillance by specialists, any progression to AGD or cancer can be detected early. - Adverse events following radiofrequency ablation therapy occur in about 10% of cases, but are rarely severe.	of radiofrequency ablation therapy until complete eradication of metaplasia. - DAG without visible lesions can be treated only with radiofrequency ablation therapy. - Surgery should not be offered.	
Tomoyuki Koike (2022)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - In the West, endoscopic surveillance every 2 to 5 years is recommended in EB patients for early detection of adenocarcinoma. - Recommended Seattle protocol. - In Japan, surveillance methods for EB have not been established and targeted biopsies only on suspicious lesions are commonly done.	- does not address DBG	- doesn't address DAG.	- does not address surveillance after eradication.
Jia Di (2020)	- It does not draw its own conclusions about the diagnosis.	- Recommended surveillance with an interval of 6 months.	- Endoscopic ablation resection recommended.	- does not address surveillance after eradication.
Fouad Otaki (2018)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - In the West, endoscopic surveillance every 2 to 5 years is recommended for EB patients for early detection of adenocarcinoma.	- It doesn't draw its own conclusions about DBG.	- Endoscopic surveillance is only recommended when there is AGD in patients with limited life expectancy and should be discontinued when life expectancy is less than 5 years.	- does not address surveillance after eradication.
Spyridon Michopoulos (2018)	- The investigation of EB in the general population is not cost-effective. - Screening of target populations recommended, but this approach has a low level of scientific evidence.	- When histology is undefined for dysplasia, the GCA recommends intense anti-reflux therapy with double-dose proton pump inhibitors to minimize inflammation and repeat endoscopy	- There is less discrepancy among pathologists as to histological diagnosis. - Confirmation of DAG by a second pathologist specializing in DAG is required.	- does not address surveillance after eradication.

		according to the Seattle protocol. - If after the second endoscopy, the degree of dysplasia remains the same, most guidelines advocate performing a new endoscopy in 6 months, reevaluation of the biopsies by a pathologist specializing in EB pathology. - Follow-up with biopsies every 1 cm once a year. - There is a great discrepancy among pathologists regarding the definition of DBG.	- Visible lesions should be resected with endoscopic mucosal resection. - Flat lesions with no visible abnormalities should be treated with ablative methods, usually radiofrequency ablation therapy is the method of choice. - Other ablative methods such as cryoablation or coagulation with hybrid argon plasma are less evaluated, but may play an important role in the future. - If after radiofrequency ablation therapy EB lesions remain, the use of argon plasma coagulation may be considered. - It is still debatable whether endoscopic submucosal resection is preferable in cases of large lesions.	
Aamir N. Dam (2020)	- Diagnostic confirmation required by a pathologist specialized in gastrointestinal pathology. - Endoscopic surveillance should use high-definition white light. - Any abnormality found in the mucosa should be submitted to endoscopic mucosal resection. - If no abnormalities are visualized, surveillance should be performed according to the Seattle protocol.	- 1st line: TEE - Surveillance is an acceptable option.	- 1st line: TEE.	- Follow-up after eradication consists of the collection of biopsies of 4 quadrants every 1 c along the original dysplastic segment and gastric cardia. - Most recurrences are detected in the distal 2cm of the esophagus. - Recurrences are treated similarly to initial treatment involving mucosal resection and ablative modalities. - Anti-reflux therapy may be associated for symptom control.
Inês Marques de Sá (2020)	- High-quality endoscopy recommended.	- The surveillance interval differs between guidelines in that they are based on	- For AGD without visible lesion, most guidelines recommend repeat	- Recommended surveillance after endoscopic treatment.

		expert opinion and the low quality of scientific evidence.	high-quality endoscopy to look for abnormalities. - If no visible lesions are found, ablation therapy is proposed by all guidelines except ESGE which proposes repeating the Seattle protocol and repeating endoscopy in 3 months and, if DAG is confirmed, ablation is recommended.	
Andrew M. Bellizzi (2018)	- The use of the Seattle Protocol is recommended - Recommended high-quality endoscopy	- This study does not draw its own conclusions about DBG.	- This study does not draw its own conclusions about DAG.	- Patients should be kept under surveillance after endoscopic eradication of EB.
Tavankit Singh, MD (2019)	- Two pathologists are needed, one of whom must be a specialist in gastrointestinal pathology. - Patient education is essential before surveillance.	- Surveillance with random biopsies of 4 quadrants every 1 cm if history and biopsy of any mucosal irregularity. - Patients with DBG who do not undergo eradication therapy should undergo endoscopy every 6-12 months.	- It is critical that maximum acid suppression is performed with a proton pump inhibitor twice daily and a histamine-2 blocker at night. - The current treatment of choice is endoscopic mucosal resection of elevated lesions for patients without severe comorbidities, followed by radiofrequency ablation of the entire affected segment. Alternatively, surveillance every 3 months can be done.	- After eradication, continued surveillance and prolonged treatment with PPIs are required. - Surveillance endoscopy involves 4-quadrant biopsies taken every 1 cm of the entire length of the segment where EB was seen prior to ablation. - The time of surveillance interval depends on the degree of pre-ablation dysplasia. - DBG: surveillance every 6 months in the first year after ablation and annually after this period if there is no recurrence. - DAG: surveillance every 3 months in the first year, 6 months in the second year and annually from the third year.
Francesco Maione (2022)	- Required use of high-quality technique for diagnostic confirmation.	- There is currently no consensus on the management of DBG. - Ablation methods are the most commonly used for flat dysplastic EB. - Endoscopic surveillance is	- It doesn't address DAG surveillance.	- does not address surveillance after eradication.

		recommended in patients not undergoing endoscopic treatment.		
Ishaan Maitra (2020)	- The gold standard method for screening is visual inspection and biopsies of mucosal irregularities according to the Seattle Protocol. - EB should be considered if a paceintis with GERD has risk factors such as advanced age, male gender, long-term history of reflux, increased frequency of esophagitis symptoms, anterior hiatal hernia, esophageal stenosis, or esophageal ulcers. - Endoscopy should be performed in patients with controlled reflux symptoms for better diagnostic accuracy. - Findings such as inflammation and ulceration considered undefined for dysplasia may be results of erosive esophagitis. Because of this, acid suppression should be offered and a new endoscopy should be performed in 6 months.	- If a histological finding of AGD is found, a new endoscopy should be performed in 6 months. - In case of diagnostic confirmation, it should be discussed which is the best treatment to follow: endoscopic surveillance (every 6 months for 2 years and then annually) or eradication therapy. - The absolute benefit of eradication therapy is not certain as the rate of progression from DBG to ACE is low. - Among the eradication therapies, the most used is radiofrequency ablation therapy. - Initial ablation has been shown to be more cost-effective than intensive surveillance.	- The ideal is to refer the patient to a specialized center in EB for endoscopic mucosal resection and eradication therapy.	- Continued vigilance recommended. - There are no long-term data on the recurrence of intestinal metaplasia or dysplastic changes in the squamous epithelium.

5 DISCUSSION

5.1 SURVEILLANCE OF DYSPLASTIC LESIONS IN BARRETT'S ESOPHAGUS

As for the definition, all current guidelines agree that for Barrett's esophagus to be characterized, there must be the presence of columnar mucosa in the esophagus instead of the squamous epithelium.[18,23] However, there is no consensus regarding the extent of this alteration for the diagnosis to be made accurately. The BSG, ACG and ESGE consider that it is necessary to have at least 1 cm of columnar mucosa extension above the proximal gastric fold, while the Japanese Society, the AGA and the Australian guideline have not determined minimum length for this definition. Finally, the ASGE does not cite criteria for the extent of the change.[18.24]

Based on these considerations based on metaplastic extension, the Prague criteria were created in order to standardize the endoscopic report of the extent of esophageal epithelial metaplasia from the

circumferential extension and maximum extension visualized.[18,23,25,26] In this analysis, at least one minute should be used for the inspection of each centimeter of Barrett's mucosa, with a particular focus on the right wall and proximal segment.[24th]

These definitions are important, because from the moment that the metaplastic cell development changes, becoming a dysplasia, this should be identified early from the routine surveillance to which these patients diagnosed with EB must be submitted.

Thus, the main function of any surveillance program is the early detection of dysplasia so that treatment is properly implemented.[23,24,25,26,27] Currently, the guidelines recommend that surveillance be performed through endoscopic examinations performed in certain periods of time. Such a disposition is important, because there is a direct relationship between the period of the examination and the detection of dysplasia, so that a complete evaluation of the mucosa and regular evaluation of the mucosa is essential for effective surveillance.[24.27]

To optimize this evaluation, all guidelines recommend the use of the Seattle Protocol, which consists of the biopsy of four quadrants obtained every 2 cm for patients without dysplasia and every 1 cm for patients with previous dysplasia. [24,25,30,31]

However, this protocol has some challenges. One is that surveillance from random biopsies shows only a small proportion of the mucosa of Barrett's Esophagus. In addition, it is a tedious and time-consuming protocol, which hinders the adherence of patients, especially those who have longer segments affected and that, therefore, the risk of progression to other prevalent cancers is higher. Thus, it has been shown that low adherence is associated with lower rates of dysplasia detection.[32nd]

Importantly, surveillance biopsies should only be obtained after resolution of an active esophageal inflammation or in cases of esophagitis previously treated with anti-reflux therapy. This is recommended because inflammation can cause the pathologist to confuse regenerative changes with the dysplasia itself, leading to misdiagnosis.[20,23,26,27,33]

Another consensus among international guidelines is that any visible dysplastic lesion, whether low-grade or high-grade, should be diagnosed by at least two pathologists, one of whom should be a specialist in gastrointestinal pathology and use a high-quality endoscopic technique to confirm the diagnosis.[13,18,20,26,27,31,33,34] This recommendation was established in order to minimize the chances of misdiagnosis, since low-grade dysplasia can often be confused with non-dysplastic EB even among experienced pathologists.[27.35]

Still, for diagnostic confirmation, the British Society of Gastroenterology (BSG), the European Society of Gastrointestinal Endoscopy (ESGE) and the Australian guideline recommend repeating the same endoscopic evaluation at 6 months.[18,23,28,30]

In particular, the American societies of the American Gastroenterological Association (AGA), the American Society of Gastrointestinal Endoscopy (ASGE), and the American College of

Gastroenterology (ACG) recommend, in addition to the consensus criteria, the use of proton pump inhibitors before the second endoscopy, with performance recommended in the interval of 8-12 weeks by AGA.[19.25]

5.2 LOW-GRADE DYSPLASIA

As for low-grade dysplasia (GBD), there are still some controversies among the guidelines regarding its approach. However, two treatments can be used for this: radiofrequency ablation therapy and endoscopic surveillance.

But first of all, it is important to emphasize that to allow informed decision-making between the doctor and the patient, before choosing the approach to this disease, patients should be informed about the risks of developing cancer in the absence of endoscopic therapy and these risks after its realization. In addition, they should be clarified about the benefits and limitations of each choice, as well as the importance of adherence to the chosen treatment.[13,25,30]

Radiofrequency ablation therapy involves the delivery of high-frequency currents to the tissue so that the heat generated results in the denaturation of the proteins and therefore in local cell death.[27] This technique stands as one of the main treatments, as it has been shown to have better effects in reducing the progression to high-grade dysplasia and has led to the eradication of intestinal dysplasia and metaplasia in a significant number of patients.[27] For these reasons, all guidelines recommend ablation over surveillance, with the exception of the AGA, the Australian guideline, and the Asia-Pacific Consensus.[19,23,28]

The randomized "SURF" study compared the efficacy of radiofrequency ablation therapy with that of endoscopic surveillance in 136 patients with DBG previously confirmed by three pathologists. As a result, this research showed that ablation decreased the risks of progression to high-grade dysplasia (DAG) and adenocarcinoma of the esophagus (ACE) by 25%, while surveillance decreased the risks by only 8.8% in the control arm over a 3-year follow-up period.[23,24,25,33,34] Similarly, the prospective randomized trial "*AIM DYSPLASIA*" demonstrated that ablation was associated with a higher rate of DBG eradication, as well as a decreased risk of progression from DBG to DAG/ACE. Therefore, the risk of progression was assessed at only 5% for follow-up with ablation at 14% with surveillance over the 12-month period.[25,33]

Based on such evidence, the ACG, the British Society of Gastroenterology (BSG), the European Society of Gastrointestinal Endoscopy (ESGE), the American Society of Gastrointestinal Endoscopy (ASGE) recommend ablation therapy for confirmed cases of DBG. However, the annual surveillance recommended by the ACG and ASGE and the surveillance every 6 months recommended by the BSG would only be an alternative management for those patients in whom the risks may be greater than the benefits.[26,27,30,35]

Despite all recommendations indicating ablative therapy as the best option, it is known that there are complications associated with it. Among them, post-procedural stenosis occurs in about 6% of cases is the most common and, together, the risk of neoplasia is not negligible after endoscopic ablation therapy, and there may be relapses.[19] Despite this, the ablation technique is the most recommended because there is a scarcity of studies comparing ablative techniques and in view of this, the current literature indicates that the risks of stenosis and other complications associated with endoscopy ablation therapy are lower.[19] Therefore, these other techniques may play an additional role in the future, namely argon plasma coagulation, cryoablation, cryotherapy, and photodynamic therapy.[19.35]

On the other hand, surveillance still remains an acceptable first-line management in some of the international guidelines. In 2019, with the aim of guiding AGA members, an expert review was commissioned, which demonstrated that both endoscopic therapy and surveillance are equally effective options for the management of patients with confirmed DBG.[13] In these patients, however, in order to rule out the presence of a visible lesion that may harbor malignancy and therefore justify an endoscopic resection, a new examination of 3 to 6 months should be performed with endoscopy with high-definition white light and, preferably, by optical chromoendoscopy using the Seattle Protocol before proceeding with the surveillance protocols.[13,24,29,33]

In view of any visible abnormality found in the endoscopic surveillance examination, endoscopic mucosal resection (REM) should be performed, since this alteration suggests a higher probability of neoplastic development.[13,24,24] A study by Peters et.al. demonstrated that the histological evaluation from the MSC led to a 49% change in the diagnosis of these evaluated lesions and alteration of the treatment plan in 30% of the cases.[24.29]

However, a major impasse for the consensus regarding the surveillance interval and the biopsy protocol of DBG is that, in most cases, these approaches are based only on the opinion of specialists, on the lack of well-defined criteria to title a professional as a specialist, on the reliability of their histological interpretation and on the low quality of scientific evidence. Therefore, such parameters continue to differ slightly between international guidelines.[19,32,35]

Therefore, the AGA recommends periodic surveillance in the range of 6 to 12 months as the first line of treatment.[13,30,31] On the other hand, the interval of only 6 months is recommended by the Australian guideline and the Asia-Pacific Consensus and supported by the study by Jia et. al.[28.30]

In this situation, surveillance would consist of an annual endoscopic examination following the Seattle protocol. If two consecutive examinations are negative for dysplasia, the regimen made for Non-Dysplastic Barrett's Esophagus should be resumed, that is, biopsies in 4 quadrants with intervals of 2 cm [25,27,30,34] and, if no dysplasia is found, surveillance should continue to be done with endoscopic examinations at intervals of 3 to 5 years.[27,30] The negative point is that, because it requires a long period of time, this biopsy protocol may be impaired by the low adherence of the patient over the years.[20.23]

5.3 HIGH-GRADE DYSPLASIA

When it comes to high-grade dysplastic lesions, all guidelines recommend endoscopic ablation therapy as a good approach option to be performed in sessions every 2-3 months until complete eradication of the change is achieved.[18,19,23,26,27,31] Despite the lack of a consensus, this eradication is generally defined as the endoscopic remission of all metaplasias and dysplasias after two negative biopsies obtained in 4 quadrants with 1cm intervals.[27] However, even in those who do not achieve complete eradication of Barrett's mucosa, the overall 5-year survival rate is good and appears to be approximately 90%.[33rd]

Demonstrating the efficacy of ablation in the scientific literature, the study by Shaheen et. al. demonstrated that patients with AGD were randomized to receive radiofrequency ablation or a sham procedure. As a result, 81% of those treated with ablation achieved complete eradication of dysplasia compared to the 19% who achieved the same outcome with the sham procedure. Similarly, eradication of intestinal metaplasia was achieved in 77% of patients with ablation versus 2% of patients with dummy therapy. Finally, 3-year follow-up results from the same cohort showed a complete eradication of dysplasia in 98% and intestinal metaplasia in 91%.[34th]

In particular, for patients with confirmed high-grade flat dysplasia, the AGA recommends in its latest 2019 update, ordering a new examination in 6-8 weeks with high-definition, white-light endoscopy to rule out visible lesions amenable to resection. This would be important because in the presence of visible lesions, resection would precede ablation, aiming at the best staging, as well as the complete eradication of the segment.[13,27,31,33,34] Thus, in these cases, an additional advantage of endoscopic resection is the availability of large tissue samples, leading consequently to better conditions for pathological evaluation and staging.[35th]

Regarding the choice of resection technique, endoscopic resection remains the preferred method according to all guidelines, although recent Japanese studies have shown fewer local recurrences for squamous cell carcinomas when endoscopic submucosal dissection was applied.[35th]

Therefore, surveillance is restricted to patients with AGD who have limited life expectancy and such follow-up should be discontinued in cases where this expectation is less than 5 years.[32,34] In this context, before the initiation of ablative therapy, AGA, ASGE, GCA and ESGE recommend surveillance every 3 months.[28.34]

Therefore, current evidence shows that it is possible both to eradicate intestinal dysplasia and metaplasia and to regress the levels of progression to adenocarcinoma[25,27] without the need for esophagectomy13,24,34. However, the main reason that esophagectomy is not the most recommended option is the scarcity of evidence of high quality of survival and recurrences after surgery, since most studies are retrospective and with small numbers.[33rd]

However, the risk of developing stenosis in about 5.6% of patients undergoing treatment by ablation or endoscopic resection recommended for AGD is still a challenge for these approaches. Thus, in an attempt to minimize these outcomes, it is recommended that patients should receive high-dose proton pump therapy to mitigate stenosis formation, following evidence of its use in reflux esophagitis.[24,33] Other serious adverse events of these endoscopic managements include bleeding in 1% and perforation rate in 0.6%. Post-procedure chest pain in the absence of these serious complications can occur from 1.5% to 5.4%.[33]

5.4 CONTINUITY OF SURVEILLANCE AFTER ERADICATION OF THE LESION

There is no evidence to support discontinuation of surveillance even after multiple negative endoscopy in both DBG and DAG cases. However, a recent study found that recurrence of metaplasias and dysplasias are uncommon. Thus, more studies are needed to determine the best surveillance strategies in patients for eradication.[24,27,30] Currently, in the same way as surveillance in cases of dysplasia, follow-up after eradication consists of the collection of biopsies of 4 quadrants every 1 cm along the original dysplastic segment and gastric cardia, and most recurrences were detected in the distal 2 cm of the esophagus.[29th]

The interval between biopsies depends on the degree of dysplasia before eradication of the lesion. The ACG and the UK's national Halo registry recommend that surveillance be done in the first and third year after eradication for DBG.[13,29,30,34] On the other hand, Singh's study et. al. states that surveillance after the eradication of DBG should be every 6 months in the first year and annually from the second year if there is no recurrence.

For cases of eradicated SAD, the ACG, ASGE and the Australian guideline recommend surveillance every 3 months during the first year, every 6 months during the second year and annually from the third year, while the ESGE recommends surveillance every 3 months during the first year and annually from the second year.[13,19,24,30,34] The UK National Halo Registry and the AGA recommend surveillance at 3 months, 6 months and 1 year after eradication.[13,24,30,34] By contrast, the Asia-Pacific Consensus does not state any recommendation in this regard.

Such evaluations for surveillance should be made from endoscopy with high-definition white light and should include careful inspection of the neosquamous mucosa and gastric cardia, as well as should follow the Seattle Protocol with the collection of biopsies of 4 quadrants every 1cm.[13.29]

In this context, a prospective cohort supported the findings of the prospective study *"AIM DYSPLASIA"* showing recurrences of Barrett's Esophagus and dysplasia respectively in 5.2 and 1.8 per 100 person-years, with most recurrences occurring in the first two years.[24] Therefore, this would be a finding that could justify the higher frequency of surveillance biopsies in the first years after the complete eradication of metaplasia and dysplasia.

In addition to prolonged follow-up with surveillance, treatment with proton pump inhibitors is recommended, mainly by the ASGE, ACG and AGA guidelines.[19,34]

If there are recurrences, it is recommended that they be treated similarly to initial treatment protocols involving mucosal resection and ablative modalities.[24,29] Together, anti-reflux therapy is recommended to achieve symptom control and absence of erosive esophagitis.[29th]

6 LIMITATIONS OF THE STUDY

For the construction of this systematic review, the selection of articles, data extraction and evaluation of the quality of information were performed by only two investigators, a fact that may be a source of bias for this study.

7 CONCLUSION

This review synthesizes more recent surveillance and treatment data of dysplastic Barrett's esophagus, concluding that there is considerable consensus among international guidelines in order to optimize good medical practice regarding the diagnosis, treatment, follow-up and stratification of this pathology.

However, there are still disagreements to be clarified. One reason for such discrepancies is based on the precariousness of scientific evidence and clinical studies that compare the approaches to dysplastic EB, especially when it comes to low-grade dysplasia.

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The road to recovery: Understanding and managing anterior cruciate ligament injuries in athletes

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ABSTRACT

Introduction: Anterior Cruciate Ligament (ACL) injuries are common among athletes participating in high-demand sports. The ACL is an essential ligament in the knee that provides stability against unwanted movements. The incidence of ACL injuries in the United States is significant, becoming a concern for athletes and sports medicine professionals. This text provides an overview of ACL injuries, including their anatomy, function, risk factors, prevention strategies, and effective rehabilitation techniques. ACL rupture can impact athletic performance and require extensive rehabilitation. Methodology: A literature review was conducted from 2010 to 2022 using the databases PubMed, Scielo, and Medline to provide an updated overview of the relationship between Anterior Cruciate Ligament (ACL) injuries and athletes. Twenty-six articles addressing the clinical, anatomical, pathological, and treatment aspects of ACL injuries in athletes were selected. These articles were published in English, Spanish, or Portuguese. The methodological quality of the articles was evaluated, and the data were qualitatively analyzed, grouping the results by similarity. The data synthesis was presented descriptively, highlighting key information about the clinical, anatomical, pathological, and treatment aspects of ACL injuries in athletes. Discussion: This

work discusses risk factors, prevention, rehabilitation, surgical treatment, psychological impact, long-term consequences, recent research, and specific considerations for female athletes related to Anterior Cruciate Ligament (ACL) injuries. Risk factors for ACL injuries include increased general joint laxity, increased anterior-posterior knee joint laxity, female sex, previous ACL reconstruction, and familial predisposition to ACL injury. The incidence of ACL injuries varies among different sports and sexes. Injury rates are higher in sports such as soccer, basketball, and baseball/softball. Injury prevention strategies are also discussed. Conclusion: Anterior Cruciate Ligament (ACL) injuries are a significant concern for athletes and sports medicine professionals. A comprehensive approach involving prevention, rehabilitation, and safe return to sport is necessary to reduce the risk of ACL injuries in athletes and prevent long-term consequences. Adequate training techniques, injury prevention programs, and effective rehabilitation approaches play a crucial role in minimizing the risk of ACL injuries in athletes. Additionally, physiotherapists play a vital role in the prevention and rehabilitation of these injuries, and it is essential for them to stay updated with the latest research to provide the most effective care to affected athletes.

Keywords: Anterior Cruciate Ligament Injuries, Anterior Cruciate Ligament, Athletic Injuries.

1 INTRODUCTION

Anterior Cruciate Ligament (ACL) injuries are one of the most common types of knee injuries experienced by athletes who participate in high-demand sports such as soccer, football, and basketball. The ACL is a vital ligament that helps support the knee joint, providing stability against anterior tibial translation (TTA) and rotational forces. The annual incidence of ACL injury in the United States alone is approximately 1 in 3,500 people, making it a significant concern for athletes and sports medicine professionals. This essay will provide an overview of ACL injuries, including their anatomy and function, risk factors, prevention strategies, and effective rehabilitation techniques.

The anatomy and function of the ACL are crucial to understanding the impact of ACL injuries on athletes. The ACL is a central ligament located in the knee joint that provides stability against ATT and rotational forces. It is considered the primary passive restraint to the anterior translation of the tibia over the femur. The ACL consists of two bundles, the anteromedial bundle (AMB) and the posterolateral bundle (PLB), which work together to provide stability to the knee joint. An ACL tear or sprain can significantly affect an athlete's ability to perform at their best and may require extensive rehabilitation. [3] [4]

2 METHODOLOGY

A literature review was performed in the Pubmed, Scielo and Medline databases. Articles published in English, Spanish or Portuguese that addressed the clinical, anatomical, pathological and treatment aspects of ACL injuries in athletes were selected. The bibliographic search was conducted between 2010 and 2022, including articles published in English, Spanish or Portuguese. The descriptors used in the search were: "Anterior Cruciate Ligament Injuries" OR "Anterior Cruciate Ligament" OR "Athletic Injuries" AND "Clinical Relevance" OR "Clinical Protocols" OR

"Pathology". Cohort studies, case-control studies and systematic reviews addressing the clinical and physiological aspects of the gut microbiota that is related to human health were included. Studies with samples smaller than 10 individuals, opinion articles, case reports and animal studies were excluded. Initially, 202 articles were selected, of which 85 were excluded because they did not meet the inclusion criteria. After reading the abstracts, a further 91 articles were excluded because they did not present relevant information for the review. Finally, 26 articles were included for the analysis.

The articles were evaluated for methodological quality and the data were analyzed qualitatively, grouping the results by similarity. The synthesis of the data was presented descriptively, highlighting the main information on the clinical, anatomical, pathological and treatment of ACL injuries in athletes. This systematic literature review aims to provide an up-to-date overview of the relationship of Anterior Cruciate Ligament injuries with athletes in general, highlighting the main clinical, anatomical, pathological and treatment strategies available in the scientific literature.

3 DISCUSSION

Several risk factors can increase the likelihood of an athlete suffering an ACL injury. These include increased generalized joint laxity, increased laxity of the AP knee joint (KT-1000), female gender, previous ACL reconstruction, and familial predisposition to ACL injury. Increased generalized joint laxity is a significant risk factor for ACL injury in both men and women, while increased laxity of the AP knee joint is associated with non-contact ACL injuries in women. Female athletes are at a higher risk of suffering ACL injuries than their male counterparts, with studies reporting a two- to ten-fold higher incidence of ACL injuries in female athletes. Finally, previous ACL reconstruction and familial predisposition to ACL injury are also significant risk factors for suffering an ACL injury. [5] [6] [7]

Prevention of ACL injuries in athletes requires a comprehensive approach that includes injury prevention programs, proper training techniques, and use of equipment. Injury prevention programs should focus on improving neuromuscular control and proprioception, strengthening the lower extremities, and correcting biomechanical imbalances. Proper training techniques can help reduce the risk of ACL injuries by emphasizing proper landing mechanics, running technique, and cutting and rotating movements. In addition, the use of proper equipment, such as knee pads, can help reduce the risk of ACL injuries. Finally, effective rehabilitation techniques, such as strengthening exercises, range of motion exercises, and proprioceptive training, can help athletes recover from ACL injuries and prevent further future injuries. [1] [2]

Preventing ACL injuries in athletes is crucial to ensuring their long-term health and athletic performance. Multicomponent preventive training programs have been shown to be effective in reducing the risk of ACL injuries in athletes. These programs usually include instruction and feedback

on the proper exercise technique for at least three of the following exercises: plyometrics, balance and stability, strength training, agility, and speed and flexibility. Neuromuscular training (NMT) injury prevention programs have also been shown to be effective in reducing the risk of ACL injuries. However, there is variation in the design of the program, which can affect its overall effectiveness. It is essential to implement injury prevention programs tailored to an athlete's specific sport and individual needs to reduce the risk of ACL injuries. [8] [9]

Effective rehabilitation approaches are essential for athletes recovering from ACL injuries and preventing further injuries in the future. A criteria-based rehabilitation protocol with an end-result measure was found to be effective in ensuring the safe return of athletes to sport and reducing the risk of reoffending. This rehabilitation approach typically includes strengthening exercises, range-of-motion exercises, and proprioceptive training. It is essential to individualize rehabilitation programs tailored to an athlete's specific needs and sporting requirements to ensure the best results. Prevention of ACL injuries during sport and physical activity can significantly decrease medical costs and long-term disability, highlighting the importance of effective rehabilitation approaches. [10] [8]

Surgical treatment is usually required for athletes with severe or complete ACL injuries to regain knee function and return to sport. ACL reconstruction (CSF) is a common treatment strategy for this injury, as many athletes aim to return to competitive sports. Pre-habilitation before ACLR should include strengthening the quadriceps, improving range of motion, and controlling swelling. Post-surgical rehabilitation should focus on restoring range of motion, regaining strength, and returning to sport-specific movements. Surgery, along with complete rehabilitation and sport-specific exercises, should result in functional stability of the knee joint. Proper post-surgical rehabilitation is crucial to prevent further injuries and ensure the athlete's safe return to sport. [11] [12] [13]

ACL injuries in athletes have not only physical effects, but also psychological impacts that can significantly affect the athlete's well-being. Studies have shown that ACL injuries are associated with anxiety, pain response, mood disorders, depression, and feelings of diminished athletic identity [14]. The psychological impact can also affect an athlete's adherence to rehabilitation programs, potentially leading to suboptimal outcomes. It is important for sports medicine professionals to provide psychological support and appropriate resources to athletes recovering from an ACL injury to promote optimal recovery outcomes.

ACL injuries in athletes can have long-term consequences that can significantly affect an athlete's quality of life. Fear of a new injury and readiness to return to sport are among the most common psychological problems athletes face during ACL recovery [15]. In addition, ACL injuries have been linked to an increased risk of developing osteoarthritis later in life [14]. It is crucial to implement effective preventive strategies and rehabilitation approaches to reduce the risk of long-term consequences of ACL injuries in athletes.

Current research on ACL injury prevention and rehabilitation is focused on developing new and effective strategies to reduce the incidence of ACL injuries in athletes and improve rehabilitation outcomes. Negative psychological responses to injury have been associated with suboptimal adherence and rehabilitation outcomes [16]. ACL reconstruction does not prevent the development of osteoarthritis, but it can improve knee kinematics and reduce secondary injuries to cartilage and meniscus [17]. Recent trends and modalities in ACL rehabilitation research include the use of virtual reality training, wearable technology, and personalized rehabilitation programs [15]. By keeping up to date with the latest research, sports medicine professionals can provide the most effective preventive and rehabilitative care for athletes with ACL injuries.

The incidence of ACL injuries varies between different sports, genders, and types of exposure [18]. In girls, the most frequent sports that result in ACL injuries are soccer (53.2%), basketball (26.5%), softball (11.4%) and volleyball (8%) [18]. In boys, comparable sports such as soccer, basketball, and baseball or softball have similar rates of ACL injury [18]. The differences in injury rates between sports highlight the importance of developing sport-specific injury prevention programs to reduce the risk of ACL injuries in athletes.

Multicomponent preventive training programs have been shown to be effective in reducing the risk of ACL injuries in athletes [8]. These programs should include instruction and feedback on the proper exercise technique for at least three of the following exercises: plyometrics, balance and stability, strength training, agility, and speed and flexibility. Neuromuscular training (NMT) injury prevention programs have also been shown to be effective. However, there is variation in the design of the program, which can affect its overall effectiveness. It is essential to implement injury prevention programs tailored to an athlete's specific sport and individual needs to reduce the risk of ACL injuries.

Female athletes are at higher risk of suffering ACL injuries than their male counterparts, with studies reporting a two to ten times higher incidence of ACL injuries in female athletes [19]. The intrinsic differences between male and female athletes that would explain why women tear the ACL more often than men are still being investigated [20]. However, female athletes are known to break their ACLs at a higher rate in certain sports, including basketball, handball, and soccer [20]. Proper training techniques and injury prevention programs that address the unique biomechanical and neuromuscular factors in female athletes can help reduce the risk of ACL injuries.

Returning to play after an ACL injury and rehabilitation requires careful consideration to ensure the athlete's safety and optimal performance. Guidelines for rehabilitation of upper and lower limb injuries, focusing on specific considerations for female athletes, were presented to assist in the safe return to sport. These guidelines emphasize the importance of addressing neuromuscular control, proprioception, and strength training to reduce the risk of further injury and optimize athletic performance. In addition, the criteria for returning to sport after ACL injury should not be based solely

on functional and patient-reported outcomes, as these may not fully reflect an athlete's readiness to return to sport. A comprehensive assessment, including physical and psychological factors, should be performed to determine an athlete's readiness to return to the game. [21] [22]

Physical therapists play a vital role in the prevention and rehabilitation of ACL injuries in athletes. The goal of rehabilitation is to return the knee to its pre-injury normalized state and achieve tissue homeostasis. Physical therapists work to restore full movement before surgery to reduce the risk of complications. During rehabilitation, they keep the injured knee at rest, improving range of motion and minimizing swelling. The use of RICE and electrotherapy can also help reduce swelling and improve tissue healing. Proper rehabilitation techniques, including strengthening exercises, proprioceptive training, and neuromuscular control, are crucial in preventing further injury and ensuring optimal outcomes. [23] [24]

ACL injuries in athletes can have a significant economic impact on players and teams. Recovery costs (COR) and potential loss of revenue due to lost games can have long-term financial consequences. Studies have shown that ACL tears in NBA players result in significant recovery costs, including medical expenses and lost productivity. In addition, the loss of income due to lost games can have a significant impact on an athlete's financial stability. These economic impacts highlight the importance of implementing effective prevention and rehabilitation strategies to reduce the incidence of ACL injuries in athletes. [25] [26]

4 CONCLUSION

In conclusion, ACL injuries are a significant concern for athletes and sports medicine professionals. A comprehensive approach to prevention, rehabilitation and safe return to sport is needed to reduce the risk of ACL injuries in athletes and prevent long-term consequences. Proper training techniques, injury prevention programs, and effective rehabilitation approaches are crucial to minimizing an athlete's risk of suffering an ACL injury. In addition, physical therapists play a vital role in the prevention and rehabilitation of ACL injuries in athletes. By keeping up to date with the latest research, sports medicine professionals can provide the most effective preventive and rehabilitative care for athletes with ACL injuries.

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Technology and innovation in enhancing primary health care: The role of digital solutions in strengthening healthcare systems

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ABSTRACT

Introduction: The implementation of digital solutions in primary health care has brought significant changes and improvements to traditional systems. However, the integration between traditional medical cultures and digital solutions remains a hurdle to be overcome. Despite this, the implementation of these solutions brings advantages such as improved access to care, increased patient engagement, enhanced efficiency, and better health outcomes. However, there are challenges to be overcome, such as resistance to change, concerns about privacy and data security, as well as infrastructure and internet access issues. Through collaboration between healthcare providers, policymakers, and technology developers, it is possible to successfully overcome these challenges and integrate digital solutions into primary health care. Methodology: An integrative literature review was conducted to analyze case studies and relevant research on the implementation of digital solutions in primary health care. Articles published between 2010 and 2023 were selected from databases such as PubMed, Scielo, and Medline, addressing the benefits, challenges, and outcomes related to digital solutions. Data analysis was performed qualitatively and quantitatively, grouping relevant information and highlighting improvements in primary health care. Objective: This scientific article aims to explore the impact of digital solutions in primary health care, comparing and contrasting traditional systems with the advantages and challenges of implementing digital solutions. Discussion: The implementation of digital solutions in primary health care has brought significant advantages, such as improved access to care, increased efficiency, and better health outcomes. However, it also presents challenges, including resistance to change, concerns about data privacy, and the need to assess cost-effectiveness. Case studies highlight both successful and unsuccessful implementations, providing valuable insights into the factors that contribute to success or failure. To harness the full potential of digital solutions in primary health care, it is crucial to consider the impact on the doctor-patient relationship, ensure effective data management and analysis, and integrate digital solutions into existing healthcare systems. Additionally, ethical considerations, adequate training for healthcare professionals, and patient acceptance play important roles in the successful implementation of these solutions. Conclusion: The implementation of digital solutions in primary health care brings various advantages, such as improved access, increased efficiency, and better health outcomes. However, it is essential to address ethical issues, such as data privacy and security, and ensure that these solutions are accepted, effective, and integrated into existing healthcare systems. Training and education for healthcare professionals play a crucial role in the successful adoption of these solutions, as well as patient acceptance and

adoption. Looking to the future, advances in digital technology have great potential to transform primary health care, provided the necessary skills are considered and there is collaboration among stakeholders. By addressing these considerations, primary health care can make the most of the benefits of digital solutions, improving healthcare delivery for individuals.

Keywords: Primary Health Care, Health Systems, Health Sciences, Technology, Innovation Management, Health Information Systems.

1 INTRODUCTION

Primary health care is an essential component of any health system, acting as the first point of contact for people seeking medical care. Although it has evolved over the years, traditional primary health care systems have their limitations, such as a lack of integration with digital solutions and the inability to meet the growing needs of patients. In recent years, the introduction of digital solutions in primary health care has brought significant changes and improvements.

Traditional primary health care systems often fail to integrate emerging technologies and digital solutions, focusing primarily on medical care and neglecting the broader aspects of health and wellness. This dichotomy between traditional medical cultures and digital solutions has hampered progress and innovation in primary health care. However, by recognizing and addressing these obstacles, the healthcare industry can work to transform traditional systems and seize the opportunities offered by digital solutions.

The implementation of digital solutions in primary health care brings several advantages, such as improved access to care, greater patient engagement, greater efficiency and better health outcomes. Digital platforms allow patients to remotely access healthcare services, reducing the need for face-to-face visits and streamlining processes. In addition, digital solutions empower patients by providing them with tools and resources to actively manage their health, leading to better health outcomes and greater patient satisfaction.

However, the implementation of digital solutions in primary health care also presents challenges. Resistance to change on the part of healthcare professionals, concerns about patient privacy and data security, as well as issues related to infrastructure and Internet access, can be barriers to the adoption of digital solutions. Overcoming these challenges requires collaboration between healthcare providers, policymakers, and technology developers.

To illustrate the successful implementation of digital solutions in primary health care, a case study will be presented. This study highlights the threats and challenges faced during the implementation process and the steps taken to address them. By addressing these challenges and implementing appropriate strategies, it is possible to successfully integrate digital solutions into primary health care practice.

2 METHODOLOGY

An integrative literature review was performed in the Pubmed, Scielo and Medline databases. We selected articles published in English, Spanish or Portuguese that addressed the case studies, analyzing the threats and challenges faced during the implementation process and the measures taken to overcome them and evaluation of relevant research on the subject, in-depth in traditional primary health care systems, as well as digital solutions implemented in this context. The bibliographic search was conducted between 2010 and 2023, including articles published in English, Spanish and/or Portuguese. The descriptors used in the search were: "Primary Health Care" OR "Health Systems" OR "Health Sciences, Technology, and Innovation Management" OR "Health Information Systems".

Relevant research addressing the potential benefits of digital solutions in primary health care, as well as the challenges faced during their implementation, was analyzed, and studies exploring topics such as improved access to care, patient engagement, efficiency and health outcomes were considered.

They were included through a systematic review of the literature, seeking relevant articles that address the implementation of digital solutions in primary health care, its benefits and challenges. In addition, case studies and research related to the theme will be analyzed.

The articles were evaluated for methodological quality and the data were analyzed qualitatively and quantitatively. The relevant information will be extracted from the selected studies and grouped according to the themes identified in the literature. The advantages, challenges, results and lessons learned from the implementation of digital solutions in primary health care will be considered. The synthesis of the data was presented descriptively, highlighting the main information of improvements in primary health care.

3 OBJECTIVE

The objective of this research is to explore the impact of digital solutions in primary health care, comparing and contrasting traditional systems with the advantages and challenges of implementing these solutions. In addition, the study aims to present a case study to highlight a successful implementation of digital solutions in primary health care.

4 DISCUSSION

Primary health care is an essential component of any health system, serving as the first point of contact for people seeking medical care. Over the years, primary health care has evolved from a focus on medical care to a more comprehensive approach that considers the overall health and well-being of individuals [1]. However, traditional primary health care systems have their limitations, including a lack of integration with digital solutions and the inability to meet the growing needs of patients [2]. In recent years, the introduction of digital solutions in primary healthcare has brought

about significant changes and improvements. This essay aims to explore the impact of digital solutions on primary health care, comparing and contrasting traditional systems with the advantages and challenges of implementing digital solutions [3]. In addition, a case study will be presented to highlight a successful implementation of digital solutions in primary health care [8].

Traditional primary health care systems have long relied on conventional methods and practices, often failing to integrate emerging technologies and digital solutions [1]. These systems focus primarily on medical care and treatments, neglecting the broader aspects of health and wellness [1]. The dichotomy between traditional medical cultures and digital solutions has hampered progress and innovation in primary health care [2]. By recognizing and addressing these obstacles, the healthcare industry can work to transform traditional systems and seize the opportunities offered by digital solutions [2]. delivery [3]. Research in this field has identified four themes that highlight the potential benefits of digital solutions in primary health care [3]. These themes include improved access to care, greater patient engagement, greater efficiency, and better health outcomes [3]. By harnessing the power of digital technologies, primary healthcare providers can overcome geographic barriers, streamline processes, and improve the overall patient experience [4].

One of the main advantages of implementing digital solutions in primary health care is the increased convenience and accessibility for patients [5]. Digital platforms allow patients to remotely access healthcare services, reducing the need for face-to-face visits and minimizing wait times [5]. Patients appreciate the convenience of scheduling appointments, accessing health records, and receiving virtual appointments [5]. In addition, digital solutions can empower patients by providing them with tools and resources to actively manage their health [6]. This shift to patient empowerment can lead to better health outcomes and greater patient satisfaction [6].

Although digital solutions offer numerous advantages, their implementation in primary health care presents challenges [6]. A major challenge is the resistance to change and the reluctance of health professionals to adopt new technologies [7]. In addition, there are concerns regarding patient privacy and data security [7]. Ensuring the confidentiality and protection of confidential patient information is crucial in implementing digital solutions [7]. In addition, issues related to infrastructure and Internet access can be a barrier, especially in rural or underserved areas [7]. Overcoming these challenges requires collaboration between healthcare providers, policymakers, and technology developers [7].

To illustrate the successful implementation of digital solutions in primary health care, a case study will be presented [8]. This case study highlights the threats and challenges faced during the implementation process and the measures taken to address them [8]. Identified threats included patient safety, quality of care, patient privacy, and dignity [8]. By addressing these threats and implementing appropriate strategies, the primary health care organization has successfully integrated digital solutions into its practice [8]. This case study serves as an example of how digital solutions can be effectively

implemented and used in primary health care settings [8]. barriers that may arise [9]. In this particular case, the goal was to build a successful system that incorporated data from electronic health records (EHR) [9]. However, the implementation of digital solutions faced several obstacles, leading to their failure [9]. A factor that contributed significantly to the failure was the lack of support and resistance from health professionals [4]. The division of health services into primary care and specialized care has created a barrier to the adoption of digital services [4]. Resistance to digital services was a substantial contributing factor to the failure to implement digital solutions in primary health care [4].]. A study analyzing the cost-effectiveness of digital solutions in the treatment of diabetics revealed promising results [10]. The study focused on participants in a special care "club" for diabetics and estimated the number of cases of blindness avoided [10]. The findings suggest that implementing digital solutions can be cost-effective to improve patient outcomes [10]. However, it is important to note that the level of cost-effectiveness may vary in different contexts [10]. Another study assessing the cost-effectiveness of implementing digital solutions highlighted the need for a business case and insight into the cost-benefit ratio to ensure successful implementation [11]. This suggests that a comprehensive understanding of the cost-effectiveness of digital solutions is crucial for their successful integration into primary health care [11].

The introduction of digital solutions in primary health care has implications for the doctor-patient relationship [12]. While the traditional face-to-face doctor-patient relationship has its advantages, adopting digital solutions can improve communication and improve patient satisfaction [12]. A study evaluating the impact of digital solutions on the doctor-patient relationship found that patients provided positive feedback regarding this aspect [13]. The use of digital solutions allowed better communication and convenience, which positively influenced the doctor-patient relationship [13]. However, it is important to strike a balance between using digital solutions and preserving traditional face-to-face interaction to maintain a strong doctor-patient relationship [12]. Healthcare professionals can improve relationships through the effective integration of digital solutions, while prioritizing personalized care and communication [12]. The integration of patient portals from primary health centers and hospitals can significantly improve data management and facilitate better patient care [14]. A study conducted in a tertiary-level mental health facility highlighted the benefits of data collection and analysis to improve the doctor-patient relationship [14]. By utilizing digital solutions, healthcare professionals can gain a better understanding of patient needs and preferences, leading to more personalized and effective care [14]. However, it is essential to address challenges such as the potential for information overload and the need for standardized data collection methods to ensure the effective use of digital solutions in primary health care [15]. Systems is a complex process that requires careful consideration and planning [16]. Sustaining patient and healthcare provider engagement with digital solutions and integrating them into current health systems and care pathways presents

significant challenges [16]. A study aimed at promoting the integration of innovative digital health technologies identified several areas for health system improvement [17]. These areas include the need for clear policies and guidelines, adequate infrastructure, and training for health professionals [17]. In addition, the study emphasized the importance of collaboration between policymakers, healthcare providers, and technology developers to successfully integrate digital solutions into existing health systems [17]. In summary, the implementation of digital solutions in primary health care brings several advantages, including better access to care, greater efficiency and better health outcomes. However, challenges such as resistance to change, data privacy concerns, and the need for cost-effectiveness must be addressed. Case studies highlight successful and unsuccessful implementations of digital solutions, providing valuable insight into the factors that contribute to their success or failure. To make the most of the potential of digital solutions in primary health care, it is crucial to consider the impact on the doctor-patient relationship, ensure effective data management and analysis, and integrate digital solutions into existing health systems. By addressing these considerations, primary health care can be transformed to better meet the growing needs of patients and improve overall health care delivery.

Ethical considerations play a crucial role in the implementation of digital solutions in primary health care [18]. It is essential to ensure that these solutions are accepted, effective and ethical and that they integrate seamlessly with other health services [18]. One of the key ethical considerations is the privacy of end users and their data [19]. Healthcare professionals have a responsibility to design digital solutions that prioritize the privacy and security of patient information [19]. In addition, there should be agreement among professional stakeholders on guidelines and ethical standards for the use of digital solutions in primary health care [19]. This includes considering issues such as consent, transparency, and data-sharing practices [19]. By addressing these ethical considerations, the healthcare industry can build trust and ensure the responsible and ethical use of digital solutions in primary health care.

Training and education for healthcare professionals are essential to ensure the successful implementation and use of digital solutions in primary care and health care [20]. A study conducted among nurses recently graduated in eIMCI aimed to track the adoption of eIMCI and explore the factors that influence its adoption [20]. The study found that adoption of clinical decision support systems (CDSSs) was more likely when they provided real-time guidance and were integrated into existing workflows [20]. This highlights the importance of training healthcare professionals in the effective use of digital solutions and seamlessly integrating them into their practice [20]. In addition, healthcare professionals need to be trained in the use of digital technologies in various aspects of their work, including health, education, work, and daily use [21]. This training should focus on developing competencies in the use of digital tools, understanding the potential benefits and limitations of digital solutions, and addressing any concerns related to data privacy and security [21]. By providing

comprehensive training and education, healthcare professionals can effectively utilize digital solutions to improve patient care and outcomes in primary care settings.

The adoption and acceptance of digital solutions by patients in primary healthcare are crucial to the success of these technologies [5]. Research has indicated that patients are more likely to adopt electronic health systems when they perceive them as an improvement over traditional methods [5]. Factors such as ease of use, perceived utility, and reliance on digital solutions play a significant role in patient acceptance [5]. A study that explored individuals' attitudes toward health care in general found that patients who had a positive attitude toward health care were more likely to adopt and use consumer e-health apps in a primary health care context [22]. This highlights the importance of patient engagement and education in promoting the adoption of digital solutions [22]. Healthcare providers should focus on addressing patient concerns, providing clear information about the benefits of digital solutions, and ensuring that patients feel empowered and supported in the use of these technologies [22].

Looking ahead, there are several possibilities for advancements and perspectives in digital primary health care that can further transform healthcare delivery [23]. For example, the integration of electronic health information exchange (HIE) systems can improve coordination and communication among health professionals [23]. This can facilitate better continuity of care and increase patient engagement [23]. In addition, advances in artificial intelligence (AI) and machine learning can support clinical decision-making and enable personalized care [24]. Predictive analytics and remote monitoring technologies also have the potential to improve health outcomes and reduce healthcare costs [24]. However, it is crucial to consider the competencies and skills required to effectively utilize these advances in digital technology [24]. Healthcare professionals need to be equipped with knowledge and training to fully leverage these technologies and ensure their responsible and ethical use [24]. In addition, collaboration between policymakers, health professionals, and technology developers is essential to drive innovation and ensure that digital solutions are aligned with the goals and values of primary health care [24].

5 CONCLUSION

In conclusion, the implementation of digital solutions in primary health care brings several advantages, including better access, greater efficiency and better health outcomes. However, it is crucial to address ethical considerations such as data privacy and security, and ensure that digital solutions are accepted, effective, and perfectly match existing health systems. Training and education for healthcare professionals play a critical role in the successful adoption and utilization of digital solutions. The adoption and acceptance of digital solutions by the patient are also key factors for its success. Looking ahead, advances in digital technology have great potential to transform primary

health care, but it is important to consider the necessary competencies and collaborate among stakeholders. By addressing these considerations, primary health care can fully harness the benefits of digital solutions and improve the delivery of health care to individuals.

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Additional effects of transcutaneous electrical nerve stimulation associated with vertebral joint mobilization on musculoskeletal variables of individuals with low back pain

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ABSTRACT

Low back pain (LBP) is a musculoskeletal complaint that can be defined as pain or discomfort referred to the lower part of the spine, between the last thoracic vertebra and the first sacral vertebra, above the upper gluteal line, and which may or may not radiate to the lower limbs. Highly prevalent, it affects about 84% of the adult population at some point in life, being classified as acute when it lasts up to 6 weeks, subacute when from 6 to 12 weeks and chronic if for more than 12 weeks 2. LBP is a public health problem, as it is related to functional disability, decreased quality of life, social and economic losses, both indirect, as it leads to absenteeism, withdrawal from work activities and/or disability retirement, and direct, due to public health costs with medical care and procedures related to LBP and its biopsychosocial consequences 3,4. The etiology of low back pain is complex and multifactorial, and can be specific when due to a known pathology or factor, and nonspecific when the causes are inevitable 5. However, they are often associated with an imbalance between the effort required to perform the activities and the insufficient capacity of the musculoskeletal system to do so 6, as well as other agents of mechanical origin, such as disc, joint, muscle, ligament and nerve alterations.

Keywords: Low back pain, Spinal joint mobilization, TENS.

1 INTRODUCTION

Low back pain (LBP) is a musculoskeletal complaint that can be defined as pain or discomfort referred to in the lower spine, between the last thoracic vertebra and the first sacral vertebra, above the upper gluteal line, and that may or may not radiate to the lower limbs. Highly prevalent, it affects about 84% of the adult population at some point in life, being classified as acute when it lasts up to 6 weeks, subacute when it lasts up to 6 to 12 weeks and chronic if for more than 12 weeks. [1] [2]

LD is a public health problem, as it is related to functional disability, decreased quality of life, social and economic losses, both indirect, by leading to absenteeism, absence from work activities and/or disability retirement, and direct, due to the costs to public health with medical care and procedures related to LD and its biopsychosocial consequences. [3,4]

[5] The etiology of low back pain is complex and multifactorial, and may be specific when due to a known pathology or factor, and nonspecific when the causes are unevident. However, these are often associated with an imbalance between the effort required to perform the activities and the insufficient capacity of the musculoskeletal system to do so, as well as other agents of mechanical origin, taking for example disc, joint, muscular, ligamentous and nervous changes. In addition, there are risk factors related to health and behavior that favor the onset of LD, such as age, sedentary lifestyle, overweight, smoking and occupations. [6 7]

Currently, there are numerous proposals for conservative interventions for the treatment of low back pain that aim at analgesia and increased functionality. Among them there are those that propose to act through the education of the individual and programs of exercises of stabilization, strengthening, stretching and mobility, such as kinesiotherapy. However, it is possible to observe a correlation between pain, decreased range of motion (ROM) and flexibility, which can increase the severity of the LD picture, lead to fatigue of the paravertebral muscles and limit functionality progressively, making it difficult to perform the proposed therapeutic exercises. [8,9] [10] [11] Thus, resources such as manual therapy and electrotherapy can act on the signs and symptoms, acting in a way to reduce the physical limitation generated by pain, thus enabling the practice of kinesiotherapy and other complementary techniques that would be limited, interrupted or postponed by the presence of pain. [12]

Transcutaneous electrical nerve stimulation (TENS) is characterized by being a current that produces electrical impulses of varying frequency, pulse duration, and intensity. Through the mechanism of the Theory of Gates, it acts by stimulating the myelinated fibers of type A, generating excitation of the interneurons in the posterior horn of the spinal cord and consequently inhibiting the nociceptive impulses of the A-delta and C fibers. There is evidence to suggest its ability to reduce pain during and after a certain time of application, and for this reason it is commonly used in clinical practice for CLBP, however there are few studies and consensus in the literature on its effects on fatigue and recovery of function. [8,13] [8] [14]

Among the techniques of manual therapy is the Central Postero-Anterior Joint (CAP) mobilization, with evidence of benefits of its application in individuals with CLBP. CAP is a mobilization technique that uses passive, rhythmic, oscillatory movements of low speed and low force, graduated in 5 levels that has its variation based on the ROM available in the joints. These movements aim to restore joint arthrokinematics, which improves mobility on joint surfaces that can result in decreased pain and greater performance of the segment where the technique is applied. [15] [16,17]

Therefore, transcutaneous electrical nerve stimulation (TENS) and Central Posteroanterior Vertebral Joint Mobilization (CAP) are used recurrently in physical therapy practice for pain relief and recovery of segmental function in the short term and may be beneficial means of complementing other therapeutic interventions, such as kinesiotherapy. Although many studies address the application of these techniques individually in low back pain, few associate them in the same protocol. Therefore, the aim of this study was to analyze whether the acute effects of Central Posteroanterior (CAP) vertebral joint mobilization combined with transcutaneous electrical nerve stimulation (TENS) differ from placebo-associated CAP on lumbar spine pain, mobility, strength, and resistance in young adult individuals. The hypothesis is that associating the two techniques would potentiate the musculoskeletal benefits.

2 METHODS

This is a quantitative, randomized study, submitted to the local ethics committee, CAAE: 59134522.0.0000.5406 and approved according to opinion 5.502.507 All volunteers signed the Free and Informed Consent Form (ICF) when they agreed with the procedure and objective of the study informed by the researchers, as well as clarification of any doubts.

2.1 PARTICIPANTS

The sample consisted of 33 adult individuals aged between 18 and 35 years, of both sexes. A sample size calculation was performed using the data of the first 10 volunteers. The calculation of the sample size was performed using the software G*Power 3.1.9.7 and was based on the data obtained in the numerical scale of pain because it is the primary outcome of the research. A power of 0.80, probability of error α 0.05, effect size of 0.48 and a dropout rate of 15% were used, indicating a total sample of 30 volunteers. Two groups were formed: Joint Mobilization Group (GMA, n=16) and Joint Mobilization Group with TENS (GMAT, n=17). Sample recruitment and collection occurred between the months of August/2022 to November/2022.

2.2 INCLUSION AND NON-INCLUSION CRITERIA

We included participants of both sexes and aged between 18 and 35 years, who had the ability to perform the activities related to the research, and who had presented at least one episode of low back pain in the last year, whether it had become chronic or not.

Individuals with Body Mass Index (BMI) above 30 kg/m², subjects who had used analgesic, anti-inflammatory, myorelaxant or antipyretic drugs up to 24 hours before the research protocol, or who were unable to complete all stages of collection were excluded from the sample.

Volunteers who had neurological symptoms, a history of fracture related to the lumbar spine, cardiovascular or cognitive impairment, skin lesions in the lumbar region, and/or metal implants in the spine would also not be included in the sample. Finally, those who did not sign the ICF would not participate. [16] [18] [13,14]

2.3 RANDOMIZATION

Randomization was employed using a computer-generated table of random numbers from 0 to 100. A number was drawn for each volunteer, with even numbers indicating it for the GMAT group and odd numbers for the GMA group.

2.4 EVALUATION PROCEDURES

The evaluations and interventions were performed in a single collection. Initially, anamnesis was performed to obtain personal data and clinical history of the volunteers, and the International Physical Activity Questionnaire (IPAC), which estimates the weekly time spent in physical activities, was applied in order to characterize the sample [19]. Then, the following evaluations were performed in the following pre-established sequence: Numerical Pain Scale (NDS), Schober test, lumbar extension dynamometry, and Biering-Sorensen test. In the first stage, five minutes after the initial evaluation, an overload protocol was performed on the lumbar dynamometer. A second evaluation was performed five minutes after the overload sequence. In the second stage, the CAP joint mobilization protocol was applied for the GMA, and the PAC joint mobilization protocol associated with the TENS for the GMAT. At the end of the intervention, a final evaluation was performed.

2.5 NUMERICAL PAIN SCALE (NDT)

The NDT was used and validated as a simple assessment instrument to quantitatively measure the perception of pain intensity. It is a scale ranging from 0 to 10 points, in which "0" represents no pain, while "10" represents the greatest possible pain. [20]

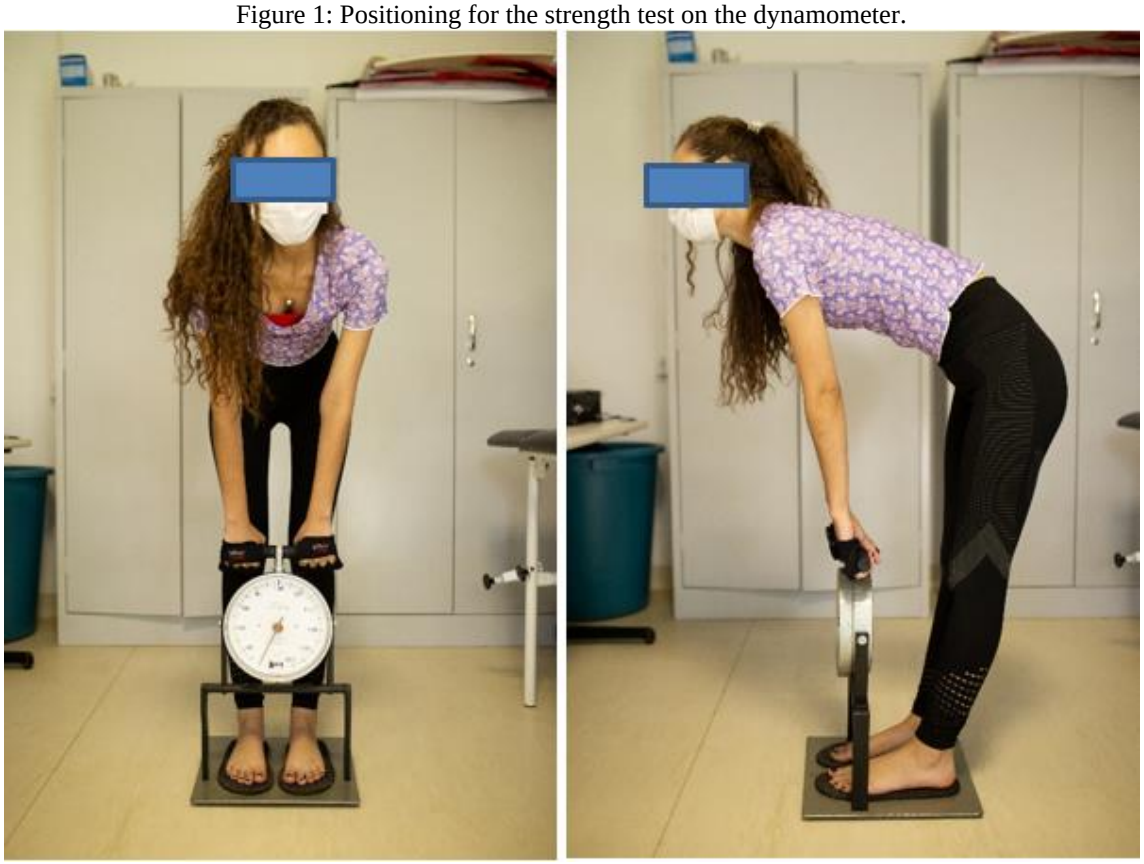
2.6 SCHOBER TEST

The Schober test was used to evaluate the mobility of the lumbar spine. With the volunteer in neutral position, a pen marking was performed in the lumbar region, taking as reference the superior posterus iliac spine. A second point was made ten centimeters above the first using a tape measure for measurement. The volunteer was instructed to flex the trunk in order to reach the ground, and in this posture the distance between the two points was verified. An increase equal to or greater than five centimeters in measurement is considered normal for lumbar spine mobility. [21]

2.7 LUMBAR DYNAMOMETRY

To measure the strength of the lumbar spine extensor muscles, the lumbar dynamometer was used. The volunteer was positioned in orthostatism on the platform of the equipment with total extension of knees, both hands supported on the bar of the equipment, elbows in extension, trunk in flexion, the head accompanying the prolongation of the trunk and gaze fixed in front (Figure 1).

Figure 1: Positioning for the strength test on the dynamometer.



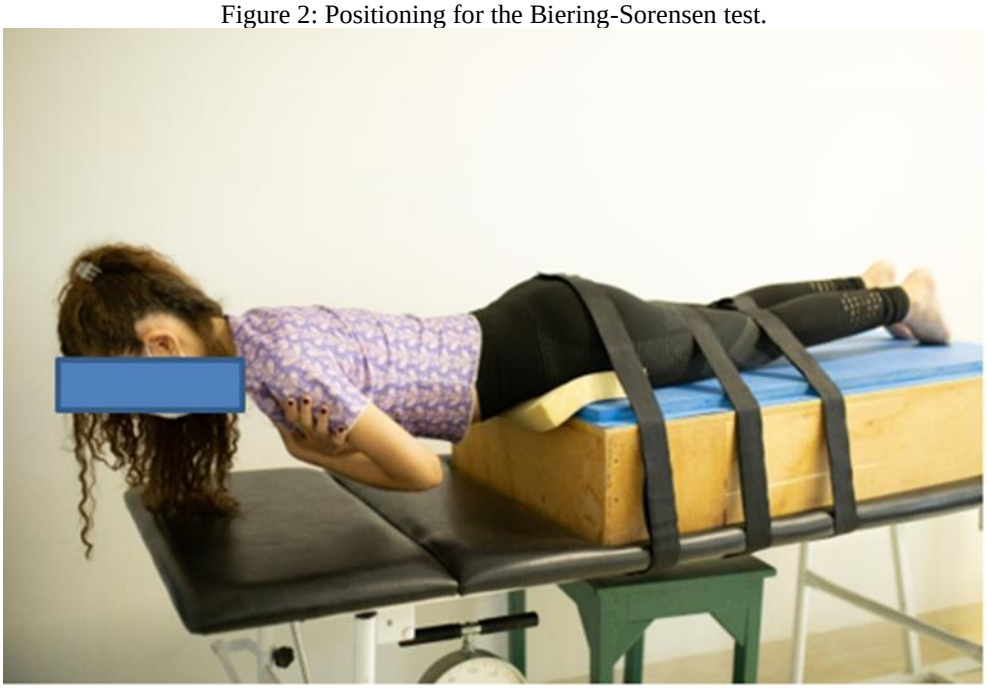
Once positioned, the volunteer was asked to perform the greatest possible force for the trunk extension movement. The commands "Strength!" and "More strength!" were standardized in order to encourage the volunteers. This test was performed three times with the submaximal strength for familiarization, and twice with the maximum force, with an interval of 1 minute between the tests. For data analysis, the highest value obtained was used. [22,23]

2.8 BIERING-SORENSEN TEST

The Biering-sorensen test was performed to evaluate the resistance of the trunk extensor muscles. The volunteer was positioned in ventral decubitus on a box above the stretcher, with the trunk suspended from the superior anterofacial iliac spine (ASIS) and with the lower limbs fixed by means of Velcro bands in the greater trochanter regions of the femur, biceps femoris and popliteal fossa. While the bands were fixed, the volunteers remained with their forearms supported in a step. At the

beginning of the test, the hands were positioned touching the contralateral shoulder, and the trunk was suspended (Figure 2). [24]

Figure 2: Positioning for the Biering-Sorensen test.



It was requested to remain in the position for as long as possible until exhaustion, with the time measured in seconds by a stopwatch. The test would also be completed if the participant did not keep the trunk in a horizontal position, due to fatigue and/or pain. The commands "You're doing well!" and "Continue!" were standardized every 30 seconds to encourage the volunteers. [25,26] [27]

2.9 LUMBAR OVERLOAD PROTOCOL

In some studies, difficulties were reported in evaluating and interpreting the performance of volunteers due to the absence or low level of pain initially presented at the time of collection. Since the purpose of this research is to evaluate the effects of two interventions on, among other variables, the low back pain of the volunteers, a sequence of overload was performed on the dorsal dynamometer, with 5 repetitions of contractions sustained for 10 seconds, intervals of 30 seconds between them, and minimum load of 75% of the value obtained in the initial evaluation (maximum force). Thus, a sharpening of the LD framework would be simulated before the application of the interventions. [4,28]

2.10 INTERVENTION PROCEDURES

2.10.1 Joint mobilization protocol

For both groups (GMA and GMAT) the same protocol of Central Postero-Anterior (CAP) vertebral joint mobilization, grade III, was applied at all levels of the Lumbar Spine. In each of the

vertebrae, from L1 to L5, 3 mobilization series were performed lasting one minute each. It was standardized to start in L5 and end in L1 each of the series.

2.10.2 TENS Implementation Protocol

For both groups, the procedures for placing the electric current were identical, changing only the intensity. To apply the Transcutaneous Electrical Stimulation (TENS), the equipment Neurodyn III, IBRAMED®, Brazil was used. In the GMAT group, conventional TENS was used with the following parameters: continuous mode; frequency of 100 Hz; pulse duration of 100 μs; maximal sensory intensity, variable so that it was tolerable to the volunteer and adjusted every 5 minutes; no visible muscle contraction; Total duration of 30 minutes. In the GMA group, placebo TENS was used, in which the volunteers were previously informed that they could or could not feel any local sensation during the application of the current. The parameters were identical to the GMAT group, however the intensity was adjusted in the minimum sensory threshold of the volunteer and, after 2 minutes, it was zeroed until completing the 30 minutes. [29] [13]

In both groups, the volunteers were placed in ventral decubitus on the stretcher, and four rectangular silicone rubber electrodes (50x55mm) were cross-applied to the paravertebral muscles bilaterally from L1 to L5, fixed with adhesive tape and with the use of conductive gel.

2.10.3 Data analysis

To analyze the effect of the intervention protocols (lumbar overload, CAP mobilization and CAP mobilization associated with TENS) on the level of pain, mobility, strength and resistance of the lumbar spine, the Repeated Measures ANOVA was used, with a mixed design (2 groups x 3 moments), followed by Bonferroni's *post-hoc* approach. Sphericity was tested by Mauchly's test. The level of significance adopted was 5%. The effect size was calculated by eta squared ($\eta^2 < 0.06$ = weak; 0.06 - 0.13 = medium; $\eta 2 \geq 0.14$ = large) for the ANOVA comparisons. [30]

3 RESULTS

A total of 33 individuals were collected and separated into 2 groups: GMA and GMAT. The results presented in Table 1 characterize the volunteers of this study and demonstrate that the groups were homogeneous in terms of anthropometry.

Table 1. Characterization of the groups [mean (standard deviation)].

		GMAT	GMA	P
n		17	16	-
Men (%)		35,29%	31,25%	-
Women (%)		64,71%	68,75%	-
Age (years)		22,59 (2,72)	21,81 (2,23)	0,195 [A]
Body mass (kg)		68,21 (9,69)	63,97 (10,85)	0,244 [B]
Height (m)		1,70 (0,08)	1,64 (0,09)	0,070 [B]
IMC ($kg.cm^{-2}$)		23,62 (2,82)	23,60 (2,83)	0,981 [B]
IPAC (%)	very active	35,29	37,50	-
	active	47,06	37,50	-
	irregularly active A	5,88	25,00	-
	irregularly active B	11,76	0,00	-

GMAT= joint mobilization group associated with TENS; GMA= joint mobilization group; IPAC= International Physical Activity Questionnaire; BMI = Body Mass Index; Kg= kilograms; cm = centimeters. [The] Mann-Whitney test; [B] T test for independent samples.

Table 2 shows that the multivariate analysis showed no significant interaction between group and moment (F= 0.775, p= 0.628, η2= 0.205, power = 0.275), nor did it show a significant effect of the group (F= 0.187, p= 0.943, η2= 0.026, power = 0.084). On the other hand, it showed a significant effect of the moment (F= 12.887, p= 0.000, η2= 0.811, power= 1) on the variables analyzed.

Univariate analysis showed a significant effect of the moment on NDT and the Schober and Biering-Sorensen tests (Table 2).

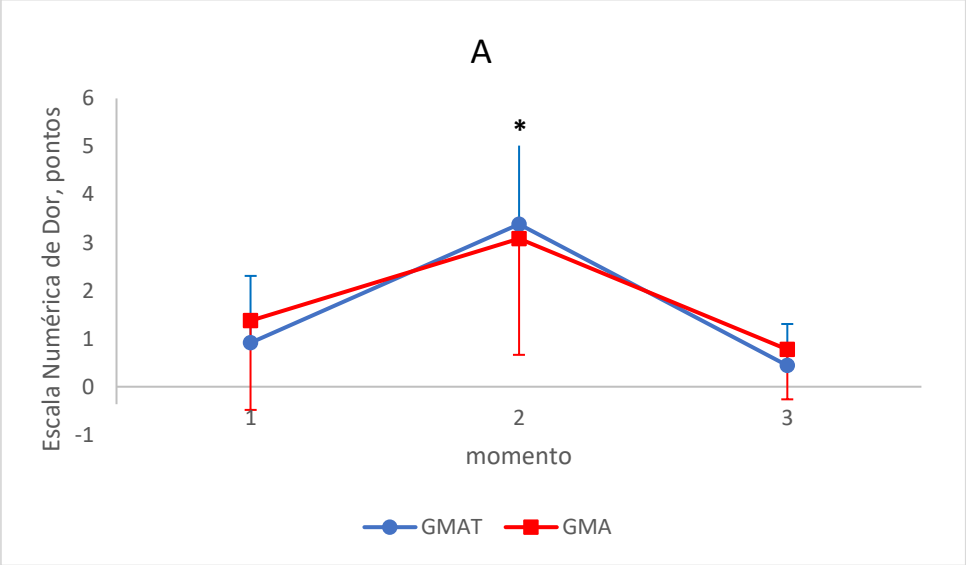
Post-hoc therapy showed a significant increase in pain level at moment 2 (p= 0.000) and, subsequently, a significant reduction at moment 3 (p= 0.000). There was no significant difference between moments 1 and 3 (p= 0.188), which indicates that the pain level was reestablished (Figure 3A). For the Schober test, it showed consecutive increases in measurements at moments 2 and 3, which resulted in significant differences for all comparisons (p= 0.000) (Figure 1B). For the Biering-Sorensen test, it showed a significant reduction at moment 2 (p= 0.001), followed by a significant increase at moment 3 (p= 0.008). There was no significant difference between moments 1 and 3 (p= 1,000), which indicates that performance was reestablished (Figure 3C).

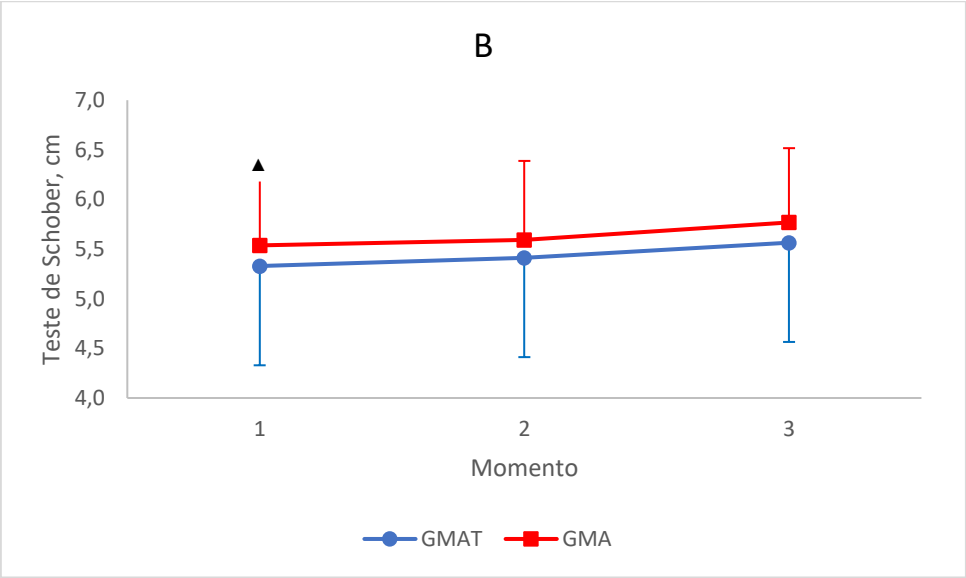
Table 2. Effect of intervention protocols on pain intensity, mobility, strength and resistance of the lumbar spine.

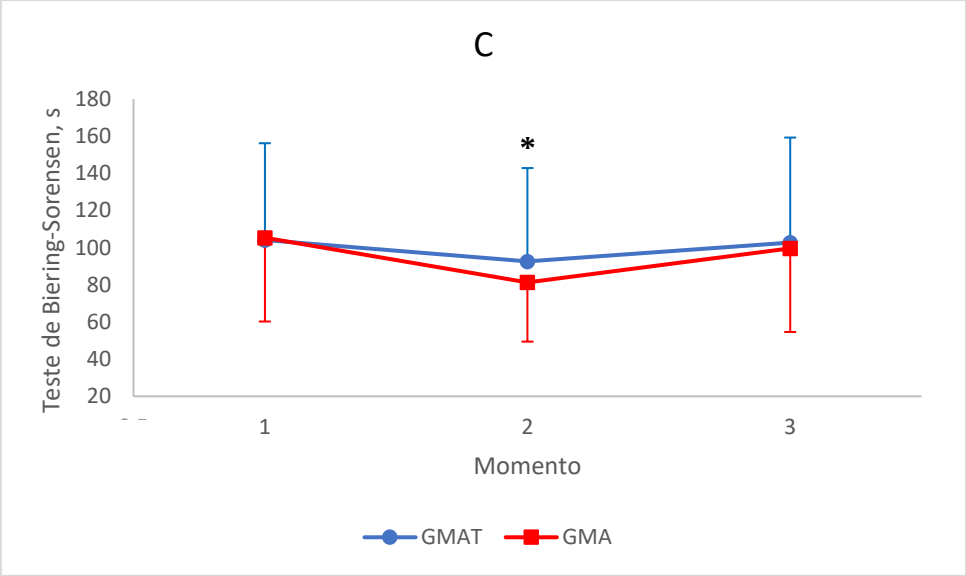
Variable	Groups		Repeated Measures Anova (ηp2)		
	GMAT	GMA	Group * Moment	Group	Moment
END 1	0,91 (1,39)	1,38 (1,86)	0,425 (0,027)	0,716 (0,004)	*0,000 (0,563)*
END 2 [A]	3,38 (1,86)	3,08 (2,42)			
END 3	0,44 (0,86)	0,78 (1,04)			
Teste de Schober 1 [B]	5,33 (0,88)	5,54 (0,83)	0,755 (0,005)	0,502 (0,015)	*0,000 (0,576)*
Schober test 2	5,41 (0,87)	5,59 (0,79)			
Schober test 3	5,56 (0,91)	5,77 (0,75)			
Dinamometria 1	78,26 (20,73)	71,16 (22,63)	0,663 (0,012)	0,520 (0,013)	0,498 (0,021)
Dinamometria 2	75,18 (23,04)	71,78 (26,21)			
Dinamometria 3	74,41 (24,63)	69,88 (22,56)			
Biering-Soresen 1	104,12 (52,10)	105,38 (45,12)	0,381 (0,031)	0,780 (0,003)	*0,001 (0,216)*
Biering-Soresen 2 [A]	92,62 (50,24)	81,31 (31,87)			
Biering-Soresen 3	102,79 (56,49)	99,56 (44,93)			

NDT = Numerical Pain Scale; GMAT= ; GMA= ; ηp2= effect size.
In italics: significant difference ($p < 0.05$).
Bonferroni post-hoc for momentum effect: [A] moment 2 is different from moments 1 and 3 ($p < 0.01$); [B] there was a difference between all moments for the Schober test ($p < 0.01$).

Figure 3. Behavior of pain level (A), mobility (B) and resistance of the lumbar spine (C) in the GMAT and GMA groups, in the three moments of evaluation. Momentum effect: * moment 2 is different from moment 1 and 3 ($p < 0.01$). ▲ all moments differ from each other ($p < 0.01$).







4 DISCUSSION

The aim of this study was to analyze whether the immediate effects of CAP joint mobilization combined with TENS differ from placebo-associated CAP on lumbar spine pain, mobility, strength, and resistance. The initial hypothesis was that the association of the two techniques would intensify the musculoskeletal benefits, however it was rejected, since there was no significant difference between the groups in the performance of the volunteers in the tests. In addition, other findings were significant: Decreased performance for the muscular endurance tests and increased pain level after the overload protocol, and improvement of GMA and GMAT for the variables of pain, mobility and muscular endurance after the interventions, suggesting the short-term efficacy of CAP mobilization in the lumbar.

Transcutaneous electrical nerve stimulation has been frequently applied as a resource for analgesia in different clinical conditions. Its application in low back pain, however, is controversial.

While some studies suggest its effectiveness in reducing pain and, consequently, increasing strength, muscular endurance and greater stabilization of the joint in the short term, others question its action when compared with the placebo effect, since they found no significant difference between both, which is similar to our results. [31,32] [33,34]

Considering the way this study was conducted, some factors may have influenced the final results. The placebo effect on TENS, as mentioned, may have influenced and been a response to the expectation and confidence of the volunteers in judging that they were receiving the treatment. Another item to be raised is the parameters adopted in the protocol, since there is no consensus in the literature on which would produce the best response, in addition to studies that indicate that the choice of the same should be made specifically for each individual, because even in similar conditions there are individual factors that can affect the TENS stimulus, taking as an example the type of pain. [33,35] [12,35] [36]

Moreover, in this study, only one CAP mobilization session associated with TENS was performed and, yet, there was no group where TENS was applied alone. For this reason, it is not possible to state whether the results would remain the same if the resource were used in isolation and/or in more sessions, as well as its long-term effects.

The objective in performing lumbar overload, previously exposed, was partially achieved in the results, since there was a decrease in muscle endurance and an increase in the level of pain after the protocol. The stability of the spine is due to the balance in the action of passive elements, such as ligaments, intervertebral discs and joint capsules, and active, represented by the musculature. When there is impairment in the function of the active components, through the induction of muscle overload, there is excessive demand on the passive components, generating structural deformations and, as a result, pain and decreased resistance, which was observed in this study. [37] [38]

It was also expected, however, a decrease in performance in the muscle strength test after the overload protocol, which did not occur. During the use of the dorsal dynamometer as a means of strength evaluation, despite the pre-test position and familiarization adjustments, activation of accessory muscles for the requested movement may occur and, thus, generate a transfer between muscle activations, making it difficult to obtain significant differences between moments. On the other hand, subjective elements such as fear of performing maximum force during the first evaluation may also have influenced. Finally, there was a significant increase in mobility after overload, which may have occurred due to the volunteers' own movement during the execution of the tests after the first evaluation, generating an increase in range of motion. [37] [39]

Although there was no significant difference between the groups, this was obtained in both for the variables of mobility, muscular endurance and, in particular, for pain level, in which a 2-point change in the NDT was observed after the interventions, which is a result considered clinically

relevant. Considering that the CAP joint mobilization intervention was performed in both groups, the efficiency of the technique is suggested. In individuals with low back pain reduced vertebral joint mobility, paravertebral muscle inhibition and functional losses are commonly found. In view of this, the mechanisms of action of mobilizations may be biomechanical and/or neurophysiological. [40] [15]

Passive and repetitive movements lengthen the contracted tissues, increase the lubrication of the articular cartilage with the redistribution of synovial fluid, as well as nutrition of the intervertebral disc, allowing greater amplitude and efficiency of movement with less pain. Hypoalgesia, in turn, can occur by the mechanism of pain gates, through the repetition of proprioceptive stimuli in the medulla during mobilizations and/or local release of endogenous opioids. The literature also points out that the technique can increase muscle recruitment, increasing the ability to produce force through the stimulation of mechanoreceptors mediated by the spinal cord, having the effect of decreasing muscle inhibition. In the present study, [41] [15] [42,43] [44] an improvement in the parameters of mobility, muscular endurance and pain level was verified after joint mobilization, which is similar in the scientific literature. However, for muscle strength there was no significant difference after a single intervention, which suggests the need to verify in future projects how this variable behaves after a greater number of sessions. [15,42,43]

The results obtained in this work contribute to the reports of previous investigations: Shum, Tsung and Lee (2013), as well as Powers et al. (2008) reported immediate effects of an intervention session with vertebral mobilization on pain reduction and stiffness in the lumbar spine; Shah and Kage (2016), as well as Cruz and Boleli (2020) found significant differences for decreased pain, increased range of motion, and increased spinal function; finally, Navega and Tambascia (2011) concluded that the technique was effective for improving quality of life, flexibility, pain and functional disability. On the other hand, our findings diverge from other studies, such as those by Thomas et al. (2020) and Tavares et al. (2017), which suggest a placebo effect of joint mobilization in chronic low back pain. [45] [46] [42] [47] [16] [48] [15]

The scientific data published so far are not sufficient to agree that CAP joint mobilization and TENS are effective resources for the treatment of low back pain. Therefore, future randomized clinical trials are necessary, with a greater number of sessions, long-term reevaluations and the presence of a control group, both for the techniques in isolation and for their association in the same protocol. Given the above, the present study corroborates and adds to the literature relevant data for the conservative treatment of low back pain.

5 CONCLUSION

The data of the present study, under the methodological conditions used, allow us to conclude that the musculoskeletal performance of young adults with low back pain submitted to PAC vertebral

joint mobilization improved in relation to pain, mobility and lumbar muscular resistance. The additional application of TENS did not result in higher gains.

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Analysis of childbirth route in pregnant adolescent, in the last decade (2010 -2020), in Ribeirão Preto-SP

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ABSTRACT
The article deals with an association between an integrative review on methods of childbirth, in ratio to their risks and benefits, and an ecological study based on the choice of route in the adolescent population of Ribeirão Preto. A total of 9727 women between 10 and 19 years old were analyzed during the period from 2010 to 2020. The study aimed to evaluate the criteria used for choosing a gestational resolution, covering possible complications and inappropriate information, justified by the incongruity between the network of health and the target public.

Keywords: Childbirth, Adolescent, Pregnancy.

1 INTRODUCTION

Adolescence is a period of physical and psychological transition in which the human being ceases to be a child and enters adulthood. Occurring in a profound and rapid way physical, mental, emotional transformation and especially the discovery of sexuality that make adolescents more susceptible to sexually transmitted infections and teenage pregnancy. [1]

Adolescence is a period of physical and psychological transition in which the human being ceases to be a child and enters adulthood. Occurring in a profound and rapid way physical, mental, emotional transformation and especially the discovery of sexuality that make adolescents more susceptible to sexually transmitted infections and teenage pregnancy. [1]. Considering that currently, adolescent pregnancy rates have been affected by significant factors such as socioeconomic status, neglect of condom use, [2] change in current values and the emergence of the contraceptive pill. [3]

Teenage pregnancy is a worrying situation due to the risks involved, both for the mother and the baby, since many studies indicate that pregnancy at this time can lead to prematurity, low birth weight, fetal growth restriction and several problems for the mother, including maternal and perinatal mortality. [4]

The mode of delivery chosen can have a significant impact on the health of both mother and baby. Cesarean section is a common delivery option for adolescent women, especially in cases of high-risk pregnancy. However, cesarean section also carries additional risks, including infection, hemorrhage, deep vein thrombosis, and uterine injury. [5]

On the other hand, the vaginal route can also present risks, especially in teenage pregnancies, because labor can be longer and more painful for adolescents, who may be more likely to need analgesia or have obstetric complications requiring intervention, such as episiotomy (cutting in the perineum). In addition, the vaginal route can increase the risk of lacerations in the birth canal, which can lead to complications such as urinary and fecal incontinence.

2 METHODS

An ecological study, conducted with the birth records of babies of mothers between 10 and 19 years old, in the periods from 2010 to 2020, contained in the Birth Information System (DataSUS) and the records of fetal deaths in the same period, which occurred in Ribeirão Preto, state of São Paulo.

3 DISCUSSION

Teenage pregnancy is a public health problem that affects millions of young people around the world, including Brazil. According to the World Health Organization (WHO), teenage pregnancy is defined as one that occurs between 10 and 19 years of age, and most of these pregnancies occur in low- and middle-income countries. [6] According to the Ministry of Health, about 17% of pregnancies in the country occur in adolescents between 10 and 19 years old. [7]

According to the Ministry of Health (BRAZIL, 2005), all women have the right to prenatal care, a service to monitor women during the gestational period in order to ensure the healthy development of pregnancy, allowing a delivery with lower risks for both mother and baby. Gestational follow-up during prenatal care is a proven benefit of protection for prematurity, intrauterine growth retardation, low birth weight, and maternal and infant deaths due to changes in health status both in the prenatal and postnatal periods, in addition to an approach in the psychosocial aspect performed by health professionals through educational and preventive activities. Women should have at least six prenatal visits, one in the first trimester, two in the second trimester and three in the last trimester. [9]

In the adolescent population, prenatal care is even more important in reducing the risk of obstetric and neonatal complications, since pregnancy in this group affects with greater prevalence young people from less favored social groups, often without family, social and partner support. [10] Studies indicate that inadequate follow-up during the gestational period conferred an increased chance of occurrence of prematurity and low birth weight. [11]

Normal childbirth can be classified as one that occurs naturally as a natural phenomenon, so it is also called natural childbirth, so that unnecessary complications or procedures do not occur throughout labor.[12]

Among the benefits found in those born by transvaginal delivery that overlap with neonates born by cesarean section are the lower complication in relation to breastfeeding, the significantly lower frequency of nosocomial infection, immediate recovery after delivery, and the lower frequency of neonates who present in the first minute Apgar of 4 to 6. [13]

Consultations during prenatal follow-up in natural childbirth are used in the health service network as tools for welcoming and bonding, in order to prepare the pregnant woman for natural childbirth, ensuring information from the beginning of pregnancy on the technical aspects of childbirth, as well as repercussions in relation to her health and that of the NB.[1] This approximation between the health system and the pregnant woman is necessary so that the rates of spontaneous delivery in Brazil does not continue to decrease, since much of this decrease is related to factors such as the belief that cesarean delivery is painless, the fear of pain during vaginal delivery, changes in the female genitalia, possibility and schedule for choosing the day of delivery.[14]

Addressing the relationship between urinary incontinence and the delivery routes, the vaginal route presents anatomical damage that can cause the integrity of the muscles and innervation of the pelvic floor, important in the maintenance of urinary continence.[15] On the other hand, the physiological changes of pregnancy, such as modification of the anatomical relations between bladder and uterus, decrease in the strength of the fascia that anchors the bladder neck and high levels of progesterone, may also be attributed to cesarean delivery.[16] Thus, despite affecting women with a history of some type of delivery, it is not possible to affirm a higher prevalence of incontinence by the route chosen due to divergence of studies.[17]

Another important factor in the high rates of cesarean sections in Brazil is the involvement of the postpartum vaginal perineum.[18] Despite the prevalence of perineal lesion in women who underwent resolution vaginally, there are variables related to the occurrence and higher degree of these lesions, among them the increase in maternal age, the number of previous vaginal deliveries, the length of the expulsive period and the vertical position at delivery.[19]

The sociocultural dimension interferes in the type of delivery, with the formation of myths, beliefs and opinions.[20] When it comes to pain, a subjective and variable phenomenon among the population, it is the objective of the health network to know the perception and characteristics of pain experienced by these women during this period in order to contribute to the process of humanization of childbirth care and assist in choosing the best method of pain management.[21] The main justification for The cesarean section of choice is the fear of pain. The insecurity of having their pain neglected and the lack of knowledge regarding the alternatives for pain relief encouraged by the WHO, such as free

movement during labor, massages, baths, acupuncture and music therapy are factors that could be reversed with an adequate integration between health professionals and women in the gestational period.[22]

Delivery by high route, or cesarean section, is defined as the birth of the fetus through an incision in the abdominal wall and another in the uterine wall (laparotomy and hysterotomy, respectively), which allows the extraction of the fetus from the maternal uterus, presenting a surgical approach. The incidence of cesarean deliveries in the world has increased significantly in recent years, where Brazil is among the countries that perform the most cesarean deliveries in the world (55.4%) [23]. This frequency has been increasing since the early 1990s, surpassing the proportion of normal deliveries and exceeding the maximum limit of 15% proposed by the World Health Organization (WHO) [24].

The main reason for choosing the upper route ends up being the little knowledge of women in relation to normal delivery, fear, insecurity and the idea that the abdominal route is the safest, since there has been improvement of the surgical and anesthetic technique, greater availability of resources to prevent fetal risks and the practicality of having a scheduled delivery [25]. Thus, the proportion of cesarean sections turns out to be unequal in the country, being more frequent in women with better socioeconomic status, older age, education and primiparous women, where the route is chosen by the patient herself and often by non-clinical factors, being associated with the idea that this route presents a better standard of care. [26] [27]. Together, the patient's choice for the vaginal route is often not supported or encouraged by the family and professionals, in which counseling during prenatal care predominates the perception that the safety of the woman does not depend on the mode of delivery chosen. [28]

However, each route presents its risk and the choice must be individualized for each case. Surgical resolution can and should be a usable resource when pregnancy presents a maternal and/or fetal risk. When for medical reasons in which there is a real need, cesarean section can bring benefits to the reduction of maternal and perinatal morbidity and mortality. [29] Pregnancy at advanced or late maternal age is considered a risk factor for cesarean delivery as a choice, while adolescence was valued as a protective factor for this. [30] Other risk factors considered are those associated with diabetes, long gestational duration, flexed and pelvic cephalic fetal presentation, low placenta, placental abruption and placenta previa, chronic or pregnancy-specific arterial hypertension and its different degrees (preeclampsia and eclampsia), incomplete prenatal care, hemorrhagic syndrome, among several other factors that should be analyzed and individualized for each patient. [31] [32]

Like any surgical procedure, cesarean section presents its post-resolution risks and presents a higher maternal and infant morbidity and mortality when compared to vaginal delivery. [33] Cesarean section when elective may present risks such as puerperal infection, anesthetic complications, lower rate of skin-to-skin contact in the first hour of life of the NB, increasing the chances of negative

perinatal outcomes, absence of breastfeeding in the first hour of life and a higher rate of hospitalization in the neonatal ICU. [34] [35]

It is evident that the rate of prematurity among adolescent parturients is higher in contrast to women over 20 years of age, mainly due to the immaturity of the reproductive system. Thus, it was evidenced that there is an increase in the percentage in the occurrence of prematurity as the age of the woman decreases and especially when prenatal care is done inappropriately. [36]. In addition, low birth weight (LBW) is the most important factor associated with perinatal mortality and morbidity, according to the World Health Organization (WHO) [36] and that early pregnancy plays a relevant role in its occurrence due to social disadvantage, biological immaturity, unhealthy behavior during pregnancy and a lower adherence of pregnant adolescents to consultations in the prenatal period. [37]. Together, there was a significant increase in the number of live births with Apgar scores lower than 7 in the fifth minute, of the order of 1.95% among adults, 3.3% in the 15 to 19 year age group and 6.0% in early adolescence (10 to 14 years). Since the Apgar score of the fifth minute is characterized as the state of oxygenation of the newborn in the antepartum and intrapartum period, it is considered an important predictor of the evaluation of the well-being and the initial prognosis of the newborn, signaling for a good state of this from values above 7. [36]

Among the clinical and obstetric complications most frequently observed in adolescent pregnancies, infections (urinary and gynecological), anemia, gestational diabetes, hypertensive syndromes (preeclampsia, chronic arterial hypertension) and Restricted Intrauterine Growth (IUGR) stood out, with urinary tract infections and anemia as the main ones due to the greater supply of nutrients for fetal development, and some general nutrient deficiencies may occur. [38]

4 FINDINGS

Aiming at a better data analysis for the study, it was divided into two groups: pregnant adolescents from 10 to 14 years old in the period between 2010 and 2020 and pregnant adolescents from 15 to 19 years old in the period between 2010 and 2020.

Regarding the first group (pregnant women aged 10 to 14 years in the periods between 2010 and 2020), 405 pregnant women were counted, of which 4 (0.98%) did not undergo prenatal care, 71 (17.53%) performed it inappropriately, 21 (5.18%) intermediately, 8 (1.97%) adequately, 88 (21.72%) more than adequately, and 213 (52.59%) did not have sufficient data in the gestational registry. Regarding the delivery routes, 311 (76.79%) were normal deliveries and 94 (23.21%) cesarean sections. Regarding the gestational age at which the delivery was performed, 22 (5.43%) of these adolescents were between the 22nd and 36th week, while 313 (77.28%) were between the 37th and 41st week and 12 (2.96%) at 42 weeks. 58 of these adolescents (14.32%) had no records of gestational age at the time of delivery. As for the babies born alive, 69 (17.03%) had weight less than 2500 grams

at birth, 51 (12.59%) had Apgar scores between 0 and 5 in the 1st minute of life and 8 (1.97%) were diagnosed with congenital anomalies. 4 (0.98%) were double pregnancies.

Regarding the second group (pregnant women aged 15 to 19 years in the periods between 2010 and 2020), 9322 pregnant women were counted, of which 38 (0.41%) did not undergo prenatal care, 1303 (13.98%) performed it inappropriately, 194 (2.08%) intermediately, 210 (2.25%) adequately, 2880 (30.89%) more than adequately, and 4707 (50.49%) did not have sufficient data in the gestational registry. Regarding the delivery routes, 6276 (67.32%) were normal deliveries and 3043 (32.64%) cesarean sections. Regarding the gestational age at which the delivery was performed, 14 (0.15%) of these adolescents were less than 22 weeks, 1108 (11.89%) were between the 22nd and 36th weeks, while 7800 (83.67%) were between the 37th and 41st weeks and 386 (4.14%) were between 42 or more weeks. 14 of these adolescents (0.15%) had no records of gestational age at the time of delivery. As for the babies born alive, 957 (10.27%) had weight less than 2500 grams at birth, 1015 (10.88%) had Apgar scores between 0 and 5 at the 1st minute of life and 145 (1.56%) were diagnosed with congenital anomalies. 128 (1.37%) were double pregnancies.

Table 1 — Pregnant women aged 10 to 14 years (2010-2020)

Total No.	40	39	42	48	45	36	41	30	31	33	20
<22 weeks	0	0	0	0	0	0	0	0	0	0	0
22-36 weeks	7	4	10	8	15	10	8	5	4	6	2
37-41 weeks	33	33	28	39	29	26	31	25	24	27	18
42 weeks	0	1	4	1	1	0	2	0	3	0	0
IG ignored	0	1	0	0	0	0	0	0	0	0	0
He didn't.	0	0	0	0	0	0	2	0	1	0	1
Inadequate NP	0	0	0	0	14	10	14	8	8	12	5
Intermediate NP	0	0	0	0	7	2	6	0	2	8	1
Adequate NP	0	0	0	0	4	0	1	0	1	0	2
PN more than adequate	0	0	0	0	13	14	13	17	15	9	7
NP not informed	40	39	42	48	7	10	5	5	8	9	4
Cesarean delivery	9	10	9	15	11	9	8	2	4	10	7
Normal Childbirth	31	29	33	33	34	27	33	28	27	23	13
Peso < 2500g	4	6	9	7	10	5	8	5	8	7	5
APGAR 0 a 5	4	5	6	5	8	7	5	4	3	2	2

Source: DataSUS.

Table 2 — Pregnant women aged 15 to 19 years (2010-2020)

Total No.	974	963	988	1018	1008	901	756	767	712	593	632
<22 weeks	2	2	2	4	0	0	1	1	1	0	1
22-36 weeks	107	114	144	123	116	94	98	91	81	65	75
37-41 weeks	856	801	788	838	835	755	624	646	602	511	544
>42 as.	6	37	54	63	55	52	33	29	29	16	12
IG ignored	3	9	0	0	2	0	0	0	0	0	0
He didn't.	0	0	0	0	9	5	9	4	3	4	4
Inadequate NP	0	0	0	0	253	215	189	177	176	149	144
Intermediate NP	0	0	0	0	43	35	30	33	19	15	19
Adequate NP	0	0	0	0	38	55	34	25	22	19	17
PN more than adequate	0	0	0	0	465	427	403	440	428	335	382
NP not informed	974	963	988	1028	110	164	91	88	64	71	66
Cesarean delivery	352	322	358	359	318	268	225	225	244	174	198
Normal Childbirth	622	639	629	669	690	633	531	542	468	419	434
Peso < 2500g	117	103	112	108	88	77	72	78	69	60	73
APGAR 0 a 5	90	85	84	90	80	69	57	60	43	46	42

Source: DataSUS.

5 CONCLUSION

According to the Brazilian Institute of Geography and Statistics (IBGE), the rate of cesarean deliveries in Brazil is one of the highest in the world, exceeding 55%. However, according to data from the Information System on Live Births (SINASC), in 2020, more than half (68.5%) of deliveries performed in the municipality of Ribeirão Preto in adolescent mothers were vaginal, with 447 vaginal deliveries, to 205 by surgery, totaling 652 deliveries of mothers between 10 and 19 years old.

It is important to identify an emergency case requiring surgical delivery and appropriate obstetric management at the time of induction when resolution by the vaginal route is decided. Since data from the Information System on Live Births (SINASC) of the municipality of Ribeirão Preto, between the years 2015 and 2020, deaths by vaginal route (51 deaths) stood out 92.7% in relation to those by surgical route (4 deaths).

Although cesarean section may be necessary in cases of emergency, it can also be performed at the option of the mother or doctor, without there being a clear indication that the vaginal route is not safe. This can increase the risks to both mother and baby, especially in the case of teenage pregnancies.

Thus, the choice of the mode of delivery ends up having a very intimate connection with the home environment, knowledge and support given to the woman in this phase. The decision generates a clinical discussion where often the woman ends up not participating in the decision-making process, becoming a choice with great influence of the professional. Many women fail to express their opinions

and desires regarding the mode of delivery because they trust the medical decision. When we talk about adolescents, this lack of autonomy at the time of choice becomes even greater, because they end up having less knowledge and less credibility.

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Hepatic and splenic evaluation by ultrasonography and elastography of fibrosis and portal hypertension in *Schistosomiasis mansoni*

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ABSTRACT
Schistosomiasis is a neglected tropical disease and an important public health problem, mainly due to its magnitude and transcendence. Although most cases are characterized as a mild infection, due to its morbidity, the untreated disease can cause economic burden and incapacitation. Periportal fibrosis (PPF) is the most common complication of schistosomiasis mansoni chronic infection and a large number of deaths are mainly caused by the rupture of esophageal varices resulting from portal hypertension (non-cirrhotic). Regarding the diagnosis and assessment of PPF and portal hypertension, different methods are applied. Although wedge liver biopsy is considered the gold standard, it is not justified in non-surgical patients, whereas percutaneous liver biopsy, even considered informative, does not have sufficient sensitivity. Thus, imaging techniques such as ultrasonography, computed tomography, magnetic resonance imaging and elastography have been applied, not only to support the diagnosis of schistosomiasis, but also to assess signs of portal hypertension. In the present chapter, an evaluation of the non-invasive imaging methods currently available for the evaluation of PPF and portal hypertension in schistosomiasis was carried out. The objectivity of elastography compared to ultrasonography is emphasized, because even though ultrasound is more frequently performed, it still has the limitation of being operator-dependent. Transient elastography (TE) has been applied more and it has shown good results in differentiating clinical forms and PPF stages, in addition to presenting potential in predicting esophageal varices. On the other hand, point shear wave elastography (pSWE) has shown more promising results in the analysis of spleen stiffness, when compared to liver stiffness. Therefore, there is a need for further studies applying liver and spleen elastography in the evaluation of PPF and portal hypertension in these patients.

Keywords: *Schistosoma mansoni*, Liver fibrosis, Elastography, Ultrasonography, Portal hypertension.

1 INTRODUCTION

Schistosomiasis is characterized as a neglected tropical disease (NTD), which affects about 230 million people in low- and middle-income countries (UZOEGBO; JACKSON; Bloch, 2022). It is therefore considered one of the indicators of poverty, as it is often associated with the lack of adequate

sanitation systems, poor hygiene conditions and because it is present in the poorest countries of the world (KARUNAMOORTHI; ALMALKI; GHAILAN, 2018; QADEER et al., 2022).

Thus, the WHO roadmap for NTDs (2021-2030) aims at the global elimination of schistosomiasis as a public health problem. Control strategies include preventive chemotherapy with praziquantel, use of standardized and sensitive diagnostic methods, as well as improvements in sanitary and hygiene conditions (WHO, 2020; WHO, 2022).

In this context, the World Health Organization (WHO) estimates that at least 251.4 million people needed preventive treatment for schistosomiasis in 2021. However, during the Covid-19 pandemic and with efforts to mitigate its impacts, there has been a reduction in the provision of NTD interventions, and consequently in treatment coverage for schistosomiasis (WHO, 2023).

In Brazil, schistosomiasis is still an important public health problem, due to its magnitude and transcendence, although the percentage of positivity for *Schistosoma mansoni* in endemic areas has remained below 4% since 2015, with 2.90% in 2018 and 3.22% in 2019 (BRASIL, 2021). Thus, it is currently observed in the Brazilian population many carriers with low parasite load, which persists among most individuals as a result of consecutive cycles of treatment and frequent exposure to the infectious agent (SILVA-MORAES et al., 2019).

However, although most cases are characterized as low-intensity infection, due to its morbidity, the untreated disease causes economic effects and disability (UZOEGBO; JACKSON; Bloch, 2022). In Brazil, there is also a high prevalence of schistosomiasis in urgent care and hospital admissions, especially in the Northeast region, and among males and in the economically active age group of the population (SILVA et al., 2022). Currently, about 20 million people suffer from complications of chronic *S. mansoni* infection. Of these, up to 42% have periportal fibrosis (PPF), considered the most frequent complication. In addition, annually, about 200 thousand deaths are attributed, mainly, to the rupture of esophageal varices resulting from portal hypertension, even with the best hospital care available (ANDRADE, 2009; GUNDA et al., 2020).

Regarding the diagnosis and monitoring of PPF and portal hypertension, these require different methods. Regarding invasive methods, wedge liver biopsy, despite being considered the gold standard, is not justified in non-surgical patients, while percutaneous liver biopsy, although it may be informative, does not present sufficient sensitivity (ROCKEY et al., 2009; SILVA et al., 2010). Imaging techniques such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and elastography, on the other hand, are used not only to aid in the diagnosis of schistosomiasis, but also to quantify PPF and evaluate signs of portal hypertension resulting from schistosomiasis (DOMINGUES; OF MEDEIROS; Lopes, 2011; OLVEDA et al., 2014a; SANTOS et al., 2018; VEIGA et al., 2017).

Therefore, a combination of a comprehensive anamnesis, a complete physical examination, along with biomarkers for liver fibrosis and the use of imaging methods seems to offer the best approach to evaluate these patients (DOMINGUES; OF MEDEIROS; Lopes, 2011; Lambertucci, 2014; SANTOS et al., 2022).

In the present chapter, the different noninvasive imaging methods currently available for the evaluation of PPF and portal hypertension in schistosomiasis mansoni will be evaluated, with emphasis on US and elastography, as well as their applications, advantages and limitations in clinical practice.

2 PERIPORTAL FIBROSIS

PPF is considered a chronic process and usually a complication of schistosomiasis. This fibrosis stems from an excessive healing response to the presence of *S. mansoni eggs in* the portal venules, resulting in embolization and inflammatory reaction in these areas (ANDRIANAH et al., 2020).

Thus, PPF is characterized as one of the drivers of schistosomiasis morbidity and mortality. However, liver fibrosis occurs and progresses differently in individuals with schistosomiasis, although they present the same parasite load and biosocial characteristics, such as age, sex and time of residence in an endemic site, suggesting, therefore, that intrinsic factors still little studied related to the host and independent of the parasite may play a decisive role in the regulation of liver fibrosis in schistosomiasis. The regulation of the progression of liver fibrosis in hepatosplenic schistosomiasis (HEE) is probably multifactorial and requires further studies incorporating this concept (DE CARVALHO, 2023; KAMDEM et al., 2018).

In addition, in patients with HEE, PPF can result from a moderate to advanced form, also called Symmers' fibrosis, and described as *pipe-stem-shaped*. On ultrasound, this fibrosis is associated with splenomegaly, with or without hepatomegaly. In endemic areas, it is possible to find patients with advanced PPF without splenomegaly, also known as the hepatic form of the disease. On the other hand, some individuals without PPF and with splenomegaly due to other causes can also be found, and without the help of US these patients would be misdiagnosed, based on clinical examination, as EHE (SANTOS et al., 2022).

Therefore, Symmers fibrosis is the most relevant feature of liver alteration in schistosomiasis mansoni and is represented by a process of fibrosis along the portal branches and within the portal spaces (ANDRADE, 2004). At the onset of the disease, granulomas around the parasite's eggs can be seen in abundance in these spaces, which disappear when the disease becomes chronic and fibrosis remains. As a consequence, there are also obstructive vascular lesions secondary to granulomas, thrombosis, phlebosclerosis and fibrous thickening of the intima (ANDRADE, 2004; LAMBERTUCCI, 2014).

In short, the main hepatic alteration caused by granulomas results from physical obstruction and tissue compression, while splenomegaly results from both chronic passive congestion and reactive hyperplasia of the reticuloendothelial system due to the very immune stimulus resulting from eggs and worms (DE CARVALHO, 2023; LAMBERTUCCI, 2014). The main clinical manifestation of HES is portal hypertension (non-cirrhosis) and portosystemic collateral circulation, notably esophageal varices (ANDRADE, 2009; COUTINHO, 1968).

In schistosomiasis, the hepatic parenchyma maintains its usual acinar structure, which is reflected in patients with preserved liver function, despite the signs of portal hypertension, but without the stigmas of chronic liver disease, unlike cirrhosis. However, in some cases, compensated HES can progress to decompensated HEE, with the presence of ascites, muscle loss and liver failure (ANDRADE, 2009). These cases of progression from schistosomiasis to liver cirrhosis, with impaired capacity for hepatocyte synthesis, are sometimes observed in clinical practice in patients who have recurrent episodes of digestive bleeding and frequent necrosis of hepatocytes (DE CARVALHO, 2023; SANTOS et al., 2022). In some cases, the appearance of venous fistulas can divert blood flow from the portal circulation to the systemic circulation (hepatofugal flow), providing chronic hepatocyte ischemia and cirrhothinization of the liver (HASHIM; Berzigotti, 2021; SILVA-NETO et al., 2021).

3 PORTAL HYPERTENSION

Portal hypertension is the main complication of liver fibrosis and is defined by an elevation of the venous pressure gradient above 5 mmHg. In HEE, periportal fibrosis by retention of *S. mansoni* eggs in the portal space and granulomatous thrombophlebitis can lead to progressive obstruction of presinusoidal blood flow at the level of terminal portal venules, and consequently to an increase in resistance in the vessels, causing portal hypertension (MASI et al., 2020).

Non-cirrhotic portal hypertension is one of the most important consequences in the natural history of schistosomiasis, since it can lead to its most serious complications such as: esophageal varices, which can cause hemorrhagic events, triggering ascites and encephalopathy, or even death. Additionally, the great splenomegaly, by immune stimulation, can increase blood flow through the splenic vein and further increase the pressure in the portal vein (DE CARVALHO, 2023; COUTINHO, 1968).

In this context, esophageal varices arise as complications associated with portal hypertension and may begin at the most distal end of the esophagus, at first thin and straight, gradually becoming more caliber, bluish, tortuous, reaching the proximal part of the esophagus. The time of formation of varicose veins depends mainly on the severity of portal hypertension, the degree of PPF and individual predispositions. The caliber of varicose veins is directly related to the risk of bleeding (BORGHERESI et al., 2021).

The gold standard for assessing the presence and severity of portal hypertension remains the pressure gradient of the free and occluded hepatic vein, however, this is valid only in cirrhotic because it does not work in cases of presinusoidal portal hypertension, as occurs in schistosomiasis. However, the recent development of non-invasive techniques through elastography offer promising alternatives in the evaluation of portal hypertension and its complications (ROCCARINA et al., 2018).

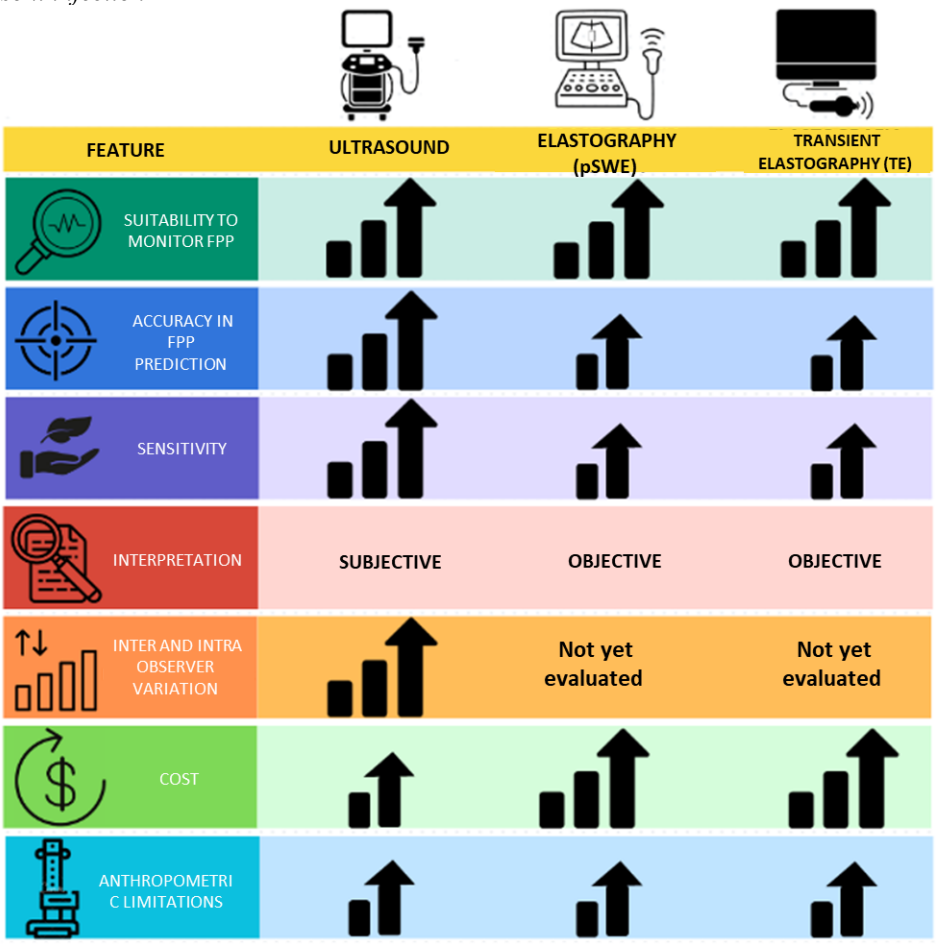
4 NONINVASIVE IMAGING METHODS FOR EVALUATION OF LIVER FIBROSIS AND PORTAL HYPERTENSION

Early detection of serious complications is of great importance in the monitoring of schistosomiasis. Thus, the use of diagnostic imaging techniques such as US, CT and MRI stand out, as each of them has a relevant role in the diagnosis and evaluation of schistosomal disease morbidity (SAH et al., 2015; WEIFENG et al., 2018).

US has been extensively used in the diagnosis of PPF and is considered the main imaging modality for the diagnosis of HES, detection of organomegaly and alteration of liver texture due to fibrosis. However, other imaging techniques, such as elastography and MRI, allow the quantification of liver fibrosis and consequent evaluation of vascular and hemodynamic changes, constituting valuable markers of staging, prognosis and response to treatment (HASHIM; Berzigotti, 2021; MASI et al., 2020). Doppler ultrasonography also enables the evaluation of portal hypertension through some of its clinical determinants: portal vein dilation, splenomegaly, presence of collateral circulation, portal vein thrombosis, portal flow measurement (HASHIM; BERZIGOTTI, 2021).

It is noteworthy that, although CT can detect low-density periportal areas with the use of contrast, and MRI is more sensitive than US, these techniques are not routinely used in the diagnosis of schistosomiasis in endemic sites, mainly due to the use of contrast, the associated risks and costs (BEZERRA et al., 2007; WEERAKOON et al., 2015). Thus, we chose in this chapter to restrict the discussion on imaging methods for the evaluation of PPF and portal hypertension, according to the reality observed in these areas, with emphasis on US, the most accessible technique, and hepatic and splenic elastography. Figure 1 summarizes the main characteristics of these imaging methods.

Figure 1. Advantages and limitations of imaging methods for the evaluation of periportal fibrosis in patients with *Schistosoma mansoni infection*.



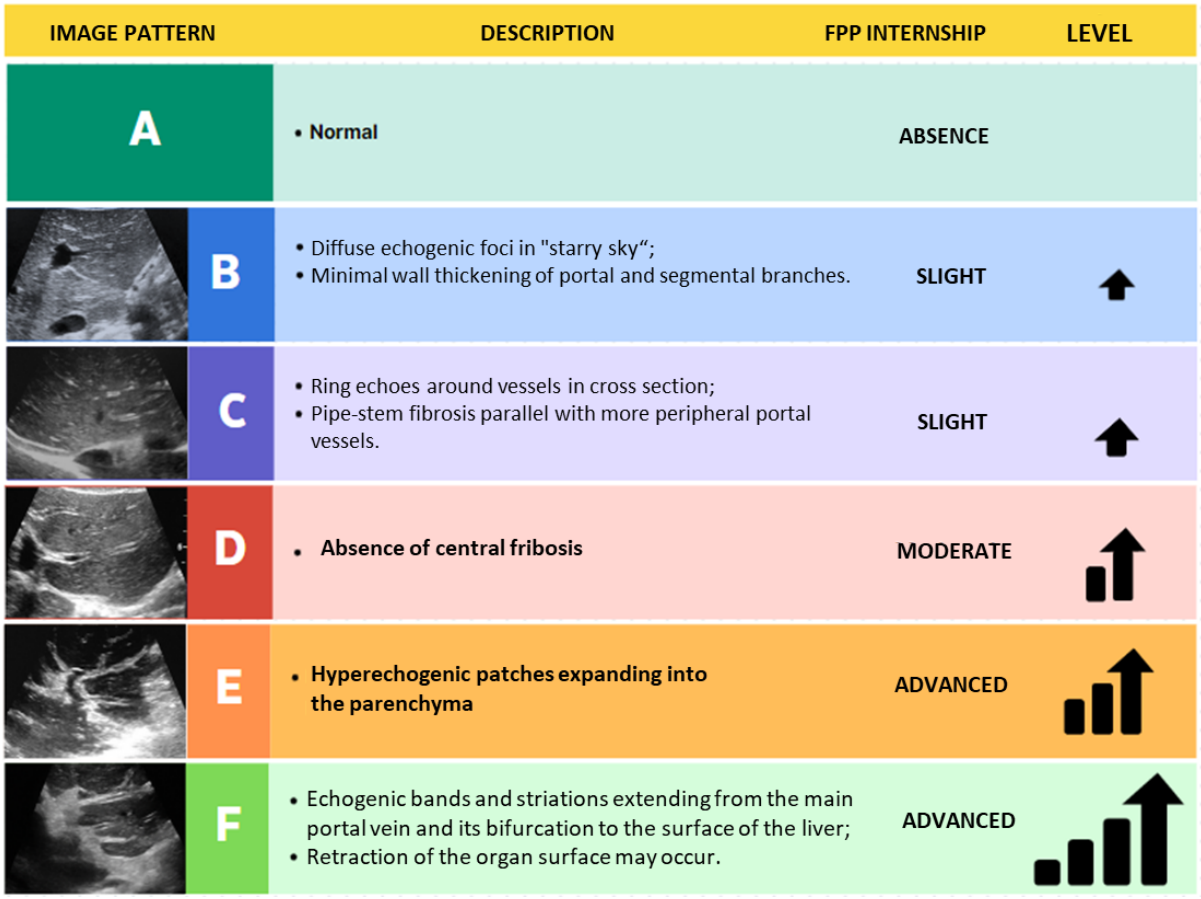
Source: The Authors (2023). Legend: PPF: periportal fibrosis; pSWE: *point shear wave elastography*; TE: transient elastography.

4.1 ULTRASOUND

Due to its practicality and reliability, US has been routinely used in the diagnosis and evaluation of patients with schistosomiasis mansoni, and has become the most well-established tool to assess PPF. This method can be applied both to demonstrate the classic characteristics of schistosomal liver injury, and to classify the patterns of PPF and the clinical form of the disease, based on the criteria of the protocol published by the WHO (WHO, 2000).

US is a simple, inexpensive and safe tool with greater sensitivity in the diagnosis of advanced PPF (Symmers fibrosis), when compared to the milder stages. Since the advent of the WHO protocol, and later the Niamey-Belo-Horizonte Protocol (2001), US has become the gold standard in the diagnosis of PPF and in the classification of its intensity (absent, mild, moderate or advanced). This evaluation is based mainly on the appearance of the hepatic parenchyma and the distribution of fibrosis from the comparison with six image patterns (A to F) (Figure 2). Other protocols previously used, such as Cairo and Managil, were abandoned due to failures in the classification of mild forms of the disease (FRIIS et al., 1996; NOOMAN et al., 1995).

Figure 2. Classification and description of periportal fibrosis imaging patterns, according to the World Health Organization.



Source: The Authors (2023). Liver ultrasound images were obtained from patients with periportal fibrosis due to schistosomiasis mansoni infection using a Siemens device and based on the Niamey standard, Pernambuco, Brazil, 2020.

The high-frequency surface probe allows the characterization of PPF and reveals a band-shaped hyperechoic periportal thickening. During the more advanced stages of PPF, pseudonodules and large patches of fibrosis secondary to extensive scarring and retraction may be observed. Other ultrasound features of HES include hypertrophy of the left hepatic lobe with atrophy of the right lobe, thickening of the gallbladder wall, and splenic nodules. In addition, US also facilitates the evaluation of consequent portal hypertension, by enabling the evaluation of portal vein dilation, splenomegaly and, occasionally, portal vein thrombosis, and also the exclusion of other intra-abdominal diseases (ANDRIANAH et al., 2020; HASHIM; BERZIGOTI, 2021).

Santos et al. (2018) demonstrated moderate to substantial reproducibility in the classification of 358 adult patients with PPF and using imaging standards according to the WHO protocol (SANTOS et al., 2018). In field studies, the use of these standards is reported as simpler and more reproducible than the application of other measures, such as the thickness of the portal branch wall and the diameter of the portal vein, which are also recommended in the WHO protocol (BERHE et al., 2006; KING et al., 2003).

Andrianah et al. (2020) analyzed the stages of PPF in 29 patients with positive serology for schistosomiasis and complications of portal hypertension, such as upper and/or lower gastrointestinal

hemorrhage and splenomegaly, by means of US and according to the degrees of periportal thickness resulting from high echogenicity. The authors identified that stage III was the most frequent in these patients (81.3%), characterized by the presence of hyperechoic periportal bands with thickness greater than 7mm and late diagnosis, followed by stage II (11.5%) and stage I (7.2%). Other findings were splenomegaly in 83.2% of cases, hepatomegaly in 48.9%, portosystemic shunt in 80.7% and ascites in 72.3%, highlighting the importance of US in the classification of PPF, in the investigation of complications such as portal hypertension and in the follow-up of these patients (ANDRIANAH et al., 2020).

In addition, more advanced portable US equipment, such as color Doppler ultrasound, allows a prediction of the prognosis of the disease from the characterization of portal vein perfusion, and thus decisions can be made about the best treatment options for complications of portal hypertension, such as portal vein thrombosis (OLVEDA et al., 2014b). It is also evident that other advances have increased US portability and decreased costs, such as tablet-based ultrasound systems with image visualization through an application, making it more feasible to incorporate this technology into a control program in endemic rural areas, as well as the identification of other diseases and referral of the population to specialized care (STRAILY et al., 2021).

Regarding the limitations of the technique, it is noteworthy that as US is an operator-dependent technique, the previous experience of the examiner is very important in the evaluation of imaging patterns and, therefore, in obtaining more consistent results. Imaging patterns B, C, and D, for example, can also be found in other diseases, such as congenital liver fibrosis, viral and autoimmune hepatitis, primary sclerosing cholangitis, and cirrhosis of the liver. Consequently, a more rigorous observer analysis is necessary to find other signs that lead to a differential diagnosis of liver fibrosis by *S. mansoni* (PINTO-SILVA et al., 2010).

In clinical practice, it is also observed that the Niamey protocol is not widely applied by all physicians who usually perform US, but only by the few who are trained and interested in research projects. It is important to emphasize the need for the evaluation of PPF by US in rural endemic areas to be performed by well-trained physicians or professionals attentive to the differential diagnosis with other liver diseases, resulting in a more efficient application of this protocol.

4.2 HEPATIC AND SPLENIC ELASTOGRAPHY

In general, focal and diffuse liver diseases are associated with structural tissue changes, leading to changes in the biomechanical properties of the liver, which can be quantified by tissue elastography. Elastography techniques can be divided into two main categories, magnetic resonance imaging-based elastography techniques and US-based elastography techniques (TARU et al., 2023). Due to the high

cost and infeasibility of MRI in endemic rural areas, US-based elastography techniques are the most widely used.

Elastography techniques have shown value in the evaluation of HES and portal hypertension, although the evidence remains limited due to the small number of patients evaluated in most studies. Hashim & Berzigotti (2021), highlighted the need for longitudinal studies with larger sample sizes to establish robust criteria to accurately assess the performance of these techniques in predicting regression and progression of the stage of PPF, in addition to identifying their cost-effectiveness in community screening (HASHIM; BERZIGOTTI, 2021).

Elastography-based techniques, such as transient elastography (TE) and point shear wave elastography (pSWE) using acoustic radiation force imaging (ARFI), have received substantial attention regarding the non-invasive evaluation of tissue mechanical properties. These techniques have emerged as complementary to US imaging in the study of liver fibrosis in many liver diseases (COSGROVE et al., 2017; DIETRICH et al., 2017), including schistosomiasis mansoni (LIMA; LACET; PARISE, 2020; PEREIRA et al., 2021; SANTOS et al., 2018; SINKALA et al., 2020; VEIGA et al., 2017, 2021).

Due to changes in the elasticity of the soft tissues of the affected organs, including the liver and spleen, using these techniques, qualitative and quantitative information is obtained that can be used for diagnostic and prognostic purposes (SIGRIST et al., 2017). In this context, the noninvasive evaluation of portal hypertension has become an issue of great interest in recent years. Recently, splenic stiffness has been identified as a potential substitute for the marker of portal hypertension in cirrhotic patients (VEIGA; WALNUT; FERNANDES, 2020). In fact, recent studies have shown that measurement of spleen stiffness by ET and pSWE correlates with liver stiffness and portal hypertension in patients with HES (PEREIRA et al., 2021; VEIGA et al., 2017). Table 1 summarizes the studies that used elastography in the evaluation of PPF and splenic stiffness in patients with *S. mansoni* and Figure 3 summarizes the cutoff points reported in the literature for these methods.

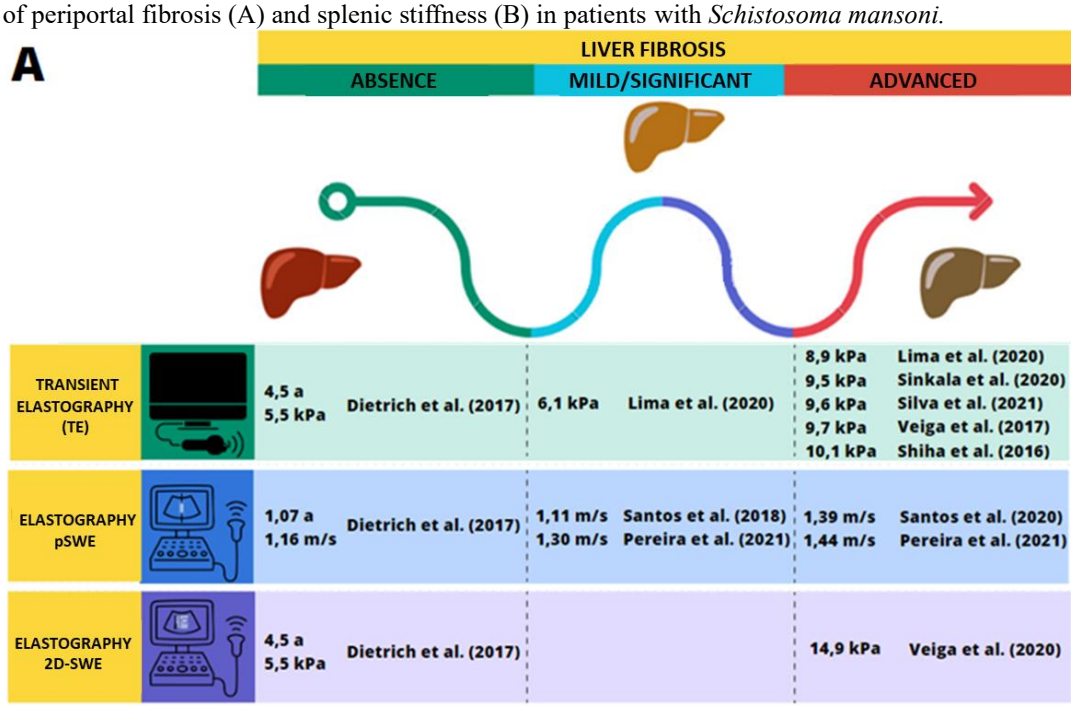
Table 1. Studies described in the literature that used elastography in the evaluation of periportal fibrosis and splenic rigidity in patients with *Schistosoma mansoni.*

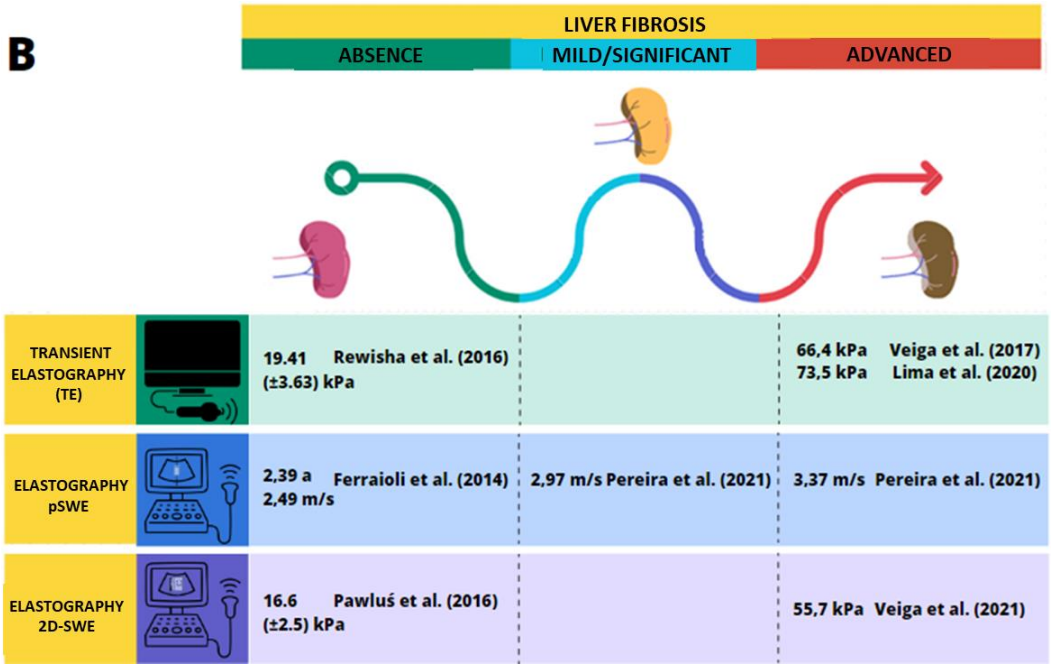
Authors	Location (Country)	Study design	Objective of the study	Number of patients	Variables	Findings
Transient elastography (ET)						
Shiha et al. (2016)	Sherbin (Egypt)	Transverse	To evaluate the accuracy of ET in the diagnosis of PPF.	Schistosomiasis: 30	Hepatic stiffness	Low accuracy in the detection of splenomegaly (36.7%) and varicose veins (37.9%)
Veiga et al. (2017)	Rio de Janeiro (Brazil)	Multicenter transverse	To describe the parameters of hepatic and splenic stiffness by ET in patients with HES and correlate with USG.	EHE: 30; HCV cirrhosis: 30; Controls: 17.	Hepatic and splenic stiffness	Association of liver stiffness with the differentiation between cirrhosis and HES, and splenic stiffness as a potential marker of portal hypertension.
Nascimento et al. (2018)	Sergipe (Brazil)	Transverse	To evaluate the correlation between APRI, FIB-4 and ET.	Chronic schistosomiasis: 17; HCV: 45.	Hepatic stiffness	Positive correlation between APRI and FIB-4 and between FIB-4 and ET in patients with schistosomiasis.
Sinkala et al. (2020)	Lusaka (Zambia)	Nested control case	To evaluate liver stiffness in patients with HEE.	EHE: 48; Controls: 22	Hepatic stiffness	Increased liver stiffness in patients with HES and positive correlation of ET with inflammatory markers.
Lima et al. (2020)	Alagoas (Brazil)	Case-control	To correlate the measurements of liver stiffness obtained by ET with the stage of fibrosis of USG.	Schistosomiasis: 117	Hepatic stiffness	Positive and direct correlation between ET and the clinical form and with the presence of fibrosis and significant fibrosis.
Silva et al. (2021)	Minas Gerais (Brazil)	Transverse	To investigate the role of ET in differentiating between HES and cirrhosis and the factors associated with hepatic and splenic stiffness in HES.	EHE: 29; Cirrhosis by NASH: 23	Hepatic and splenic stiffness	Higher levels of hepatic stiffness, splenic in the group with HES and association with varicose veins and DVT.
Nardelli et al. (2022)	Rio de Janeiro and Minas Gerais (Brazil)	Multicenter transverse	To investigate noninvasive methods in the prediction of esophageal varices in patients with HES.	EHE: 51	Hepatic and splenic stiffness	Variables related to the spleen were shown to be predictors of esophageal varices in patients with HES and non-cirrhotic portal hypertension.
pSWE						
Santos et al. (2018)	Pernam-buco (Brazil)	Transverse	Evaluate the performance of pSWE in predicting significant FPP and determine the best cutoff point.	Chronic schistosomiasis: 358	Hepatic stiffness	pSWE was able to accurately differentiate between light FPP and significant FPP.

Pereira et al. (2021)	Pernam-buco (Brazil)	Transverse	To evaluate the morbidity of schistosomiasis by hepatic and splenic pSWE and relate it to USG parameters.	Chronic schistosomiasis: 74	Hepatic and splenic stiffness	Positive and direct correlation between the FPP pattern and the spleen-only pSWE values. Significant correlations between splenic pSWE values, longitudinal and transverse lengths of the spleen, and portal and splenic vein diameters.
2D-SWE						
Veiga et al. (2021)	Rio de Janeiro (Brazil)	Transverse	To analyze the correlation between single and multiple measurements of liver and splenic stiffness and the variability of these measurements among the hepatic lobes.	EHE: 26 patients	Hepatic and splenic stiffness	Higher values of liver stiffness in the left lobe when compared to the right lobe and conclusion that a single measurement would be sufficient to assess splenic and hepatic stiffness in patients with HES.

Source: The Authors (2023). Legend: APRI: Index of the ratio of aspartate aminotransferase to platelets; HEE: Schistosomiasis, Hepatosplenic; NASH: Nonalcoholic steatohepatitis; FIB-4: Fibrosis-4 index; PPF: Periportal Fibrosis; HCV: Hepatitis C Virus; pSWE: Point shear wave elastography; TE: Transient elastography; USG: Ultrasonography.

Figure 3. Cutoff points reported in the literature for transient elastography (ET) and shear wave elastography (SWE) in the evaluation of periportal fibrosis (A) and splenic stiffness (B) in patients with *Schistosoma mansoni.*





Source: The Authors (2023).

With regard to the limitations of the method, we highlight the cost, the difficulty of availability of the equipment in endemic areas. As well, there is a need for a greater number of studies with hepatic elastography and more detailed studies in relation to splenic elastography.

4.2.1 Transient elastography (ET)

Similarly to most liver elastography techniques, ET performs the measurement of shear wave velocity using a transient force, however, it stands out as the only quantitative elastography method that has not been integrated into a standard ultrasound system and uses an external impulse mechanism (DIETRICH et al., 2017; TARU et al., 2023). It is worth mentioning that in the evaluation of schistosomiasis mansoni with ET, in which liver fibrosis is not diffuse, there is the possibility of triggering the wave impulse on top of a periportal fibrosis beam and, consequently, obtaining overestimated values.

The velocity of the shear wave is obtained through 10 valid measurements, with interquartile range (IQR), and interquartile / median ratio (IQR/M) ≤30%. The more rigid the tissue, the higher the values of liver stiffness, calculated in kilopascal (kPa), while lower values indicate a more elastic liver. In the healthy population, a liver stiffness of about 4.5–5.5 kPa is reported (DIETRICH et al., 2017; TARU et al., 2023) and splenic of 19.41 (±3.63) kPa (REWISHA; ELSABAAWY; ALSEBAEY, 2016).

Initial studies in patients with schistosomiasis mansoni, conducted by Shiha et al. (2016), evaluated the use of ET in 30 patients infected with *S. mansoni,* and reported that this method was not useful in the diagnosis of PPF or esophageal varices, but that it would be necessary to confirm these

findings in a larger group of patients, as well as to evaluate the applicability of ET in cases of prehepatic portal hypertension, such as portal vein thrombosis and congenital hepatic fibrosis (SHIHA et al., 2016).

On the other hand, Veiga et al. (2017) when comparing 30 patients with HEE, 30 cirrhotic patients with hepatitis C virus (HCV) infection and 17 controls (negative serology for hepatitis B and C and no history of liver disease), through ultrasound and transient elastography, observed that schistosomal patients had significantly higher liver stiffness (9.7 kPa) than the control group (3.7 kPa), however, lower than the cirrhotic (27 kPa). Therefore, this assessment may be a useful tool to differentiate cirrhosis-related portal hypertension from that of HES. The authors also highlighted that spleen stiffness was associated with the diameter of the right hepatic lobe, spleen and portal and splenic veins, as well as with the resistance index of the splenic artery and congestion of the portal vein. Thus, in view of these findings, they suggested that splenic stiffness could be a potential surrogate marker for the evaluation of portal hypertension in schistosomal patients (VEIGA et al., 2017).

Similarly, Sinkala et al. (2020) when comparing 48 adults with HES and 22 healthy individuals, identified that the former had greater liver stiffness when compared to the control group. The authors also verified positive correlations between inflammatory markers and liver stiffness, suggesting that HES results in changes in both periportal and parenchymal fibrosis and that the evaluation of liver stiffness may be useful in identifying fibrosis in these patients (SINKALA et al., 2020).

The other studies with ET, conducted only in patients with schistosomiasis mansoni, without co-infection with other liver diseases, sought to compare it with indirect noninvasive markers of liver fibrosis, such as the indices of aspartate aminotransferase ratio over platelets (APRI) and fibrosis-4 (FIB-4) (NASCIMENTO et al., 2018) and with the findings of US (LIMA; LACET; PARISE, 2020). Nascimento et al. (2018), when investigating 17 patients with schistosomiasis 45 patients with chronic hepatitis by HCV, reported a positive correlation between the results of APRI and FIB-4 and between FIB-4 and elastography in patients with schistosomiasis, suggesting that noninvasive methods for diagnosis and monitoring of liver fibrosis in this group have good acceptance. Similarly, Lima et al. (2020), when evaluating 117 adult patients from endemic areas with schistosomiasis, using the Niamey protocol, reported that ET was effective in the diagnosis of PPF, being able to identify advanced forms of the disease and predict the risk of clinical complications in endemic regions.

Regarding the measurement of splenic stiffness by ET, some studies have shown that it can predict the presence and size of esophageal varices, as well as clinical complications in compensated cirrhosis (BARANOVA et al., 2011; NIELSEN et al., 2017; OLVEDA et al., 2014a). Consequently, this measure can also be a predictor of bleeding from esophageal varices in HES and used in the prevention of complications of schistosomiasis mansoni (SILVA et al., 2021).

With regard to this aspect, Silva et al. (2021) compared 29 patients with HEE and 23 with liver cirrhosis secondary to nonalcoholic steatohepatitis and identified lower levels of liver stiffness, and higher levels of splenic stiffness and the controlled attenuation parameter (CAP) in the group with HES. In addition, high splenic stiffness in patients with HES has been shown to be associated with esophageal varices, portal venous thrombosis, previous bleeding of these varicose veins and metabolic disorders (SILVA et al., 2021).

Similarly, Nardelli et al. (2022) evaluated 51 HES patients using ET and identified some spleen-related variables as predictors of esophageal varices in patients with HES and non-cirrhotic portal hypertension: the measurement of splenic stiffness, the diameter of the splenic vein, the index of the measurement of splenic stiffness in relation to platelets (SSPS), the varicose vein risk index (VRS-modified) and the platelet count index in relation to spleen diameter (SRP) (NARDELLI et al., 2022).

In general, in patients with compensated advanced chronic liver disease, the combination of ET ($\leq$ 20 kPa) with platelet count ($\geq$ 150x109/L) is recommended to rule out the presence of varicose veins requiring treatment (DE FRANCHIS et al., 2022)). Roccarina et al. (2017) suggested that the evaluation of specific cutoff points associated with etiology to rule out clinically significant portal hypertension is an unmet clinical need and that incorporating splenic stiffness measurements into noninvasive algorithms and improved measurement scales may improve the noninvasive diagnosis of portal hypertension in these patients (ROCCARINA et al., 2018).

As limitations of ET, it is noteworthy that some changes in liver tissue, such as edema, inflammation, cholestasis, congestion and infiltrative diseases can interfere in the values of liver stiffness, regardless of fibrosis, therefore, these factors should be considered when evaluating the results. Thus, although the examination can be performed by a technical professional, the clinical interpretation should be performed by a specialist who considers the demographic data, etiology of the disease and the biochemical profile of the patient (BOURSIER et al., 2008; DIETRICH et al., 2017; TARU et al., 2023).

4.2.2 Shear wave elastography (SWE)

In SWE, the shear wave velocity is measured, which can be performed at a specific point (pSWE) or at multiple sequential points (2D-SWE, 3D-SWE), chosen as the region of interest – ROI and which are generated using acoustic radiation force (ARFI). While ET uses an acoustic mechanism of external impulse, in ARFI, this impulse is internal, providing a measure of tissue elasticity in meters per second (m/s) or kPa. Thus, the higher the velocity of the shear wave, the greater the hepatic stiffness. In the healthy population, normal values between 1.07 and 1.16 m/s are reported for hepatic pSWE (DIETRICH et al., 2017), and between 2.39 and 2.49 m/s for splenic (FERRAIOLI et al., 2014). With regard to 2D-SWE, 4.5 to 5.5 kPa for liver stiffness (DIETRICH et al., 2017) and 16.6

(±2.5) kPa for splenic (PAWLUŚ et al., 2016) are considered normal . Similarly to ET, in pSWE 10 valid measurements and an IQR/M ratio ≤ 30% are usually required, while in 2D-SWE, there is a need for at least three measurements (DIETRICH et al., 2017; TARU et al., 2023; Villani et al., 2023). However, if these are obtained in m/s the IQR/M should be ≤ 15% (BARR et al., 2020).

In initial studies evaluating pSWE compared to US standards in patients with schistosomiasis mansoni, Santos et al. (2018), analyzed PPF in 358 patients infected with *S. mansoni and* highlighted that this technique could be useful in the diagnosis of advanced forms of schistosomiasis, since ARFI was able to accurately differentiate between mild PPF and significant FPP (SANTOS et al., 2018).

When assessing the morbidity of schistosomiasis mansoni in 74 patients by means of hepatic and splenic elastography (pSWE) and relating it to US parameters, Pereira et al. (2021) reported that as the pattern of PPF progressed, the values of splenic pSWE increased significantly. In addition, these authors observed significant correlations between splenic pSWE values, longitudinal and transverse lengths of the spleen, and portal and splenic vein diameters, indicating the potential of splenic pSWE in the evaluation of morbidity in these patients. These findings, however, were not observed through hepatic pSWE (PEREIRA et al., 2021).

With regard to 2D-SWE, Veiga et al. (2021) analyzed the correlation between single and multiple measurements of liver and splenic stiffness and variability of these measurements among the hepatic lobes of 26 patients with HEE. The authors identified higher values of stiffness in the left lobe when compared to the right lobe and reported an excellent correlation between the first measurement and the median of four measurements in both the hepatic and spleen lobes, concluding that a single measurement would be sufficient to assess splenic and hepatic stiffness in patients with HES.

Regarding the diagnosis of esophageal varices due to portal hypertension, although no studies evaluating patients with schistosomiasis mansoni using SWE have been reported, Hristov et al. (2023) sought to establish whether liver stiffness measured by 2D-SWE could be used as a predictor for the presence and severity of esophageal varices in 86 cirrhotic patients. The authors reported a sensitivity and specificity of 100% in the differentiation between patients at high risk of esophageal varices (grade 4), when compared to the other grades (1 to 3), and suggested that 2D-SWE could be used as a noninvasive method of evaluation in these patients. For the other grades, upper GI endoscopy remains the method of choice (HRISTOV et al., 2023).

As limitations of SWE, the same interferences related to changes in liver tissue stand out, such as edema, inflammation, cholestasis, congestion and infiltrative diseases. The interpretation of elastography results is also a limitation, since in schistosomal patients it is an unusual technique and there are still no well-established protocols (BOURSIER et al., 2008; DIETRICH et al., 2017; TARU et al., 2023). The need for an experienced physician/professional to obtain measurements of liver and splenic stiffness is also highlighted, since this method is integrated into a standard ultrasound system.

5 CONCLUSIONS

Based on what was evaluated in the present chapter, it is highlighted that US and hepatic and splenic elastography are important methods for the evaluation of PPF, tissue stiffness and portal hypertension in schistosomiasis mansoni. In addition, these techniques have been highlighted, mainly because they are non-invasive, when compared to the gold standard, and have a medium cost. The objectivity of the results of elastography in relation to ultrasonography is also highlighted, because although the latter is widely used, it still has the limitations of being operator-dependent and the difficulties of operators in adhering to the Niamey protocol.

When comparing the performance of ET and pSWE in patients with schistosomiasis mansoni, it is noteworthy that ET has been more used and with better results when compared to pSWE in the differentiation of clinical forms and stage of fibrosis, besides being promising in the prediction of esophageal varices. The pSWE, however, has shown better results in the analysis of splenic stiffness when compared to the hepatic one. There are still few studies applying 2D-SWE elastography in the evaluation of patients with schistosomiasis mansoni. In general, we highlight the need for further studies using elastography in the evaluation of portal hypertension and, consequently, the prediction of the presence of esophageal varices and risk of digestive hemorrhage in these patients.

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Evaluation of nursing management reasoning using the concordance test script

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ABSTRACT
Objective: to develop, apply and analyze an instrument for the evaluation of managerial reasoning in nursing in situations of uncertainty based on the concordance test script.
Method: cross-sectional study, carried out in the cities of Botucatu and Lins, state of São Paulo, Brazil. The instrument, based on the theory of agreement of scripts in the form of situations in the dimension of nursing management, was elaborated by three specialists (panel of questions), validated by fourteen specialists in nursing management (reference panel) and applied to fifty students of the last semester of the undergraduate nursing course. Data collection was done electronically, both for the reference panel and for the students The analysis was quantitative through descriptive statistics, analytical and reliability test through Cronbach's alpha. Results: construction of the instrument with one hundred situations of the nursing management process. Validation of all situations by the reference panel that guided the comparison of students' answers. The mean score of the reference panel was 77.06, higher than the mean score of the group of students, which was 67.67, with p=0.0004, demonstrating statistical significance. Data reliability was analyzed using Cronbach's alpha, which was 0.95. Conclusion: the concordance test script proved to have good applicability to evaluate managerial reasoning in nursing in the context of uncertainties, significantly evidencing that the reference panel presents less variability in its answers than the students.

Keywords: Education, Decision-making, Management of professional practice, Nursing evaluation, Nursing.

1 INTRODUCTION

The Law of Guidelines and Bases that governs nursing education designates that professionals must be critical, reflective, dynamic, active and able to understand the new demands and the real needs of the country. In these guidelines, the need to develop competencies (knowledge, skills and attitudes) in: health care, decision-making, communication, leadership, administration and management and permanent education is highlighted.[1] Among these competencies, those that refer to the nursing management process stand out.

A study2 showed that undergraduate nursing courses prepare students for the development of actions of promotion, prevention, management and nursing techniques, in line with the generalist training proposed in these guidelines.

The managerial competencies, from the perspective of nurses, contemplate leadership, communication, permanent education in health and the need for professional experience for the

performance of functions that include the prediction of materials, dimensioning and scales of nursing staff, organization of the work environment; emphasis on teamwork, in order to achieve the quality of care provided.[3]

For the development of managerial competencies, the formative process is complex, as it comprises elements that are subjective and present in the political microspace of interactions between teachers and students in the classroom and between social actors in the field of practice, as well as interaction in the socio-economic, cultural and political context of the society where they are inserted.[4]

A study that mapped the competencies (knowledge, skills and attitudes) in relevant managerial themes during the nursing graduation concluded that in the field of knowledge, the largest number of specific managerial competencies listed and the smallest gaps were verified. Skills and attitudes had the largest *gaps*, suggesting that they are less apprehended in the disciplines of Nursing Administration by the students, thus inferring that there is a need for transformations in the management education of nurses.[5]

Decision-making as a managerial competence of nurses is presented in the ability to evaluate and decide the most appropriate conducts based on evidence, which is in line with the clinical reasoning process. Understanding it is part of the dynamics for teaching managerial competencies in practical situations, which are permeated by situations of uncertainty.[6]

The evaluative methods currently proposed, such as written tests and multiple choices, have great capacity for scientific technical measurement, however, when directed to the evaluation of decision-making skills, they are faced with totally ineffective methods, subjugating the student's ability to discuss practical solutions that have a high degree of uncertainty.[6]

In this sense, the ability to make decisions under uncertainty and solve ill-defined problems are paramount elements of professional competence.[7]

In this perspective, the instruments available for the evaluation of clinical nursing reasoning have great limitations, since they are tests with very well defined questions and solutions. The available tools escape from the reality found in professional practice, because real situations are often faced with poorly defined situations permeated with uncertainties.[8]

Studies based on the script agreement framework, *using* script theory, have brought a new dynamic to evaluate decision-making in these situations through the *Script Concordance Test* (SCT).[7, 14]

The SCT is a written test, widely used in medical schools and related fields. The tests present clinical scenarios of professional life, with circumstances permeated with incomplete information, complex and with a high degree of uncertainty.[9]

However, the use of TSS in nursing is still incipient, with all studies conducted outside Brazil. One of the studies8 considers that it is necessary to ensure that new nurses are prepared to perform

clinical evaluation competently, and nurse educators are challenged to develop effective teaching methods for the development of skills and reasoning in clinical evaluation in nursing students.

In the SCT examiners are presented with a brief description of an authentic case, followed by a series of questions for judgments regarding diagnostic options and conducts, when new elements of information are provided.[14]

Through a survey in the literature, the use of TSS in clinical reasoning was identified, however, with regard to the management process there are gaps, because there are no studies on the reasoning for the decision-making process of nurses using this test. These gaps, combined with the experience of researchers in the teaching of undergraduate nursing courses in the area of nursing management, aroused the interest in answering the following question: Can the TSS contribute to the instrumentalization of reasoning in the dimension of management in undergraduate nursing?

It is believed that the use of a validated instrument can contribute to the instrumentalization of the evaluation of this competence and guide the teaching of nursing education. Thus, the objectives of this study were: to develop, apply and analyze an instrument for the evaluation of managerial reasoning in situations of uncertainty based on the *Script Concordance Test* (SCT).

2 METHOD

This is a cross-sectional quantitative study conducted in the state of São Paulo, Brazil.

The first stage consisted of the construction of an instrument based on the theory of script agreement, in the form of real cases in the dimension of nursing management. These cases were elaborated by a group of nursing management specialists who constituted the panel of questions.

Studies recommend that the components of the panel for the elaboration of the questions are not numerous, and may consist of two to three people[9-11]. Thus, three professors who are experts in the area of management from different public universities in the State of São Paulo were asked to collaborate in the construction, analysis and suggestions of the tests.

The scenarios and situations constructed were guided by the nurse's managerial competencies and did not contain all the necessary data for their resolution, corroborating with the situations experienced in professional practice.

The dimensions of management addressed are independent of each other, and were built with the intention of raising doubts and enabling a reflection to answer them.

After the construction of the instrument, the pilot application stage was carried out. This application was performed before sending the instrument to the specialists in the area of nursing management who constituted the reference panel. To this end, the instrument was sent to five professors, specialists, with experience and degree in nursing management. The participants in this stage did not participate in the question panel and the reference panel. This phase aimed to improve

the instruction for solving the tests, detect failures and enable adjustments that were necessary. In this stage, content validation was performed.

After the pilot application, the instrument was finalized and the specialists of the reference panel were selected, from the curricula inserted in the Lattes Platform considering the following inclusion criteria: being a nurse, with specialization and or strictu senso post-graduation in the area of nursing management, with experience and professional performance for ten years or more. A total of 30 specialists from several higher education institutions with undergraduate nursing courses in the country were invited, 14 agreed to participate in the study, answered the tests and the answers were analyzed in order to establish the reference for the case scores.

After the construction of the scores by the reference panel, the instrument was applied to the undergraduate students of the last semester of the nursing graduation. For the undergraduate nursing students, 58 invitations were sent to the students considering the inclusion criteria: to be attending the last semester of the graduation and to have successfully completed the nursing management discipline. Of the students invited, 50 agreed to participate in this study by answering the questionnaire.

The instrument was adapted to the electronic format, using *Google Drive*, and both the specialists, who constituted the reference panel, and the students answered the questions through this format.

Subsequently, the resulting data were grouped and compared with the data obtained through the responses of the reference panel, attributed by the Likert scale.

Data analysis was performed using descriptive data statistics, with frequencies and percentages for the categorized variables and means, medians and standard deviation for the continuous quantitative variables. To verify the consistency of the questionnaire, Cronbach's alpha was performed. Cronbach's alpha is used to estimate the reliability and internal consistency of a scale, that is, to assess the dimension in which the items of the instrument are correlated.[15th]

Data normality was verified using the Shapiro-Wilk test. As normality was evidenced, we chose to use a generalized linear model followed by Tukey to verify the difference between the score that represents the responses of students and specialists. All statistical analyses were conducted using SAS *software* version 9.2 for *Windows* with a significance level of 5%.

The study complied with national and international standards of ethics in research involving human beings, receiving a favorable opinion from the Research Ethics Committee, ensuring the anonymity of the participants and the clarification of the research.

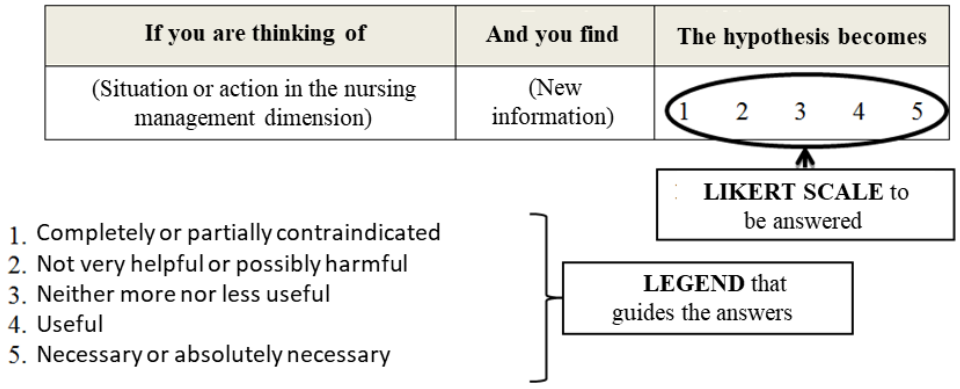
3 FINDINGS

The construction of the scenarios and situations of the decision-making process contemplated three parts, following the guidelines proposed by the *guidelines13*, shown in Figure 1. The first column

presents an action, or conduct within the scope of management. The second column, a new piece of information to guide the decision-making process. The last column is formed by a five-point Likert scale, which represents the possibilities of decision making in the face of each new piece of information.

The following is the structural model of the situations as well as the scoring scale:

Figure 1: Structural model of the situations and their scores.



20 scenarios and 100 situations were elaborated. All of them were described thinking about the decision-making processes through the managerial competencies of nursing, as shown in scenario 14 with situations 52, 53, 54, 55 and 56, presented as an example in chart 1.

Table 1 - Description of scenario 14. Botucatu, SP, Brazil.

Scenario 14: Nurse of the emergency sector forwards to the nursing management a request for a review of the personnel dimensioning, alleging expansion of the functional sites without adequacy of the professional quantity.		
If you're thinking of	And you find	The hypothesis becomes
52- Use pre-sizing to ascertain the need	Expansion of the emergency department due to the establishment of a reference in trauma	1 2 3 4 5
53- Expand humanized care strategies	Hiring a nurse for triage with risk classification	1 2 3 4 5
54- Prevent adverse events	Absence of mid-level professionals due to maternity and sick leave without replacement	1 2 3 4 5
55- Establish provisional measures to supply the necessary quantity	Possibility of establishing the modality of paid shifts	1 2 3 4 5
56- Evaluate current quantitative for new sizing and provision of human resources	Institution committed to the reform of the unit, with no financial resources for new hires at the moment.	1 2 3 4 5

Caption:
1. Contraindicated completely or partially
2. Not very helpful or possibly harmful
3. No more and no less useful
4. Useful
5. Necessary or absolutely necessary

To evaluate the scores, the aggregate score method was used. In this methodology, any answer

given by an expert has a value of its own, even if there is no agreement with the other experts. The score of each item is made according to the frequencies given for each point of the Likert scale.

This scale maintains agreement with the *script theory* and demonstrates the variability of answers offered by experts in the decision-making process through situations of uncertainty.

To form the aggregate score, the frequencies in which the experts' answers were marked in each of the situations were verified (Table 1). Then, for each of the situations, the score value was obtained. This value was used to score the instrument.

Table 1. Example of the frequency in which the answers were marked by the specialists for the formation of the score, Botucatu, SP, Brazil.

Frequency of responses	S01	S02	S03	S04	S05
Answer 1	0	0	0	1	0
Answer 2	2	0	1	1	2
Answer 3	0	1	2	1	2
Answer 4	3	8	3	5	4
Answer 5	9	5	8	6	6

S01= situation 1; S02= situation 2; S03= situation 3; S04= situation 4; S05= situation 5.

According to the example shown in table 1, considering situation 2 (S02), answer option 4 presented the highest frequency of choices by nursing management specialists. This frequency of responses (eight) was then considered the reference value or modal value for this situation. Thus, the score for each response of S02 was obtained by dividing the number of times this response was marked by the reference value. In this sense, the score of answer option 1, for situation 2, is 0/8; for answer choice 2, 0/8; for answer choice 3, 1/8; for answer choice 4, 8/8; and for answer choice 5, 5/8. Thus, the score values for the responses of situation 02 were formed, as can be seen in table 2.

Table 2. Example of scores calculated using frequency and reference value, Botucatu, SP, Brazil.

Calculation of Scores	S01	S02	S03	S04	S05
Answer 1	0,00	0,00	0,00	0,17	0,00
Answer 2	0,22	0,00	0,13	0,17	0,33
Answer 3	0,00	0,13	0,25	0,17	0,33
Answer 4	0,33	1,00	0,38	0,83	0,67
Answer 5	1,00	0,63	1,00	1,00	1,00

S01= situation 1; S02= situation 2; S03= situation 3; S04= situation 4; S05= situation 5.

The calculation was also performed to demonstrate the performance in relation to the maximum possible score (100 situations = 100%) for each of the research groups. The group of students presented a 65% performance, while the group of specialists presented a 77% performance.

Through descriptive and analytical statistical analysis, the means, medians, standard deviations (SD), minimum (Min.) and maximum (Max.) values and the variation of the scores of the groups

(specialists and students) that answered the test were obtained.

All specialists (N=14) and students (N=50) answered all items (N=100). The group of specialists presented a mean of 77.06, with a median of 76.68 and standard deviation of 6.70. The minimum score for this group was 67.29 and the maximum score was 87.21. In the group of students, the mean was 65.97, with a median of 67.67 and a standard deviation of 10.46. In this group, the minimum score was 36.50 with a maximum of 83.71. The variation of the scores was higher in the group of students (47.21) than in the group of specialists (20.23).

The hypothesis of normality of the distributions was tested and confirmed by the Shapiro-Wilk test (SW) with scores in the specialist (p=0.5655) and student (p=0.2395) groups.

Following the hypothesis of normality of the samples, the Tukey test was used to compare the mean total scores of the groups of specialists and students. The mean score of the group of specialists (77.06) was higher than the mean of the scores of the group of students (67.67), with *p=0.0004.*

The Cronbach's alpha coefficient, considering all participants in this study, for the total number of items (N=100), was 0.95.

4 DISCUSSION

During the elaboration of the scenarios and situations, the objectivity, clarity and precision of the same were emphasized, ensuring the clear description of the object of study, but with incomplete contents and with a high degree of uncertainty.[7-12,13] These scenarios and situations were described through the practical and daily experience of the professional nurse in the performance of the management process.

The scenarios are short, with challenging situations due to their context of uncertainty. Even experts have found it difficult to provide a single answer to the problem because the data are incomplete, or because multiple options would be possible, or because there is no consensus in the literature on the strategy to follow.[13]

The literature emphasizes that SCTs are case-based tests, consisting of short scenarios where each learner needs to interpret whether new information contributes to the decision-making process.[16]

The structure of the situations was assigned through the theoretical framework *of the Concordance Test Script*, using three columns, where the first presented a nursing management situation, in the second column a new information and in the third, a numerical sequence of the Likert type, as highlighted in the literature.[7-14,16-17].

For scoring, a Likert scale was used to contextualize the uncertainty, where it was possible to score from 1 to 5, where 1 referred to complete or partial contraindication, 3 as neither more nor less useful and 5 to full agreement with the hypothesis.

The use of the scale through the aggregate method has demonstrated a substantial variability of

specialists, according to the practical context of professional life. This sense, a comparative study between the use of the traditional method and the aggregate method, the latter proved to be of great importance to contextualize the practice of reasoning in situations of uncertainty.[11,16]

The formation of a reference panel is a feature of the *Concordance Test Script*. In this research the reference panel corroborates quantitatively with other studies that indicate the need for the reference panel with 10 to 20 members, which guarantees the reliability of the scores.[13-14.17]

The reference panel of this study was characterized as multicenter, comprising specialists from eight different institutions, with sufficient experience time to ensure reliable scores for replication. The recommendation guide discusses the importance of ensuring professionals with experience and aptitude in the area of study to enable an effective reference panel, which corroborates the methodology of this study.[13]

It was significantly evidenced ($p=0.0004$) that the reference panel presented less variability in its answers than the students. It is inferred that this result is associated with a better ability of specialists to make decisions, because deciding, solving problems and thinking critically are learned skills that improve with practice and consistency.[18th]

The instrument presented good data reliability using Cronbach's alpha of 0.95. The validity of an instrument depends on some variables such as the object of study, the objectives of the instrument and the population to be examined. In this study, validation was performed by expert evaluation, through content validation.[19]

The application of the instrument in online format facilitated the process of application of the instrument, but the fact that the electronic form used does not allow the partial saving of the data associated with the extension of the instrument elaborated, may have been difficult to acquire new specialists since these, in most situations, are involved in numerous research and simultaneous activities.

Even with these difficulties, the electronic format proved to be efficient for the process of data collection and analysis, enabling a dynamic monitoring and treatment of all research.

The managerial dimensions proposed in the performance of the TSS are corroborated in the literature, since they comprise the theme that permeates the management process in nursing that is exclusively performed by the nurse.[20th]

The nurse's managerial work process often goes through situations that require decision-making through a thorough evaluation of the professional's previous knowledge, who in turn needs to do it responsibly, because his decision will directly affect health actions.[21]

The central theme of nursing management evaluation in the context of uncertainties emerges from decision making, since everything a nurse does requires decision making.[22]

The results of this study are innovative in the Brazilian context, since the use of TSS in the

nursing management process was not found in the literature. It is understood from this research that other studies can be carried out, expanding the possibility of teaching strategies for the managerial decision-making process that is permeated by situations of uncertainty.

The limitations refer to the use in a single context of nursing students, as well as the small number of participating students. Also due to the impossibility of comparing in the literature the results of this study in the scope of the TSS applied in the area of nursing management.

5 CONCLUSION

We developed 20 scenarios and 100 situations for the evaluation of managerial reasoning in situations of uncertainty based on the TSS analyzed and validated by a panel of experts (panel of questions, participants of the pilot study and reference panel).

The study provided evidence that TSS provides a reliable and objective means of evaluating reasoning. In the context of nursing education, it demonstrates a viable strategy to evaluate reasoning in students.

The application of the TSS in two different moments of training demonstrated the lowest variability of the data and the highest score among the specialists, allowing them to be detected by the scores, thus affirming the need for a standard *of experts* in the reference panel, which will certainly enable the future use of this instrument in teaching.

Although the TSS is widely discussed in related areas and with extensive international publication, the study is a pioneer in the teaching of Brazilian nursing.

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Marijuana & Mental Health: Therapeutic effects and risks of medicinal and hedonistic uses

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ABSTRACT
The paper addresses the therapeutic effects and risks of the medicinal and hedonistic uses of cannabis on mental health. Preliminary historical and psychosocial aspects of marijuana use and the right to health are preliminarily considered. It points below to the complexity and diversity of medicinal therapy in different situations: epilepsy; Alzheimer 's; anxiety; depression; psychosis and autism; chemical dependence. And finally, the hedonistic use of marijuana, considering psychosocial aspects, sociability and sensitivity.

Keywords: Mental health, Medical cannabis, Psychosocial aspects, Therapeutic effects and risks, V Medical Cannabis Course of UNIFESP.

1 INTRODUCTION

The present text, final work of the V Course of the Medical Use of Cannabis (2021), was elaborated based on the records of the classes and the systematization of readings of bibliographic survey carried out by this author, psychologist and doctor in education, with emphasis on those related to the theme *Marijuana & Mental Health*. We seek to focus on the therapeutic effects and risks of the medicinal and hedonistic uses of cannabinoids and/or marijuana (MALCHER-LOPES; RIBEIRO, 2007; ZUARDI; CRIPPA; GUIMARAES, 2008).

After this Introduction, we address, in the following items, separately, the medicinal and hedonistic use, although, to a certain extent, the boundary between the medicinal therapeutic effects and those related to well-being is not so clear. The latter are usually related to what is conventionally called "recreational use". But here we prefer to adopt the term "hedonistic use", because we consider it more comprehensive and consistent with an equally comprehensive conception of health.

1.1 HISTORICAL AND PSYCHOSOCIAL ASPECTS OF MARIJUANA USE

There is a huge variety of historical aspects reported about the properties, use, and domestication of the plant commonly termed marijuana. The same can be said for the contexts and psychosocial effects of its use (CASTILLA, 2007).

There are several denominations of cannabis, and a long historical process of domestication of the plant and its uses in different countries and times, as well as in different religious orders: Hinduism, Taoism, Buddhism, Rastafari. And yet, in rituals of the Mexican tribes (Tepehua) and Candomblé (Aula 2 – 10/03/2021 - Profa. Renata Monteiro -pharmacist).

It is recorded that in 1899 the Merck Manual already contained clinical indications of marijuana use (Class 4 – 03/23/2021 – Prof. Eliane Nunes). There is a history of the use of the plant and some of its medicinal uses (Epilepsy, Parkinson's, Glaucoma, Chronic Pain, Alzheimer's, Cancer, Sclerosis, Autism, and even Depression, Anxiety and AIDS Symptoms). Then there was strong propaganda against, from the end of the 1920s until years later, with the influence of the racist perspective of the American Anslinger (1937) (Aula 3 – 16/03/2021 – Prof. Paulo Morais).

The historical and cultural representations of the cannabis plant are diverse. As an example in the literature, we can mention Schultes and Hofmann, who refer to marijuana as "Plantas de los dioses". Historical aspects are very old. You can take us back to the year 770 BC. The Brahmins made use of marijuana in the meditative processes of sacred texts. In Mesopotamia there was the religious use of "sacred incense." The use as an anesthetic for minor surgeries, mixed with other products such as datura and wine was also characterized as an ancient historical practice. In Nepal there had since time immemorial the cult of God Shiva, venerated, pointed out as the one who discovered and taught the recipes of *Cannabis.* In India, marijuana was consumed by shamans in the form of a drink to induce trance states. Marijuana is given different names throughout the ages and spaces. It is used and termed as ganja in the Rastafarian cult. This religious-cultural practice or psychosocial phenomenon is relatively well known to other cultures. *Reggae and* some musicians such as Peter Tosh and Bob Marley, are world-famous icons or symbols of Rastafarian culture (Lecture 6 – 06/04/2021 – Profa. Eliana Rodrigue). Hence the correct designation of the existence of a "cannabis culture" (CASTILLA, 2007).

Some studies bring detailed reports on the history of marijuana in the world and in Brazil (CARLINI, 2019; 2006), of marijuana consumption in Brazil (PEREIRA; SHAH; SHIGAKI; LARA, 2018) and about social representations and stigmas in relation to its users (SOUSA, 2013), often mixed with structural racism (ALMEIDA, 2019) (Aula 10 – 04/05/2021 – Prof. Michael Dantas). It is known that the motto of prohibitionism and the politics of wars in Brazil was historically related to racism, police violence and the mass incarceration of the poor, black and peripheral; and that when such social conditions intersect with that of the female gender, other aggravating elements are presented, both historical and current (Aula 8 – 20/04/2021 – Profa. Luciana Boiteux; Class 10 – 04/05/2021 – Profa. Breeze Lima). This meant and means, in addition to a prejudiced attitude, a simplification about the multiplicity of motives and forms of use by different social segments, as diverse as they are difficult to be circumscribed to certain particularities and singularities of classes, groups, age group, or even of social circumstances and influences, the media and government campaigns, among others, even by researchers who tried to do so (PEREIRA; SHAH; SHIGAKI; LARA, 2018). Sousa (2013) points out that negative if not stigmatized narratives of marijuana prevail, despite being conveyed, in daily life and in the media, through a multiplicity of references, from that of merchandise of trafficking, through

that of object of use of celebrities, to its mention and debate as a pharmacological, therapeutic or even "recreational" or "entertainment" product. What is perceived is that the wealth of narratives and references, despite the predominant, degrading if not moralistic character, indicate a polemical and polysemic social construction of marijuana, compatible with its undeniable historical, cultural and psychosocial diversity (CASTILLA, 2007).

Raphael Mechoulam, an Israeli researcher, in the article "Early phytocannabinoid chemistry to endocannabinnoids and beyond", contrary to the myths and prejudices surrounding the plant, revealed, in 1964, from the isolation of delta 9 tetrahydrocannabinol (THC), its therapeutic and anticonvulsant effects. Mechoulan synthesized CBD and THC (Lecture 4 – 23/03/2021 – Prof. Eliane Nunes). In Brazil, the physician and researcher Eliseu Carlini, began his studies on marijuana in 1952, by the Escola Paulista de Medicina. Since then, and in numerous subsequent studies (CARLINI, 2019; 2006; CARLINI; ROBERTS; GALDURÓZ 2004; CARLINI; MASUR, 2004), indicated the anticonvulsant property of cannabis, among others. In the 80's there was interruption of studies (prohibition). UNIFESP, however, develops research on medicinal use in its Observatory. The Journal Observes Marijuana can be an important access to information, as can the episodes of the Miniseries "Marijuana Through Time." One of them deals with the political aspects of marijuana (Class 6 – 06/04/2021 – Profa. Eliana Rodrigue).

In 1992 there was a remarkable discovery: that of the endocannabinoid anandamide, the "substance of happiness", produced by the brain. And in 1993, the identification of CB1 and CB2 receptors. These discoveries could revalue, but always in the midst of all kinds of ebbs and flows, and oppositions of all kinds (moralistic, prejudiced, unjust/legalistic), the historical aspects of the use of the plant for medicinal purposes (MALCHER-LOPES; RIBEIRO, 2007).

We understand that the health of the individual is linked to the health of the social being, to modes of sociability in which human rights are non-negotiable. But the history of civilization and societies rigs welfare conditions for economic interests, and relations of power and domination create a series of obstacles to healthy psychosocial conditions, or worse, engender pathogenic psychosocial conditions. in which subjects in conditions of vulnerability and poverty, or ethnic-racial and gender conditions, are predominantly harmed.

1.2 FROM HUMAN RIGHTS TO CIVIL DISOBEDIENCE

Human Rights are basic and indispensable rights for human life on the planet. Such rights do not admit of any distinction of social class, color, gender, nationality, religion, sexual orientation or of any other kind that nullifies the fundamental rights of a person. The articles of the Universal Declaration of Human Rights express them accurately. It is an official document prepared and approved by the UN Commission on Human Rights in 1948. Composed of a preamble and 30 articles,

they aim to guarantee the social well-being and dignity of humanity. We indicate some of the fundamental rights, such as the right to life, liberty, health, which are mixed with others, such as political, legal, educational and freedom of expression rights.

Article 1 reads that "all human beings are born free and equal in dignity and rights"; Article 2 states that "every human being has the capacity to enjoy rights and freedoms," "without distinction of any kind, whether of race, color, sex, language, religion, political or other opinion, national or social origin, wealth, birth, or any other condition." Article 3 is short and dense: "every human being has the right to life, liberty and personal security." Articles 4 and 5 repudiate slavery and any cruel condition that human beings may be subjected to. Article 11 points out that "every human being accused of a criminal act has the right to be presumed innocent" and that "no one shall be guilty of any action or omission which, at the time, did not constitute an offense under national or international law." Article 12 asserts that "no one shall be subject to interference with his or her private life." Articles 19 and 20 indicate, respectively, that: "every human being has the right to freedom of opinion and expression" or "freedom to have opinions without interference and to seek, receive and transmit information and ideas"; and the "right to freedom of peaceful assembly and association." Article 25 points out that "every human being has the right to a standard of living capable of ensuring for himself and his family health, well-being, including food, clothing, housing, medical care and the indispensable social services." And it is also worth highlighting a complement to Article 27, given the purposes of this text: "every human being has the right to participate freely in the cultural life of the community, to enjoy the arts and to participate in scientific progress and its benefits." We will not dwell on it, because this set of solid propositions is enough to justify how plausible civil disobedience can be in the face of the unscientific and restrictive prohibitions of the medicinal and/or hedonistic use of cannabinoids and/or marijuana.

Prohibitionism hurts fundamental rights. International drug policy instituted a global regime of control from the second world war, but we can refer to a "prehistory" of the "war on drugs", exemplified by the "Temperance League" in the US, of a moralistic character and religious orientation. Before the institutionalization of this policy, there was the force, in the USA, of Prohibition (1919-1936). The global politics or regime of control characterizes a model of moral and ideological social control that aims to persecute producers, sellers, and consumers. There are countries with total control, such as Japan. In Brazil, the user is distinguished from the trafficker. In the Netherlands there is a de facto legalization. And Canada and Uruguay are legalization *in jure*. The Shanghai Commission was the landmark of international control or policy. Prohibitionist control starts from the presumption of trafficking (aprioristic condemnation). In this case, in Brazil, it characterizes violation of the Federal Constitution. And we reiterate, it goes against the Declaration of Human Rights. The rigidity of the prohibitionist model ignores scientific studies on the medical therapeutics of cannabis. The UN, it is

worth noting, fights prohibitionism and defends regulation (Lecture 8 – 20/04/2021 - Prof. Cristiano Maronna).

The National Drug Act is not restricted to the issue of crime. It institutes a national system of drug policy. Establishes norms for the repression of production and trafficking. And it indicates drugs as dangerous. This is opposed to the principles of freedom, autonomy and citizenship, that is, to the principles or values proclaimed in the law itself; principles contradictory to the core of the law (repression) and its criminal nature. The purpose of the law refers to misuse and inclusion – which could refer us to due use (and exclusion). It provides for involuntary hospitalization (by a family member or legal guardian, or even by a health professional, in the absence of one of these). Quite contradictory to the issue of autonomy and freedom of the user. It removes fundamental rights and considers the user as a devoid or unreasonable being. The unconstitutionality of the cultivation ban prescribed by the National Drug Law is being discussed. Distributing without marketing can carry a criminal penalty of 5 to 15 years. Sowing can also be considered a crime, if so discretioned its distribution by the police authority. The law implies a high rate of incarceration due to the framing as traffickers of many who could be considered users. There are sentences whose duration supplants that decided by the late trial. There is a high cost of prohibitionism that could be invested in social policies (GORDHANDAS, 2014). Prohibition still implies low quality of drugs, which tends to further burden the public health system (Aula 8 – 20/04/2021 - Prof. Ítalo Coelho de Alencar).

Prohibitionism or "drug crime" can be considered historically recent (early twentieth century). There are several examples of criminalization in Brazilian history, even when medical use was admitted. Drug addiction was progressively considered as a disease, under the focus of the user as a patient to be criminalized. The so-called "sanitary", "hygienist" model was constituted, which advocated mandatory hospitalization, in the name of the sick and public order. A medical-police system. A stigmatizing and exclusionary control. International conventions have been accumulating and overlapping since approximately 1940, with sanctions, reprimands and civil interdictions. The sanitary model was later replaced by the war model, even before the dictatorial period. In this, the user was then equated with the trafficker. A vision of an authoritarian "social danger of drugs" was naturalized. And addiction was conceived as "mental illness." Many studies point to such criticisms, such as those of Luisa Saad ("Fumo de negro: a criminalização da marijuana no pós-abolição"), Nilo Batista ("Critical introduction to Brazilian Criminal Law"), Saulo de Carvalho ("The criminal drug policy in Brazil: criminological and dogmatic study of Law 11.343/06") and Luciana Boiteux ("The Brazilian antimodel: prohibitionism, incarceration and penal selectivity in the face of drug trafficking") (Aula 8 – 20/04/2021 - Prof. Dr. Luciana Boiteux).

In the face of prohibitionism, the confrontations of fundamental human rights and pertinent questions of the unconstitutionality of some laws in Brazil in the face of the Federal Constitution, civil

disobedience presents itself as a justifiable prerogative. And this struggle for the right (denied) is also a struggle for health. Civil disobedience can be understood as a tool to overcome unjust laws. Thoreou was the originator of the term (USA, 1949). Historical personalities fought them, such as Gandhi in India (struggle for independence) and Luther King in the USA (struggle for civil and black rights). This is a right of resistance. A right of exception. Or still, a legitimate act, because it was erected on the principle of what is just, and which became famous in King's phrase about the "moral duty to disobey unjust laws" (Lecture 5 – 30/03/2021 – Prof. Patricia Milani)

1.3 HEALTH IS RIGHT, RIGHT IS HEALTH

Health problems are socially determined. It is not possible to isolate the disease as something circumscribed to a biological organism, as if it existed in an environment devoid of economic, political, moral, cultural and social clashes. As if there were no conflicts and antagonisms in a class society. Mercantile values often overlap with pro-life values. There are such problems in all areas. Even the struggle and civil disobedience in favor of the health and freedom of the cultivation of cannabis for medicinal purposes are interposed industrial interests, which forge the production of the synthetic cannabinoid, even though the extracted cannabinoid phytopharmaceutical has greater safety of use. The point is that rights are a condition for health. Hence the maxim that health is right, and right is health.

Legalization is necessary under several arguments. And the prohibition compromises three dimensions of use: substance (which can be degraded), body (inadequate dosages) and society (with increased violence). Legalization and regulation can protect at-risk groups and respect users. The use of medical cannabis in some diseases and the reasons and arguments that support its advocacy for science are expressed by the Movement for the Regulation of Medical Cannabis (MOVRECAM). There is a relationship that can be established between prohibition and the absence of regulation that stimulates the illegal market, violence, repression and corruption. Planting can favor the best use of the active ingredient and the "committee" or "entourage" effect of marijuana. In addition, it can correct the social imbalance of access to cannabis. The prohibitionist policy and the war on drugs historically falls on the poor, blacks and peripherals (Aula 1 – 02/03/2021 – Prof. Sidarta Ribeiro).

Health problems of different origins could benefit from the medicinal use of cannabis, as well as avoiding medications with unwanted side effects. This is the case with sportsmen, for example. Or Cannabidiol (CBD) can act in the prevention of injury in high-performance athletes. Many athletes prefer the use of CBD over painkillers and anti-inflammatories. It is necessary to debate what is or is not harmful to the athlete. In 2018 the World Anti-Doping Agency (WADA) withdrew CBD as doping. We emphasize that there is chemical dependence and side effects of analgesics and anti-inflammatory drugs and heart and kidney health risks. Cannabidiol is an alternative to ibuprofen. It can be used not

only in chronic pain, but also for ostearthritis and fibromyalgia. Or even, to accelerate recovery after physical exercises of athletes. CBD assists in the maintenance of homeostasis. Several athletes of different modalities have made or are making medicinal use: Andrew Flansky, triathlete, for injury to the hip flexor tendon (athlete reported improvement in hip, anxiety and sleep); Martellus Bennet, American football; Billy Kemper, Company *EcoScience*, which he sells (he used it for his mother with cancer, initially, and then for himself, in place of painkillers, and referred to improvement for usual problems of flight routines and time zones, as it helps with sleep). Bob Burniquitis, skateboarder; Nate Diaz, MMA fighter, for healing and inflammation (vaporized use); The NBA's Kareem Abdul-Jabbar. And yet, the case of Ross Rebagliati, *snowboarder*, who lost a gold medal on charges of use/doping, but was later proven to have been passive inhalation and regained the medal. CBD can be considered a mild remedy and of low acute toxicity, indicated as anxiolytic, analgesic, antioxidant and active neuroproducer (Aula 4 – 23/03/2021 - Prof. Raul Thame de Toledo Almeida)

There are a diversity of social and contextual issues related to the social and medicinal use of cannabis. Health is a question of citizenship, of struggle for rights, and not a practice circumscribed to medical-biological expertise. Health involves social, medicinal and legal aspects. Civil and political rights can be related to citizenship and identity of the social being. Social and health rights are provided for in the Federal Constitution. The WHO's notion of health is related to full well-being. There are collective interests related to the popular medical cannabis movement. It is important to recognize the authenticity of the popular cause, popular education and the black and women's movements. The work of Paulo Freire highlights the importance of social action aimed at emancipation from oppression (Aula 5 – 30/03/2021 – Profa. Patricia Milani). The aforementioned civil disobedience and the moral duty to fight unjust laws is also articulated to an educational practice by Mandela, in a phrase equally famous to that of Luther King: "education is the most powerful weapon of changing the world." Father Ticão (deceased, one of the protagonists of the Course that gives rise to the present work) was moved by social ideals such as this, as well as those previously mentioned, Luther King and Gandhi. And Sidarta Ribeiro considers the prohibition of the therapeutic use of cannabis a colossal historical error on a planetary scale. In the country we have more than 10 thousand patients registered with ANVISA and more than 20 thousand linked to some cannabis association. The WHO indicates the safety and efficiency of the medical use of cannabis and defended its removal from the list of proscribed or prohibited substances. Domestic cultivation and extraction of oil from the plant is a right to health and life. And the cultivation itself does not materialize crime (Lesson 5 – 30/03/2021 - Profa. Deborah Garcia).

PL 399/2015 does not contemplate domestic cultivation. It is important, for the movement to decriminalize the cultivation of cannabis sativa for personal therapeutic use, the signing of PLS 4514/2017. A survey by SBEC in Brazil points to the following data: 79% in favor of medicines from

the plant; 87% aware of the possibility of use as a remedy for diseases; but only 41% know which diseases and 9% know someone who has used them; 91% of respondents without religion support the distribution by SUS (percentiles of 81% for Catholics and 70% for evangelicals). A total of 27 countries removed cannabis from Annex IV of the 1961 Convention on Narcotic Drugs (against 25 and 1 abstention, Brazil among them). The reclassification had been recommended by the WHO. Brazilian regulations are restrictive. And there is a high cost of medication (Mevatyl at 2,800 reais a box). In this way, the struggles for the inseparable right-health pair proliferate, such as those of the manifesto of support for cannabis research, which can be done by the link http://bit.ly/2LBiK5O (Aula 4 – 23/03/2021 - Profa. Eliana Nunes).

2 THE THERAPEUTIC EFFECTS AND RISKS OF THE MEDICINAL USE OF CANNABINOIDS AND/OR MARIJUANA FOR MENTAL HEALTH

2.1 THE COMPLEXITY AND DIVERSITY OF THERAPEUTICS AND CANNABINOID PROPERTIES

The therapeutic-medicinal use of cannabinoids in mental health should be selective and parsimonious, that is, one should select well the oil or product according to the behavioral issue to be treated, and always with caution regarding the dosage so that it is neither insufficient nor beyond what is necessary. The selectivity refers us to the multiple cannabinoid properties of the plant and the different medicines derived from them, as well as to the attention to the "entourage" effect that may or may not be present in the chosen drug. And due to this selection occur the variations regarding the dosage, or evolution and management of the dosage.

There are many diseases in which the medicinal use of cannabis can be beneficial, some of them from the field of mental health (epilepsy, Alzheimer's) and public health (cancer) of great interest. Benefits and risks should be investigated and directed to selectivity and dosage. In the case of epilepsy, for example, traditional treatment leads to the reduction of "neuronal firings," but at the expense of drowsiness. In this disease one can use the cannabinoid, which produces dissynchrony, without generating the lethargy of the torpor of the traditional treatment. Studies are not assertive in frequent pathologies, as in the case of cancer. Although such a health problem does not integrate the field of mental health, it should be noted that a discussion focused on the issue of mental health problems cannot fail to point out that there is no pathology that does not involve the behavioral and psychodynamic factor. In the case of cancer, the medicinal use can mitigate side effects of chemotherapy (pain, lack of appetite, sleep problems), and some studies even point to antitumor properties, although there are controversies, and this neuroprotective aspect is very important in the approach to mental health pathologies (Aula 1 – 02/03/2021 - Prof. Sidarta Ribeiro).

The effects of the different drugs, properties and forms of use should always be taken into account on the basis of selectivity and parsimony. An important question is whether it would be better to allow planting so that there is the use of the whole plant and its "entourage" effect or only use of the active principles. It is considered that the whole plant can further expand the range of research and uses. At the same time, in the field of mental health, caution must be exercised, according to the pathology, in the use of the drug whose THC principle is operative. It is also worth considering that the legalization of active ingredients could maintain greater control of some risks. There are risks of use and risk groups. Early and abusive use in adolescents and young people is not recommended. And the use in the elderly tends to be more beneficial than in other age groups (Aula 1 – 02/03/2021 - Prof. Sidarta Ribeiro).

There are differences between the isolated cannabinoids and those from the extract. Ethnopharmacology addresses the perception of communities of substances that interact with their organisms. The *Cannabis sativa* is from the family *cannabacea*. There are two subspecies: sativa and indic. In relation to the various types of plants, there are hybrids (male and female in the same plant). Hermaphrodites are rarer, such as C99 or Cinderella 99. The male plant has a low concentration of THC (e.g., hemp, which is rich in fiber). The female plant has a large amount of resins with medicinal richness. There are 3,000 varieties of the same family. There are narcotic properties (hedonistic use) and therapeutic properties (medicinal use) (Lecture 6 – 06/04/2021 - Prof. Dr. Eliana Rodrigues).

The prescription, use and management of cannabis-derived products should be carried out with the aid of pharmacogenetics. Pharmacogenetic testing is useful for treatment choices. The chronic and abusive use of THC can generate psychotic symptoms or schizophrenia in predisposed individuals (polymorphism in a reduced portion of individuals). In this pathology the question of the selectivity of the property of the drug is fundamental. In the case of anxiety, THC can be beneficial, and dosage is key. A former marijuana smoker before treatment whose medicinal oil is used for pain, for example, may benefit from pain reduction but feel more anxious if THC metabolism is reduced. The hypothesis of behavioral and metabolic polymorphism should be considered. The finding of such a condition leads to adjustments or management of treatment in order to avoid adverse effects of anxiety. Pharmacogenetics improves clinical decision-making and optimizes benefits. It helps to avoid adverse effects and saves time and money with treatment (AULA 15 – 08/06/2021 – Prof. Dr. Fabrício Pamplona).

The properties of the drugs vary according to plant, form of cultivation and extraction. Only the discussion of trichomes and terpenes would lead us to a series of considerations that are beyond the scope of this work. Parthenocarpic infrutescence is the scientific name for the fruit of marijuana. Trichomes are secretory glands rich in THC. Terpenes (a substance present in the plant that has taste and smell) are secondary metabolites, and flavonoids, bioactive compounds. At UFRJ, a

standardization of the extraction process was developed (the first regulated and standardized extraction in Brazil). It was sought to obtain at each harvest an extraction with the same concentration of cannabinoids and terpenes (standardization of the product). The purest extract is golden in color. Despite the diversity of drugs we can consider, generically, that by influencing the activity of the cannabinoid system we can interfere in almost all diseases that affect humans. But we must highlight possibilities of contraindications, and in the focus of this work, the need for caution in the administration in cases of tendency to psychosis, bipolar disorder, anxiety, phobia, paranoia, adolescence (amotivational syndrome) and schizophrenia (CLASS 19 – 06/06/2021 – Prof. Renata Monteiro).

Terpenes (secondary metabolites) are volatile and aromatic chemical compounds. Myrcene is one of the most common terpenes in marijuana. It is a natural oleofinic organic compound that associated with CBD reduces pain. Linalool has therapeutic potential in the case of Alzheimer's. Terpenes are produced by plants, animals, microbes and fungi, with the most diverse purposes. More than 40,000 species are known. They are arguably the largest and most diverse class of naturally occurring organic products (class of natural hydrocarbons). In plants they are part of the natural or specialized metabolites. Medicinal properties such as: inhalation of certain terpenes associated with improved mood and emotional well-being stand out; antitumor, anti-inflammatory, antifungal, antibacterial, antioxidant effects, as well as pain relief, bronchodilation, muscle relaxation and neuroprotection (AULA 19 – 06/06/2021 – Prof. Lu Cannabier) (AULA 19 – 06/06/2021 – Prof. Lu Cannabier).

Marijuana has 1500 compounds and 177 cannabinoids. Cannabis sativa of the female gender during the reproductive phase produces parthenocarpic infrutescences. We can highlight two compounds: THC and its therapeutic action: bactericidal, anti-inflammatory, analgesic, corticosteroid, immunoregulatory, neuroprotective, brain regeneration and proliferation of neurons in the hippocampus; and CBD: serotonin balancer (Lecture 2 – 10/03/2021 - Profa. Renata Miller)

As demonstrated by Israeli researchers Raphael Mechoulan and Shimon Bem-Shabbat on the "entourage" effect, all the natural components found in cannabis (cannabinoids, terpenes) combine synergistically with increased beneficial effects. That's because the effects of cannabis compounds alone aren't as effective as when they act synergistically. About Myrcene, in addition to the anti-inflammatory properties (which help in reducing swelling in lesions and improving the immune system response) there is aid for relaxation, sleep quality and anxiolytic and antidepressant effects (increased dopamine), providing positive feelings and reducing excessive (anxiogenic) activity of the nervous system (AULA 19 – 06/06/2021 – Prof. Lu Cannabier).

As already mentioned, one of the great discoveries after the effects of THC in the history of marijuana studies (especially the anticonvulsant), was the existence of the endocannabinoid system.

Its action is referred to by the metaphor of the "maestro of the organism" (diverse, metabolic, immune systems) and its neuroprotective potential is discussed in the field of application to mental health pathologies.

The endogenous cannabinoid system (ECS) includes receptors, endogenous ligands, or endocannabinoids themselves (such as anandamide, AEA and 2-arachdonoyl glycerol, 2-AG), and enzymes. The cannabinoid molecule is recognized by a receptor. The receiver produces responses that generate ion channel opening and effects. THC is a partial agonist of CB1, like other cannabinoids or phytocannabinoids. The synthetic cannabinoid is a full agonist and has a response of greater amplitude. The safety range of cannabinoids is wide (Lecture 3 – 03/16/2021 - Prof. Paulo Morais). The theme is vast and includes biochemical knowledge that goes beyond the limits of the systematized knowledge for the elaboration of this work.

The discussion on the use of marijuana for mental health benefits includes relevant contributions, such as those of Malcher-Lopes and Ribeiro (2007), "Marijuana, brain and health", and of studies organized in the collection "Cannabis and Mental Health: a review on the drug of abuse and the drug" (ZUARDI, CRIPPA, GUIMARÃES, 2008). In this collection, we highlight Part IV, dedicated to Cannabis and Psychopathology (includes texts on anxiety, psychosis, mood, post-traumatic stress), and Part V, in which cannabis is made explicit as a drug of abuse, which differs from hedonistic use, to be considered in the next item.

The broadest and most basic discussion on drugs is carried out by Carlini and Masur (2004), and on cannabinoid substances in medicine we have the relevant systematization of Carlini, Rodrigues and Galduróz (2004), but because of the limitations of this work, they will not be presented.

Malcher-Lopes and Ribeiro (2007) present a table entitled "Pharmacological properties of cannabinoids present in marijuana", as well as a Glossary at the end of the book that "translates" technical-scientific terms. We extracted from the table only the pharmacological properties of the two most well-known cannabinoids: THC and CBD. We present: which are only THC; which are from THC and CBD; and which ones are just from CBD. We highlight in bold those directly related to mental health-disease processes:

THC Antipyretic

Antiviral THC

THC Appetite Stimulator

Hipotensor THC

Psicotrópico THC

Analgésico THC e CBD

Ansiolítico THC e CBD

Anticonvulsivo THC e CBD

Antiemético THC e CBD

Antiinflamatório THC e CBD

Antioxidante THC e CBD

Antitumorígeno TCH e CBD

Imunodepressor THC e CBD

Neuroprotetor THC e CBD

Sedative THC and CBD

CBD Antipsychotic

Antispasmodic CBD

If the use of cannabis in mental health problems deserves to be discussed with regard to the specificities of such problems, it is worth mentioning that the issue of anxiety and depression, just to stay in two aspects, affects numerous other pathologies in which cannabis can be administered (either in the treatment of the disease or the symptom). Thus, we consider it important to mention possible biopsychic benefits of the use of cannabis in a pathology that does not concern mental health (although it can be considered a psychosomatic disease) and that is responsible for the death of a significant number of individuals and populations: cancer. Cannabis in cancer can act as: appetite stimulant; antitumor effects; anti-nausea and anti-vomiting action (induced by chemotherapy). For some patients can act as protective action in peripheral neuropathy, analgesic (reduces doses of opioids); for others, they may have a beneficial effect on anxiety, depression and sleep. The dosages and known composition of the oils should be well observed, to avoid risks in place of responsive effects (Class 9 – 27/04/2021 – Prof. Dr. Paula Dall'Stellaasil).

Given the general considerations presented here, with emphasis on the issue of selectivity, parsimony and propriety of the uses and management of cannabinoid drugs, we will present, albeit synthetically, some of their characteristics in specific mental health issues, such as: the anticonvulsant effect in epilepsy; the neuromodulatory action and on memory in the use in Alzheimer's; the possibilities and precautions of use as an anxiolytic; the challenges and risks of use in depression; and the use of CBD as a medicinal cannabinoid in psychosis and autism.

2.2 THE ANTICONVULSANT EFFECT IN EPILEPSY

The anticonvulsant effect is characterized as the best known and perhaps best proven in medicinal studies of cannabinoids. It was discovered in 1839. The treatment of epilepsy with cannabinoids can be considered an ancient promise for a better future. Records of cannabis use for epilepsy (seizures, seizures), pains etc., date back to 2700 BC in China and 1000 BC in India. Irish physician Brook discovered the use for pain, cholera, tetanus, and seizure in 1843. In 1973, Brazilian physician Carlini discovered the anticonvulsant property of CBD in rats. And a clinical trial in 1980

(Cunha et. al.) finally confirmed this property. There is increased endocannabinoid neural action and limitation of the spread of epileptiform neuronal activity. In the long term, there is also, in theory, a neuroprotective role of phytocannabinoids. Lutz et. al. indicate increased endocannibinoids in response to epileptiform activations, corresponding to a "natural" containment of hyperarousal. Geffrey pointed to a positive interaction of cannabidiol with clobazan. There are many studies with CBD and need for more studies with *Full Scream*. Holanda and Polona (2017) pointed out in a double-blind randomized study a reduction of 43.95% of seizures. The high number of patients refractory to conventional treatments shows that the search for new treatments is essential and that these are essential to increase the quality of life. The high incidence of side effects, added to the high costs/difficult accessibility, drives the search for new therapeutic strategies that increase patient adherence (AULA 13 – 05/25/2021 – Prof. Ortale Trainotti). Since it is necessary to expand studies and that can be more detailed, which is valid for most studies on the medicinal use of cannabis, an unfortunate legacy of the senseless prohibitionism in relation to the plant and scientific research.

The pharmacological effects on epilepsy were addressed by Israeli researcher Mechoulan in "*Cannabinoids in health and disease*." This, together with Prof. Dr. Carlini (former professor of UNIFESP, deceased, renowned and widely recognized reference in marijuana research,), published, in 1978, a study of the effects of CBD for epilepsy (Aula 4 – 23/03/2021 - Profa. Eliana Nunes).

Epilepsy should be distinguished from epileptic seizure. While epileptic seizure refers to abnormal neuronal activity, epilepsy concerns a heterogeneous group of neurological disorders that have a chronic tendency to epileptic seizures. The (acute) crises demand a therapeutic approach to the triggering factor. Whereas epilepsy has as its object of treatment the seizure threshold. There are epileptic seizures of different types: focal (neuronal networks of a single cerebral hemisphere) and generalized (2 hemispheres) that are more exuberant (e.g., tonic-clonic crisis; absence crisis) (AULA 13 – 25/05/2021 – Prof. Giovanni Ortale Trainotti).

Epilepsy affects all ages. It is the second neurological disease in young adults (the first is migraine). Worldwide, it affects 1% of the population. It is higher in developing countries where there are, among others, a higher number of prenatal diseases. The goal (not always achieved) of conventional treatment is seizure control without side effects. There are 25 antiepileptic drugs (which is an indicator of the difficulties of treatment that achieves the indicated goal). The following problems are identified in conventional treatment: high incidence of side effects (sleep, drowsiness, changes in appetite and weight, mood swing, paresthesia or "tingling", visual changes and variations in neuroendocrine axes); high cost; poor accessibility and low adherence; frequent drug interactions (AULA 13 – 25/05/2021 – Prof. Giovanni Ortale Trainotti).

Regarding the prognoses, it is known that the longer periods of uncontrolled crises and the greater durability of the crises have negative prognostic effects. The higher incidence of crises

generates psychosocial losses and a higher risk of depression and mortality. Sudden death occurs in 1 in 1000 patients/year, especially in young adults. Even with a wide range of medications, 1 in 3 patients continue to have seizures. "Resistant epilepsy" (denomination for cases in which maximum doses of 2 drugs have already been tried without success) affects 35% of cases. These are the so-called "refractory cases" (AULA 13 – 25/05/2021 – Prof. Giovanni Ortale Trainotti). So what's the option? Cannabis medicines. Throughout the course, mothers whose children suffered from several epileptic seizures on the same day and who did not obtain results with conventional treatment, made their testimonies about the very positive results of cannabis treatment.

The therapeutic medicinal use of cannabis in epilepsy is discussed in a scientific article by Mattos et.al. (2017). The authors conducted a survey of studies from 1940 to 2015. They indicate, based on such systematization, the use of CBD for seizures. They point out that the improvements vary from total to partial. They argue that it is an effective treatment, without adverse and toxic effects. And yet, without creating tolerance, dependency or abstinence. Finally, they emphasize that the control of seizures prevents brain damage, in order to modify what would be the natural history of the disease.

2.3 THE ACTION ON MEMORY AND QUALITY OF LIFE AND THE USE IN ALZHEIMER'S

Alzheimer's is a neurodegenerative disease and the most common of the dementias related to senility or pathological aging. It affects more women than men and affects mainly in the 75 to 80 years, 80 to 85 years (MANZARO, 2017).

There is a forecast of the increased longevity of the world's population that indicates that by 2050 there will be twice as many elderly people as in 2010. From the age of 85 there is a 40% chance of having Alzheimer's. There are 50 million demented people in the world. And by 2050 that number could be 152 million. The disease is more common than you might think: 1 in 10 people over the age of 65 has Alzheimer's. The use of cannabis medicine can act from favoring better quality of life (restorative sleep, better appetite, improvement of common pains in old age), through its modulating action of the body and its metabolism, to neuroprotective effects that can slow down mnemic or memory losses. The effects of cannabis use are not antagonistic to those of conventional drugs and the necessary deepening of research seems quite promising for the prevention and treatment of the disease.

The term "dementia" is a generic name. In order to be able to fit in case of dementia requires at least 2 of the following symptoms: memory problem, language problem, executive dysfunction, attention dysfunction and social cognition abnormality. Alzheimer's is not a sudden disease, on the contrary, it is progressive and insidious. It involves progressive synaptic and neuronal loss, as well as plaque accumulation of beta-amyloid proteins. We can indicate 10 signs, namely: memory impairment that disrupts everyday life, difficulties in planning and problem solving, difficulties in completing familiar tasks, confusion with time and place, difficulty in understanding visual information and spatial

relationships, problems with words in speech or writing, not knowing where to put things (losing the ability to "redo steps"), difficulty judging, withdrawal from work or social activities, change in mood and personality. And the following risk factors: age (highest risk factor), family history (mainly first-degree relatives), genetics (risk genes; deterministic genes), head trauma, diabetes, hypertension, cardiovascular disease, hypercholesterolemia, sedentary lifestyle and smoking. Prevention factors are: reduction of risk factors (e.g., control of the diseases mentioned), regular physical exercise, healthy eating (whose guideline may be based on the *slogan* "peel more, unwrap less"), social connections, keeping mentally healthy, regular sleep, avoiding tobacco and avoiding excess alcohol (AULA 13 – 25/05/2021 – Prof. Denise Lufti Pedra).

There are other neurodegenerative dementias with some converging symptoms, but with distinct characteristics, such as: frontotemporal dementia, corticobasal degeneration, traumatic encephalopathy syndrome, Huntington's disease, Lewy body dementia, progressive supranuclear palsy. And yet, non-degenerative dementias: vascular dementia, normal pressure hydrocephalus, vitamin B12 deficit, hypothyroidism, depression, infectious dementias (AULA 13 – 25/05/2021 – Prof. Denise Lufti Pedra) (MANZARO, 2017).

Regarding the possible beneficial effects of the use of cannabinoid medication, in addition to well-being (quality of life, sleep, appetite), it is worth mentioning some considerations about the endocannabinoid system, albeit briefly. It is a system of homeostasis that regulates our entire organism. Cannabis replaces the deficient endocannabinoid (e.g., anandamide; aracdonoyl ethanolamine). The actions of what are called receptors are known: CB1 in the central nervous system (modulation of neurotransmitter activity) and CB2 (reduces inflammation and preserves bone mass). The neuromodulation of the endocannabinoid system amplifies or attenuates the action of neurotransmitters (AULA 13 – 25/05/2021 – Prof. Denise Lufti Pedra).

There are common or specific properties of cannabidiol and THC, as well as CBD. CBD is: antibacterial, antitumor, anticonvulsant, anti-inflammatory, antioxidant, antipsychotic, neuroprotective, bone growth promoter, anxiety and depression reducer, nausea and vomiting reducer, intraocular pressure reducer, spasticity and muscle spasm reducer, and relieves chronic pain. And THC is: antitumoral, anti-inflammatory, antioxidant, neuroprotective, reducer of anxiety and depression, reducer of nausea and vomiting, stimulator of appetite, reducer of intraocular pressure, favorer of sleep (reparative), sedative, reducer spasticity and muscle spasm, and relieves chronic pain (AULA 13 – 25/05/2021 – Prof. Denise Lufti Pedra).

In relation to Alzheimer's, CBD: reduces the formation of beta-amyloid protein and blocks the pathway that leads to the accumulation of the TAU protein. And THC: reduces amyloid beta protein. Synthetic cannabinoids also have a positive effect; through activation of CB2 receptors help remove beta-amyloid protein from human brain cells; through CB1 receptors block the formation of

neurofibrillary tangles of TAU protein. In rats, synthetic cannabinoids blocked the release of pro-inflammatory substances and TAU protein targeting CB2 receptors. In mice with AD (Alzheimer's disease), the combination of CBD and THC results in memory preservation and improves learning capacity. The therapeutic effects of THC and CBD may be indicated, even with studies still advancing. THC reduces agitation and aggressiveness, competitively inhibits acetylcholinesterase (such as conventional drugs used in the early/mildly moderate phases), decreases glutamate release with decreased neurotoxicity in the neurodegenerative cascade (such as conventional medications used in the moderate/severe phases), improves depression and fatigue, increases hunger and improves taste, decreases pain and disconnects pain and suffering. And CBD: improves memory, anxiety and sleep, decreases neuroinflammation (has antioxidant and neuroprotective effect) and has antipsychotic (reduces agitation) and anticonvulsant effects (AULA 13 – 25/05/2021 – Prof. Denise Lufti Pedra).

Linalool, as previously mentioned, is potentially effective for Alzheimer's. Article published in the journal Neuropharmacology indicates reversal of mental and emotional degradation: "reverses histopathological features and restores cognitive and emotional functions through an anti-inflammatory effect." Being touted as a "candidate" for Alzheimer's prevention for preclinical studies. Researcher Elthan Russo points to the following synergistic effects of Linalool: Linalool + THC: sedative and analgesic effects; Linalool + CBD + THCV + CBVD: anticonvulsant effect; Linalool + CBG: anxiolytic effect; Linalool + CBD: analgesic effect. (CLASS 19 – 06/06/2021 – Prof. Lu Cannabier).

It is worth mentioning that the use of cannabis, from the perspective of integrative health, should always consider contextual aspects, as well as the before and after the prescription. Patients who are refractory or have ineffective results from the treatment of Alzheimer's and other pathologies (autism, epilepsy) tend to benefit, in different ways and degrees, from the medicinal use of cannabis. But we should not pay attention only to the signs and symptoms of the disease, nor should we consider it as an isolated problem. It is necessary to contextualize it, to take its set and context. It is important to consider the environment in which the problem/disease is situated. It is very important that the patient is involved with the strategies of his treatment and, in the case of Alzheimer's, the role of the family is fundamental, given the cognitive weakness and discernment that affects the patient. The initial use of cannabis should be cautious: "start low, go slow", are slogans (Lecture 7 – 13/04/2021 - Profa. Carolina Nocetti). Self-care and body awareness are important aspects to enhance the benefits of medicinal use, and despite the challenges for such a condition in AD, the systematic care of the patient by family members and professionals, as well as cognitive stimulation activities, combined with exercise practices (consistent with the physical and psychological state of the patient) are recommended and greatly favor quality of life (MANZARO, 2017).

Nocetti and Ribeiro (2020) point to cannabis as an adjuvant drug in the treatment of AD. In general, the review articles, and the insufficiency if not lack of studies with humans, or even the very complexity of the elements involved (genetic and individual/singular aspects; the endocannabinoid system; the paradoxical effects of drugs and their interactions with the organism, its systems and brain – see later discussion on the use of anxiety and depression) prevent more assertive indications. Nevertheless, authors such as Carvalho and Mello (2020) tend to highlight more possible benefits, and in this case, indicate the use of cannabidiol for AD. In a literature review article, they point out that the limited efficacy of drugs used in AD in combating the degeneration of neurons, senile plaques and neurofibrillary tangles, motivate research on the identification of the therapeutic potential of cannabidiol. They point out that improvements are observed in "social recognition" and "learning", and although they emphasize that "studies with human beings" are necessary to "evaluate the safety and efficacy" of this "phytocannabinoid", they even mention that there is "reduction and recovery of memory deficit" (in this case, in the treatment of mice) (CARVALHO; MELLO, 2020). The perspective of Carvalho and Mello (2020) is based on the line of research integrative and complementary health practices. Systematized studies indicate symptom relief, predominantly, but also refer to the reduction of neuronal inflammation that may have broader ramifications. Although they indicate promising aspects, they recognize even in reference to animal studies, that the damage caused to memory is not reversed.

Camargo Son et. al. (2019) in a review article from 2007 to 2017 address the use of cannabidiol and delta 9-TH in Alzheimer's and Parkinson's. Promising therapeutic effects indicate: reduction of motor and cognitive symptoms; neuroprotective action. The results are explained by the antioxidant, CB1 receptor antagonist and activation of PPAR-gamma receptors. They consider adverse effects such as drowsiness and dry mouth. Further research on therapeutic and adverse effects is recommended, with higher doses and periods of exposure so that substances can be considered a more effective and safe therapeutic option.

Marsicano et.al (2002) focus on the endogenous cannabinoid system in the extinction of aversive memory. It is known that AD patients have very significant recent memory impairments, and as we have seen, not reversible, only potentially attenuated in their progressive rate of degradation (by conventional and cannabis drugs, which act in a relatively similar or non-antagonistic way, as previously exposed), and that curiously some memories and negative emotional conditioning tend to persist. It is about such memories and conditionings that Marsicano et. al. refer to the same pointed out by Malcher-Lopes and Ribeiro (2007):

> The amygdala acts on the emotional response, the formation of aversive (negative) memories, and the perception of fear and stress. The presence of CB1 in the amygdala is responsible for the erasure of traumatic memories and this helps to explore the relaxing effects and decreased anxiety caused by marijuana. In some people, depending on the dose and emotional state, the

> action of marijuana on the amygdala can generate opposite effects, with the transient emergence of paranoid thoughts (MALCHER-LOPES; RIBEIRO, 2007, p.55).

Malcher-Lopes and Ribeiro (2007) address many aspects related to marijuana and the brain, from its natural history and in Brazil, to considerations about the endocannabinoid system and marijuana as both medicine and toxic. The mental and neurobiological effects are explained, the "cascades of biochemical reactions (p.44), the effects on sleep and dream, "sexual appetite" (p.72), "immune effects" (p.74), "anticonvulsants" (p.82) and neuroprotective (p.83). Regarding the administration of THC in animal models of Alzheimer's, they indicate that there is inhibition of neurodegenerative and its symptoms, in addition to having beneficial effects on the behavioral disorders and lack of appetite present in this disease (p.84).

Malcher-Lopes and Ribeiro (2007, p.135), who refer to the neuroprotective aspects and anti-inflammatory effects, among others, understood as constitutive of numerous possibilities and therapeutic potentialities and well-being of the use of cannabinoids, mention that there is a "flexibilization" of "neuronal groups", in a passage in which they indicate "typical mental effects" of marijuana:

> The antiepileptic action, the short-term memory deficits, the perceptual alteration that converts even the most common stimuli into novelty, the loss of attention, the altered sensation of the passage of time, laziness, the increase in creativity and contemplative attitude, all these mental effects typically caused by marijuana may derive directly from the flexibilization of coordination between neuronal groups (MALCHER-LOPES; RIBEIRO, 2007, p.135).

For our part, we emphasize that in the most diverse studies on cannabis and mental health (ZUARDI, CRIPPA; GUIMARÃES, org., 2008), the consideration of the need for more research with human beings, and the deepening of existing ones, despite the prohibitionism that hinders them, are recurrent. It is necessary to recognize, under the necessary rigor of scientific caution, that, while some findings are consolidated, others increasingly seem to be plausible in the short, medium and long term. Thus, we align ourselves with Malcher-Lopes and Ribeiro (2007, p.63) who, when they argue that the "endocannabinoid system" is one of the "main conductors in the orchestration of vital functions", or even when they consider that marijuana produces "complex" effects and indicative of the "fantastic potential of the endocannabinoid system as a target for new remedies"; being challenging the task of directing its effects and using them selectively (MALCHER-LOPES; RIBEIRO, 2007, p.64).

2.4 POSSIBILITIES AND PRECAUTIONS OF USE AS AN ANXIOLYTIC

The use of medical cannabis in psychiatry is controversial in cases of psychosis and depression, more so in the former than in the latter. Admissibility in all cases must be well understood and analysed. The precaution in the use of cannabis in anxiety, whether as a specific behavioral disorder or as a problem related to other diseases and health conditions, also deserves to be highlighted. One of the

aspects known to be important to be properly considered is the dosage. Nevertheless, it can be pointed out that the anxiolytic (anxiety-reducing) property of cannabis is undoubted, provided that it is well managed and properly managed.

We can consider the use of cannabis medication in cases of anxiety and obsessive-compulsive disorders (OCD). Anxiety can be considered an adaptive response to a threat. When excessive (in itself, or depending on the objective situation), it becomes problematic.

As in all discussions about the use of cannabis in mental health problems (as well as in other health-disease processes), it is worth some considerations about the endocannabinoid system, this time in relation to receptors and retrograde lipid neurotransmitters, especially 2-AG and anandamide. The CB1 and CB2 receptors are coupled to the G protein, and act respectively on the nervous and immune systems (and others). The receptivity of CB2 can be amplified by different substances (e.g. pepper). Enzymes such as amide hydrolysis and COX-2 synthesize and degrade endocannabinoids (AULA 12 – 18/05/2021 - Prof. Eduardo Perin).

Regarding anxiety disorders, the DSM-5 separated them from OCD and post-traumatic *stress* . Anxiety disorders affect 29% of the population in the USA. The action of CBD and THC on anxiety is already relatively well studied. CBD provides a decrease in anxiety in its action on the CB1 receptor, is anti-inflammatory in its action on CB2, and decreases pain and anxiety in its action on serotonin. THC acts to decrease anxiety through the CB1 receptor. It is noteworthy that this occurs with low doses, which provide a decrease in anxiety and pain, as well as provide metabolic gains of the autoimmune system and bone growth. The vanilloid receptor is biphasic and anxiogenic when hyperactivated. At low dose it is anxiolytic. The reversal of high- and low-dose effects is valid for both THC and CBD, that is, it is beneficial at low dose (decreases anxiety) and harmful at high dose (increases anxiety). Acting on CB1 can extinguish fear memory and decrease responsiveness to *stress*. THC and CBD reduce the anxious behavior of rodents after conditioned fear. In humans the effect under basal anxiety is limited, and more effective in situational anxiety. Study of the U inverted in 5 groups, one of them placebo and others with different dosages of CBD to evaluate effects of anxiety (in this case, specific to the act of public speaking of people without problems) demonstrated that CBD is best in moderate doses (neither high nor low). The action of CBD and THC may be beneficial for anxiety, sleep, social anxiety disorder ("social phobia") and obsessive-convulsive disorders (OCD) and obsessive-convulsive symptoms (OCS) (CLASS 12 – 05/18/2021 - Prof. Eduardo Perin).

There are clinical case reports of patients who did not get answers and/or suffered side effects with traditional medications and who obtained improvements with the use of different types and doses of cannabis oils. In one of the classes, Professor Eduardo Perin reported a case of a patient with anxiety crises, which occurred when he migrated to the state of São Paulo. The patient had used clomipramine (tricyclic antidepressant), with worsening, and sought medical attention. The psychiatrist used *Full*

Screem with this patient (with a predominance of CBD), started with a few drops, and gradually increased until 12, when then the seizures ceased, but the patient then still did not leave the house. With yet another slight increase in the dose this improved, without the aid of psychotherapy. The professor also mentioned clinical cases described by Shindler et al., from 2008: a case of OCD and major depressive disorder, which obtained benefit with THC; and another, weighted as risky treatment, with symptom or trace of psychosis and OCD, in which THC improved OCD and did not worsen "psychosis." It was inferred from the clinical descriptions of the professor that there are different symptoms associated with anxiety disorders as the case may be, and that treatments should be zealous in terms of dosages and composition, having favorable results when well administered in terms of their anxiolytic effects and associated symptoms (such as sleep/insomnia) (AULA 12 – 18/05/2021 - Prof. Eduardo Perin).

The discussion about the use of cannabis in anxiety occurs in conjunction or articulated with the discussion about its use in depression, so that in the following item we present some systematizations that we made based on some scientific articles selected by us.

2.5 THE CHALLENGES AND RISKS OF USE IN DEPRESSION

The therapeutic use of cannabinoids in psychiatry and its main advances was systematized in an article by Crippa, Zuardi and Hallack (2010), researchers at USP in Ribeirão Preto. The authors, whose analyses are also developed in the aforementioned collection "Cannabis and Mental Health", Part IV "Cannabis and Psychopathology" (ZUARDI, CRIPPA, GUIMARÃES – org., 2008), made a survey of studies and literature reviews on the therapeutic use of the following cannabinoids: cannabidiol, rimonabant, delta-9-tetrahydrocannabinol and analogues. Cannabidiol has therapeutic potential as an antipsychotic, anxiolytic and antidepressant. Delta-9-tetrahydrocannabinol (THC) and analogues have anxiolytic effects on cannabis dependence and are adjuvants in the treatment of schizophrenia, although more studies are needed. Rimonabant, on the other hand, was effective in the symptoms (physiological and subjective) of cannabis intoxication, besides being an adjuvant in the treatment of smoking. But the potential side effects of this antagonist – induction of depression and anxiety – limit its clinical use. That is, if in epilepsy the anticonvulsant effect is already well accepted and the clinical responsiveness positive, and if in anxiety the dosage of cannabinoids is known to be a fundamental element to generate therapeutic effect (and avoid risk of potentiating it), in the different forms or pictures of depression and psychosis, other issues are (re)posed and demand greater caution. As we pointed out, selection and parsimony are part of the psychiatric clinic, and are not recommendations that are limited only to the use of cannabis. It is therefore necessary to point out that, although the "cannabinoids" have "demonstrated that they may have broad therapeutic interest in

psychiatry", "more controlled studies" are needed to conform the "findings and determine the safety of these compounds" (CRIPPA; ZUARDI; HALLAK, 2010, p.56).

The indication of cannabidiol or CBD presents, according to Crippa, Zuardi and Hallak (201, p.59), strong evidence (controlled clinical trials in humans) in schizophrenia, and moderate evidence in psychoses associated with Parkinson's or induced by cannabis, being the same valid for anxiety in healthy subjects, anxiety induced by cannabis or derived from social anxiety disorder; And yet, there is "some evidence," based on animal studies, on cannabis withdrawal syndrome and depression.

Animal studies suggest that the antidepressant and mood-stabilizing effect present in CBD is mediated by activation of the 5-HT receptor. This cannabinoid, Like the standard antidepressant imipramine, it decreases the immobility time of animals submitted to the forced swim test. According to the authors, "since CBD has been shown to have anticonvulsant, anxiolytic and antidepressant effects, it was hypothesized that this cannabinoid would have a pharmacological profile similar to mood-stabilizing drugs" (CRIPPA; ZUARDI; HALLAK, 2010, p.61). But studies of patients with bipolar affective disorder (BAD) have suggested, in turn, that "CBD is not effective for the treatment of manic episodes in BAD" (CRIPPA; ZUARDI; HALLAK, 2010, p.61).

The use of the cannabis plant is referred to as a reliever by patients with anxiety and depression, but controlled clinical trials with delta-9-THC and analogues have not been sufficiently conducted. If in anxiety one dosage can be beneficial and another can intensify it, in depression euphoria can also be induced in certain doses. For Crippa, Zuardi and Hallak (2010, p.62), the "paradoxical findings" of delta 9-THC "could be explained by the observation that its effects on anxiety and mood seem to be dose-dependent", with "low to moderate doses" demonstrating "anxiolytic and euphoric properties", and "higher doses" being "anxiogenic". Genetic and individual factors still need to be better understood; despite "promising indications" for the relief of "psychotic and mood symptoms," "it is prudent to discourage the use of these cannabinoids in these conditions": "an alternative could be the cautious exploration of the beneficial effects of the mixture of delta 9-THC and CBD, which is already used in some neurological disorders" (CRIPPA; ZUARDI; HALLAK, 2010, p.61).

Saito, Wotjak and Moreira (2010) address the pharmacological exploration of the endocannabinoid system and the new perspectives for the treatment of anxiety disorders and depression. These are literature review studies. The authors point out that studies on the pharmacological profile that led to the discovery of the endocannabinoid system in mammals indicate that endocannabinoids modulate a "diversity of brain functions, including anxiety, fear, and mood", so as to exert "effects of the anxiolytic and depressive types" (SAITO; WOTJAK; MOREIRA, 2010, p.7). The conclusion they present refers to experiments with animals, in which it is indicated that "drugs that facilitate the action of endocannabinoids may represent a new strategy for the treatment of anxiety disorders and depression" (SAITO; WOTJAK; MOREIRA, 2010, p.7).

Endocannabinoids are "endogenous binding substances" and the "development of novel pharmacological compounds" that target "receptors or the synthesis and degradation of ligands has revealed several complex brain functions" (SAITO; WOTJAK; Moreira, 2010, p.8). The authors argue that "drugs that amplify endocannabinoid action" imply a "more subtle strategy" for "pharmacological interventions" than "direct activation of cannabinoid receptors" (SAITO; WOTJAK; MOREIRA, 2010, p.9). Some compounds that interfere with the endocannabinoid system have potential advantages and disadvantages. Among the pros for depression, CB1 and CB2 agonists, TRPV1 antagonists, endocannabinoid uptake inhibitors AM404, VDM11, UCM707, OMDM and AM1172 stand out (SAITO; WOTJAK; Moreira, 2010, p.10). The authors report that in the so-called "major depression" the levels of endocannabinoids AEA and 2-AG, in the few studies that were measured, were reduced: "from a set of few exceptions, most of the preclinical and clinical data support a scenario in which attenuated endocannabinoid signaling promotes the occurrence of symptoms similar to those of anxiety and depression" (SAITO; WOTJAK; Moreira, 2010, p.11). Low doses of delta 9-THC and synthetic analogues have properties similar to anxiolytics and depressants, and at the behavioral level, they alleviate the "consequences of inevitable stressors and animal models of depression": "in addition, cannabinoids increased neutrofin levels, induced hippocampal neurogenesis, and suppressed stress hormone secretion" (SAITO; WOTJAK; Moreira, 2010, p.11). The paradoxical effects of cannabis use and The action of cannabinoid receptor agonists are explicitly mentioned by the authors:

> Although therapeutic applications for these substances can be envisioned, there are major obstacles that limit their applicability in the clinic. For example, treatment with cannabinoids can cause addiction and tolerance, induce sedative effects, and impair learning and memory. In general, low doses tend to induce anxiolysis [behavioral state of tranquility], whereas higher doses may induce opposite effects. The reasons for these differences are yet to be determined. They could be attributed to dose-dependent actions in different brain regions and neural populations. In addition, high concentrations of cannabinoids can lead to desensitization/internalization of CB1 receptors, thus resulting in lower endocannabinoid signaling. It is tempting to assume that such processes are responsible for the paradoxical effects of cannabis use on emotional responses such as episodes of anxiety and panic. To work around these problems, future studies may try to target the allosteric site of the CB1 receptor (SAITO; WOTJAK; Moreira, 2010, p.11).

TaThis considerations, however, do not prevent them from pointing out that the "uptake and/or hydrolysis of anandamide represents promising pharmacological targets", whether for the therapeutics of "depression" or for "anxiety disorders", since the effects induced by these "endocannabinoid enhancers" differ "from those of direct CB1 agonists, especially by avoiding "ubiquitous activation" (endocannabinoid action is restricted, temporally and spatially); nor to conclude that the "malfunction of the endocannabinoid system may promote the development and maintenance of psychiatric disorders such as depression, phobias and panic disorder"; thus, the expectation remains that "CB1 agonists or anandamide hydrolysis inhibitors exert antidepressant and anxiolytic effects", which should be better considered by other studies (SAITO; WOTJAK; Moreira, 2010, p.12).

2.6 THE USE OF CBD AND THE MEDICINAL CANNABINOID IN PSYCHOSIS AND AUTISM

As mentioned before, the endocannabinoid system governs and modulates body and behavior. The deficiency of the same can be suppressed and by the use of cannabis medicine. Phytocannabinoids are neurostabilizers that act on the problems arising from endocannabinoid deficiency. Among the uses in clinical practice can be highlighted those related to pain, mood disorders and insomnia, as well as lack of appetite and nausea. This is true in psychosis and autism. In the case of psychosis the indication is only of the drug based on CBD, because the use of THC can be harmful and stimulate typical symptoms of this pathology, such as delirium and hallucinations. In the case of autism, careful management does not rule out whole oil. The renowned researcher, Russo, was one of the pioneers in considering the aforementioned "collective effect" or "*entourage effect*", which concerns the collective action of cannabinoids, arguing that the use of whole oil is better than synthetic (cannabinine oil). Regarding the therapeutic use in psychiatry, there is an important group from USP in Ribeirão Preto, focusing on synthetic CBD. There are analgesic, antidepressant and antipsychotic effects, similar to those of "atypical antipsychotics" (Lecture 4 – 03/23/2021 - Profa. Eliana Nunes).

Autism or ASD (Autism Spectrum Disorder) is a pathology whose studies have had remarkable development and in which the use of cannabinoids seems to be promising, acting positively on the quality of life, food and interactivity of its carriers.

There is a multifactorial complexity and cause of autism, expressed in the film's title "Autism Riddles." We highlight the importance of food in the treatment of autism, which can make it one of the indicative aspects of cannabis use. There are several comorbidities of ASD (Autism Spectrum Disorder). The use of cannabinoids in autism, as in epilepsy, is justified mainly because of their action as a neurostabilizer (Lecture 6 – 06/04/2021 - Profa. Eliana L. Guerra Nunes)

There are reports of significant improvements in marijuana use in cases of autistic children in several studies. It is worth mentioning the need to treat inflammation together, as well as microdosing for beginners; or the need for precaution with psychoactive effects. Low doses can have good effects. The first oil indicated, is the rich in CBD. This can be replaced by the complete oil at a later stage. ASD includes many syndromes and use of different oils. There is a need for live pharmacies in addressing autism and other diseases that can benefit from the use of *cannabis* (Lecture 6 – 06/04/2021 - Profa. Eliana L. Guerra Nunes).

2.7 THE USE OF LOW THC CBD IN TREATMENT FOR CRACK ADDICTION

The University of Brasilia (UnB) conducts scientific studies with cannabis at the Center for Drugs and Associated Vulnerabilities. The use of CBD with low THC content in the treatment for crack addiction is investigated and recommended. Therapeutic use is indicated both in acute crises and in withdrawal. A work is developed in the CAPS of Ceilândia. Treatment of addiction can be crack,

alcohol, and marijuana itself. In the case considered here, we focus on the report of the study and clinical experience of the treatment of crack addiction presented in one of the classes by Profa. Andrea Galassi (Class 11 – 11/05/2021- Prof. Andrea Galassi).

Some delusional symptoms, difficulty sleeping and lack of appetite, present in the acute crack crisis, are attenuated with the use of marijuana. Crack users themselves have noticed such an effect. Thus, this mobilized clinical studies. The use of CBD can provide longer periods of abstinence and improve quality of life, by providing better sleep and nutrition. Chronic user anxiety and depression can also be treated with CBD. The medicinal use can also provide resumption of daily social and work activities, and decrease the frequency of crack use and the side effects of the drugs that are used in its conventional treatment (Aula 11 – 11/05/2021- Profa. Andrea Galassi).

In the research carried out, two groups were compared: one made use of cannabidiol; and another of the traditional medicines (antidepressant, anxiolytic and mood stabilizer). The research was conducted with non-hospitalized patients. That is, with people in a situation of routine life preserved. Unlike, therefore, double-blind randomized studies with patients disconnected from their context (inpatients). This professor highlighted the importance of the research being carried out in the real context of the user's life. And he pointed out that it is consistent with the health care model whose basis is the territory. He criticized the idea that marijuana is the "gateway" to other drugs, and referred to it being the "exit door" of crack. He also criticized the segments of Psychiatry that point to crack addiction as a "disease of the brain", because dependence is contextual and multifactorial, he argued. He also reported that the study showed positive results. The cannabinoid use group had benefits. He considered that different clinical pictures demand applicability of different cannabinoids. But that in the research had only one type: CBD low THC. Questions remain open as to whether a drug with a higher THC content could not increase the benefits, or even be better for some clinical cases and not for others. Distinct applicability exists for different contexts and clinical conditions. It is necessary to be able to take into account these adjustments and specificities. Thus, we point out the need for advances and deepening on the use of cannabis in the treatment of crack addiction (Aula 11 – 11/05/2021- Profa. Andrea Galassi).

We also consider it important to consider the importance of the medical use of cannabis in harm reduction, referred to in one of the classes by Profa. Sheila Dantas (Coordinator of the Federation of Therapeutic Cannabis Associations in Brazil and President of the Cannabis League in Paraíba), user of medical cannabis for rheumatic pain, as well as for refractory epilepsy and autism of her child (Aula 11 – 11/05/2021- Profa. Sheila Dantas).

Harm reduction is a strategy to minimize harm from substance use. It does not aim at prohibition or abstinence, but also at the promotion of health, dignity and respect for the human person. The harm reduction policy emerged in the 1980s when HIV was transmitted by injecting drug users.

The positive results achieved with the distribution of syringes and guidelines allowed an expansion of the harm reduction policy for other problems related to mental health (Aula 11 – 11/05/2021- Profa. Sheila Dantas).

The right of associativism entails the exchange of information and discussion on the reform of drug policy, a need pointed out in the introductory item of this work when we consider cultivation through the right of civil disobedience. When supported by associations, users of medical cannabis have greater guarantees of using more appropriate oils and dosages, as well as better quality substances. We must face the dismantling of harm reduction policies and the defense of the current Bolsonaro government of a diametrically opposed policy, of compulsory hospitalizations and forced abstinence. There is restriction on freedoms and "therapeutic communities" that are characterized as spaces of mistreatment. Associations are a form of organization of people with common goals and benefits; are governed by Civil Law, private law associations, non-profit, which does not prevent them from having revenues (community of associated property). The Associations enable support for patients and harm reduction. Support for patients, especially in regions where there are no doctors and access to cannabis therapy. Associations reduce misuse and misinformation. Reduce risks such as: inadequate dosages; inappropriate type of oil (e.g., contaminated oils, made from "pressed marijuana"; counterfeit oils); violence to which the buyer can be subjected in trafficking. And benefits: orientation to cultivation; "solidarity or associative cultivation"; "covering" lack of medicine from growers at home who have eventual crop problems; dissemination of knowledge and experiences. And finally, but not last, they play an important social role in breaking prejudices and paradigms, in the critical discussion about the reform of drug policy and in the reception of users (Aula 11 – 11/05/2021- Profa. Sheila Dantas).

3 THE HEDONISTIC USE OF MARIJUANA

3.1 SOCIABILITY AND PSYCHOSOCIAL ASPECTS

Historical and psychosocial dimensions related to the use of marijuana were treated in the Introduction of this work, and now we resume them in the sense of discussing the hedonistic use, a term considered more comprehensive and engaged than the "recreational use". We understand hedonistic use as beyond individual or narcissistic pleasures, even if it also involves them. We have preliminarily addressed some of the class reports to indicate the marijuana-sociability relationship. And then other systematizations, especially those inspired by the work of Malcher-Lopes and Ribeiro (2007)

The "Green Prophet", founder of the Cannabis Cultural Association of São Paulo (ACuCA-SP), made mention, in his report in one of the classes of the course, to the "recreational use" (which in his case later expanded to the religious and therapeutic uses). The speaker mentioned participations in 2009 in the Marijuana March (legitimized in 2011 by the Supreme Court), in the creations of the "Pain

Collective" (Unnumbing Reason, in 2010) and "Breathe Harm Reduction: Green Prophet" (2011), which denotes the imbrication of hedonistic use with different forms of sociability. This aspect was also evident in the following years. In 2012, he promoted the foundation of the Cannabis Association of São Paulo (ACuCa). In 2015 he participated in the Cannabis (Online Congress on Cannabis). And yet, in 2016, he ran for alderman; which was repeated in 2018 and 2020, this time in a collective candidacy ("Ganja Coletiva") (Aula 11 – 11/05/2021 - Prof. Fernando "Profeta Verde").

ACuCa was considered the first and perhaps only cannabis association in Brazil with cultural bias, that is, not related to therapeutic medicinal use. There is evidence of a cannabis social movement that seeks the modification of the drug law and the participation of the "voices of cannabists" in the laws. The communitarian character in favor of balance in the game of social forces is characterized as a counterpoint to economic interests. The socialist perspective merges, in the trajectory of the speaker, with cannabis associations, considered a tool for the construction of a new drug policy that invites participation, solidarity, cooperation and collective decisions, in the sense of a transforming force of society (Aula 11 – 11/05/2021 - Prof. Fernando "Profeta Verde").

The imbricated relationship between marijuana and sociability was also made explicit in the mention of the history of cannabis associations and clubs, such as the "Hashish Club" in France, which proclaimed the use of cannabis as a way to give light to artistic productions. He also referred to the "Diambistas Club" in Maranhão. In this one they make wheels in which they smoke and sing. In the group's sayings: "they invigorate the soul", "they bring the joy of living". He also mentioned the social cannabis clubs in Spain, in order to indicate the clubs as a fusion between associations, production, distribution and consumption. He indicated that there are different types of cannabis associations: activist, cultural, medicinal, political, professional and religious. They make different social actors interact and mobilize critical opinions on marijuana, prohibition, regulation and legalization, among others (Aula 11 – 11/05/2021 - Prof. Fernando "Profeta Verde").

The issue of marijuana and sociability was also made explicit in the participation of professors Angela Aboin (Mãesconha) and Prof. Keka Richie (ACuCa) in the Course.

Professor Keka Richie addressed the theme Associativism and Sociocracy. He presented associativism as an instrument for a community to come out of anonymity and gain social, legal and political expression in favor of the collective. Reported on organizational and financial aspects of an association. He mentioned the work of collective construction of the Statute of an association. He pointed to diversity as the great richness of the collective. He pointed out rules of sociocracy as the consideration of the interest of all people and the unanimous acceptance of all people in the decisions. The decisions have a popular basis. And there is collective power and intelligence. Consent is of the whole. Sociocracy obeys the following principles: effectiveness, evidence, consent, continuous improvement, equivalence, total transparency and accountability. Its benefits are inclusive governance,

adaptability, flexibility, engagement and stimulation of creativity. The speaker concluded her presentation by pointing out that the activist soul of sociocratic associativism acts in favor of the collective and common good, being critical of white, elitist and sexist society (Aula 12 - 18/05/2021- Profa. Keka Richie).

Prof. Angela Aboin, known for being a mother of an autistic child, in turn, emphasized the importance of the anti-asylum struggle and the deleterious effects of the institutionalization of different clinical conditions of different complexities, and under which there are prejudices and mistreatment in diverse social environments. He mentioned *the slogan* "to lock up is not to treat", recalling the commemoration of the day of the anti-asylum struggle. He pointed out that an articulation between the struggle for medical cannabis and anti-asylum is important. He defended the humanization of CAPS and mental health. He described and criticized the history of asylums, asylums and hospitals and their "strategy" of withdrawal from social life. He mentioned the importance of movements for inclusion. He compared the holocaust and dictatorship to asylums as spaces of mistreatment. He argued about the need for welcoming and human contact for mental health. He referred to the well-known case of 60,000 deaths in the Barbacena Hospital, as well as to the occurrence of cases of rape, abuse, starvation and doping in patients in numerous situations of institutionalization. And yet: of "loss of identity" and curtailment of freedom. He reiterated criticism of institutionalization and mechanical restraints (use of helmets, straitjackets, bindings), lobotomy and electroshock. He argued that there is safe, well-tolerated and effective use of cannabis in ASD, according to recent studies. He pondered that there is no treatment for central issues of autism, but rather a better neurological environment for the development of the child, modulation of neurons, decrease in anxiety, anguish and depression, improvements in mood, sleep, communication, or even stereotypy and management behavior in ASD. He concluded by pointing out that cannabis medicine opens new perspectives of life to autistic patients and children and to others who have been institutionalized and treated inhumanely for years (Aula 12 - 18/05/2021- Profa. Angela Aboin).

3.2 SENSITIVITY AND CREATIVITY

The discussion about the sensitivity and creativity sharpened through the use of marijuana is reported by users and we can point out subjective and objective aspects related to this perception. As Gabeira (2007) points out, there are many myths surrounding marijuana and its use, nonsensical effects and attacks and defenses that indicate that this habit, disseminated throughout the world, has relations with the social reality (specificities of the use and vision of marijuana in Brazil) and the most diverse dimensions and political positions.

We consider that chronic and abusive use can lead to distortions of users' perceptions. But on the other hand, there are numerous reports of artists and users, whose controlled or moderate hedonistic

use refers to the sharpening of sensitivity and creativity, which should not be neglected. Thus, we will consider, albeit briefly, some scientific aspects addressed in the book "Marijuana, brain and health" (MALCHER-LOPES; RIBEIRO, 2007).

Malcher-Lopes and Ribeiro (2007, p.53) address the action of THC on "brain circuits" called "base nuclei" and the presence of CB1 in the cerebellum. They explain that in the "nucleus *accumbens*" the CB1 receptor is abundant; it is the region of the brain that participates in the "anticipation and processing of the sensations of pleasure and reward" (MALCHER-LOPES; RIBEIRO, 2007, p.54). The "action of the active principles of marijuana" in this region "may be behind the amplification of the pleasures that marijuana causes, including the pleasure of eating, laughing and the pleasure of an affective or sexual relationship" (MALCHER-LOPES; RIBEIRO, 2007, p.54). But such pleasures, he warns, can also contribute to the case of "abusive use and psychological dependence of the drug" (MALCHER-LOPES; RIBEIRO, 2007, p.54; p.95; Melman, 1992; FIRMINO; QUEIROZ, 2009).

Malcher-Lopes and Ribeiro (2007) consider that the most immediate mental effect of marijuana is the "relief of mental and physical stress", and also indicate: "inner peace" and "empathy", facilitation in "interpersonal relationships", intensification of "emotions and perceptions" and enrichment of "visual perception" (p.104); "more flexible associations of concepts, ideas and emotions" that favor creativity" and "elaboration of metaphors" (but which can also hinder "logical and objective reasoning") (p.105).

The authors present a detailed characterization of marijuana as a "tonic": cannabinoids promote a "disorganization of neuronal processing" that has as a consequence a "facilitation of the restructuring of memory traits", thus making it easy to understand that their use "facilitates the creative process and the generation of *insights*" (p.141-142). The tonic thus acts as an "appetite stimulator", "relaxing" and aphrodisiac", while allowing the "deepening of the sensory experience", "enriches the appropriation and production of the arts" and "favors states of low anxiety", reducing "social tensions" in different contexts (in "prisons" and "dance parties") through its "anti-stressful action" (p.142)

3.3 THE DISTINCTION BETWEEN THE WELL-BEING OF HEDONISTIC USE AND ENJOYMENT AS A SYMPTOM

The hedonistic use of a socializing and engaged character, which promotes well-being, can develop, however, an unwanted facet, in which it is characterized as dependence and abuse. As Malcher-Lopes and Ribeiro (2007, p.56) point out, "the abusive and chronic use of marijuana can generate reversible memory deficit, lack of motivation and depression."

According to the psychoanalytic perspective, pleasure and displeasure are inseparable and related to the contradictions of the subject of the conflict and to the antithetical pair: life drives and death drives. As Melman (1992) points out, the use-symptom of marijuana is related to subjective and

social issues, such as the death drive and delinquency, which is understood rather as a social symptom related to abandonment than to a deformation of character, as conservative and uncritical discourses insist on the social inequalities of the capitalist order. The author resorts to the Lacanian concept of enjoyment, in which there is a differentiation and opposition to the common use of the word, usually related to pleasure.

Freudian and psychoanalytic discussions about the pleasure principle are well known, which is not only related to the pursuit of pleasure, but also to avoiding displeasure; and yet, we emphasize, to what lies beyond the pleasure principle, which refers us to the repetition compulsion and the death drive directed to the self itself (FREUD, 1985). It is to this situation that the notion of an unbearable excess of pleasure that reaches the social and erotic body is related, or even a kind of violated pleasure, although divorced from its rule and principle, by giving in to displeasure. The discussion is complex and involves the understanding of the cleaved subject and its conflicts and ambivalences, aspects that should not be unduly "psychologized", since the separation between individual psychology and social psychology is a great misconception, as Freud (1985) considers in his classic text of 1921, "Psychology of the Masses and Analysis of the Self" (title that receives different translations according to editions/translations that are used).

The discussion of this dimension of the use-symptom or use-enjoyment of marijuana leads us to the issue of abusive and chronic use, addressed by several authors, such as in Part V of the collection organized by Zuardi, Crippa and Guimarães (2008), as well as by Malcher-Lopes and Sidarta (2007) who, as previously exposed, differentiate marijuana as a tonic from marijuana as a toxic and drug that can generate psychological dependence. Chronic use and dependence can also cause, especially in adolescents and young people, the amotivational syndrome. But chronic and dependent use should not be confused with hedonistic use and the search for experiences by adolescents and young people, since the notion that such a search necessarily leads to the "ladder of drugs" or to an inexorable pathological destiny, contrary to the hedonistic use that promotes sensitive experience and well-being, as previously addressed, it is a gross error, which integrates the myths about marijuana and its use, eloquently addressed by Gabeira (2007, p.28).

Fermino and Queiroz (2009) refer to the frequent view that the use of marijuana would be related to obtaining pleasure or relief from the conflicts or ills of existence. And they consider that the Freudian reading situates marijuana as a "palliative" or "vehicle that produces a certain refuge" (FERMINO; QUEIROZ, 2009, p.253). And they question about such a function, its validity and effectiveness.

The authors mention studies that indicate that "psychoactive substances" are consumed "in various cultures for therapeutic, religious purposes and, due to the hedonistic character present in the history of humanity, as a way of obtaining pleasure" (FERMINO; QUEIROZ, 2009, p.253).

They ponder or problematize this possibility of "pleasure", because, by seeking the "relief" of the "situation that bothers them, it corners the subject" (FERMINO; QUEIROZ, 2009, p.254). And they also mention the conception that "drugs reveal a symptom, denounce problems of our society"; and they take up Freud's comment, in "The Malaise of Civilization," about the soothing effect of "toxic substances" (FERMINO; QUEIROZ, 2009, p.254).

The authors consider, without moral judgment, that the drug, in theory, could increase pleasure and decrease displeasure. But they problematize such a view. And they argue that in practice consumption assumes a "very contradictory character" (FERMINO; QUEIROZ, 2009, p.255). They exemplify cases in which one user reported that without the drug he was sad, and another who could only face the work in which he felt discriminated against when he smoked a joint. From "worry buffer" or "relaxing and anxiolytic mechanism", they ponder, the use is diluted in everyday life, changing "mood", "working capacity" and even "reasoning" (FERMINO; QUEIROZ, 2009, p.255). The issue of abstinence, psychological dependence and amotivational crisis are indicated under the metaphor of the "car without fuel" (FERMINO; QUEIROZ, 2009, p.255).

As we have pointed out, the authors reject the moralistic bias. They point out the inevitability of suffering. And they argue about another way of dealing with it than the use – dependent, we point out – of marijuana. Reason is then argued as a more effective form of suffering relief or even possible recourse in the pursuit of happiness (plausible, not idealized) (FERMINO; QUEIROZ, 2009, p.255).

According to Fermino and Queiroz (2009, p.257), the "reflective understanding, that is, reason", is what allows an experience in which there is the possibility of discernment between an idealized happiness and another plausible. As they argue, this possibility of being happy, under the mediation of reason, is distinguished from "naïve hedonism" (FERMINO; QUEIROZ, 2009, p.257).

There would then be another enjoyment distinct from the symptom-enjoyment, referred to by the authors as a satisfaction, or experience of the meaning of life in its course, and not as something essentialized. Therefore, a living of a "continuous reflective and active exercise, in search of a good living that implies moments of connection to projects, ideas and people" (FERMINO; QUEIROZ, 2009, p.258).

Therefore, based on the reflections presented here, we can indicate the pertinence of distinguishing between a symptomatic narcissistic-hedonism, which ranges from an inability to deal with frustrations to as a refuge from social issues of fact of difficult acceptance, from an objectifying, binding hedonism, entangled in the collective struggle, since the individual struggle against social hardships is in fact too costly. As well as distinguishing interactive and creative (not merely "recreational") hedonistic uses from uses that, although liable to be considered hedonistic, assume as their main mark dependence or chronicity.

4 FINAL CONSIDERATIONS

In the present work, we seek to articulate the content of the classes to the systematizations of readings carried out under the focus of mental health and the benefits and risks of the therapeutic-medicinal and hedonistic uses of cannabis.

In Introduction we address the historical and psychosocial aspects of marijuana use and human rights and civil disobedience. We proclaim that cannabis health is a right and the right is a social and institutional aspect that promotes biopsychosocial health.

We were able to present a series of considerations about the therapeutic effects and risks of the medicinal use of cannabinoids and/or marijuana for mental health. This item was the one that we highlighted the most in the present study. When addressing the complexity and diversity of therapeutics and cannabinoid properties, we advocate the parsimonious and selective use of medications. We develop analyses on neurological pathologies: the anticonvulsant effect on epilepsy and the cannabis action on memory and quality of life in Alzheimer's disease. Next, we consider the use of cannabis in mental-behavioral disorders, namely: the possibilities and precautions of use as an anxiolytic; the challenges and risks of use in depression; the use of CBD and the medicinal cannabinoid in psychosis and autism; and use of CBD low THC in the treatment of crack addiction.

We indicate the importance of management and caution in the prescriptions and dosages of the different compositions of cannabinoids according to pathologies and individual, psychosocial and genetic conditions of patients, according to scientific knowledge. We consider that there are paradoxical effects of cannabis, some consolidated scientific knowledge and others to be better investigated. And we regret that the medicinal potential of cannabis in the endocannabinoid system has not been as developed as it could be due to a narrow-minded if not prejudiced prohibitionism.

We end with the discussion of the hedonistic use of marijuana, in order to consider the marijuana relationship, sociability and psychosocial aspects. We also indicate several aspects of the hedonistic use of marijuana related to well-being, social interactions, sensitivity and creativity. We highlight marijuana as a tonic. Consideration of such aspects did not prevent us from considering the unwanted facet of abusive use and dependence. It is necessary to make clear the distinction between the well-being of hedonistic use and narcissistic-pathologizing hedonistic use; distinguish marijuana as a tonic from marijuana as toxic; or even, the social-subjective well-being of what we call self-absorbed enjoyment, a kind of symptom of social and psychosocial malaise.

We conclude that the use of marijuana and cannabinoid drugs holds promise in promoting good social, psychosocial and subjective being, and the existing risks elements to be always considered, being a challenge to society and science to better know them, in a multi, inter and transdisciplinary perspective (ABRAMD, 2006), always far from the marks of prejudice, moralism, prohibitionism, structural racism and stigmas.

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Cannabis & Alzheimer's: From adjunctive use in symptoms to neuromodulatory therapy

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ABSTRACT
This paper addresses the adjuvant use and neuromodulatory therapy of cannabis in Alzheimer's. It preliminarily considers the effects and risks of the medicinal use of cannabis, the anticonvulsant effect in epilepsy and the prospects for use in Alzheimer's. He argues for neuromodulatory use in Alzheimer's, in addition to the more restricted use to placate symptoms. And it concludes by pointing to the half-open perspectives and more recent investigations about the neuroprotective character of cannabis.

Keywords: Alzheimer's, Medical cannabis, Neuromodulation, Neuroprotection, VI Medical Cannabis Course of UNIFESP.

1 INTRODUCTION

The present text, Final Work of the VI Course on Medical Cannabis (August to December 2021), was elaborated based on class records and systematization of readings of bibliographic survey carried out by this author on the theme *Cannabis + Alzheimer's*. The present study was preceded by another (SILVA, 2021), entitled *Marijuana & Mental Health***:** *therapeutic effects and risks of medicinal and hedonistic uses* (Final Work of the V Course on Medical Cannabis). We seek to deepen the general knowledge so far developed of the use of cannabis in the field of mental health, we resume some premises and syntheses reached, and then dive into the challenge of understanding the paths already trodden and the still to tread of the medical use of cannabis in Alzheimer's.

1.1 ON THE EFFECTS AND RISKS OF THE MEDICINAL USE OF CANNABINOIDS FOR MENTAL HEALTH

Initially, we highlight two aspects related to the therapeutic effects and risks of the medicinal use of cannabinoids in mental health: the possibilities and precautions of use as anxiolytics; and the challenges and risks of use in depression (SILVA, 2021).

The use of medical cannabis in psychiatric pathologies is controversial. Caution in the use of cannabis is redoubled in importance in cases of psychosis, anxiety and depression. But to limit ourselves to the first two, we emphasize that the dosage is of paramount relevance. The anxiolytic

property (anxiety reducer) exists, as long as it is well managed and properly managed. Treatments should be zealous in terms of dosages and composition.

Crippa, Zuardi and Hallack (2010) address the therapeutic use of cannabinoids in psychiatry. If the anticonvulsant effect in epilepsy is well accepted and there is positive clinical responsiveness, in anxiety and depression some caveats are common. The dosage is a relevant factor for therapeutic or negative effect in these cases. The dosage is always something relevant, a fundamental element to be considered in the management of the prescription. We only highlight that it is highlighted when it comes to the use in anxiety and depressive disorders. And the dosage is always relative to a certain type of drug. It is necessary in each case to select the best drug indication, taking into account its composition and the clinical picture in question. As we pointed out in a previous study (SILVA, 2021), selection and parsimony are fundamental in the psychiatric clinic:

> If in anxiety one dosage can be beneficial and another can intensify it, in depression euphoria can also be induced in certain doses. For Crippa, Zuardi and Hallak (2010, p.62), the "paradoxical findings" of delta 9-THC "could be explained by the observation that its effects on anxiety and mood seem to be dose-dependent", with "low to moderate doses" demonstrating "anxiolytic and euphoric properties", and "higher doses" being "anxiogenic" (SILVA, 2021, p.).

Murillo-Rodriguez, Pandi-Perumal, and Monti (2021) contribute to a number of current discussions on psychiatric use in the dossier "Cannabinoids and neuro psychiatric disorders." In the present work we will refer to one of the articles, related to recent advances on the neuroprotective potential of cannabinoids in Alzheimer's (PÉREZ-OLIVES, RIVAS-SANTISTEBAN; LILLO; NAVARRO; FRANCO, 2021). The topic of cannabinoids in neuropsychiatry is also explored in James' (2021a) clinical guide.

1.2 DIVERSITY OF CANNABINOID PROPERTIES AND COMPLEXITY OF THERAPEUTICS

The various cannabinoid properties act on concrete beings, contexts, and it is recommended that the Therapeutic-medicinal use of cannabinoids in mental health is always selective and parsimonious. The complexity of the therapy demands it.

The medicinal properties vary according to plant, form of cultivation and extraction. Malcher-Lopes and Ribeiro (2007) detail the pharmacological properties of different cannabinoids. We consider here only the two most covered: THC and CBD. THC is Antipyretic, Antiviral, Appetite Stimulator, Hypotensive and Psicotropic. And both THC and CBD are: Painkiller; Anxiolytic; Anticonvulsant; Antiemetic, Anti-inflammatory, Antioxidant Antitumorigen, Immunodepressant, Neuroprotective and Sedative. And they are specifics of CBD: Antipsychotic; Antispasmodic.

In the case of Alzheimer's, as well as other pathologies, the entourage effect of the interaction of the two cannabinoids tends to be considered as having the best therapeutic effect. We will highlight

in this work the neuroprotective aspect and the cannabis potential to lead the mastery of the organism, particularly, the neuromodulation harmonized to neurogenesis and homeostasis.

1.3 FROM THE ANTICONVULSANT EFFECT IN EPILEPSY TO THE PROSPECTS OF USE IN ALZHEIMER'S

In our previous study we already pointed out the anticonvulsant effect as "better known and perhaps better proven in medicinal studies of cannabinoids" (SILVA, 2021, p.12). The action on seizures cannot be understood as merely on the symptom. When a seizure is resolved, or its high frequency, especially in cases refractory to conventional medications, not only one symptom is reached, but the progressive etiology of the disease itself, concomitantly. An effect that ignites great hope. A better future for various health problems. In which more comprehensive actions of cannabis, in addition to the more immediate, circumscribed and/or already verified therapeutic effects, can be unveiled.

The action of cannabis on Alzheimer's raises many expectations. In the reduction of discomforts and symptoms, promotion of well-being and quality of life, is one of them. But hypotheses are also launched about acting on memory, and therapeutic effects, let's say, more daring and comprehensive.

The Disease of Alzheimer's (AD) is the most common neurodegenerative disease of dementias related to senility (MANZARO, 2017). In this work we consider that cannabis medicine can improve quality of life. Promote restorative sleep. Improvement of appetite and pain. But our fundamental question is: how would its modulating action of the organism and its effects on metabolism take place? Can neuroprotective effects slow down mnemic or memory losses? These are questions necessary for the deepening of investigations that bring relatively promising hypotheses for the prevention and treatment of the disease and that do not limit the use of cannabis to the placation of symptoms.

In class 12 of the VI Course of 10/26/2021, Professor Sidarta Ribeiro made mention of the "cannabinoid revolution". It addressed the neurobiological mechanisms of THC, tuned to the CB1 receptor, and CBN, an oxidized, non-enzyme-based product of THC, tuned to the CB2 receptor. He pointed out the use of the cannabinoid in diseases related to excess neural synchronization, such as epilepsy. Such an excess generates the seizure. In this disease the cannabinoid can desynchronize without impairing neuronal activity, unlike conventional medicine, which lowers activity but generates drowsiness. It considered several positive aspects of the use of cannabinoids, in the immune response, appetite, sleep, anxiety, emotion, pain, locomotion, cardiovascular and respiratory functions, intraocular pressure, inflammation, reproduction, sex, as well as pointed to *remodeling of neural circuits*, formation of new memories, extinction of traumatic memories, *neuroprotection, neurogenesis,* perception, motor coordination, flow of thoughts, creativity, emotion, etc. (emphasis added). It considered diseases with decreased neurogenesis (such as depression and Alzheimer's) and the

mitigating effects with the use of medical cannabis. In addition, decreased oxidative stress, neuroinflammation and the formation of amyloid plaques and neurofibrillary tangles typical of Alzheimer's disease (AD). Already *in live* "The use of medical cannabis in dementia processes" (11/11/2021), Professor Sidarta reiterated the potential for cannabis cell regeneration and new synapses in the face of decreased connectivity. He clarified the accumulation of malformed proteins and neural circuits in AD. He referred to the genesis of connections, that is, he argued that phytocababinoids promote neurogenesis and plasticity. In relation to the problems of cognition, there is the triad: delay; mitigate; rescue. He mentioned that there is a mismatch between the clinic (use for years in Canada, for example), and the scientific evidence. Mismatch between the clinician and the published. And under the metaphor *of Ippon* (a term that means in martial arts the last or perfect blow), he admitted that with regard to AD - unlike what happened with epilepsy, based on the findings of the Israeli PhD Raphael Mechoulan - a "Ippon article" has not yet been published, which could be considered a full proof of therapeutic efficacy.

Nevertheless, more recent studies by the renowned Mechoulan on cannabinoids in health and disease (KOGAN; MECHOULAN, 2007), as well as others, indicated by Professor Siddhartha in that class, are encouraging. We are referring to the contributions of *in vivo evidence* study for therapeutic properties of cannabidiol (CBD) for Alzheimer's disease (WATT; KARL, 2017). And two others about the decrease in neurogenesis. One of them addresses the CB1 receptor of cannabinoids in rats (JIN; XIE; KIM; PARMENTIER-BATTEUR; SUN; MAO; CHILDS; GREENBERG, 2004). Jim et.al (2004) indicate that pharmacological studies suggest the role of the cannabinoid receptor, CB1, in the regulation of adult brain neurogenesis. And another, also experimental with rats, which indicates promotion of neurogenesis of the embryonic and adult hippocampus, in order to produce anxiolytic and antidepressant effects (JIANG; ZHANG; XIAO; CLEEMPUT; JI; BAI; ZHANG, 2005). Jiang et. al. (2005) investigated the synthetic cannabinoid HU210.

In the study by Watt and Karl (2017), like several others, the accumulation of beta-amyloid protein plaques and hyperphosphorylation of the tau protein in AD is indicated. Beta-amyloid comes from a larger protein present in the fatty membrane of nerve cells. The plaques block signaling between cells at synapses or even activate immune cells that cause inflammation. And the hyperphosphorylation of the tau protein blocks the intracellular traffic of proteins (neurotrophic; functional) so as to generate loss or decrease in axonal or dendritic transport in neurons. That is, there is neuroinflammation and oxidative stress. The authors point out that conventional remedies do not stop or reverse the disease. And that cannabidiol (CBD) is proven (*in vitro*) to be a phytocannabinoid with neuroprotective, anti-inflammatory, and antioxidant properties. A potential multifunctional treatment option for Alzheimer's is thus being investigated. In this case, the study investigated the *in vivo* effects of CBD on animals. It points to CBD's ability to reduce reactive gliosis and neuroinflammatory response. And not only. It

can also produce neurogenesis. Also, reversal and prevention of the development of cognitive deficits in rats with AD. They point out that such potentialities are more promising when the CBD-THC combination. But they do indicate that research is needed to assess the long-term potential of what they describe about CBD.

2 CANNABIS IN ALZHEIMER'S DISEASE (AD): IN ADDITION TO ADJUNCTIVE USE, NEUROMODULATORY PROTAGONISM

Alzheimer's is progressive and insidious. It involves progressive synaptic and neuronal loss. The beneficial effects of the use of cannabinoid medication, in addition to well-being in aspects such as food, sleep, pain, interaction and behavior, may occur due to its action on the deficiency of the endocannabinoid system, which influences metabolism, homeostasis and the nervous and immune systems.

2.1 USE TO PLACATE SYMPTOMS

We can consider a type of use more aimed at placating symptoms. Liu, Chau, Ruthirakuhan, Lanctôt & Herrrmann (2015) point to case studies in which THC reduces symptoms of agitation and aggressiveness characteristic of AD. Ruthirakuhan, Lanctôt, Vieira & Herrrmann (2019) in a meta-analysis evaluated effects of natural and synthetic cannabinoids. They point to the reduction of the symptom of agitation with the use of synthetic THC, but with an adverse effect of sedation.

Nocetti and Ribeiro (2020), in a broader perspective, also address the use of cannabis in AD. They consider it as an "adjuvant" drug (in the title of the article) and an "adjuvant" medication (in the body of the text) in the treatment of AD. We will return to this point, for a reflection on this subtle difference between these adjectives in the title and body of the text, and the possible reason for their use, since neuromodulation is considered, competently and explicitly, by the authors.

In general, the multiple references to disease harm reduction and symptom mitigation can perhaps be explained by the fact that many articles are reviewed, there are insufficient human studies, and there is no complete proof of the comprehensive therapeutic potential of cannabis in Alzheimer's. There is still a complexity of genetic variables, individual / singular, and many processes still under investigation regarding the endocannabinoid system (MOREIRA, 2008). We shall also return to these hypotheses.

But is the use of cannabinoids limited to placating major or secondary symptoms of the disease, to being an adjunct to other treatments, or merely a specific form of palliative care? Or yet, to limit oneself to providing some situations of well-being? Let's see what some studies tell us.

Carvalho and Mello (2020) point out that the limited efficacy of drugs used in AD in combating the degeneration of neurons, senile plaques and neurofibrillary tangles motivate research on the

identification of the therapeutic potential of cannabidiol. They seek to demonstrate cannabidiol as a therapeutic "alternative" (CARAVALHO; MELLO, 2021, p.1). The term "alternative" also appears in the title of the article by Lemos, Barcelar and Fialho (2017), who criticize the adverse effects of conventional drugs. If they indicate that it is an "alternative", apparently without positioning themselves in favor of cannabis being a protagonist of the therapy, they indicate not only the action of delaying the progressive effects of Alzheimer's, or of applicability on "neuropathic pain", "nausea and vomiting" (in these cases in patients using chemotherapy), but also more substantive reductions than the mere attenuation of symptoms, such as that of excitotoxicity" (cause of Alzheimer's neural injury), decreased neural damage, protection of cells from nitrosative stress, and even CBD's ability to "create new neurons," "retrieval of memories," "improve cognition," protect the nervous system, and "antioxidant" action (LEMOS; BARCELAR; FIALHO, 2017, p.3).

Oliveira, Moraes and Fattori (2021, p.1-2) refer to the articles by Nocetti and Ribeiro (2020) and Lemos, Barcelar and Fialho (2017), and follow them in a similar line: they refer to the "reduction of the adverse effects of conventional drugs"; also in relation to the use of medicines and products, they consider it "alternative or complementary", and also mention "delay" of the "progressive effects of AD" and "neurodegeneration", and also, "creation of new neurons." They refer to the amyloid hypothesis of the "complex pathological cascade" that "culminates in disseminated synaptic and neural dysfunction"; hypothesis that has as "key process an imbalance between the production and clearance of peptide A-Beta", "dysregulation in synaptic structure and function", "oxidative stress" and "alteration of homeostasis" (OLIVEIRA, MORAES, FATTORI, 2021, p.4). And they affirm: "it becomes necessary to search for *supporting resources*" (OLIVEIRA, MORAES, FATTORI, 2021, p.6, our emphasis). The final highlight of the article is also highlighted, in which they refer to "endocannabinoid signaling" and the *"modulation* of various brain functions", as well as the "neuroprotective effects of cannabinoids" (OLIVEIRA, MORAES, FATTORI, 2021, p.6-7, our emphasis).

Some terms of specialized titles in the discussion of the topic *Cannabis & Alzheimer's* of relevance can be briefly highlighted: Cao et. al. (2014) refer to the "potential" of the therapeutic effects of THC in AD. Esposito et. al. (2006a) refer to the inhibition factor of cannabidiol in Beta-Amyloid and Tau Protein. In another article, Esposito et. al. (2006b) indicate again the same factor of inhibition of Beta-Amyloid, this time analyzing physiological and biochemical mechanisms involving the CB1 receptor. And detailed discussions about cannabinoids and reduction of structural and not merely symptomatic pathological aspects of AD, which require deepening that is beyond the scope of this work, are presented by Aso et. al. (2003; 2012; 2015) and Tolón et. (2009).

Camargo Son et. al. (2019) address the use of cannabidiol and delta 9-TH in Alzheimer's and Parkinson's. Indicate reduction of motor and cognitive symptoms. But in addition, also the

neuroprotective action. The results are explained by the antioxidant effects, CB1 receptor antagonists and PPAR-gamma receptor activation. They consider adverse effects such as drowsiness and dry mouth. Further research on adverse therapeutic effects is recommended, with higher doses and periods of exposure, so that the substances can be considered more effective and safe therapeutic options.

Marsicano et.al (2002) focus on the endogenous cannabinoid system in the extinction of aversive memory. It is known that AD patients have significant recent memory impairments, not reversible and only potentially attenuated in their progressive rate of degradation (by conventional and cannabis drugs, which in this aspect act in a non-antagonistic way). And that interestingly some memories and negative emotional conditioning tend to persist. It is about such memories and conditionings that Marsicano et. al. refer to. The same is pointed out by Malcher-Lopes and Ribeiro (2007), whose quote below refers us again to the important memory of management, dosage, under the principles of selectivity and parsimony:

> The amygdala acts on the emotional response, the formation of aversive (negative) memories, and the perception of fear and stress. The presence of CB1 in the amygdala is responsible for the erasure of traumatic memories and this helps to explore the relaxing effects and decreased anxiety caused by marijuana. In some people, depending on the dose and emotional state, the action of marijuana on the amygdala can generate opposite effects, with the transient emergence of paranoid thoughts (MALCHER-LOPES; RIBEIRO, 2007, p.55).

So, still that there are many allusions to effects of placating symptoms, in some cases are reductions of symptoms related to something much more comprehensive and that, in this sense, suggest a therapeutic cannabis action also much more comprehensive.

It is worth considering one more example: the use for sleep induction (symptom of insomnia, also related to anxiety) or combating irregular or turbulent sleep. James (2021b) addresses the use of cannabis in sleep. What is clear, is that this use is much broader than the more immediate, to placate symptoms. It is not only achieved insomnia or sleep turbulent. The action takes place on the circadian cycle. That is, it acts positively in the orientation of the organism between day and night, in the hormonal production in wakefulness and sleep. As seen in the Class of the day 27/11 with professors Nivaldo Vanni and Guilherme Martins, cannabis can act in order to compensate for the deficiency of the hormone melatonin, which regulates the cycle. Cannabis extract nabiximols is pointed out by James (2021b) as having a beneficial effect in coping with sleep disorders. It is also pointed out that endocannabinoids 2-AG and anandamide (AEA) modulate the activity of sleep-associated neurotransmitters, including GABA and glutamate. Still, the CB1 receptor develops its activity during REM sleep.

Before we synthesize aspects of neuromodulatory use in the following item, it is worth making some comments and systematizations about the important article, already briefly alluded to, by Nocetti

and Ribeiro (2020), entitled "Use of cannabinoids as an adjuvant in the treatment of Alzheimer's Disease".

Nocetti and Ribeiro (2020, p.1) characterize the symptoms in Alzheimer's in the Abstract of the article: "neuroanatomical and biochemical changes in the cerebral cortex". And when they comment that "drug treatment" (conventional) "has little efficacy in more advanced stages of the disease", they refer to the search for "adjuvant resources" (medication canabbica) (NOCETTI; RIBEIRO, 2021, p.104). It is curious the use of the term "adjuvant" in the title and the "coadjuvant" in the Abstract, and this is repeated on page 2 in the following statement: "It is evident the need for resources *Supporting* capable of reducing the adverse effects of conventional pharmacological therapies, thus benefiting AD carriers" (NOCETTI; RIBEIRO, 2021, p.105, emphasis added).

If we turn to the dictionary, we find a distinction between "adjuvant" and "adjunct". Adjuvant is what provides help, help. Being that, in pharmacology, it is said of the drug that, administered with some other, or added to the formula of this, reinforces its action. Well. Already supporting is said to what helps, assists or contributes to a common goal. But it also has a second meaning, not of the pharmacological area, but of cinema and radio: it is said of actor or actress who plays a secondary role.

When we take the article as a whole, or even confining ourselves to the Abstract, when referring to the endocannabinoid system, there is something that is relatively out of touch, whether we stick with the term adjuvant or stay with the adjuvant, namely: "The endocannabinoid system has gained scientific *prominence* as a *therapeutic target* in the treatment of Alzheimer's disease" (NOCETTI; RIBEIRO, 2021, p.104, emphasis added). We assert that such prominence is given by cannabis medicine, since only cannabis acts directly on this "target". And if that's the "target," cannabis would be, let's say, under metaphor, the lead actor, not the supporting actor. This does not invalidate the proposition of conciliatory possibilities with conventional treatment; and we can understand the most common meanings and synonyms of the terms adjuvant or coadjuvante (help; help). We also know, as in the case of inflammation-pain, that we can combine corticosteroids and cannabis, reducing side effects of the former by lowering its dose and including cannabis, aiding the anti-inflammatory-analgesic action, and also adding the beneficial effects of cannabinoids (sleep; food; anxiety). In this case, cannabis "helps" the corticosteroid. Using a metaphor again, we can consider that the husband who says he "helps" to wash dishes, certainly has not overcome the macho attitude. And so we ask: how long would we be limited to the auxiliary use of the cannabinoid? We don't want to forge an all-or-nothing stance; And we also know that there are cases where the corticosteroid is definitely replaced by cannabis, and others where the two are reconciled. How will the use of cannabinoids evolve in the case of AD? Will it ever be possible, with the development of research and evidence that is more rigorous and consistent and more consistent, to have cannabis medicine as its protagonist therapeutic

agent? This is what we want to problematize, without at any time failing to recognize the relevance and richness of the contents worked on in the article.

Therefore, we consider that the term "adjuvant" may bring some misunderstanding, and that the "adjuvant" is the most appropriate. It should also be in the body of the text and not just in the title. For it would be more consistent with the path that unfolds with the "cannabis revolution", to use the term used by Professor Siddhartha. Path that we identify in the following passage from Nocetti and Ribeiro (2021, p.104): "The modulation of the endocannabinoid system presented high therapeutic potential", "because it was able *to slow* the progression of Alzheimer's disease, *reducing* neuroinflammation, the accumulation of beta-amyloid protein and the hyperphosphorylation of tau protein". To which they add: "The *neuroprotective* effects of cannabinoids favor *neurogenesis,* attenuate neuropsychiatric symptoms and improve memory, behavior and learning" (NOCETTI; RIBEIRO, 2021, p.104, emphasis added). On the one hand, reduction, decrease, attenuating aspects of suffering and pathology, and on the other, modulation, neurogenesis, and even as we have seen, mentioned by other authors, "creation of synapses", that is, factors that go beyond the palliative aspects, and that clearly indicate a health-promoting action - which, in the face of a degenerative pathology, will always have a mitigating effect - there would not be, in this distinction, a negation of this aspect.

We consider that the non-existence of the scientific article "Ippon", in the humorous Professor Sidarta's expression - undoubtedly the result of prohibitions and prejudices that hinder the parsimonious and selective use of cannabis in health, and particularly in mental health (SILVA, 2021) - has weight in a certain oscillation between the emphasis of cannabis as a merely additional element to conventional treatment, collaborative with conventional medicines and / or symptom placation (both of the symptoms of the disease and of the side effects of conventional medicines themselves), and the emphasis on its asset *potential* comprehensive therapeutics. Yes, the *potential*, there is still a need to point out with some caution what is glimpsed with cannabis in AD (and that as we have pointed out, differs from the *"status"* achieved by its use in epilepsy). The still circumscribed scope of clinical scope and its mismatch in comparison with objective scientific scopes, in randomized double-blind studies, the need for dialogue with skeptical views with cannabis medicine, may indeed require a prudent stance.

For our part, it is only necessary to explain that we use the term supporting in this work with a connotation different from that of Nocetti and Ribeiro (2021), and that, although we problematize it, we consider it understandable, if not necessary. Here we use the connotation closest to secondary, to the sense of the artistic area. For it is our intention to try to indicate what is unfolding, even if at the risk of projecting something that takes a long time, or that does not even occur in the way we can conjecture today. Nevertheless, whatever the result that there may be of cannabis and the endonacabinoid system as its therapeutic target par excellence, which only the future will tell us, we

consider it necessary to assert the statement that one can no longer go back on the hypotheses and discussions about neuroprotective, neurogenic and neuromodulatory actions. And if a certain caution is needed, and a step or two steps back, boldness is also necessary, for this is the "cat's leap" of many of the social transformations.

2.2 NEUROMODULATORY USE

The use of cannabis as a neuromodulator in AD is distinguished from the use of symptom easing or adjuvant use by its greater scope in terms of the organism, related pathologies and etiological complexity.

Malcher-Lopes and Ribeiro (2007) present considerations about the endocannabinoid system and marijuana. The mental and neurobiological effects, the "cascades of biochemical reactions" (p.44), the effects on sleep and dream, "sexual appetite" (p.72), as well as the "immune effects" (p.74), "anticonvulsants" (p.82) and neuroprotective (p.83) are explained. Regarding the administration of THC in animal models of Alzheimer's, they indicate that there is inhibition of neurodegenerative and its symptoms, in addition to having beneficial effects on the behavioral disorders and lack of appetite present in this disease (p.84).

Malcher-Lopes and Ribeiro (2007, p.135), who refer to the neuroprotective aspects and anti-inflammatory effects, among others, understood as constitutive of numerous possibilities and therapeutic potentialities and well-being of the use of cannabinoids, mention that there is a "flexibilization" of "neuronal groups", in a passage in which they indicate "typical mental effects" of marijuana:

> The antiepileptic action, the short-term memory deficits, the perceptual alteration that converts even the most common stimuli into novelty, the loss of attention, the altered sensation of the passage of time, laziness, the increase in creativity and contemplative attitude, all these mental effects typically caused by marijuana may derive directly from the flexibilization of coordination between neuronal groups (MALCHER-LOPES; RIBEIRO, 2007, p.135).

Thus, we align ourselves with Malcher-Lopes and Ribeiro (2007, p.63) who, when they argue that the "endocannabinoid system" is one of the "main conductors in the orchestration of vital functions", or even when they consider that marijuana produces "complex" effects and indicative of the "fantastic potential of the endocannabinoid system as a target for new remedies"; being challenging the task of directing its effects and using them selectively (MALCHER-LOPES; RIBEIRO, 2007, p.64).

CBD reduces the formation of beta-amyloid protein and blocks the pathway that drives the accumulation of the TAU protein. And THC reduces amyloid beta protein. Synthetic cannabinoids also act positively, through activation of CB2 receptors that help remove beta-amyloid protein from human brain cells; and through CB1 receptors, which block the formation of neurofibrillary TAU protein

tangles. In rats, synthetic cannabinoids blocked the release of pro-inflammatory substances and TAU protein targeting CB2 receptors. In mice with AD (Alzheimer's disease), the combination of CBD and THC results in memory preservation and improved learning capacity. The therapeutic effects of THC and CBD may be indicated, even with studies still advancing. THC reduces agitation and aggressiveness, competitively inhibits acetylcholinesterase (such as conventional drugs used in the early/mildly moderate phases), decreases glutamate release with decreased neurotoxicity in the neurodegenerative cascade (also conventional drugs used in the moderate/severe phases), improves depression and fatigue, increases hunger and improves taste, decreases pain and disconnects pain and suffering. And CBD: improves memory, anxiety and sleep, decreases neuroinflammation (has antioxidant and neuroprotective effect) and has antipsychotic (reduces agitation) and anticonvulsant effects. In summary, all the benefits in terms not only of symptom allaying, but also of action on the health of the organism can be related to the modulation of the activities of neurotransmitters (Lecture 15 - Course VI - 11/23/2021 - Prof. Denise Lufti Pedra).

And Nocetti and Ribeiro (2021, p.105) also emphasize such a neuromodulatory role. When considering the pathophysiology of AD, we highlight, among other aspects, the "neuroanatomical alterations of the cortex", the "oxidative stress", the "neuroinflammation", the "calcium dysregulation", the "mitochondrial dysfunction", the "alterations of cholinergic transmission in the hippocampus" and "alterations of the homeostasis of the cytosolic calcium and the Wnt pathway". And they emphasize the neuromodulatory action of this neurotoxicity. When considering the endocannabinoid system (ECS) indicate that "ECS activation leads to neuroprotection", "reducing neural damage, inflammation and oxidative stress" (NOCETTI; RIBEIRO, 2021, p.105).

> In general, activation of cannabinoid receptors protects the hippocampus and granular neurons against excitotoxicity and glucose deprivation. The beneficial effects of cannabinoid receptor activation can be used effectively in the treatment of AD. Based on this information, the objective of this study is to evidence, from the review of preclinical (in *vivo and in* vitro) and clinical studies, the therapeutic potential of SEC in the treatment of AD (NOCETTI; RIBEIRO, 2021, p.105).

In the development and discussion of the article deepen the explanations about the modulation of the SEC. They address the regulation of synaptic transmission. CB1 receptors (located at neuronal endings) act as "modulators of excitatory or inhibitory neurotransmission", whereas CB2 receptors (located in immune system cells) "modulate cell migration and cytokine release" (NOCETTI; RIBEIRO, 2021, p.106). They also clarify that "endocannabinoids" are "lipid compounds" derived from the "degradation of the phospholipid membrane", and that they "act as neurotransmitters" (NOCETTI; RIBEIRO, 2021, p.106). And they add: "The increase in tonic of SEC" plays a "neuroprotective role" in "neurodegenerative processes," so that "cannabinoid activation" promotes "brain homeostasis and neuronal survival" (NOCETTI; RIBEIRO, 2021, p.106). Therefore, the

argument of an action far beyond the supporting one is evident, especially if we consider the critical connotation that we proposed to the use of this adjective. This is consolidated in the conclusion, in which they assert that the "modulation of the SEC, through the daily use of small doses of cannabinoids" implies an increase in the "neurogenic potential", in addition to "improvement of memory and behavior" (NOCETTI; RIBEIRO, 2021, p.108).

3 NEW PATHS TO ALZHEIMER'S: IS NEUROPROTECTIVE CANNABIS HERE TO STAY?

If assertiveness about the comprehensive therapeutic potential of cannabis in AD and health still has limitations, we can look at the question in another way, and instead of simply questioning it, ask: is it possible to go back to what has already been raised of hypotheses, debatES and clinical experiences that refer to neuroprotective action? Our answer to the question is no.

James (2021a) in his chapter on cannabinoids and neuropsychiatry describes the functioning of the endocannabinoid system and mentions: neuroprotection, and its action on oxidative stress, inflammation and mitochondrial dysfunction, among other aspects; neurogenesis, the formation of new neurons, with benefits to brain plasticity and limbic system functions (emotions; memory; behavior); and anxiolytic action.

Pérez-Olives et. al. (2021) address advances in the neuroprotection potential of cannabinoids in Alzheimer's (and also in Parkinson's and Huntington's disease). They indicate the delay of neuronal death and the existence of microglia activation as a protective phenotype. The cannabis extract SativexTM is referred to as approved for human therapy, and that such condition has favored studies on natural and synthetic cannabinoids. And, consequently, the expansion to cope with neurodegeneration and removal of intraneural amyloid in the case of AD.

The neuromodulatory action is related to the neuroprotective and vice versa, and both to the anti-neurodegenerative potential. The SEC study is here to stay. You can't turn your back on him. Although there are still many investigations to better understand the SEC and its relations with the nervous system, immune, metabolism and homeostasis. As already pointed out, lipid and mitochondrial dysregulation deserve special attention in the case of AD and its neurodegenerative processes.

For Moreira (2008, p.47), the "endogenous cannabinoid system" is one "of the most recent neurotransmitter systems studied, with many aspects to be elucidated". Among them the "enzymatic processes" of "synthesis and inactivation" of "cannabinoids" (MOREIRA, 2008, p.47). With this, it will be possible to develop compounds that act in these stages. The question of the role of CB1 and CB2 is also mentioned, as well as findings that unfold in relation to CB3. The "endocannabinoids" interact with "other systems", "such as opioids, dopamine, gamma-aminobutyric acid and glutamate" (MOREIRA, 2008, p.47). They are "modulators of these neurotransmitters", and some functional

aspects are still obscure (MOREIRA, 2008, p.47). Understanding the mechanisms of action of cannabinoids and especially the physiology of the cannabinoid system can shed light on pathological conditions in which this system is unbalanced, such as Alzheimer's. And, consequently, expand "new pharmacological approaches" that can be "transformed into therapeutic benefits" (MOREIRA, 2008, p.48).

Nocetti and Ribeiro (2021), as previously mentioned, indicate the SEC as a therapeutic target for Alzheimer's. They indicate that the "lipodromic analysis" points to low levels of anandamide (AEA). This reduction is inversely proportional to beta-amyloid protein levels.

> This relationship suggests that cognitive function is affected by AEA deficiency, which is regulated by peptide levels of beta-amyloid. In addition, changes in enzyme activity related to the synthesis/degradation of endocannabinoids have also been observed in the brains of AD patients. Previously, an increase in FAAH enzyme activity was observed in glial cells associated with neuritic plaque, as well as in peripheral blood mononucleated cells. This event may contribute to the degradation of AEA in senile plaques (NOCETTI; RIBEIRO, p.7).

Studies indicate the "neuroprotective, antioxidant, and antiapoptotic effect of CBD" in "cell culture" exposed to "beta-amyloid neurotoxicity" (NOCETTI; RIBEIRO, p.7). There is "reduced production of ROS" and "lipid peroxidation" (NOCETTI; RIBEIRO, p.7).

> Much of CBD's effects involve intracellular mechanisms closely linked to neuronal physiology. In hippocampal neurons, for example, CBD stimulates increased intracellular calcium concentration via mitochondrial uptake/release and activation of L-type (voltage-dependent) calcium channels. CBD is able to significantly reduce oxidative and nitrosative stress and neuronal damage promoted by the deposit of beta-amyloid protein, attenuating tyrosine hydroxylase depletion, dopamine levels, GABA and the *modulation* of induced nitric oxide synthase (iNOS) expression, decreasing the production of NADPH oxidase from ROS. Rajesh et. al. (2007) observed that pretreatment with CBD attenuated mitochondrial superoxide generation induced by lack of glucose concentration and NF-kB activation, along with expression of ICAM-I and VCAM-1 adhesion molecules in human coronary artery endothelial cells. These results suggest that CBD may exert a *desirable neuroprotective*, antioxidant, and anti-inflammatory role for the treatment of AD (NOCETTI; RIBEIRO, p.7-8, emphasis added).

In this way, one can see the level of detail that research has already achieved, and how the conjecture of a future treatment of AD under the reins of cannabis medicine makes sense, provided thatMany obscure or insufficiently understood aspects can be elucidated.

3.1 HALF-OPEN PERSPECTIVES, HYPOTHESES AND INVESTIGATIONS

As we have tried to demonstrate, the neuroprotective potential of cannabis in AD leads us to neurogenesis, or even to a complex metabolic action of neuromodulation. Regarding this broader possibility of the action of cannabis medicine in Alzheimer's, some studies point out important aspects, hypotheses that incite new debates, so that we seek here to indicate some paths that can provide new paths to Alzheimer's.

We have selected, for the discussion of this item, four articles whose points raised seem important to us for the fabric of new research and deepening. Points that can be connected and aligned by a wire that allows better grounding the neuroprotective and neurogenic potential, or, synthetically, neuromodulation and homeostasis.

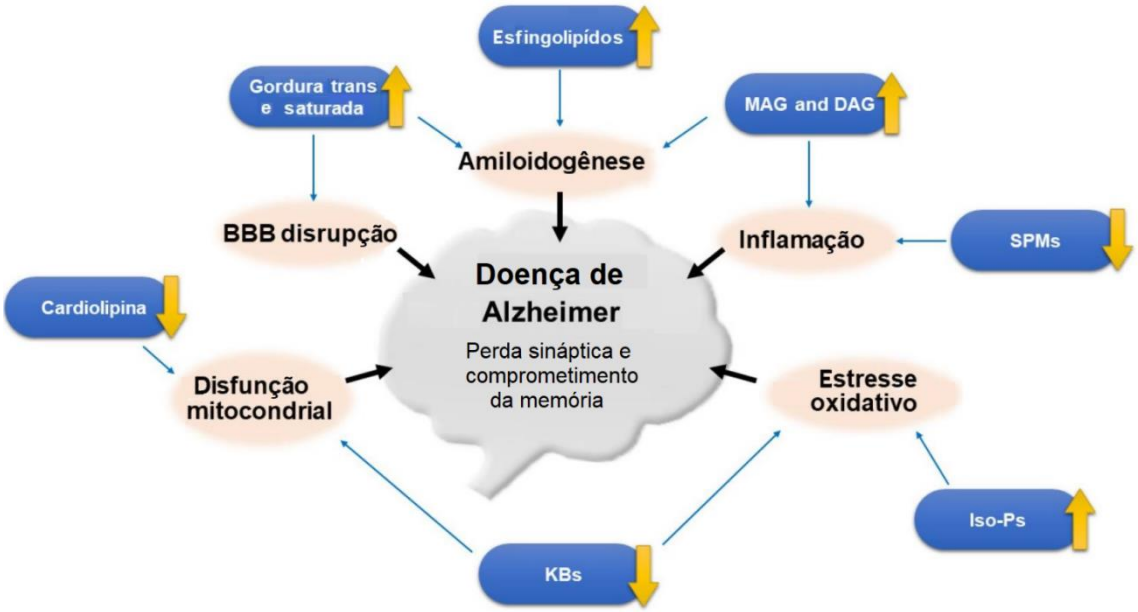
Kao, Ho, Tu, Jou & Tsai (2020, p.1) point to an analysis of lipid peroxidation so as to shed light on exaggerated inflammation and "aberrant lipid metabolism". Cadas, Gaillet, Beltramo, Venance & Piomelli (1996), in turn, deal with the biogenesis of anandamide. The release of this bioactive lipid is considered from an analysis of the mechanisms of its biogenesis. The understanding of lipid metabolism does not dispense with the discussion of elements related to brain energy. Castro, Martins and Tufi (2010) address the crucial role of mitochondria in providing energy to the brain. They indicate the relevance of mitochondrial stress in neurodegeneration. In a complementary way, Rao, Carlson and Yan (2013) specifically address the mitochondrial permeability transition pore as a potential drug target for neurodegeneration.

KAO, HO, TU, JOU & TSAI (2020) point out that knowledge of the connection between lipids and AD is crucial to unravel its metabolic aspects. AD is referred to as an "intriguing disease" in which there is "disruption of lipid homeostasis" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). They point out that lipids are basic components of cell membranes. They play a role in brain health and function. The interruption of lipid homeostasis generates neurological disorders, in the case of AD, neurodegeneration. The authors consider recent advances in lipid analytical methodology to be necessary and promising. His considerations are based on the observation of "fatty acid changes at the level of lipid rafts" and "lipid peroxidation in the initial stage of AD" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). Lipid peroxidation is pointed out as the main manifestation of oxidative stress in the CNS.

As we pointed out, in Alzheimer's there is "accumulation of amyloid protein in plaques due to overproduction or impaired elimination of β-amyloid peptides (Aβ)" and "deposition of neurofibrillary tangles (NFTs)" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). This results in synaptic loss and neurodegeneration. The authors indicate lipids as responsible for "50% of dry brain weight" and "basic structural component of neuronal cell membranes" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). As an early AD event, they identify "cerebral lipid peroxidation", which characterizes an "aberrant lipid metabolism" (KAO; HO; YOU; JOU; & TSAI, 2020, p.1). Patients with AD have increased "lipoid granules (adipose inclusions)" in "cells of the central nervous system (glia)." Lipids are mediators of immune responses, and the "permeability of the blood-brain barrier (BBB)" is higher in the elderly: "Cerebral hypoperfusion" and "loss of BBB integrity" result in "reduced energy availability and disrupted synapses, leading to impairments in memory and learning" (KAO; HO; YOU; JOU; & TSAI, 2020, p.3).

AD is a disease with "exaggerated inflammation" and "impaired inflammatory resolution"; resolution is regulated by "lipid mediators" (specialized pro-resolution mediators - SPMs) whose anti-inflammatory properties restore "inflammatory resolution and homeostasis" (KAO; HO; YOU; JOU; & TSAI, 2020, p.7).

"Dysregulated lipid homeostasis" is associated with aging and contributes to the "pathogenesis of AD" (KAO; HO; YOU; JOU; & TSAI, 2020, p.18). We present the figure elaborated by the authors on the roles of lipids in the pathogenesis of AD. As they state, "the mechanisms linking lipid dysregulation" and Alzheimer's "consist of changes in the gut microbiota and gut-brain axis, neuronal signaling pathway, BBB disruption, mitochondrial dysfunction, oxidative stress, and inflammation"; Such aspects lead to "synaptic loss" and "memory impairment." Lipids, illustrated below, play "essential roles in pathogenesis," and are proposed as "biomarkers" (KAO; HO; YOU; JOU; & TSAI, 2020, p.18).



Roles of lipids in the pathogenesis of AD (In: KAO; HO; YOU; JOU; & TSAI, 2020, p.18).

As it turns out, the discussions of Kao et. al. (2020) on the roles of lipids in pathogenesis can be related and compared to those of the other authors of the three articles referred to in this item.

Cadas, Gaillet, Beltramo, Venance & Piomelli (1996, p.3934), in their approach to the biogenesis of anandamide, precisely indicate the role of this lipid as cannabinoid substances. Anandamine, according to the authors, may derive from the "cleavage of the precursor phospholipid NAPE" (CADAS et. al., p.3934). NAPE levels in neurons are regulated by ions. Such "regulation" can maintain the supply of "carabimimetic N-acylethanolamines" during the "synaptic activity and primary target neurons of the release of these bioactive lipids" (CADAS et. al., p.3934).

Castro, Martins and Tufi (2010, p.1), who emphasize the crucial role of mitochondria in providing energy to the brain, consider that their "deterioration" can have "harmful consequences" on the "function and plasticity of neurons", and consequently, on the "pathogenesis of neurological disorders" (CASTRO, MARTINS; TUFI, 2010, p.1). Mitochondria are subjected to high stress. Thus, the authors seek to understand the "mitochondrial stress control pathways", and thus better understand neurodegenerative processes (CASTRO, MARTINS; TUFI, 2010, p.1).

Rao, Carlson and Yan (2013, p.1267) indicate that the "mitochondrial permeability transition pore (mPTP)" plays a "central role" in "changes in mitochondrial structure and function". This leads to the neuronal lesion typical of AD. "The interaction of amyloid beta peptide with CypD potentiates mitochondrial and neuronal disturbance," Rao et states. al. (2013, p.1267), in order to bring interesting complements to the analysis of Castro, Martins and Tufi (2010)

Thus, we leave open to the experts some paths that can be aligned between these points of these four important articles briefly considered here.

3.2 CONNECTIONS AND PLASTICITIES

Malcher-Lopes and Ribeiro (2007, p.53) address the action of THC on "brain circuits" called "base nuclei" and the presence of CB1 in the cerebellum. They explain that in the "core *Accumbens*" the CB1 receptor is abundant; It is the region of the brain that participates in the "anticipation and processing of the sensations of pleasure and reward." (MALCHER-LOPES; RIBEIRO, 2007, p.54). They also present a detailed characterization of marijuana as a "tonic": cannabinoids promote a "disorganization of neuronal processing" that has as a consequence a "facilitation of the restructuring of memory traits", thus making it easy to understand that their use "facilitates the creative process and the generation of *Insights*" (MALCHER-LOPES; RIBEIRO, 2007, p.141-142). The tonic, they continue, acts as an "appetite stimulator" and "favors states of low anxiety", reducing "social tensions" in different contexts through its "anti-stressful action" (MALCHER-LOPES; RIBEIRO, 2007, p.142). Thus, such aspects can also be considered as potentially beneficial to Alzheimer's patients. When considering the "neurobiological effects of marijuana," they consider that CB1 activation promotes "reduced activity of inhibitory neurons," which enables "more active circuits." (MALCHER-LOPES; RIBEIRO, 2007, p.124). Finally, but not last, they consider that the joint results of studies from the last three decades suggest that "endocannabinoids" regulate "hippocampal modifications" by "*Modulation* of the activity of inhibitory neural networks that control the greater or lesser organization of memory processing" (MALCHER-LOPES; RIBEIRO, 2007, p.126).

And if the studies, with all the gaps and challenges still to be overcome, already indicate such elements, what will be said of the results that will come in the next three decades? Therefore, the paths are open to, perhaps, erect the protagonism of the neuromodulatory role of cannabis in Alzheimer's.

Connections and plasticities are key words that emerge from the conjectures that, for now, we can glimpse for coping with such a complex and intriguing disease.

4 FINAL CONSIDERATIONS

The future belongs to God, say the religious. While others say that history is made by men and that the social practices they lead produce transformations and advances, in historical cycles of alienation and estrangement guided by properties intrinsic to the development and ontology of the social being (LUKÁCS, 2010). We adopt this second perspective. And we ponder that nothing advances or transforms without difficulties. This is how they should or can occur. Counterpoints and dialogues are necessary for there to be solid foundations of our social constructions. And these never become eternal. In the scientific and health field, we can easily identify the contradictions, advances and setbacks of the processes of discussion, legitimation and consolidation of different perspectives of promotion, prevention and care. In the present work we seek to indicate supporting and protagonist aspects of cannabis in the treatment of Alzheimer's. And we emphasize the importance of making the neuromodulatory role predominant (neurogenic; neuroprotective; neurostabilizing). Parsimony and boldness. Dialogue and affirmation. Thoughtfulness and enthusiasm. These are necessary and intrinsic psychosocial components to the irreversible advancement of cannabis medicine, and by extension, cannabis medicine in the treatment of Alzheimer's. Psychoanalysis revolutionized the understanding of the therapeutics of neuroses, and later of psychoses, and even today there are those who question its scientificity. The Freirean perspective revolutionized the understanding of educational processes, and even today there are those who despise it or even label it as left-wing or other bizarre and unreasonable adjectives. These were contributions that took very important steps. And even if they still provoke resistance, they are irreversible, whether you believe them or not. Both Sigmund Freud and Paulo Freire were tireless in their trajectories, in the sense of assuming dialogical postures with what was faced (or even denied), without ever giving up their ethical convictions, and the practices and objectives they achieved. His achievements marked epochs and generations, but they never occurred in an ideal way and not even without mishaps, as indicated in his works "Terminable and endless analysis" (FREUD, 1985) and "Pedagogy of hope" (FREIRE, 2018). Similarly, this is the case with the achievements of the medicinal use of cannabis. With the contents and reflections systematized in this work, we hope to make our modest contribution to a more promising future for the life and health of Alzheimer's patients, with the hope that this can happen with the strengthening of cannabis medicine, since we risk saying that this is essential to the former.

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Relationship between e-cigarette use and oral health: An integrative literature review

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ABSTRACT
The objective of the present study was to detect oral problems associated with the use of electronic cigarettes in the literature. This is an Integrative Literature Review, formulated with the aim of investigating the complications and risks to oral health related to the use of electronic cigarettes. It was based on the protocol for systematic reviews PRISMA Flow Diagram. Data were collected from the Latin American and Caribbean Health Sciences Literature Electronic Database (Lilacs), Medline and Pubmed. Decs/Mesh descriptors were used in the form: "Electronic Nicotine Delivery Systems" OR "Vaping" AND "Oral Health". 196 works were identified in the bases and only 16 articles remained, which are part of this integrative review. It has been observed that over time, the use of electronic devices can result in periodontal diseases, dental caries, oral infections, and oral cancers, affecting both the functionality and appearance of the stomatognathic system. For this reason, it is essential that the dentist guide patients about the care and prevention necessary to minimize the possible damage caused by electronic cigarettes to oral health.

Keywords: Electronic cigarette, Oral health, Vaping, Electronic Nicotine Delivery Systems.

1 INTRODUCTION

The habit of smoking is recognized as an epidemic disease that causes physical, psychological and behavioral dependence similar to what occurs with the use of other drugs such as alcohol, cocaine and heroin (BRASIL, 2020). Increasingly popularized, the Electronic Devices for Smoking - DEFs, also known as *vape, electronic cigarettes,* pod, *among others, emerged as an alternative to stop the use of conventional cigarettes, but ended up evidencing a major health problem.*

According to the Pan American Health Organization (PAHO) indicators for the year 2019, the tobacco epidemic is responsible for the deaths of more than 8 million people per year, with more than 7 million of these deaths resulting from direct tobacco use and more than 1.2 million deaths being the result of non-smokers exposed to secondhand smoke. The institution also states that the new tobacco and nicotine delivery devices pose a threat to the control of the epidemic.

The devices with attractive designs and use of tasty essences, which exude flavored smoke, do not cause bad breath or spread gray and seek to attract, above all, young people, stimulating, in many cases, the duality in the consumption of conventional and electronic cigarettes (BARRADAS *et al.*, 2021).

According to the National Cancer Institute (INCA, 2016), the electronic cigarette device includes: a battery, a liquid storage tank, a resistance responsible for heating the liquid, a wick that absorbs the liquid and a nozzle that is used by the user to inhale the aerosol produced. The liquid contained in the storage tank can contain a variety of substances, including nicotine, flavors, and chemical additives. The resistance is usually made of a high-temperature resistive wire, such as kanthal, and is wrapped in organic cotton to absorb the liquid. The battery is responsible for providing the energy needed to heat the resistance and produce the aerosol.

When the user vacuums the device, a sensor detects the airflow and heats the liquid from the cartridge, causing it to evaporate. The steam releases the nicotine to the user, and a portion of the vapor can be released into the ambient air when the user exhales. The steam temperature reaches 40-65°C. According to information from manufacturers, a cartridge can generate from 10 to 250 jets, which could correspond, depending on the brand, to 5-30 cigarettes (KNORST *et al*., 2014).

Based on current global evidence, the use of nicotine e-cigarettes increases the risk of a range of health harms, such as: poisoning, seizures, addiction, trauma and burns (caused by explosions) and respiratory diseases (including Severe Acute Respiratory Syndrome – SARS – and Electronic Cigarette-Induced Lung Injury – EVALI) (INCA, 2023)

It becomes practically inevitable the comparison between conventional cigarettes and DEF 's, however, there is little widespread knowledge about the harms of the latter both systemically and restricted to the oral cavity. In this way, there is the concern of researching about the devices in order to list if the damages caused are similar, aggravated or diminished.

In Brazil, the marketing, importation and advertising of all types of electronic devices for smoking are prohibited by the National Health Surveillance Agency, ANVISA, since August 2009 (ANVISA, 2016). In this perspective, it is necessary to understand that the problems surrounding the use of these devices, whether in the social or individual sphere, can have numerous influences on the oral health of users.

The growing popularization of the devices and the false sense of non-malignancy of their effects on the body, especially in the oral region, motivated the researchers to carry out this research.

The objective of the present study is to point out the relationship between the use of electronic cigarettes and oral health, through the identification in the existing literature of the main points that health professionals, especially dentists, need to have knowledge to offer scientifically based information and a more complete treatment for their patients.

2 METHODOLOGY

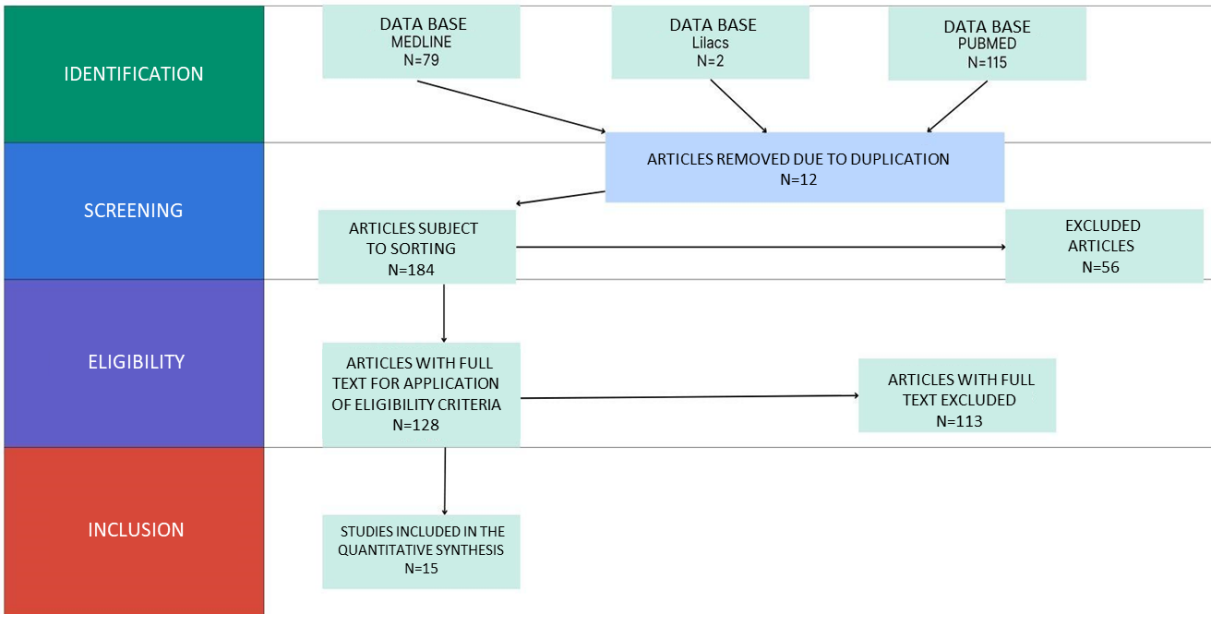
This is a qualitative and descriptive study, based on database research from the perspective of the integrative review, starting from the following guiding question: What are the risks and complications in oral health associated with electronic cigarettes?

It was necessary to define the data sources to convey reliability for the investigation. The survey was anchored in the protocol for systematic reviews PRISMA Flow Diagram. Data were collected using the Electronic Database of Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature Analysis and Retrievel System Online (MEDLINE) and PUBMED. The descriptors Decs/Mesh were used in the form: "Electronic Nicotine Delivery Systems" OR "Vaping" AND "Oral Health". The search, reading and selection of scientific articles that interested the theme were carried out.

Thus, the inclusion criteria were: (1) types of productions: original articles, published in full and available electronically; (2) Temporal framework: papers published from January 2018 to December 2022; (3) Languages: Portuguese, English or Spanish. On the other hand, to ensure that only the relevant works were considered, the works denominated as "gray literature" were excluded, as well as those that did not meet the objective of this study, duplicates and those that mixed other pathologies.

A total of 196 works were identified in the databases, where 12 were removed due to duplicity, 56 were excluded because they were not within the established filters and 112 were not in accordance with the intention of this study. Thus, 15 articles remained, upon full reading and which are part of this integrative review, as shown in the diagram below.

Figure 01 - Flowchart of the description of the methodology.



Source: Prepared by the authors.

3 RESULTS AND DISCUSSION

Based on the above, image 1, the studies used in this integrative review are cited in the following table.

Table 01 - List of selected articles according to author, year, type of study, database and category.

Author/year	Type of study	Database	Category
IRUSA *et al*. (2022)	Cross-sectional study	MEDLINE	Changes in tooth structure
CATALA-VALENTIN *et al.* (2022)	Laboratory study	MEDLINE	Changes in tooth structure
THOMAS *et al*. (2022)	Longitudinal study	MEDLINE	Changes in the periodontium
XU *et al*. (2022)	Longitudinal study	MEDLINE	Changes in the periodontium
VEMULAPALLI *et al.* (2021)	Cross-sectional study	MEDLINE	Changes in tooth structure
KLAWINSKI *et al.* (2021)	Case report	MEDLINE	Cellular changes
HONG; MAINOUS (2021)	Cross-sectional study	MEDLINE	Cellular changes
TOMMASI *et al*. (2019)	Cross-sectional study	MEDLINE	Cellular changes
TOMAR *et al*. (2019)	Literary review	PUBMED	Changes in tooth structure
ALQAHTANI *et al*. (2020)	Cross-sectional study	PUBMED	Changes in saliva

EBERSOLE *et al.* (2020)	Literary review	PUBMED	Cellular changes
PANDARATHODIYIL *et al.* (2021)	Cross-sectional study	PUBMED	Changes in saliva
CICHOŃSKA *et al.* (2022)	Cross-sectional study	PUBMED	Changes in saliva
CICHOŃSKA *et al.* (2019)	Cross-sectional study	PUBMED	Changes in saliva
DE LIMA *et al*., (2023)	Cross-sectional study	PUBMED	Cellular changes

Source: Prepared by the authors.

3.1 CELLULAR CHANGES

The in *vitro study* by De Lima *et al*., 2023) demonstrated in the laboratory how *e-liquid* – also called juice, is a mixture composed of nicotine, flavorings and solvent – can alter oral cells and their implications from a panel of normal oral epithelial cell lines, oral squamous cell carcinoma and mouse oral cancer. The authors point out that this exposure alters the structure and survival of oral epithelial cells, increasing cases of cell death and tumor invasion, and may induce changes consistent with the epithelial-mesenchymal transition, thus increasing the metastatic competence of oral squamous cell carcinoma.

In the same vein, Tommasi *et al*. (2019) aimed to determine the effects of e-cigarette and conventional cigarette use compared to non-smokers from oral epithelial cells to assess cancer-causing potential. They used as a method the collection of these oral cells and the sequential analysis of the collected RNA. In this study, they concluded that e-cigarette users, as well as conventional users, have significant dysregulation of key genes in the oral epithelium converging to cancer-related functions.

Approaching this discussion, the review by Ebersole *et al*. (2020) lists the chemical substances that are emitted and those that can be formed in electronic devices and their effects on the oral cavity. Among them, reactive nitrosamines and carbonyls stand out, with great carcinogenic potentials, in addition to the impurities present in the liquid that, together with the breakage of the wick, can lead to the release of arsenic and silica.

Hong and Mainous (2020) made an association between e-cigarette use and oral human papillomavirus infection from the National Health and Nutrition Examination Survey (NHANES) study between 2013 and 2016 with full oral HPV DNA testing and questions about tobacco use. They resulted in a higher likelihood of HPV-16 infection in dual users, *vape* and conventional cigarettes. From this, they came to the conclusion that there is a significant relevance between electronic and oral HPV-16 infection, responsible for most cases of oropharyngeal cancer.

In this perspective, Klawinski et al. (2021) described the case of a previously healthy 19-year-old young adult who presented with an ulcerative lesion of the side of the tongue that did not heal and swelled progressively. The authors provided clinical care and collected the data to describe the case.

The patient, who had an extensive history of e-cigarette use and no other carcinogenic risk factors, developed aggressive and unresponsive HPV-negative squamous cell carcinoma in the oral cavity and underwent total glossectomy, radiotherapy and chemotherapy but developed metastasis.

3.2 CHANGES IN SALIVA

The pilot study by Alqahtani *et al.*, 2020) intended to analyze the modifications present in the saliva of DEF'S users compared to never tobacco users through the evaluation of inflammatory cytokines and metabolite profiles. To this end, they collected salivary samples and applied a questionnaire to both groups. As main results it was evidenced that the users of this product present ongoing inflammation compatible with gingivitis, but the alterations found could be used only to identify risk factors.

The works of Pandarathodiyil *et al.* (2021) and Cichonska *et al*., (2019; 2022) compared e-cigarette smokers, conventional and non-smokers (control group) for different purposes.

Pandarathodiyil *et al.* (2021) examined the levels of the enzyme lactate dehydrogenase (LDH) among recruits, since it can be used to detect pathologies in the oral mucosa. The research participants were located from an advertisement and after screening their saliva was collected and measured with a calorimetric LDH assay kit to later make the statistical comparisons. In this study, salivary LDH levels in *pod* users were higher compared to the smoking and control group, indicating greater degradation of oral epithelial cells.

On the other hand, Cichonska *et al*. in their 2019 study, aimed to understand the impact of e-cigarettes on the bacterial properties of saliva. In this research, the volunteer participants underwent screening and then saliva was collected for laboratory and statistical analysis. These indicated that IgA levels in vape users were not significantly lower than in the control group and lysozyme levels were also decreased. Lactoferrin levels were increased. Proving that there are changes in the oral environment of vaper smokers.

Approaching this discussion, Cichonska *et al.* In 2022, they intended to study the physicochemical changes of saliva by comparing the 3 groups mentioned. The saliva of the screened participants underwent laboratory tests to check the pH and concentration of proteins, calcium and phosphates. As a result, they noticed that e-cigarette users have altered pH, amount of protein, calcium and phosphates compared to the other two groups.

3.3 CHANGES IN THE PERIODONTIUM

The electronic cigarette is an alternative to traditional tobacco that has gained popularity in recent years among young adults, However, the relationship between EC use and oral health is still little known. Thus, the research conducted by Martell *et al.* (2020) aimed to investigate the knowledge

of EC e-cigarette users about the impact of the use of these devices on oral health. The research was conducted with 220 EC users, who were interviewed in order to evaluate the knowledge and perception about the impact of the use of FB on oral health. The results were analyzed using descriptive and inferential statistics. The results of this research indicate that FB users have little knowledge about the oral problems associated with the use of EC. However, most participants are willing to discuss the effects of vaping on oral health with dental care professionals and would potentially reduce or quit if they believed it was harmful to oral health. These results highlight the importance of user awareness and education about the effects of vaping on oral health.

Clinical studies have also demonstrated an association between e-cigarette use and the presence of signs of inflammation in the periodont. A recent study Thomas SC *et al*, (2022) compared clinical and demographic measures between e-cigarette users, conventional cigarettes and non-smokers, and found that the progression of periodontal severity was significantly worse for e-cigarette users and conventional cigarettes than for non-smokers.

In addition, e-cigarette use may promote a healthier microbiome compared to conventional cigarette smokers, but not as healthy as that of nonsmokers. According to the study Xu *et al*. (2022) in order to investigate the effect of e-cigarette vapor on the structures of the saliva bacterial community, performed with 101 patients with periodontitis. The results showed that e-cigarette users showed enrichment of bacteria of the genera Dialister, Selenomonas and Leptotrichia, which were correlated with high levels of pro-inflammatory cytokines, including IFN-y, IL-1ß and TNF-α, thus contributing to oral microbiome dysbiosis and disease progression.

E-cigarettes are often promoted as a healthier alternative to traditional tobacco, but recent studies indicate that it can have detrimental effects on oral health, including the periodont. E-cigarette vapor contains a variety of chemicals, such as glycerin, propylene glycol, nicotine in varying concentrations, and flavoring agents, these toxic compounds can affect periodontal tissue and the oral microbiota Thomas SC, *et al.* (2022).

However, it is relevant to note that there is no consensus in the scientific literature about the effect of electronic cigarettes on the periodont. The peculiarity of the periodontal microbiome of the electronic cigarette reinforces the need for further research on this relatively new microbial community, resulting from the adoption of a recent human habit. It is necessary to investigate how biotic and abiotic components act synergistically in oral health and disease to better understand this relationship.

3.4 CHANGES IN TOOTH STRUCTURE

Tooth decay is a multifactorial disease that involves a complex interaction between the oral microbiota, diet, host, and environmental factors. Recently, the use of e-cigarettes has become popular

as a safer alternative to smoking. However, studies have shown that e-cigarettes can pose risks to oral health, including the association with tooth decay.

A systematic review study conducted by Irusa, *et al.* (2022) evaluated the relationship between e-cigarette use and tooth decay. The authors concluded that e-cigarette use is associated with a higher prevalence of tooth decay. According to research conducted by Xu, *et al*. (2022) the results obtained indicated that flavored essences, compared to unflavored ones, are more harmful to biofilm formation and the growth of oral commensal bacteria. This may be related to the presence of sugars and other additives in e-cigarette liquids, which can be fermented by oral bacteria, leading to the production of acids that erode tooth enamel.

In addition, a study by Thomas SC, *et al.* (2022) showed that e-cigarette vapor can affect the integrity of the dental biofilm and increase the adhesion of oral bacteria to the surface of teeth. This can contribute to the development of tooth decay and other oral diseases. In this sense, the research conducted by Abhilash Vemulappalli, *et al,*. (2021) indicates that it is possible to observe a correlation between the use of vaporizers and double smoking with an increase in the prevalence of untreated dental caries.

However, the lack of regulation on the composition of e-cigarette liquids makes it difficult to assess the long-term effects of their use.

4 CONCLUSION

Based on the presented studies of current research and discussions on the effects of e-cigarette use on oral health, a number of symptoms from microscopic to macroscopic levels are observed, affecting not only oral health, but also adjacent systems regarding excessive e-cigarette use. Therefore, it is crucial to highlight that this review offers a comprehensive view of the harms caused by the use of e-cigarettes, which can include from cellular changes, problems in saliva, in the periodont, to the evolution to oral cancer.

The importance of health professionals addressing the subject during interventions in school environments, colleges, medical and dental consultations is highlighted, raising awareness and encouraging the reflection of individuals about the damage to physical and oral health caused by the consumption of electronic cigarettes and other tobacco products and that they are encouraged to seek safer alternatives. In addition, future studies should be conducted to investigate the specific changes associated with e-cigarette use on systemic and oral health, as well as to compare the effects of e-cigarette and conventional cigarette use.

Given all this information, it is important to emphasize the relevance of this study for public health, since it provides important evidence for decision-making about the use of e-cigarettes and the prevention of their harmful effects on oral and systemic health. In this sense, this investigation

contributes to the advancement of scientific knowledge on the subject, as well as to the awareness of the population about the risks associated with the use of electronic cigarettes.

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Performance of the pharmaceutical professional during the COVID-19 pandemic

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ABSTRACT

The COVID-19 pandemic has impacted not only the population, but also health systems around the world. Hospitals and care networks have been caught up in one of the biggest public health challenges of recent times: a novel coronavirus. In this scenario, pharmaceutical professionals perform an essential function since they are easily accessible to the population through drugstores and pharmacies and are able to offer guidance in the fight against the disease. Thus, the objective of the present study was to observe and report the services and performance of the pharmaceutical professional during the COVID-19 pandemic around the world. To this end, a bibliographic review was performed with a targeted search of scientific articles during the month of June 2020 in the PubMed and Scielo databases. The data were presented in the form of a comparative table containing the objectives of the articles, country of origin and dates of publication, as well as a description of the activities of the pharmaceutical professional cited in the different studies. Based on the results, it was observed the importance of the performance of the pharmaceutical professional in the hospital, community and clinical spheres, during the pandemic, both in the direct care of the patient and in the pharmacotherapeutic contribution in team. Therefore, the role of the pharmacist in the fight against COVID-19 is essential not only in dispensing the drug in pharmacies, but also in the primary care of the patient with reliable guidance and avoiding unnecessary trips to hospitals.

Keywords: Pharmaceutical services, Pharmaceutical care, COVID-19.

1 INTRODUCTION

The coronavirus pandemic has been responsible for one of the biggest global public health crises, affecting many countries around the globe. The World Health Organization (WHO) characterizes COVID-19 as a pandemic on March 11, 2020, with the first case detected in December 2019 in the city of Wuhan, China. According to the WHO, the coronavirus belongs to a large family of viruses that can cause illness in animals or humans through respiratory infections such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Regarding the symptoms of COVID-19, the WHO highlights fever, dry cough and tiredness as the main ones, with about 80% of people recovering from the disease without needing hospital treatment and 1 in 5 people who contract the virus become seriously ill. Higher risk is attributed to older people or those with associated comorbidities such as high blood pressure, heart and lung problems, diabetes or cancer (WHO, 2020). The transmission of the coronavirus occurs mainly from human to human through respiratory droplets, having an incubation period of 1 to 14 days before the onset of symptoms and

therefore social distancing is important in order to prevent community transmission and try to maintain control of the pandemic (ZHENG S. et al., 2020).

The COVID-19 scenario brings unprecedented sanitary conditions and enormous pressure on health systems around the world. As a result, chronic patients are affected while they may have difficulty accessing health services for routine treatment and medication management. Therefore, pharmacies and drugstores are useful facilities to facilitate the access of these patients, as well as the contribution of pharmacists to help alleviate the burden on already overburdened health systems (KRETCHY I. et al, 2020). In this context, it is important to highlight the duties of pharmacists as one of the most accessible health professionals to the general public and who have much to offer in assisting and combating COVID-19. For example, with direct pharmaceutical assistance to patients with chronic diseases, guidance and rational use of medications, as well as forms of disease prevention (HEDIMA E. et al., 2020).

Clinical pharmacists are accustomed to performing pharmaceutical care in their work environment in order to ensure the safe and effective use of their patients' medications. However, in the context of the pandemic, as in other public health emergencies, work strategies need to be adapted according to the spread of the disease, where sometimes information and resources to guide professionals are lacking (LI H. et al., 2020). Based on the above, the present work aims to observe and report the main services and performance of the pharmaceutical professional during the COVID-19 pandemic, around the world.

2 MATERIALS AND METHOD

The present study is a literature review on pharmaceutical services related to the COVID-19 pandemic. The review consisted of the targeted search of scientific articles during the month of June 2020 based on the PubMed and Scielo databases, using the keywords: pharmaceutical services, pharmaceutical care, COVID-19. The results of the bibliographic survey were tabulated according to the objectives of the articles, country of origin and date of publication, comparing the performance of the pharmacist in the different studies.

3 RESULTS AND DISCUSSION

The database search resulted in 198 results in ScienceDirect and 59 results in PubMed. After excluding articles that did not contemplate the desired theme, 14 and 11 articles were obtained from each database, respectively. Among the 25 articles included, 8 were selected for analysis of the competencies of the pharmacists cited and direct comparison (Table 1). As expected, Chinese articles were the most incident, but not unique: research groups from countries in the United Kingdom, Pakistan, Africa, Iran, were also present. Among the areas of activity of the pharmacist observed,

community pharmacy (5 articles) stood out, followed by hospital pharmacy (2 articles) and clinical pharmacy (1 article). Regarding the activities performed by pharmacists, the most cited were: evaluating the safety, efficacy and rational use of medicines, informing about COVID-19, advising on medications, screening suspects of the disease and patient care in order to relieve the burden on the health system as well as integrating health teams collaborating in relation to pharmacotherapy.

Table 1 - Main articles resulting from the search in the PubMed and ScienceDirect databases

Article	Goal	Location, date	Cited activities
SONG Z.et al. Hospital pharmacists' pharmaceutical care for hospitalized patients with COVID-19: Recommendations and guidance from clinical experience. *Research in Social and Administrative Pharmacy.* 2020.	Discuss the role of hospital pharmacists in providing pharmaceutical care to hospitalized patients with COVID-19 and promote patient care and management during the pandemic.	Beijing, China 3, April/2020	Hospital pharmacist-drug adjustment- evaluate drug safety and efficacy -monitor drug interactions -offer emotional counseling -help collect data on the efficacy and safety of vaccines
LI H. et al. Fighting against COVID-19: Innovative strategies for clinical pharmacists. *Research in Social and Administrative Pharmacy.* 2020.	Investigate the prevention and control measures of clinical pharmacists during the outbreak of novel coronavirus, summarize the roles and responsibilities of clinical pharmacists.	Beijing, China 6, April/2020	Clinical pharmacist-industry leadership-inform about medicines-promote the rational use of medicines-work in collaborative teams-rationally analyze the situation-ensure the safety and rational use of medicines.
ZHENG S. et al. Recommendations and guidance for providing pharmaceutical care services during COVID-19 pandemic: A China perspective. *Research in Social and Administrative Pharmacy.* 2020.	Discuss the role of community pharmacists in pharmaceutical care during COVID19 and promote prevention, control, and safe use of medications in the community's patient population.	Beijing, China 26, March/2020	Community pharmacist-dispense medications to the patient-pay attention to self-protection and the patient-be readily available for consultations-guide equivalent therapeutic substitution -assist in the identification of suspicious patients -home care consultation -orientation of patients with chronic diseases-inform about delivery services
HEDIMA E. et al. Community Pharmacists: On the frontline of health service against COVID-19 in LMICs. *Research in Social and Administrative Pharmacy.* 2020.	Highlight additional functions and activities related to the public health response that can be performed by community pharmacists that can help reduce pressure on general practice and other areas of the health service.	Nigeria, Africa 17,April/2020	Community-accessible pharmacist for underserved populations -refer patients when needed-inform about COVID-19-promote rational use of medicines
YING W. et al. Drugs Supply and Pharmaceutical Care	Summarize drug supply management practices and pharmaceutical	Jilin from China 6, April/2020	Hospital pharmacist - monitor of adverse reactions-participate in multidisciplinary

Management Practices at a Designated Hospital During the COVID-19 Epidemic. *Research in Social and Administrative Pharmacy.* 2020.	services in coping with COVID-19		consultation-manage drug supply-manage use of off-label drugs-promote pharmaceutical care
BUKHARI N. et al. Pharmacists at the frontline beating the COVID-19 pandemi. *J Pharm Policy Pract.* 2020	Establish 10-step protection guidelines for pharmacy teams.	Pakistan and United Kingdom April 20, 2020	Community pharmacist-perform triage services-see patients to reduce the burden on hospitals and doctors' offices-provide home deliveries
KRETCHY I. et al. Medication management and adherence during the COVID-19 pandemic: Perspectives and experiences from low- and middle-income countries. *Research in Social and Administrative Pharmacy.* 2020.	Highlight the pharmaceutical care practices of community pharmacists to patients with chronic diseases during this pandemic.	Ghana, Africa 15, April/2020	Community pharmacist-manage chronic conditions-promote medication adherence-ease the burden on health systems -screen suspected patients -rational use of medications during the pandemic-review prescribed pharmacotherapy-inform about COVID-19
AMERI A. et al. Tele-Pharmacy: A New Opportunity for Consultation in COVID-19 Pandemic. *Health Policy and Technology.* 2020.	(Letter to the editor, outline) Dissertation on the importance of telepharmacy in the COVID-19 pandemic.	Iran June 14, 2020	Community pharmacist-perform consultation by telepharmacy-reduces adverse effects and interactions to drugs-promote drug efficacy and cost reduction.-review the patient's profile and perform medication adequacy.

A study by Song et al. (2020), brings some functions of the pharmacist in the hospital environment during the pandemic: to participate in evidence-based decision-making about medications, assisting physicians in the formulation and adjustment of drugs in patients with COVID-19, as well as monitoring and evaluating the safety and efficacy of these drugs. According to the authors, the clinical pharmacist should also monitor drug interactions, offer emotional counseling and psychological support to patients with the disease. In addition, when it comes to participants in vaccine-related clinical trials for COVID-19, hospital pharmacists should help clinicians monitor adverse manifestations and reactions after vaccination, assist in collecting data on the efficacy and safety of vaccines during pharmaceutical care. In addition, the International Federation of Pharmacy (IFP) guidelines emphasize that as a member of healthcare professionals, the hospital pharmacist has a responsibility to join the medical collaboration team and provide pharmaceutical care services to COVID-19 patients in order to improve the level of drug therapy and promote overall control of the pandemic (SONG et al., 2020).

Already Zheng et al. (2020), brings the activities of the pharmacist in community pharmacy: performing the dispensing of medicines to the patient during the COVID-19 pandemic paying attention

to self-protection (use of PPE), as well as patient protection (checking if he is wearing a mask and performing hygiene properly). According to the authors, pharmacists should be readily available to provide consultations on self-protection, guide an equivalent therapeutic substitution at the time of dispensing, in case the pharmacy is lacking the prescribed drug, in order to avoid additional trips to other pharmacies. Another activity of the pharmacist in drugstores during the pandemic is to assist in the identification of patients suspected of coranavirus based on clinical symptoms (cough and fatigue and history of travel to places with cases of the disease in the last fourteen days). If this patient is identified, the pharmacist should encourage him to seek immediate medical treatment, and may offer reconciliation of medications, home care consultation for these patients in order to support their recovery at home. Another very important function of pharmacists is the active guidance of patients with chronic diseases in order to improve the adherence to medications of these patients by encouraging self-monitoring: to realize the effectiveness and safety of therapy, to instruct patients to take their medications in the usual dosage, to monitor blood glucose, blood pressure, when applicable, emphasizing the importance of disease control to avoid unnecessary hospital visits during the pandemic. Finally, authors bring the importance of the pharmacist informing patients about the availability of drug delivery services at home, preventing them from leaving home.

Study by Li et al. (2020), brings from the activities of Chinese clinical pharmacists who created a Manual of Rational Use of Medicines to help frontline physicians understand and apply in the treatment of patients with COVID-19, including use and dosage, solvents, precautions, adverse reactions, drug interactions, dose adjustment for special populations (pregnant women, children, elderly, dialysis patients). In addition, clinical pharmacists participated in evidence-based evaluations of the efficacy of drugs for SARS and MERS respiratory syndromes with the aim of finding references for the treatment of COVID-19, evaluating the indications and efficacy of antiviral drugs such as lopinavir, ritonavir, interferon, chloroquine in the prevention and treatment of COVID-19, deciding which drugs can be nebulized, optimal dosage, route of administration. In addition, Hedima et al. (2020) cites that in the face of the pandemic, domestic and foreign clinical pharmacists have collaborated through their expertise in pharmacology and therapeutics to actively participate in COVID-19 medical activities. In many rural or underserved communities, pharmacists are the most accessible and patient-first contact health professionals when there is often a shortage of doctors. According to the authors, both hospital pharmacists and clinicians or those in community settings (such as pharmacies and drugstores) are qualified and trained to treat infectious diseases and can guide with reliable information and advice during the pandemic. Due to the creation of a bond between pharmacists and customers (very common in community pharmacies or drugstores), the movement of individuals to obtain information is reduced and consequently a possible spread of the virus.

Pharmacists also often have a good relationship with doctors and hospitals to properly refer patients when needed (HEDIMA et al., 2020).

Another important possibility of action of the pharmacist during the pandemic is telepharmacy, according to Ameri et al. (2020). According to the authors, with the COVID-19 pandemic, the use of information technology in health services, such as telemedicine, has been revolutionized. In fact, this feature provides virtual consultations, preventing direct contact with the patient and, consequently, a possible transmission of the virus. Telepharmacy is part of telemedicine and refers to the provision of pharmaceutical services within the scope of their responsibilities by maintaining spatial distance with patients or other health professionals. Thus, the pharmacist can communicate with patients for medication consultation, for example, through real-time videoconferencing technology (KANE-GILL et al. 2019). This tool can help reduce adverse effects or undesirable drug interactions as well as promote therapy effectiveness and even cost reduction (AMERI et al., 2020). In addition, telepharmacy is also a strategy to increase access for underserved populations with COVID-19 in rural areas. The pharmacist can give consultations on diet instructions, self-protection, disease monitoring, medications after discharge, and other guidance for recovered patients (LI et al., 2020). According to Ameri et al. (2020), although telepharmacy does not solve all problems, it is a modern and adequate approach to strengthen the relationship between pharmacists and health professionals or to consult with patients with COVID.19.

4 CONCLUSIONS

In fact, the different activities and attributions of the pharmacist were visibly praised during the pandemic, gaining greater visibility both within the health teams in patient care and in society as a whole. Pharmacists from the various areas of activity (hospitals, pharmacies and clinics) play an exclusive role when it comes to pharmacotherapy, in order to ensure the effectiveness and safety of the treatment. New resources such as telepharmacy, successfully employed during the pandemic, may continue to be valuable tools for pharmacists to access more underserved populations. Pharmaceutical services proved to be indispensable in the treatment of patients hospitalized for COVID-19, in addition to the valuable guidance of these professionals assisting in the primary care of the population and collaborating with the Health Networks.

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Functional capacity of post-Covid-19 patients: Impacts of a rehabilitation program

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ABSTRACT
Introduction: COVID-19 is an acute respiratory infection caused by the SARS-CoV-2 coronavirus, potentially serious, highly transmissible and globally distributed. Pulmonary rehabilitation can contribute to the relief of symptoms and the improvement of the functional capacity of patients affected by the infection. Objective: To evaluate the effects of a rehabilitation program on the functional capacity of post-COVID-19 patients. Methods: This is an exploratory, experimental, descriptive research with a quantitative approach. The research took place at the post-COVID-19 Rehabilitation Outpatient Clinic, located at the University of Vale do Taquari - Univates. At the evaluation, the participants performed the following functional tests: the 6-minute walk test (6MWT), the manovacuometry, the 10-meter walk test (10MWT), the digital dynamometry, the Medical Research Council (MRC) dyspnea scale and the Post COVID-19 Functional Status Scale (PCFS). Subsequently, participants underwent a 12-week exercise-based rehabilitation protocol. Quantitative data were analyzed using descriptive statistics and comparisons were performed using the paired t test, considering the significance of $p \leq 005$. Results: After complying with the protocol, the patients showed an increase in the distance covered in the 6MWT, higher gait speed in the 10MWT, greater respiratory and peripheral muscle strength, lower dyspnea index and better functional status. Conclusion: The exercise-based outpatient rehabilitation program was able to improve the functional capacity of individuals with post-COVID-19 syndrome.

Keywords: Physical therapy, covid-19, 6-minute walk test, covid-19 pandemic, functional capacity.

1 INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the outbreak caused by the novel coronavirus (SARS-CoV-2), which characterized a Public Health Emergency of International Importance, therefore pandemic, with high transmissibility and rapid lethality on all continents[1–2]. The novel coronavirus is the seventh member of the family of coronaviruses that infect humans and whose disease has been termed COVID-19.

First detected in December 2019 in the city of Wuhan, China, this virus causes a disease whose clinical picture ranges from asymptomatic infections to severe respiratory conditions, called COVID-19.

In Brazil, the first case was reported on February 21, 2020[4]. Worldwide, since the first case revealed in Wuhan, China, at the end of 2019, until June 15, 2020, 7,283,289 cases and 431,541 deaths have been confirmed. In the same period, America occupied the first place in the ranking, with 3,841,609 cases and 203,574 deaths[2–5].

Already looking for more recent data, according to the World Health Organization (WHO) until May 25, 2022, 521,127,460 cases of covid-19 have been confirmed worldwide, of which 30,846,602 in Brazil. Regarding deaths, 6,263,321 were confirmed worldwide, of which 664,872 were confirmed in Brazil.

In Rio Grande do Sul, until the same date, 2,408,431 cases of Covid-19 and 39,472 deaths have been confirmed.

Physical therapy and pulmonary rehabilitation assist patients in recovering from the damage caused by COVID-19, making them return to society more quickly and safely.

According to Lima et al.[8] physiotherapy aims to promote both cardiorespiratory function, which is physical conditioning, which can be stimulated through the use of the exercise bike and the treadmill; and the musculoskeletal aspect, through active activities, which include resistance exercises.

Barker-Davies et al.[9], state that pulmonary rehabilitation (PR) is considered the gold standard for rehabilitation of patients with respiratory diseases, because the method uses physical exercise, education and behavioral modification for physical and psychological improvements.

In this sense, PR is indicated for post-COVID-19 patients, as it is able to reduce symptoms, increase functional capacity and improve quality of life, even for irreversible damage to the lungs.

The goal of pulmonary rehabilitation, in the short term, is to relieve dyspnea and anxiety, which in the long term, improves the patient's quality of life[7-10].

Given the severity of the dysfunction seen in patients with covid-19, rehabilitation is critical to improve physical and cognitive fitness, as well as decrease the risk of disability and morbidity[11].

According to the Cardiopulmonary and Metabolic Rehabilitation Guideline (2006), it is imperative that public health centers have their own places to guide physical exercise, with structure and human resources trained for the care of patients eligible for the extra-hospital phases of Cardiovascular, Pulmonary and Metabolic Rehabilitation (CPMR)[12].

Given the importance of post-COVID-19 functional capacity recovery, rehabilitation in a prepared outpatient setting becomes indispensable.

Thus, it is expected that individuals submitted to a rehabilitation program, with a closed exercise protocol, of time equal to or greater than 12 weeks, achieve important functional recovery.

Therefore, the present study aims to analyze the effects of a rehabilitation program on the functional capacity of patients enrolled in the post-COVID-19 Rehabilitation Outpatient Clinic of Univates.

2 METHODS

This study is an exploratory, experimental, descriptive and quantitative research. The research was conducted at the post-COVID-19 Rehabilitation Outpatient Clinic, located on the premises of the Clinical School of Physical Therapy of the University of Vale do Taquari - UNIVATES, Lajeado-RS.

The population of this study was selected by convenience, composed of individuals of both sexes, over 18 years of age, affected by COVID-19, recruited to participate in the rehabilitation program of the manifested dysfunctions post-COVID-19, directed from the health network of the municipalities of the 16th Regional Health Coordination (CRS) of RS. All participants signed the Free and Informed Consent Form (ICF) (APPENDIX A).

To calculate the sample size, we considered a probability of error ⍺=0.05, effect size of 0.5 and power of analysis of 80%, arriving at the value of 12 patients.

The software used for sample calculation was GPower version 3.1.9.2 for Windows (University of Düsseldorf, Düsseldorf, Germany).

The study's inclusion criteria were individuals with a prior diagnosis of COVID-19; in rehabilitation period of manifested dysfunctions post-COVID-19; individuals with or without hospitalization; of both sexes; aged between 18 and 95 years.

Users who did not present at least three altered conditions in the evaluation process were excluded from the study; who had a previous disease requiring physiotherapeutic care of a specific area; who refused to sign the Free and Informed Consent Form (ICF); and who exceeded the limit of 3 fouls during the service period.

The study consisted of individuals who had contact with the post-COVID-19 Rehabilitation Outpatient Clinic of Univates, located in the Clinical School of Physical Therapy of UNIVATES.

This contact was made via referral from their referral health network, via e-mail, whatsapp, telephone call or in person at the service, referring to having post-COVID-19 dysfunctions.

Data collection was carried out during the months of August, September and October 2022, through the analysis of the medical records of patients previously inserted in the Tasy system, including identification information, disease characteristics, functional assessment and reassessment tests and associated comorbidities.

Initially the individuals were part of a waiting list, and the time to be called varied according to the number of vacancies available at that time.

After having gone through the waiting process, when necessary, the participants were called to the evaluation phase, in which a complete anamnesis was performed, followed by the application of

the functional tests. After 12 weeks, the patients were submitted to the reassessment stage, to compare the results initially obtained in the functional tests.

The research instrument was the application of functional tests at the beginning of the rehabilitation process of patients in the post-COVID-19 Outpatient Clinic and after patients completed the four face-to-face phases of the pre-established exercises of the rehabilitation protocol, totaling at least twelve weeks.

The functional tests established were: the 6-minute walk test (6MWT), manovacuometry, digital dynamometry, the 10-meter walk test (10mMT), THE Medical Research Council (MRC) dyspnea scale and the Post COVID-19 Functional Status Scale (PCFS).

2.1 6-MINUTE WALK TEST – 6MWT

The 6MWT was performed according to the standards of the *American Thoracic Society*[13]. The patients had to travel the longest distance in the period of six minutes, in order to assess functional capacity.

The vital signs monitored, before and immediately after the test, were peripheral oxygen saturation (SpO2), blood pressure (BP), heart rate (HR), sensation of dyspnea and muscle fatigue, using the BORG CR10 scale, modified exertion BORG (06-20) [14].

The 6MWT is performed as follows: in a flat corridor of 30 meters in length, with marks every three meters, the patient is instructed to travel the greatest possible distance in a period of six minutes at his own speed, but trying his best to walk as far as possible in that time.

In this interval, the person can stop if necessary, and should report from the visualization of the Borg Scale, identifying (pointing) the level of discomfort, which will be noted by the researcher (academic), the appearance of chest discomfort, dizziness, severe dyspnea, imbalance, blurred vision, pain in the limbs or back, numbness or tremors, or any other symptom. At the end, the distance covered by each patient [13–15] will be recorded in meters.

2.2 MANOVACUOMETRY

Muscle weakness occurs due to the immobility of the individual in bed; however, hypotrophy is noticeable to a greater extent in the respiratory muscles than in the peripheral ones.

Respiratory muscle strength can be assessed by means of maximal respiratory muscle pressures, measured by means of a manovacuometer. It is a low-cost and easy-to-perform test that measures negative and positive pressures (MIP and MEP) [16].

Maximal expiratory ($_{\text{MEP max}}$) and inspiratory ($_{\text{MIP}}$ max) pressures are an estimate of the force produced by the $_{\text{inspiratory and expiratory}}$ muscles, respectively.

And to perform such measurements, the manovacuometer is used. The MEP_{max} is the measure of positive pressure generated by the contraction of the expiratory muscles from the total lung capacity, that is, the patient is instructed to perform a maximum inspiration followed by a forced expiration against the buccal of the manovacuometer, thus causing the device to record the value of the maximum expiratory pressure reached by the patient.

The$_{MIP\ max}$ is the measurement of negative pressure obtained through inspiratory effort from the residual volume, that is, the patient is instructed to perform a maximum expiration followed by a maximum inspiration against the buccal of the device, causing the device to record the values referring to MIPax[17].

An MVD 300 Globalmed digital manovacuometer was used. The patient was instructed to perform a maximal inspiration, against an occluded valve, from the residual volume, for the measurement of the $_{MIP}$; for the determination of the $_{MEP}$, the patient will perform a maximum expiration from the total lung capacity, against the referred valve of the manovacuometer, being recorded the peak pressures. For both measurements, three maneuvers will be performed, considering the highest value (cmH$_{2O}$) and being performed with the individual sitting comfortably, without restrictions to lung expansion, such as tight clothing, among others[18].

2.3 MEDICAL RESEARCH COUNCIL (MRC) DYSPNEA SCALE

The dyspnea scale of the Medical Research Council (MRC) is an instrument that assesses the sensation of dyspnea during the activities of daily living (ADLs) of individuals, and is widely used in the international literature, mainly because it is easy to apply and understand. The scale has been widely used in individuals with sequelae of COVID-19[19]. This scale is composed of five items, and the patient chooses the item that corresponds to how much dyspnea limits their ADLs. Its original version has been described and validated in the English language, as well as the Portuguese[20] version.

2.4 PORTABLE DIGITAL DYNAMOMETRY

The measurement of the maximum voluntary handgrip strength, or simply manual dynamometry (DM), consists of a simple and objective test that has as its principle to estimate the function of skeletal muscle. The internal consistency of the strength measurements exerted by different muscle groups supports the use of DM to characterize the general muscular functional status. It is a test usually performed with a portable device - dynamometer - being a quick and little invasive procedure. It is worth mentioning that its cost, ease of use and size are important factors that justify the present diffusion of the use of the digital dynamometer[21].

Among the portable dynamometers, we highlight as an example the portable pressure dynamometer, from the English *Hand-Held Dynamometry - HHD,* which uses compression to evaluate

the force. For its use, the HHD should be placed between the evaluator's hand and the part of the patient's body being evaluated[22]. Thus, the HHD was used to perform the dynamometry test in the participants, in order to obtain peripheral muscle strength values.

2.5 10 METER WALKING TEST

It consists of the gait speed test. The patient walks for a distance of 14 meters, first at natural speed, using their usual assistive devices, footwear and orthotics. Only the central 10 meters will be used to mark the travel time, since the initial and final two meters will be used for the acceleration and deceleration of the gait. Individuals can be classified as home ambulation (lower 0.4m/s), community ambulation (between 0.4 and 0.8m/s) and complete community ambulation (greater 0.8m/s).

2.6 POST COVID-19 FUNCTIONAL STATUS SCALE - PCFS

The Post-COVID-19 Functional Status Scale (PCFS) was recently translated into the Brazilian Portuguese and has been an excellent strategy to assess limitations after SARS-COv-2 infection.

The PCFS scale covers the full extent of functional outcomes, as it is focused on the limitations of daily tasks/activities at home or at work/school, as well as changes in lifestyle.

This questionnaire can be self-applied, or there is the possibility of a flowchart for application. The scale has 6 possible gradations from 0 (zero: no symptoms), 4 (four: severe functional limitation), to 5 (five: death). It can be applied at hospital discharge and also in outpatient follow-up to assess and monitor functional status[23].

After the evaluation, the selected patients were submitted to a pre-established exercise protocol based on the Brazilian Guidelines for Functional Rehabilitation.

This protocol was divided into 4 phases, presented in Chart 1. After the completion of the exercise protocol, the patients underwent a reassessment process to analyze the effects of the rehabilitation program on patients participating in the post-COVID-19 Rehabilitation Outpatient Clinic.

The demographic data of the study were presented descriptively and the quantitative data were presented as mean and standard deviation (SD), with comparisons performed through the paired Student's t-test and two-way ANOVA. The software used for the analyses was GraphPad version 7.0 for Windows (San Diego, California, USA). $P \leq 0.05$ was considered statistically significant.

3 FINDINGS

Throughout the process of recruitment and application of the protocol, we had some losses and withdrawals on the part of the participants. Initially, a total of 17 patients were evaluated, with 2

dropouts, 1 death and 2 patients who could not finish the protocol due to absences. Thus, we concluded the analyses with the participation of 12 patients, totaling 29.4% of loss.

At the time of the evaluation and anamnesis of the study participants, demographic data were collected and are shown in Table 1. Through the analysis of the results, it was possible to perceive an increase in peripheral and respiratory muscle strength, when comparing the values of the evaluation and reassessment at the end of the protocol, as shown in Table 2.

Regarding functional capacity, we noticed that the patients, after being submitted to the rehabilitation protocol, obtained better performance in the 6-minute walk test (6MWT) and 10-meter walk test (10-meter walk). Data shown in Figure 1.

In addition, we noticed that the patients presented a better functional status and a reduction in the dyspnea index after the protocol (Figure 2).

4 DISCUSSIONS

The present study sought to analyze the effects of a rehabilitation program on the functional capacity of post-COVID-19 patients. The results showed a significant improvement in the functional capacity of all participants who were submitted to the exercise protocol in the period of 12 weeks or more, with improvement evidenced through the increase in the distance covered in the 6MWT and 10mwt, as well as in muscle strength (dynamometry), dyspnea level (MRC) and increased respiratory muscle strength (manovacuometry).

In a study conducted by DAYNES et al[24] (2021) participants underwent a post-COVID-19 rehabilitation program (aerobic training, upper and lower limb strengthening, and home orientations).

These individuals had persistent symptoms of dyspnea, fatigue and reduced exercise capacity. After the completion of the exercise protocol, with a frequency of twice a week, in the period of six weeks, the participants obtained a considerable improvement in functional capacity and in the decrease of fatigue.

These data are similar to the data obtained in the present study, both for the performance of the exercise protocol covering aerobic training and strengthening of upper and lower limbs, and for the frequency of visits being twice a week, in addition to the improvement in the functional capacity of the individuals.

According to the study developed by SILVA, PINA, ORMOND[25] (2021), which is a review of the literature, in the rehabilitation process of post-COVID-19 patients, mediations of aerobic exercises, progressive resistance training for strength gain, balance, diaphragmatic breathing exercises, respiratory muscle training and stretching of the same, involving the intercostal muscles, were recommended, muscles of the abdominal wall and other muscles that aid respiratory function.

Thus, the exercise protocol adopted by this study follows the recommendations found in this literature review, which aimed to offer the participant the opportunity to resume functionality and autonomy.

In a study conducted in Switzerland by BETSCHART *et al*[26] (2021), containing 12 post-COVID-19 patients, it was demonstrated that individuals affected by COVID-19 had decreased functional capacity evidenced through the 6-minute walk test (6MWT), especially patients who developed the severe form of the disease. When these patients were submitted to an outpatient pulmonary rehabilitation program, with physiotherapeutic intervention twice a week, nine of the 12 participants showed clinically significant improvement in the 6MWT results. These data are similar to the findings of our study, in which all participants showed significant improvement in the results of the 6MWT.

In the study by TOZATO *et al*[27] (2021) consisting of 4 case series, participants underwent a post-COVID-19 rehabilitation exercise protocol consisting of aerobic exercise and resistance exercise. The participants obtained important cardiovascular recovery, reduced sensation of dyspnea on exertion, increased peripheral muscle strength and functional independence reported and also observed throughout rehabilitation.

The participants also obtained changes in the distance covered in the 6-minute walk test (6MWT), showing an increase of 16%, 49%, 67% and 94% from Case 1 to Case 4, respectively, thus indicating an increase in functional capacity and improved prognosis, regardless of severity. Similarly, the present study identified an increase in the distance covered by all individuals in the 6MWT, with a high percentage in most cases.

MACHADO et al.[28] 2021, conducted a study in Belgium, validating the PCFS scale, and demonstrated in the course of their study the validity of the application of the PCFS Scale in individuals in the post-COVID-19 period. The fact that the PCFS Scale can be easily used is a great advantage, facilitating its wide implementation.

In the study developed by IMAMURA et al.[29] 2021, composed of a series of retrospective cases, they aimed to describe an outpatient program developed at the Institute of Physical Medicine and Rehabilitation of the Hospital das Clínicas of the Medical School of the University of São Paulo. In their study, it was demonstrated that the PCFS is a tool that can be used as an important outcome variable in the rehabilitation process, in addition to the 10-meter walk test.

A clear trend of improvement of the PCFS and the 10-meter walk test was observed in patients undergoing the rehabilitation process, but there was no significant difference, but the p values obtained indicate that this difference may be a trend, presenting as a limitation the small number of participants. These data are similar when compared to those obtained in the present study, but here it was possible

to observe a significant reduction in the PCFS scale and in the time required to complete the 10-meter walk test.

The reduction in respiratory muscle strength (RMS) was reported in a study by Huang *et al.*[30] (2021), in which approximately 30% of COVID-19 patients were considered severe or critical, and more than half had decreased RMS. According to Nogueira *et al.*[31] (2021) muscle weakness is one of the main complaints of post-COVID patients. In their study, 25% of post-COVID patients had this complaint, which occurs due to the inflammatory response to the virus, related to loss of muscle strength and sarcopenia, as well as malnutrition and prolonged period of immobilization in bed. This pattern was also found in the present study, evidenced by the results of a significant decrease in RMS in nine of the 12 participants.

In the present study, after the patients went through the exercise protocol and performed the respiratory muscle training using PowerBreathe, the participants presented a statistically significant increase in respiratory muscle strength, indicated by the results of manovacuometry, at the time of reassessment. The same occurred in the study by LIU, Kai *et al*.[32] (2020), in which participants, after 6 weeks of respiratory rehabilitation in the intervention group, achieved statistically significant improvements.

Regarding the values obtained through the MRC scale, it was possible to observe that there was a significant reduction in the perception of dyspnea after the participants had completed the rehabilitation protocol. The study by BATISTA *et al.*[33] (2021) presented similar results, in which patients, after undergoing a post-COVID-19 syndrome rehabilitation protocol in primary care, obtained a significant improvement in the sensation of dyspnea (mMRC) and fatigue in performing their ADLs, compared to the period before the disease.

In another literature review study, developed by OLIVEIRA, MACEDO[34] (2021), it is described that functional impairments in critically ill patients are directly related to the length of stay in the ICU and prolonged mechanical ventilation. Seven days of bed rest can already reduce muscle strength by 30%, with an additional 20% loss of remaining strength each week. In the present study, it was possible to observe an important increase in muscle strength after the completion of the rehabilitation protocol. The muscle weakness identified in the evaluation of most participants was also related to the history of hospitalization.

Even with all the important findings, the present study has some limitations, which make it necessary to continue research in the area of rehabilitation of post-COVID-19 patients in order to identify the effects of rehabilitation programs. The main limitation is the small sample size and the high level of losses. Nevertheless, the lack of a control group and the blinding of both the participants and the professionals involved ended up interfering in the quality of the final evaluations. Another

important point was the lack of an evaluation of the levels of anxiety and depression of the participants, remaining as a suggestion for future studies.

5 CONCLUSIONS

The infection caused through COVID-19 generates functional and hemodynamic repercussions to the individual, thus generating significant impairments in functional capacity and, consequently, in activities of daily living and work, negatively impacting the quality of life of the user.

The rehabilitation program consisting of physical exercises, based on principles of cardiovascular and pulmonary rehabilitation showed positive results for all participants, with improvement in functional capacity, even with the variability of the severity of post-COVID-19 cases.

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TABLE AND FIGURES

Table 1. Exposure protocol

REHABILITATION PROTOCOL
Evaluation:
Anamnesis and application of functional tests.

Phase I (attendance 1 to 6)
- Aerobic training (60% of HRmax.): treadmill or stationary bike (20 min, if possible);
- Joint mobilization exercises.
Phase 2 (attendance 7 to 12)
- Aerobic training (70% of HRmax.): treadmill or stationary bike (20 min, if possible);
- Respiratory muscle training (20% to 60% of maximum strength):
- Powerbreathe
- Global muscle strengthening exercises (20% of maximum strength)
Phase 3 (anticipation 13 to 18)
- Aerobic training (80% of HRmax.): treadmill or stationary bike (20 min, if possible);
- Respiratory muscle training (20% to 60% of maximum strength):
- Powerbreathe
- Dynamic exercises of global muscle strengthening (30% of maximum strength):
Phase 4 (attendance 19 to 24)
- Aerobic training (90% of HRmax.): treadmill or stationary bike (20 min, if possible);
- Respiratory muscle training (20% to 60% of maximum strength):
- Powerbreathe (2 sets of 8 to 12 repetitions).
- Dual task and circuit exercises:
STEP 1: Warm-up;
STEP 2: Circuit;
STEP 3: stretching.
Revaluation:
Reapplication of functional tests.

Source: From the author (2022).

Table 1. Sample characteristics

Muscle group	Mean ± SD (%)
Age (years)	61 ± 9.3
Weight (kg)	85 ± 14
Height (m)	1.75 ± 0.14
BMI (kg/m2)	31 ± 7,3
Women, n (%)	7 (63,6)
Men, n (%)	4 (36,4)
Education, n (%)	
Incomplete fundamental	6 (54,5)
Medium	1 (9,1)
Incomplete high school	1 (9,1)
Superior	3 (27,3)
Profession, n (%)	
From home	3 (27,3)
Retired	3 (27,2)
Educator	1 (9,1)
Company Administrator	2 (18,2)
Teacher	1 (9,1)
Shoe reviewer	1 (9,1)
Medications, n (%)	
Yes	10 (90,9)

No	1 (9,1)
Physical Activities, n (%)	
Yes	4 (36,4)
No	7 (63,6)
Smoker, n (%)	
Yes	0 (0)
No	11 (100)
Alcoholic, n (%)	
Yes	0 (0)
No	11 (100)
Associated Diseases, n (%)	
Yes	9 (81,8)
No	2 (18,2)

Source: Study data (2022)

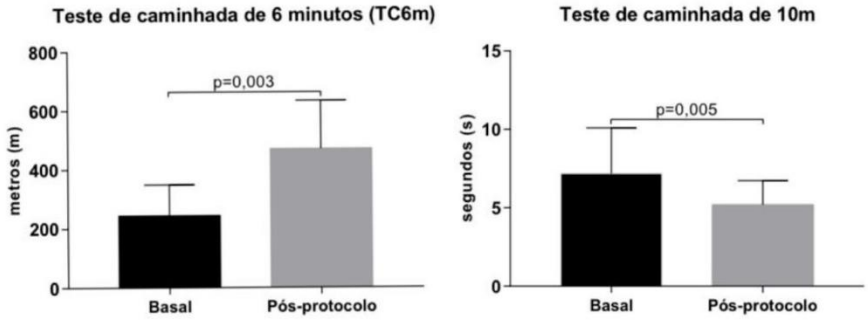
Table 2. Muscle strength – Dynamometry (kgf)

Muscle group	Basal	Post-intervention	*P* (Test t pareado)
Palm grip D	25,4 ± 11,9	33,9 ± 11,7	0,029*
palmar grip E	24,3 ± 10,9	30,8 ± 12,7	0,027*
Elbow flexors D	17,5 ± 6,4	20,8 ± 5,2	0,0006*
Elbow flexors E	17,2 ± 4,9	20,3 ± 4,8	0,004*
Elbow extenders D	12,5 ± 3,2	15,8 ± 5,0	0,0007*
Elbow extenders E	12,5 ± 3,6	14,6 ± 3,7	0,0001*
Rot. Inter. Shoulder D	13,2 ± 4,6	16,0 ± 5,2	0,019*
Rot. Inter. Shoulder E	13,9 ± 4,9	17,2 ± 5,3	0,009*
Rot. Ext. Shoulder D	11,0 ± 3,6	11,8 ± 3,3	0,069
Rot. Ext. Shoulder E	9,7 ± 3,3	12,2 ± 3,8	0,001*
Knee extensors D	17,5 ± 5,2	23,4 ± 7,0	0,0003*
Knee extensors E	17,7 ± 5,4	23,1 ± 7,4	0,0007*
Knee flexors D	13,4 ± 4,1	23,4 ± 7,0	0,0001*
Knee flexors E	13,1 ± 3,3	23,2 ± 7,2	0,0001*
Hip adductors D	9,4 ± 2,7	12,9 ± 3,2	0,0009*
Hip adductors E	10,1 ± 3,1	12,4 ± 3,8	0,012*
Hip abductors D	9,8 ± 2,5	13,9 ± 2,6	0,0001*
Hip abductors E	9,6 ± 2,4	14,5 ± 2,6	0,0001*
PImáx	-80 ± 34,6	-114 ± 41,1	0,007*
PEmáx	68 ± 31,5	94 ± 36,3	0,004*

Source: study data (2022).

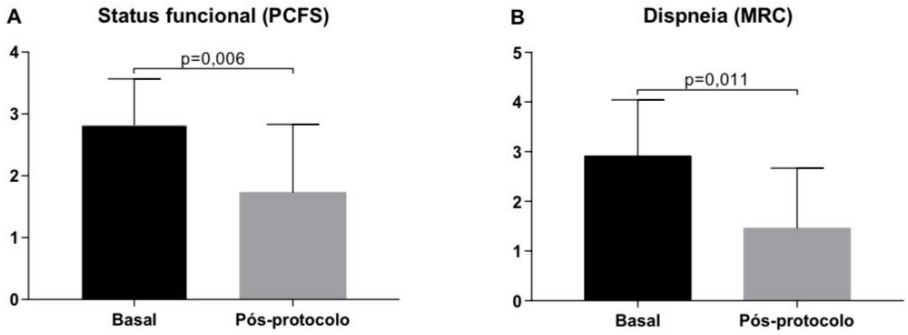
Values presented as mean ± SD. MIP (maximal inspiratory pressure); MEP (maximal expiratory pressure). Paired t-test*.

Figure 1:



Values presented as mean ± SD. Paired t-test.

Figure 2:



Values presented as mean ± SD. Paired t-test.

SEVEN publicações acadêmicas

Toxicological analytical methods for metals identification in cosmetics

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ABSTRACT
BACKGROUND: Cosmetic Toxicology involves the study of substances contained in beauty products that can accumulate in the body such as lead (Pb), aluminum (Al), cadmium (Cd), nickel (Ni), mercury (Hg), chromium (Cr), copper (Cu), zinc (Zn), iron (Fe). These substances reach tissues and the bloodstream and can cause long-term damage such as hormonal disorders and carcinogenic events. OBJECTIVES: To evaluate the toxicological analytical methods commonly used in the identification and/or quantification of heavy metal cosmetic ingredients. METHODS: A literature review was conducted with a targeted search of scientific articles during the month of June 2019 in the PubMed and Scielo databases published between 2009 and 2019, using the keywords: toxicology, cosmetic, metal. RESULTS: Spectrometry is the most widely used toxicological method in the detection of heavy metals in cosmetics and presents good accuracy and reliability. In the analyzed studies, several spectrometry variations were used, such as Atomic Absorption Spectroscopy, Inductively Coupled Plasma Atomic Emission Spectrometry, Optical Emission Spectrometry. Among the products analyzed for metals, lipstick was the most prevalent cosmetic (in 69% of cases), followed by eye shadows (in 38.4% of articles). CONCLUSIONS: The presence of heavy metals such as Pb, Al, Cr, Cd seems to be widely present in cosmetics such as lipsticks and eye shadows, at levels above the considerable safe.

Keywords: Cosmetic, Metals, Toxicology, Method.

1 INTRODUCTION

Toxicology refers to the study of exposure to chemicals as well as the adverse effects resulting from this interaction (HAYES et al., 2017). Toxic agents are those originating from heavy metals such as aluminum, cadmium, lead, arsenic, mercury which can accumulate causing deleterious effects in the long term (NORDBERG et al., 2007). The study of toxicology includes food, occupational, social, environmental, drug and cosmetic toxicology, the latter of which has gained prominence in the last 20 years given the increase of 4.5% in the production of cosmetics in the world per year (FISCHER et al., 2017). In addition, cosmetic toxicology is related to environmental toxicology (plants used in the production of products may be contaminated with heavy metals) and social toxicology (cosmetics are absorbed by individuals through the skin or ingestion) (BOCCA et al., 2014).

It is estimated that an adult uses, on average, nine types of cosmetics per day, exposing themselves to more than 120 chemicals that can accumulate in the body and even cause disease (*Environmental Working Group-EWG).* Examples of cosmetics that may include harmful substances

include antiperspirants (containing aluminum), makeup (containing lead), toothpaste (containing fluoride), henna capillary (containing ammonia), creams and lotions (containing aluminum, lead). Also, additives that give color to cosmetics can be contaminated by metals such as Pb and Hg (EWG, 2007). These products should, in theory, be inert and not cause harm to health, however the intentional or accidental presence of chemicals is unfortunately a reality in cosmetics (BOROWSKA et al., 2015).

Toxic metals present in cosmetics can be retained in the tissues, acting directly on the skin or be absorbed reaching the bloodstream, accumulate in the body, exerting toxic effects and reaching organs (BOCCA et al., 2014). In addition, topical effects such as allergic and systemic contact dermatitis may occur due to exposure to metals present in cosmetics (FILON et al., 2009). Some of the long-term effects of metal damage include increased risk of cancer, reproductive problems and development of neurological disorders, cardiovascular, kidney and kidney problems, contact dermatitis and hair loss (LIU et al., 2013). Data from Pineau et al. (2014) indicate that the aluminum present in antiperspirants presents a health risk and should be reduced. The authors indicate a strong relationship of this metal with carcinogenesis and the development of breast cancer based on evidence of accumulation of the metal in the mammary gland. Also, preservatives like parabens are harmful given their interference with the hormonal system, increasing the risk of hormonal disorders like obesity, infertility, thyroid, breast cancer (NOWAK et al., 2018).

In view of the potential toxicity of cosmetics and their adverse effects on organisms and the environment, it is of paramount importance that there is control over the presence and concentration of heavy metals in these products. Therefore, the aim of the present study was to evaluate the toxicological analytical methods commonly used in the identification and/or quantification of heavy metal cosmetic ingredients.

2 MATERIALS AND METHODS

The present study is a literature review on the toxicological analysis techniques used in the detection of substances in cosmetic products. The review consisted of the targeted search of scientific articles during the month of June 2019 based on the PubMed and Scielo databases and published between the years 2009 to 2019, using the keywords: *toxicology, cosmetic, metal.* The results of the bibliographic survey were tabulated and described in a table to exemplify the techniques employed, elements analyzed, as well as to discuss the results.

3 RESULTS AND DISCUSSION

In view of the potential toxicity resulting from the repeated and progressive use of cosmetics, the present work sought to observe the toxicological analytical methods employed in the detection of heavy metals in these products, through a scientific literature review. The search results in the PubMed

and Scielo databases (presented in Table 1) were satisfactory and totaled 13 studies that directly contemplated the theme. A study by Atz and Pozebom (2009) performed the toxicological detection of metals in cosmetics such as eye shadow and lipstick, using the methods Graphite Furnace Atomic Absorption Spectrometry (GFAAS) and Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-OES). The authors observed the presence of the trace elements Cr (1.29%), Ni (106 µg/g-1) and Cu (9.90%), and the concentrations investigated in lipstick were below those found in eye shadows, probably due to the basic matrix of lipstick composed of waxes and oils - where inorganic oxides are present in lower concentrations.

Among the articles surveyed, lipstick was the most prevalent cosmetic (in 69% of cases), followed by eye shadows (in 38.4% of articles), because, according to Orisakwe (2013), these items are more "dangerous" due to their greater absorption and ingestion given the proximity of the mucous membranes. The same author conducted a study in Nigeria to assess the levels of metals Pb, Cd, Ni, Cr, Hg in lipsticks and other cosmetics and noted that the detected levels of lead and cadmium were higher than the permissible limits in water and food (15 ppb and 5 ppb – parts per billion, respectively). In addition, based on the dermal toxicity study in albino rats by Tsankov et al. (1982) where the maximum permissible concentration of lead should be ≈10 ppm (parts per million) only 2 (4%) of the 50 cosmetics tested by Orisakwe (2013) showed the appropriate level of lead (>10ppm).

Study conducted in Jordan, evaluated the levels of metals as Pb, Cd, Ni, Al in lipsticks, eye liner, mascara, facial base and observed high levels of these constituents in the products. According to the authors, Pb was detected in all eye shadow samples evaluated with concentrations up to 153.89 ± 17.03 ppm (when the ideal would be up to 15 ppb) (FARRAD et al., 2015). In addition, the Ni concentration was detected in the eye shadow up to 31,909 ± 3.34 ppm being a factor for increased allergic eye infection and important cause of eczema on the hands (ORISAKWE et al 2013). The permissible limits of Pb, Cd, Cr for water and food are 15, 5 and 100 ppb (GONDAL et al 2010), evidencing that concentration for these elements in this study is much higher than the allowed limits. Therefore, according to Farrad (2015), the daily and continuous use of these cosmetics can result in the accumulation of metal levels in the human body above the permissible limits, causing harmful effects to individuals in the long term.

Data from Liu (2013) demonstrated the presence of lead in 75% of the products analyzed, with an average concentration of up to 1.32 ppm (within acceptable). However, even some items presenting individually acceptable levels of metals, the author argues that when added 10 products tested, the acceptable daily dose of metals would be far beyond the ideal - indicating the harmful effect of the accumulation of products. Also, a study by Gondal (2010) showed that the concentration of several toxic carcinogenic contaminants (lead, chromium, cadmium and zinc) were present in lipstick samples in Saudi Arabia with levels above the permissible safety limits, which is a cause of great concern.

According to Liu (2013) the level where there is no observed adverse effect (NOAEL) for Pb is 2.86 µg/day, Al is 125 mg/day, Cd is 19 µg/day, Ni is 1.12 mg/kg-day and Cu is 426 µg/kg-day, but the cumulative effect of ingestion and exposure to these compounds can be very harmful. For example, Cd and its compounds are considered carcinogenic to humans and their inhalation exposure is associated with lung cancer and chronic oral exposure to kidney and bone damage, according to Liu (2013).

In addition, animal studies indicate that young animals may absorb more Cd than adults and be more susceptible to bone deficiencies (OGOSHI et al. 1989) and feeding rats and mice with high Cd levels (1 to 20 mg/kg/day) has demonstrated low birth weight and behavior and learning problems (Agency for Toxic Substances and Disease Registry/USA, 2008). Heavy metals can also arise during the production chain process. For example, various ingredients derived from non-organic plant sources, such as cottonseed oils and rice derivatives, may contain metals such as Pb and Hg (EWG, 2007). Also, Co Cr and Ni, are potent skin sensitizers to cause dermatitis, while As, Cd, Hg, Pb and Sb are highly toxic with many long-term effects (THYSSEN, 2010).

TABLE 1. List of studies involving toxicological analysis of metals in cosmetics, searched in the PubMed and Scielo databases between 2009 and 2019.

Method	Substances analysed	Cosmetic product analyzed	Reference
Graphite Furnace Atomic Absorption Spectrometry (GFAAS) Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-OES)	As, Cd, Co, Cr, Cu, Ni, Pb	Eye shadow Lipstick	Atz, Pozebon. 2009.
inductively coupled plasma mass spectrometry (ICP-MS)	Pb	Lipstick	Hepp et al., 2012
Atomic Absorption Spectrophotometer	Pb, Cd	Lipstick	Nkansah et al. 2018.
Flame emission spectrophotometer	Pb, Cd	Lipstick	Ziarati et al., 2012.
Parent-Indutious Plasma Mass Spectrometry (ICP-MS)	Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Zn, Sb, Se	lipstick, eyeliner, henna, eyeshadows, cream, moisturizers and facial powder.	Al-Qutob et al., 2013.
Parent-Indutious Plasma Mass Spectrometry (ICP-MS) Plasma-coupled atomic emission spectrometry (ICP-AES)	Ag, As, Ba, Be, Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sn, Sr, Ti, Tl, U, Zn, Zr, Nb, Rb, Sb, Se	lipstick, eyeliner, eye shadows, mascara.	EMAD et al., 2015.

Electrothermal Atomic Absorption Spectrometry Inductively Coupled Plasma Optical emission spectrometry Flame Atomic Absorption Spectrometry Cold Steam Atomic Absorption Spectrometry	As, Cd, Cr, Cu, Hg, Mg, Mn, Ni, Sr and Zn	Shampoo, hair gel, body milk, Hair conditioner and body oil	Lavilla et al., 2009
Plasma-coupled atomic emission spectrometry (ICP-AES) and ICP-MS	Ni, Cr	Dead Sea Mud (cosmetic ingredient)	Ma'or et al., 2015
Atomic absorption spectroscopy	Pb, Cd, Hg	Plants used in cosmetics	Fischer et al., 2017
Atomic Absorption Spectrometer	Pb, Cd, Ni, Cr, Hg	Creams, lotions, facial powders, soaps, eye shadow and lipsticks	Orizakwe et al., 2013
UV-VIS spectrophotometry and complexation reactions in solvent mixtures to generate chromophore species	Al, Fe, Cu	Eye shadow	Almeida et al., 2019
Plasma-coupled atomic emission spectrometry (ICP-AES)	Al, Cd, Co, Cr, Cu, Mn, Pb, Ni, Ti	Lipsticks	Liu et al., 2013
Laser Induced Break Spectroscopy (LIBS)	Pb, Cd, Cr, Zn	Batons	Gondal et al., 2010

4 CONCLUSION

The constant and widespread use of cosmetics by the population raises a warning about the potentially toxic and cumulative ingredients that can cause long-term harm. In view of the ability of absorption of toxic metals by the body to reach organs, it brings the concern with the toxicity of these products. In addition, it is necessary to evaluate the safety of the use of these cosmetics as well as the precise knowledge of the concentrations of the ingredients present. In this sense, cosmetic, environmental and social toxicology is of great relevance as it studies the effects of toxicants on cosmetic products as well as on the environment and effects on individuals. Based on the data obtained in the present review, it can be concluded that heavy metals such as lead, aluminum, cadmium are widely present in cosmetics such as lipsticks, eye shadow, eyeliner, creams and may influence the increased risk of diseases such as cancer and other hormonal, behavioral and fertility disorders. Therefore, it is of paramount importance that there is supervision by health agencies in order to ensure

safe parameters of cosmetic constituents, for example, through reliable toxicological analytical methods.

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Geochemical aspects of heavy metal fractionation in eucalyptus soils

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ABSTRACT
Aspects of heavy metals fractionation (Cu, Cr and Co) in main eucalyptus cultivated soils were investigated after total extraction by alkaline fusion and selective sequential extractions. The study aimed to identify the major geochemical fractions and phases involved in metal complexation. Possible pollution classes were investigated through index of geo-accumulation (Igeo), considering the local natural background level. Among the main soils, Typic Hapludox showed the highest concentrations of these metals. However, there was no contamination according to the calculated Igeo. The selective sequential extractions showed that, for most analyzed soil, there was a predominance of these metals in the residual phase (> 80%), compared to the bioavailable fraction, and in this case, an association with the geochemical phase of Fe oxides. Cultural treatments, performed in this region during the eucalyptus cultivation, did not have residual effects in terms of heavy metals in soils.

Keywords: Heavy metals, Micro-watershed, Sequential extractions, Index of geo-accumulation.

1 INTRODUCTION

The heavy metals introduced into the earth system can come from various sources such as industrial waste and domestic sewage, mining activities, atmospheric depositions, agricultural practices, etc. In the soil they can be distributed in different compartments or fractions and their mobility and bioavailability will depend on their total concentrations, and the form in which they are associated with the solid phase, according to Tessier et al. (1979). Selective sequential extraction allows inferring about the potential for remobilization of heavy metals between labile fractions, mainly to distinguish between the natural and anthropogenic origin of soils and river sediments (Ure et al., 1993). The degree of pollution or toxicity of heavy metals in soils and sediments can be assessed in terms of the concentrations of these metals in the natural geochemical background (*background*), usually obtained in deep soils, without contamination, as proposed by Müller (1979), using the geoaccumulation index. The present work aimed to investigate the partition of heavy metals Cu, Cr and Co in the main fractions and geochemical phases in soils cultivated with eucalyptus, identifying the possible classes of pollution.

2 AREA OF STUDY

The studied area is located in São Paulo between the parallels 23o16'30" and 23o17'30" S and the meridians 48o25´30" and 48o26´30" W at an average altitude of 624 m and area of 1.6 km2, being composed of six plots planted with *Eucalyptus grandis* Hill Ex Maiden of varying ages and occupying 68.7% of the total area. The rocks of origin of the soils belong to the São Bento Group, Pirambóia formation. The main soil classes found were: Dystrophic Red Latosol, clayey phase (LVd); Ortic Quartzarenic Neosols (RQo) and Dystrophic Tb Haplic Cambisols (CXbd). In the study area, agricultural inputs were used for more than ten years of successive annual applications for planting fertilization and cover fertilization in the cultivation of eucalyptus trees.

3 MATERIAL AND METHODS

Soil sampling was carried out in triplicate with the aid of a Dutch auger in stainless steel, at depths of 0-10, 10-20 and > 50 cm. The composite samples were air-dried, homogenized and sieved for the fraction of 63 □m. The method of total extraction of heavy metals used was that of alkaline fusion (Samuel et al., 1985). Heavy metals were analyzed by ICP OES, including white metals and international reference material Soil-7 (IAEA) in triplicate.

The procedure of selective sequential extraction of heavy metals was performed according to the method proposed by Leleyter & Probst (1999), and allowed to identify the association of each heavy metal with the labile fractions, S1 (soluble in water), S2 (exchangeable), S3 (carbonate), S4 (oxides Mn), S5 (oxides Fe) and S6 (organic matter) by means of successive extractions of the phases. The residual fraction was calculated from the difference between the total content of the sample and the sum of the leachable fractions (S1 to S6) and considered as labile or bioavailable fraction.

To characterize the natural geochemical background, Cu, Cr and Co concentration values were used in the soil samples CXbd, LVAd, LVd and RQo at depths > 50 cm. In comparative terms, the average concentrations of the Earth's crust of these heavy metals were used, according to Taylor & Mc Lennan (1985), with concentrations of 25, 35 and 10 □g g^{-1}, for Cu, Cr and Co, respectively.

4 RESULTS AND DISCUSSION

The results of the mean concentrations (± standard deviation) in □g g^{-1} of Cu, Cr and Co were 17.6±9.1; 27.1±4.2 and 9,2±4,1 for soil samples CXbd, LVAd and RQo, ndepths of 0-10, 10-20 and > 50 cm, respectively. For LVd, the mean concentrations were 206.9±0.9; 89.4±1.1 and 184.1±3.9 respectively, for the depths studied.

Lows were observed *Igeo* for all soils (0-10 cm) concerning Cu, Cr and Co, when the local natural geochemical background was considered, showing no occurrence of pollution. However, when the chemical composition of the Earth's crust was considered, moderate to strong pollution classes

were verified for the LVd soil and especially for Co and Cu. At depths of 10-20 cm they presented results similar to those observed for the shallower soils and when the local natural geochemical background was used, there were no possible toxicities of these metals. Likewise, elevated *Igeo* were observed when the weighting parameter of the Earth's crust was used, identifying possible pollution problems for Co and Cu.

From the results obtained from the selective sequential extraction of Cu, Cr and Co, it can be verified (LVAd and LVd) that Cu and Co were preferentially in the residual fraction (80 %) at the depth of 0-10 cm with bioavailability lower than 20 %. For Cu there was a predominance of the geochemical phase associated with Fe oxides for the LVAd soil and an equilibrium between the geochemical phases of Fe oxides and organic matter for the LVd soil. Cr was relatively more bioavailable for LVAd soil (50 %) being mainly associated with the phases of Fe, exchangeable oxides and organic matter, and LVd soil presented about 30 % of bioavailability with association with Fe oxides.

To the ground CXbd, Cu and Co presented preferentially in the residual fraction (84%) with bioavailability lower than 16 and 20 %, respectively, with predominance of the geochemical phase associated with Fe oxides, only being observed a relative influence of organic matter for Co at depth (> 50 cm).

The Cr presented a high percentage of bioavailability (> 40 %) being preferentially associated with Fe oxides, and also present in the exchangeable phases and organic matter, evidencing the relative ease of interaction and availability. For the RQo soil, Cu and Cr were preferentially in the residual fraction, with respective averages of 83.4 and 66.8 %. The bioavailability observed was mainly related to Fe oxides. Co showed high bioavailability in this soil, especially on the surface, being associated with Fe oxides and organic matter, showing to be only soluble in strong acids.

5 CONCLUSION

The LVd soil presented concentrations of Cu, Co and Cr above the CETESB quality reference values and the average concentrations of the Earth's crust, however, the calculations of the *Igeo*, did not present any evidence of contamination. The use of selective sequential extraction of Cu, Co and Cr allowed to verify for all soils, a predominance of the residual fraction in comparison with the bioavailable fraction, even in the case of LVd, with preferential association to the phase linked to Fe oxides. Thus, it was not possible to verify that the use of agricultural inputs over 10 years in the cultivation of eucalyptus brought contamination of Cu, Co and Cr in the studied area.

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Hospital management: Operational audit as a strategic tool for waste control

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ABSTRACT
Currently, there is a shortage of financial resources in the hospital environment, the pursuit of management excellence is becoming increasingly present and growing. The audit is a hospital management tool in the sense of maintaining the institutions financial sustainability, including the processes maintenance involve the assistance and, mainly, the paying sources and the providers of hospital medical services. The objective of this work was to demonstrate that the operational health audit can act as a strategic hospital management tool to control waste. The study was carried out through a literature review. The Operational Audit allows the hospital manager to identify ways to favor of the service qualification without adding costs to the care provided and charging correctly according to the hospital care record. This study makes it clear that the audit used as a management tool in health institutions achieves satisfactory results both in waste control and in strategic actions. It is noteworthy that the study was limited to bibliographical research aiming to analyze the operational audit as a management tool for health organizations. In this way, it is suggested for future research done evaluating health organizations regarding the performance of the operational audit to improve its performance, through the reduction of waste.

Keywords: Audit, Hospital Management, Strategies, Waste.

1 INTRODUCTION

Currently, due to the scarcity of financial resources in the hospital environment, the pursuit of management excellence has become increasingly present and growing and, in this context, is inserted for the continuous evaluation of management processes (TEIXEIRA*, et al.,* 2018).

As organizations, public and private, begin to expand their internal and external activities, the need begins to emerge for a professional who can assist managers in the process of supervising the activities performed, aiming at efficiency in management (AMARAL, BERTEGANI; 2018). Therefore, the excellence of organizational performance depends on the quality of the execution of managerial functions, which guide the type and amount of efforts that will be placed in each operational area to achieve the strategic goals (SENGER, 2021).

The manager of an organization performs a number of different functions, which are related to planning, deciding, acting, controlling and proceeding to lead the activities of third parties. But before

planning, the manager of the organization needs to obtain data and information, to later make decisions that must be managed. To carry out the planning it is necessary, in addition to data and information, work team, time and, among other resources, the help of management tools, which may be the hospital audit one of them (ASSI, 2020).

In this context, the operational audit can be conceived as an essential activity to organize and develop a management with a more active, participatory character and demonstrating forms of control (AMARAL, BERTEGANI; 2018). Therefore, auditing becomes a highlight and is directly linked to minimizing risks and the security of reliable data of health organizations and their professionals.

The hospital audit is considered a management and inspection instrument more appropriate to the needs of information management in the hospital environment, being seen as an area of the organization that provides information to the decision-making process. Thus, the audit works to minimize or resolve risks of possible errors or organizational fraud, through suggestions for improvements in internal controls (MASSON; SOUZA; SARTORI, 2018).

Thus, the audit supports the performing professional for the need to detect the errors that burden the costs related to excessive waste. From this, it promotes a quality service, verification, observation and analysis of how to generate means that favor the development of institutional goals within a proposal that relates cost/benefit and quality of care in hospitals. The professional responsible for this work, analyzes the processes, conducts actions that use resources to achieve correct and impactful objectives in the performance of the organization, achieving an effective result and financial return in a sustainable way and with social responsibility (ASSI, 2020).

In this context, there is a need to use specific technical tools that enable the manager to take a strategic position, ensuring the survival of the organization. Thus, the objective of this study is to demonstrate that the operational audit in health can act as a strategic tool of hospital management for the control of waste. The article was elaborated through a literature review, seeking to conceptualize the theme and prove the usefulness of auditing as a management tool for hospital organizations, leaving for future research the proof of results through empirical studies.

Therefore, the theme is relevant, because it allows the hospital manager to identify ways to favor the qualification of the service without adding costs to the care provided and the collection correctly according to the medical record of hospital care. Still, this article contributes to academia, since it is a subject that involves strategic issues of health organizations and the importance of internal or operational audit as a tool in the process of resolving hospital costs and, therefore, can be used as a strategy to control costs and improve the quality of service.

2 OPERATIONAL AUDIT IN HEALTHCARE ORGANIZATIONS

The operational audit, both in the health sector or in other diverse areas, becomes a management tool that, when well used, helps in the reduction of institutional expenses, in the evaluation of the quality of the services provided and in the development of the work between sectors. As presented by Evangelista, Bezerra (2021), the audit is a control review system to inform the management teams about the efficiency and effectiveness of the programs under development, and its function is not only to indicate failures and related problems, but also to point out suggestions and solutions assuming, therefore, an educational character.

Thus, the operational audit is defined as the systematic and formal analysis of activities developed by professionals not involved in its execution, with the objective of ensuring compliance, quality and control in a function, process or health institution (SOUZA, *et al,* 2010).

Health audit activities aim to ensure the quality of care provided to patients, respecting technical, ethical and administrative standards. The function of the auditor should not only be seen as a means to reduce costs, it can also be perceived as an ally, to ensure the quality of care (EVANGELISTA, *et al*., 2021). Therefore, the health audit can be classified, according to Brazil (1998), regarding its execution, for example:

- Analytical audit: audit model that is carried out through the analysis of reports, processes and documents, which aims to assess whether health services or systems meet the previously defined norms and standards;
- Operational audit: audit model that aims to verify processes and documents compared to the legal and normative requirements that regulate the Unified Health System (SUS) and Health Operators (PAHO) and the activities related to the health area, through the direct examination of the facts, documents and situations.

In relation to its nature, the health audit can be classified, according to Brazil (1998) in regular or ordinary audit, which is performed routinely with a view to the analysis and verification of the specific phases of an activity, action or service; and special or extraordinary audit, which is carried out to meet the findings of complaints and indications of administrative irregularities.

The audit can also be grouped as to the form of intervention in internal audit, where the audit performed by qualified auditors of the audited organization itself, which has the function of examining the controls and evaluating the efficiency and effectiveness of management. This area of auditing aims to promote improvement in operational controls and resource management (Brasil, 1998); and external audit, where the audit performed by auditors or independent company hired to verify the activities and results of a particular organization. It is the examination of the financial statements or of some specific area or predefined procedure as an object of special work (Brasil, 1998).

According to Brasil (1998), the audit can be grouped into:

- Retrospective audit or audit of hospital bills: it is performed after the discharge of the patient and consists of the verification of all the procedures that were performed during the period of hospitalization;
- Concurrent audit: it is performed during the hospitalization of the patient and consists of the monitoring and authorizations of procedures performed in the hospitalization process;
- Prospective audit: consists of the evaluation of medical procedures before the patient's hospitalization.

Therefore, the audit carried out in health organizations consists of the evaluation and systematic analysis of the procedures performed during the time of hospital stay and post-hospital discharge, being carried out by professionals trained for the correct verification of the quality of the care provided (TEIXEIRA, et al. 2019). That is, auditing in organizations is related to a cycle of improvements in the quality of efficiency and effectiveness of health care. Thus, it is developed through actions to adapt the care practice, quality of care provided and minimization of costs in waste (KAURA, 2016).

3 MANAGEMENT OF HEALTHCARE ORGANIZATIONS

Hospital management aims, as a general rule, to coordinate and standardize its work and institutional environment. However, when considering a health care institution, management stands out among the others, since it contains the most diverse sectors, with the most different professionals and with multiple services involved (SILVA, ESPÍRITO SANTO, 2013). Therefore, the excellence of business performance or its malfunction, depends on the quality of the performance of the managerial functions of the organization, which guide the type and amount of effort undertaken in each operational area to be developed (ANDRADE, SICHESKI, 2017).

According to Barbará, *et al. (2008),* the management process is characterized as a set of coordinated activities, aiming to control and direct a group of people and install processes with responsibility, authority and defined relationships. Given this, we consider the current situation in which we live, both with technological advances and the process of globalization, institutions to remain in the market, understood that they need to focus on organizational objectives and goals as a purpose for success. Therefore, in order to reap good results, institutions need to have a well-structured management. Therefore, one can use, according to Catelli (2011), the form of the planning, execution and control click, that is, to apply the PDCA cycle (Plan - Planning, Do - Execution, Check - Verification and Action - Action). The PDCA characterizes the efficiency in solving problems of a cycle by making improvements from stages (SHIBA, 1997), as observed in Figure 1.

Figure 1 - PDCA - Process Control Method



Source: Andrade, Sicheski, 2017.

Therefore, the PDCA, represents the resolvability in the efficiency of a cycle, from the problems of an organization, that is, it performs improvements by stages and repetitiveness of the cycles of improvements until when it is necessary (SHIBA, 1997). Fieg and Senai (2002) state that the application of this quality tool can be used in all sectors of an organization, as it helps in the optimization of the process, including internal audit. It is worth mentioning that to improve performance, the organization must have an action plan, this contributes to the orientation and solution of problems, prioritizing the actions to be developed, designating responsible and verifying the fulfillment of the tasks.

With regard to hospital management, Meyer Júnior, Pascucci and Mangolin (2012) define hospitals as multiprofessional organizations composed of different specificities, emergency needs marked by interdependence between sectors, professionals and a strong social mandate. Neves (2009) states that health institutions are environments with advancement in information technology, process optimization, excellence in management, professional efficiency and customer satisfaction. Thus, hospital management does not differ from other organizations.

In the midst of an environment that presents constant changes and competitiveness, hospitals are defined by Stacey (1996) as complex systems that are in continuous transformation. According to the author, for this phenomenon of updating to happen, innovation has become a condition to remain in the competitive market.

The scholar Dussault (1992) considers hospital management as one of the most complex activities. To assist in management and decision-making and control, auditing plays a key role in

hospital management. The audit has the role of making the systematic and formal evaluation of the activities developed, by someone not directly involved in the execution, to analyze, check and determine if this activity is in accordance with its objectives.

Therefore, the internal hospital audit is part of a process of systematic investigation, which according to Chiavenato (2004) contributes a lot to health organizations, through the review of exercise control, of the most diverse areas involved in the process.

4 HOSPITAL AUDIT AND MANAGEMENT

The importance of auditing in hospital management is due to the diversity of professionals who perform it and how specific, complex and how much it collaborates in the management of health services. Thus, it contributes to hospital management as it drives the achievement of results for management (Souza, *et al.* 2010). Thus, the use of auditing as a management tool should contemplate the requirements inherent to the management process such as planning, monitoring, evaluating health actions and services, intensifying the training and permanent education of all those involved in the process (BAZZANELLA, 2013).

The hospital audit service can also be inserted in an educational process, which undertakes to explain to the performing professional for the failure in the process, the reason for the non-compliance generated. In addition, the audit becomes responsible for the efficiency of the financial control of the hospital organization.

As pointed out by Souza, *et al.* (2010), the audit of hospital bills has a primary function for determining the costs and profits of the organization, being a management mechanism for decision-making processes, as it interferes directly and fundamentally in the quality of care provided to the patient. The authors maintain that the main objective of the audit is to evaluate consumption and charges made to patients or service providers. According to Castilho, *et al.* (2015), the increase in hospital costs has been an object of attention by hospital managers and health professionals. The tendency of hospital organizations, both public and private, is to invest in the audit of hospital bills seeking adequate remuneration for the care provided.

Martins (2000), considers cost as the expense related to good or service used in the production of other goods or services. In health services there are costs with human resources, with materials (syringe, needle, gloves, equipment used in the production of care), medicines and with the hospital structure (physical space, furniture, water, electricity, telephone), among others. Hospital costs are fundamental work instruments for the optimization of hospital operations, alerting management to any results that require correction (YANO, 2020). Cost information is useful in the hospital sector when it enables the understanding of its behavior, and the identification and development of waste containment strategies.

In this sense, the audit is used to identify problems related to the care and management processes (RODRIGUES, *et al., 2018*), to which it contributed both to the situational diagnosis and to the proposition of strategies in obtaining relevant information for managerial decision-making. Therefore, the use of auditing by management to assist in the implementation of improvement of care and management processes was subsidized by changes and/or incentives for the implementation of protocols and/or clinical guidelines (MARTINS; ANGELO, 2020). Therefore, this implementation aims to adjust conducts and make changes in professional practices, monitoring indicators to qualify care and adjust the use of resources. The use of clinical auditing helps to understand the expenditure of the care provided and can contribute to important cost savings, resulting from the analysis of indicators and use of resources (JOHRI, *et al.,* 2017).

The analysis based on the financial losses evidences problems arising from the assistance. Thus, an intervention tool can be used, such as the process control method – PDCA, to reduce waste rates, improve performance, provide subsidies for cost management in the care and management processes (RODRIGUES, *et al.,* 2018). Therefore, waste is part of every area of a healthcare organization. According to Aranha, Vieira (2001), waste is considered any and all resources that are spent to perform a certain product or service, in addition, one should consider the extra consumptions, such as raw material, materials, time, energy and money, because it is an addition to the normal costs of the product / service.

In health organizations, waste is related to inputs such as materials, medicines, especially injectables, seen as the sources of greater expenditure within institutions. According to Brasil (2002), waste related to the health area needs the attention and knowledge of all professionals directly or indirectly involved in the process. Therefore, for a better understanding of what happens in the health institution in relation to waste, greater attention should be paid to this, where they may be related to excessive and unjustified amounts of the use of materials and medicines, also of human resources/labor, work methods, equipment/machinery, input rates and suppliers.

Given this, the audit has a fundamental role in this process, seeking to examine them and make proposals to minimize them through the records found. In this context, the absence of this information and/or the inadequate filling with inconsistency in the notes, interfere directly in the generation of financial losses, since they cannot prove whether in fact certain inputs were used (MORAIS, GONÇALVES, AMARAL, 2017).

Thus, it is necessary to identify what are the main reasons that generate waste in the health institution, so that strategies can be identified and implemented to avoid failures in this process (SPIGOLON, *et al.,* 2019). However, the audit aligned as a hospital management tool provides financial sustainability of organizations, including the maintenance of processes involving care and, mainly, the paying sources and providers of hospital medical services.

Therefore, the audit is a strategic management tool, used to minimize and control waste. In order to be successful, in relation to this objective, in the health organization, it is necessary to carry out regular specialized audits specific to the sector in focus. These audits should use programs and procedures developed by professional auditors, in order to avoid nonconformities and undue charges, in addition to contributing to reduce the percentage of waste and measurement of data.

5 FINAL CONSIDERATIONS

The present study sought to demonstrate that the operational audit in health can act as a strategic tool of hospital management for the control of waste, and the audit plays an important role within organizations. Thus, it becomes an important gauge and evaluator regarding internal controls regarding their efficiency and effectiveness, advising managers through information and data collected in a technical way.

The audit has an important role in the analysis of hospital performance through the verification of records and the verification of costs, thus contributing to the improvement in the control and economic-financial balance of the hospital organization. Therefore, the hospital audit activity has stood out as a management and inspection instrument more appropriate to the needs of information management in the hospital environment. This model for measuring results meets the specific information needs of each manager and other users.

This study makes it evident that the audit used as a management tool and the elaboration of instruments to perform analyses in health institutions, achieves satisfactory results both in the control of waste, as in strategic actions from the institutional indicators by the management team and in the permanent education with the professionals involved in the care provided to the patient.

It is noteworthy that the article was limited to a bibliographic research aimed at analyzing the operational audit as a management tool for health organizations, without proceeding with a case study or analysis in hospital organizations to corroborate the results presented from the literature review. Thus, it is suggested that future research be done evaluating health organizations regarding the performance of the operational audit to improve their performance through the reduction of waste.

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Prognosis of patients with intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma undergoing liver transplantation

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ABSTRACT
Cholangiocarcinoma (CC) is the most common of tumors of the biliary tree, according to its location is classified as intrahepatic, perihilar, and distal. Intrahepatic CC (ICC) constitutes about 5-10% of all CC. Although rare, its incidence has been increasing in several parts of the world. The mixed tumorhepatocellularcarcinoma/cholangiocarcinoma (HCC-CC), which is also rare, presents histological findings of both hepatocellular carcinoma (HCC) and iCC in the same nodule. Patients with a presumptive diagnosis of HCC on imaging tests undergo liver transplantation when, in fact, they have iCC or HCC-CC. A consensus meeting of the 2014 European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) contraindicated liver transplantation (LT) in patients with iCC or HCC-CC. However, recent studies suggest that careful selection of patients with very early iCC have similar survival rates to patients transplanted by HCC, suggesting that early iCC patients should be considered for liver transplantation. Similar results were obtained in patients with HCC-CC; however, it would seem that the cutoff could be extended to 5 cm considering other post-LT variables

Keywords: Liver Transplant, cholangiocarcinoma, hepatocellular carcinoma, prognosis, recurrence, survival.

1 INTRODUÇÃO

Cholangiocarcinoma (CC), a tumor of the epithelium of the bile ducts, is the most common of the biliary tree tumors, representing 10% to 25% of malignant tumors of the liver.[1]

CC originates anywhere in the biliary tree, from the intrahepatic bile ducts – Hering canals – to the whole doc (bile duct that originates from the junction of the common hepatic duct with the cystic duct and that flows into the ampoule of Vater - second portion of the duodenum).

Anatomically they are classified as intrahepatic, peri-hilar (at the confluence of the bile duct in the hepatic hilum), and distal (lower half of the choledoc). By the growth pattern, they are classified as mass-forming – mass effect – infiltrative – growing along the periphery of the bile duct - and intra-ductal (inside the bile duct). [2,3]

Intrahepatic CC (iCC) constitutes about 5-10% of all CC. [4-6] Although rare, incidence rates have increased in the last four decades in different regions of the world. [7-11]

For example, the incidence of iCC is high in Asia. A Thai study [12] reported age-adjusted rates of 100/100,000 inhabitants among men and 50/100,000 inhabitants among women.

In the West, age-adjusted rates range from 0.5 to 2.0/per 100,000 inhabitants. [12] In the United States, between 1992 and 2000, the incidence of iCC increased by 4%. [13] Population-based studies in that country, using data from Surveillance, Epidemiology, and End-Result (SEER), described increases in the incidence of iCC three to five times more compared to other anatomical subtypes between 1973 and 1997 and then between 1975 and 1999. [7,14]

Similar form data was described in European and Japanese cohorts. [15-17] The iCC shows a predominance by the male sex with a male/female ratio of 1.2-1.5:1 and rarely occurs before the age of 40. [13]

The mixed tumor HCC-CC presents histological findings of both hepatocellular carcinoma (HCC) and iCC in the same nodule. [18]

Mixed HCC-CC tumors are rare, and it is estimated that their incidence among malignant liver tumors varies between 1% and 4.7%. [19] HCC-CC presents the same histological characteristics as iCC. [20]

Although imaging tests suggest a diagnosis of iCC [21-23], identifying these tumors is a challenge because they are not commonly seen, and because HCC and iCC can coexist in separate nodules in the same liver.

Consequently, patients with a presumptive diagnosis of HCC on imaging tests undergo liver transplantation when, in fact, they may have iCC or HCC-CC. [24,25]

2 PATHOGENESIS

Cholangiocarcinoma is a primary biliary cancer that develops from the malignant transformation of cholangiocytes rather than hepatocytes, which form the most common liver cancer, hepatocellular carcinoma. [26,27]

Precursors of CC are:

1. Intraductal papillary mucinous neoplasm of the bile duct: This is classified according to the extent of cellular atypia, reflecting the spectrum of precursor lesions of pancreatic cancer. [26,27]
2. Biliary intraepithelial neoplasia: This is the most common form of CC, which is a macroscopic lesion similar to its pancreatic counterpart. [26,27]

Conversion of normal to malignant biliary epithelium through one of these precursor lesions likely requires a gradual accumulation of successive genetic abnormalities, similar to the sequence of events underlying colorectal carcinogenesis. However, the level of understanding of the molecular pathogenesis of CC is significantly lower than that of other gastrointestinal cancers. [26,27]

The molecular pathogenesis of cholangiocarcinoma involves different signal transduction pathways. At the molecular level, carcinoma precursors remain poorly characterized, although they appear to harbor mutations in p53 and loss of SMAD4. [26,27]

A variety of molecular defects have been described in samples of invasive tumors of the biliary tract, involving:

1. Oncogenes: RAS, ERBB2, BRAF, EGFR, PIK3CA, CTNNB1
2. Tumor suppressor genes: p53, SMAD4, CDKN2A.

The abnormal expression of KRAS is found in 45% to 54% of intrahepatic CCs; and in 10% to 15 % of extrahepatic CCs. The presence of these genetic alterations seems to be associated with a more aggressive tumor phenotype. [26,27]

2.1 EXTRAHEPATIC CHOLANGIOCARCINOMA

Perihilar CC is the most common subtype of cholangiocarcinoma and represents approximately 60% of malignant neoplasms of the biliary tract.

Most cases occur spontaneously, and although chronic inflammation and biliary stasis have been identified as risk factors, the precise etiology remains unclear. [2]

Specific genetic mutations that have been identified include K-ras, C-myc, p53, and Bcl-2. K-ras mutations in particular have been reported in up to 60% of patients and are seen more frequently in perihilar tumors larger than 3 cm and patients with lymph node metastases; they are often associated with poor survival. [2]

2.2 INTRAHEPATIC CHOLANGIOCARCINOMA

In intrahepatic CC, the KRAS mutation is frequently seen. About 20% of intrahepatic CCs have a loss-of-function mutation of the P53 oncogene.

In addition, mutations in isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) have recently been seen in 10% and 23% of cases [2] Mutations in the gene encoding isocitrate dehydrogenase 1 (IDH1) have been identified in 25% of intrahepatic CCs but not in extrahepatic CCs or gallbladder carcinomas.

The frequency of mutations in the IDH1 and IDH2 genes was higher than the combined frequency of activating mutations in other genes (e.g., AKT1, KRAS, NRAS, and BRAF) in intrahepatic CCs; suggesting the potential to target this pathway in intrahepatic CC. [2]

3 DIAGNOSES

When diagnosing CC, which is a form of CCA, (write out CCA) it is necessary to consider three possible scenarios, (a) asymptomatic cholestatic pattern, with symptoms or imaging findings related to a hepatobiliary malignancy, or a patient with known ulcerative colitis. (27)

Risk factors include age (between 50-70 years), increased incidence, (increased incidence of what?), male sex, and Asian ethnicity (possibly about liver staves' infection) (12). At the time of taking the medical history, it is important to investigate a history of gallstones, inflammatory bowel disease, and hepatitis. (28)

Biochemical analysis showed elevated alkaline phosphatase at twice the normal levels. Elevated GGT and bilirubins, as well as chronic biliary obstruction by an intrahepatic CC, can also alter the values of transaminases and INR (spell out this and other abbreviations the first time they are used and then use the abbreviations as much as necessary). It should be noted that these changes are not specific to CCA in that they are also altered in other pathologies, so it is necessary to make an adequate differential diagnosis. (12)

Symptoms such as weight loss, malaise, choluria, pruritus, among others, may be present in these patients, all being nonspecific, but suggesting an obstructive process of the bile duct secondary to a neoplastic process. However, clinical symptoms of CCA do not usually appear until the disease is at an advanced stage. (28)

In the analysis of the tumor antigen CA 19-9, values higher than 100 U /ml, provides a sensitivity for CCA between 50% and 70%. However, its usefulness may be limited by the false positives that can occur in benign diseases of the gallbladder and bile duct (29).

There are other tumor antigens such as carcinoembryonic antigen (CEA), matrix metalloproteinase-7, and a cytokeratin-19 fragment, which can be elevated in CC, but have a low sensitivity, and specificity and are only present on a subset of tumors.

Thus, they are not useful in clinical practice. (30) These data suggest that a combination of these tumor antigens can increase the sensitivity and specificity of CC detection up to 90% so an adequate clinical decision should be made. (31)

If a patient presents an elevation of liver enzymes that cannot be explained, complementary imaging studies should be performed.

These include magnetic resonance or magnetic resonance cholangiopancreatography, which are the ones of choice since they offer a sensitivity of 88% and a specificity of 75% to 85%. even if contrast is available to perform the imaging study, the sensitivity will increase by 10% as long as there are no contraindications, such as kidney failure or allergies.

The underscored sentence is not clear. When pathological findings in these studies such as a mass, ductal dilation, stenosis, among others are found, an invasive evaluation with sampling for histopathological studies is recommended. (32) In patients who have liver masses, iCC should be differentiated from other possible causes, the use of contrast and the characteristics of the images may help differentiate the type of pathology. (33)

The differentiation between an HCC and an iCC is that the latter presents a progressive uptake in both arterial and venous phases. (33) Magnetic resonance imaging can help differentiate between these two tumors, although it is not always definitive. (34)

If a lesion such as iCC is suspected, the metastatic disease should be evaluated, so the request for a chest tomography is important. (35)

Perihilar tumors are less frequent than iCC, which in imaging studies are presented as well-defined or nodular masses.

The involvement of the portal vein and the hepatic artery can be evaluated by a CT scan, with a sensitivity of 89% to 92% and 83% to 93% respectively. (35)

However, magnetic resonance cholangiopancreatography is the preferred imaging study for its ability to better characterize the biliary tree as well as the extent of the lesion. (32)

In patients suspected of perihilar cholangiocarcinoma, endoscopic retrograde cholangiopancreatography (ERCP) has become the test of choice for tissue diagnosis. (37) It can be used as a complement to intraductal ultrasound for the visual confirmation of lesions that are difficult to characterize.

Among physicians with experience to perform this study, the sensitivity reaches 93%, although practical use is limited by the difficulty in collecting tissue samples for cytology or detecting regional adenopathy. (38)

A Chronic inflammatory cholangiapathy such as primary sclerosing cholangitis (PSC), is characterized by progressive cholestasis, fibrosis, and stenosis, (39). Patients who suffer from it are twice as likely to develop cancers such as CCA, CRC, and HCC compared to the general population. (40)

The main cause of mortality in patients who have been diagnosed with PSC is CC (40) and the lifetime risk is approximately 10% to 15%, with an annual incidence of approximately 1%(41). Initial

reports indicate that, within one year of diagnosing PSC, 50% present with CCA (42). This finding suggests that the diagnosis of primary sclerosing cholangitis is made only after the development of malignant stenosis.

When a primary PSC has recently been diagnosed or there is a high suspicion of it being present, studies such as magnetic cholangiopancreatography and laboratory studies (liver tests and a CA 19-9) are the initial steps indicated. Such tests have two purposes, to identify any possible malignant stenosis and two to be a baseline in the case of laboratory changes, symptoms, or imaging in the future. (43)

4 TREATMENT AND PROGNOSIS

4.1 LIVER RESECTION

The treatment of choice for iCC is surgical resection. North American researchers [44] evaluated 270 patients with iCC, of whom 82 underwent surgical resection. At a mean follow-up of 26 months, disease-free survival was 36 months, with a recurrence rate of 62%. Liver tumors, regional lymph nodes, and large tumors were independent predictors of poor recurrence-free survival.

Similarly, a study conducted in South Korea [45], with 64 patients undergoing surgical resection, showed median recurrence-free survival of 12.3 months, recurrence in 41 patients, and a 5-year survival rate of only 39.5%. In the multivariate analysis, the presence of metastatic lymph nodes (HR 3.31) and the degree of tumor differentiation (HR 3.15) were significantly associated with poor survival.

A French multicenter study [46], using retrospective analysis, compared the outcomes of cirrhotic patients diagnosed with iCC or HCC-CC ≤ 2 cm undergoing LT or liver resection between 2002 and 2015.

The diagnosis of iCC or HCC-CC was incidental in 100% of patients undergoing LT and in 81% of patients undergoing hepatectomy, of this group only 5 (19%) patients had a previous histological diagnosis of iCC or HCC-CC. [46]

Regarding prognosis, after a follow-up of 25 months, no significant difference was found between liver resection and LT regarding overall survival in 1, 3, and 5 years (P=0.17) However, recurrence-free survival (RFS) rates were statistically higher (P=0.004) in the group that underwent LT in 1, 3, and 5 years (87%, 79% and 75% versus 69%, 45% and 36%, respectively). The rate of tumor recurrence was statistically lower in the LT group compared to liver resection (18% versus 46% P = 0.01). Therefore, for patients with tumors ≤ 2 cm, LT presents better results in liver resection. [46]

According to the International Liver Transplantation Society (ILTS) consensus guidance, liver resection continues to be the first-line treatment for patients with iCC. However, if the tumor lesions are ≤ 2 cm the LT can be considered. [47]

However, if the tumors exceed this cut-off, LT with curative intent can only be offered if the disease remains stable after neoadjuvant treatment. [47]

4.2 LIVER TRANSPLANTATION

A consensus meeting of the EASL in 2014 and the AASDLD guideline contraindicated liver transplantation in patients with iCC or HCC-CC due to the high recurrence rates and low recurrence-free survival rates recorded so far. [48,49]

However, recent research has shown encouraging results in patients submitted to LT, in addition, groups of researchers have identified a subgroup of patients with histopathological diagnosis of very early iCC who may benefit from LT with results like other causes.

De Martin et al. [46], using retrospective data from 3 French centers compared the outcomes of cirrhotic patients diagnosed with iCC or HCC-CC undergoing LT or liver resection. The authors concluded that for tumors ≤ 2 cm overall survival showed no difference between LT and liver resection, but the LT group showed RFS rates in 1, 3, and 5 years older and a lower recurrence rate.

In the same study, a subgroup analysis was performed with 45 patients with tumors □ 2 cm but ≤ 5 cm, 21 of them underwent LT and 24 liver resections.

After a follow-up of 24 months, there was no statistically significant difference in overall survival between LT and liver resection at 1, 3, and 5 years (88%, 65%, 65% versus 95%, 58%, and 35%, respectively, P = 0.41) In the multivariate analysis, the largest tumor diameter was the only associated prognostic factor are survival (HR 1.11; 95% CI, 1.03-1.19; P = 0.005) [46].

Regarding RFS rates despite being higher in the LT group, there was no statistical difference when compared with the liver resection group (P=0.06), recurrence rates in this subgroup of patients were lower in the LT group but without statistical difference. (P=0.06).

In the multivariate analysis, 3 factors were associated with lower tumor recurrence: tumor differentiation (HR, 4.16; 95% CI, 1.37-12.66; P = 0.01), median size of the largest nodule (HR, 1.10; 95% CI, 1.02-1.73; P = 0.007), and LT (HR, 0.23; 95% CI, 0.07-0.82; P = 0.02) [46].

Despite the LT, showing some advantage in the prognosis of these patients, the authors suggest prospectively confirming these results, as well as coining efforts to assess pre-LT tumor differentiation. [46]

In a recent study [50], the authors compared the results after LT of patients transplanted for suspected HCC in imaging tests and that the histopathological analysis of the explant showed to be, in fact, iCC.

After a 35-month follow-up, the cumulative risk of recurrence at 1, 3, and 5 years was 7%, 18%, and 18% respectively for the very early iCC group and 30%, 47%, and 61% respectively in the advanced iCC group (p 0.01).

Survival rates at 1, 3, and 5 years for patients with very early iCC (single tumors ≤ 2 cm) were 93%, 84%, and 65% respectively, and in the group with advanced iCC (□ 2 cm tumors) were 79%, 50%, and 45%, respectively (p 0.02).

Thus, the results suggest that liver transplantation could be an effective form of treatment in patients with early iCC. [50]

A retrospective multicenter study [51] studied the risk factors for tumor recurrence after liver transplantation of cirrhotic patients diagnosed with CCI in the histopathological analysis of the explant.

The authors concluded that patients with very early CCI – single tumors ≤ 2 cm have very satisfactory survival rates in one, three, and five years, being 100%, 73%, and 73% respectively. The factors associated with tumor recurrence were higher number and tumor size, microvascular invasion, and poor degree of tumor differentiation. [51]

North American researchers, [52] using propensity-matched analysis, compared the post-LT hepatic results of patients diagnosed with HCC-CC versus HCC in the histopathological study of the explant.

Patients with HCC-CCA were matched 1:3 with patients with HCC for the pretransplant (pre-LT AFP levels and cumulative radiologic tumor diameter) and posttransplant variables (diameter of the tumor in the explant, grade of tumor differentiation, and vascular invasion). Considering the pre-LT variables, there was no statistically significant difference in recurrence rates in 1, 3, and 5 years between recipients with HCC-CC and HCC (16%, 50%, and 50% versus 14%, 19% and 22%, P=0.07), as well as a clear trend for lower rates of override and RFS, but, without statistical significance. [52]

Considering the post-LT variables, the results were similar, patients with HCC-CC had slightly higher recurrence rates but without statistical significance (P=0.13) and equivalent rates of general survival and RFS, in the same way, without statistical significance. [52]

According to the results, the authors suggest that tumor differentiation would play an important role in the post-LT prognosis since patients with low-grade and moderately differentiated HCC-CC would have excellent survival with a low risk for post-LT recurrence when compared with patients with HCC of the same characteristics. In this way, identifying the histopathological characteristics of the mixed tumor would allow these patients to be listed for LT under well-defined criteria. [52]

Recent research, [53,54] points to similar results and suggests that patients with HCC-CC could be considered potential candidates for LT provided they have a judicious evaluation. Variables such as vascular invasion, tumors □ 2cm "early stage" and multifocal disease, were associated with worse post-LT outcomes.

Despite these results, the ILTS expert panel continues to consider that there is insufficient evidence or experience and that before including patients with HCC-CC formally as potential

candidates it is necessary to identify prognostic factors that allow improving the selection and thus the post-LT results. [55]

5 CONCLUSIONS

Currently, iCC and HCC-CC are considered absolute contraindications to LT, by their worse prognosis, recent research suggests that better selection and evaluation of candidates would improve post-LT outcomes.

Although these studies have followed retrospective outlines, the use of propensity-matched analysis applied in most analyses has provided greater methodological rigor and confidence in the results obtained.

In all studies, the diagnosis of iCC and HCC-CC in patients undergoing LT was made by histopathological study of the explant.

Regarding the iCC, the results are satisfactory – the overall survival and RFS in 5 years for very early tumors – ≤ 2 cm, has been acceptable. However, the 2 cm cut-off is extremely limited, due to the challenge of its preoperative radiological diagnosis, for this reason, researchers suggest that these results be validated in multicenter and prospective studies.

Regarding HCC-CC the conclusions are more encouraging, the results after transplantation are like those obtained in patients transplanted by HCC. In this subgroup of patients, the degree of tumor differentiation plays an important role since the best results have been observed in patients with well-differentiated tumors.

Other variables related to prognosis have been tumor invasion, multifocal disease, and tumor size - ≤ 2 cm.

Although the 2 cm cut-off seems safe, researchers showed adequate results in a subgroup of patients with tumors □ 2 cm and ≤ 5 cm, in this way, patients with mixed tumors could be considered potential candidates, however, it is mandatory

Prospectively identify prognostic factors that allow improving the selection and thus the post-LT results.

On the other hand, transplant oncology is an emerging discipline that aims at multidisciplinary work between transplant oncologists, hepatologists, gastroenterologists, transplant hepatobiliary surgeons, interventional radiologists, and immunologists to expand and improve post-transplant outcomes in different types of cancer.

Conflict of Interest

The authors declare no conflict of interest.

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Perception of factors associated with overweight and obesity in individuals with special needs: An action of food and nutrition education

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ABSTRACT
Obesity is a public health problem whose etiology is multifactorial and requires knowledge about determining factors for its emergence. Food and nutrition education (NEC) actions are relevant for understanding and diagnosing this situation in its complexity. The study evaluated the perception of factors associated with overweight and obesity through written and confidential expression in individuals with special needs practitioners of hippotherapy of the IF Goiano- Campus Urutaí. The method was qualitative and the results espresso in a cloud words. In this study, the number of factors related to mental health cited by the individuals is highlighted, the words "anxiety" and "depression" received prominence and also appeared the terms "emotional" and "relationship with food", in addition, were mentioned "lack of physical activity", "inadequate diet" and "genetics". It was concluded that the diagnostic intervention was effective in showing that obesity and overweight are dependent in which the individuals presented satisfactory perceptions about the relationship of biopsychosocial factors and weight gain and obesity.

Keywords: Overweight, obesity, individuals with special needs, action of food and nutrition education.

1 INTRODUCTION

Food and Nutrition Education (EAN) is a nutritional intervention strategy that aims to promote reflection and collective dialogue that contribute to the learning of the target audience through educational resources (BRASIL, 2021; RODRIGUES et al., 2020). Thus, the EAN can be applied in different life cycles and public as a measure of creation and maintenance of healthy eating habits, and

consequently, prevention of comorbidities such as obesity (BRAZIL, 2012; DE CASTRO, DE LIMA, ARAUJO, 2021). With the focus on improving the quality of life of the assisted population, EAN strategies can be applied to individuals with special needs (RACHID, 2019).

For this public, food education actions are relevant to reduce behaviors that can be generated by characteristic aspects of a given picture (DE PAIVA, GONÇALVES, 2021). In this case, EAN activities have the potential to develop skills related to the act of eating and working with issues that guide their perception (MILANE, BORTOLOZO, PILATTI, 2022). The emphasis on the perception of these individuals is relevant because it promotes discussions about known and unknown factors of any theme, pointing out possible gaps in this population (DE CASTRO, DE LIMA, ARAUJO, 2021; RACHID, 2019).

In addition, it is worth noting that the population with needs presents characteristics that make them more prone to the appearance and development of nutritional disorders, so a personalized approach is essential (LOPEZ, 2017; BERTAPELLI et al, 2017). Among the eating disorders, there is food selectivity, monotonous feeding, swallowing difficulties, physical dependence to feed (LOPEZ, 2017). Thus, the approach of different forms of intervention can help maintain an adequate nutritional status in this population (LEITÃO et al, 2022)

The promotion of awareness and information actions using the EAN as a tool, considering the particularities of the individual with special needs assisted, is of great value for the promotion, maintenance and/or recovery of health through eating habits. Thus, the objective of the study was to collect data on the reasons associated with overweight and obesity according to the perception of people with special needs practicing hippotherapy at the Federal Institute of Goiano- Urutaí Campus.

2 THEORETICAL FRAMEWORKS

Obesity is a public health problem that increasingly affects society, causing significant impacts both for individuals and for society as a whole. The exponential growth of obesity rates is related to several factors, such as the change in eating habits, sedentary lifestyle and easy access to ultra-processed and poorly nutritious foods (DIAS et. al, 2017).

The data presented in the new edition of COVITEL (2023), a telephone survey of risk factors for chronic non-communicable diseases in times of pandemic, reveal an alarming picture in relation to the younger population, specifically between 18 and 24 years old. This age group emerges as a leader in obesity factors, with a significant increase in the number of overweight young people. In addition, habits harmful to health, such as excessive time in front of screens, high consumption of soft drinks and artificial juices and the lack of inclusion of fruits, vegetables and greens in the diet, further aggravate this worrying scenario (COVITEL, 2023).

According to a survey conducted on the website of the Food and Nutrition Surveillance System (SISVAN), which monitors diet and nutritional status in Brazil, in 2019, approximately 10% of children between 5 and 10 years of age were overweight than recommended for their age. In addition, according to the WHO Atlas of Childhood Obesity, it is estimated that by 2030, about 22.8% of children aged 5 to 9 years and 15.7% of children aged 10 to 19 years in Brazil will be obese (LOBSTEIN; BRINSDEN, 2019).

Corroborating this scenario, the Brazilian population as a whole has been going through a worrying nutritional transition, where we have observed an increase in the consumption of ultra-processed foods to the detriment of in natura and minimally processed foods. This change in dietary patterns has led to a reduction in malnutrition rates, however, it has resulted in a growth of overweight and obese people. This scenario is particularly prevalent in the young public, where a diet characterized by foods high in sodium, fats and sugar is predominant, while natural and healthy foods are little consumed (IDEC, 2021).

To combat the growth of obesity, food and nutrition education (EAN) strategies are key. These strategies aim to guide the population on the importance of a healthy and balanced diet, providing information on the proper choice of foods and the benefits of a balanced diet. Thus, the EAN is consolidated as an effective tool in the promotion of healthy habits and, consequently, as a way to prevent and combat obesity and its diseases (SANCHES; GREGGIO, 2022).

When analyzing the growth and feeding process of children and adolescents with special needs, it is possible to notice that it differs greatly from the general population. Most special needs can affect food and nutrition, because their physical and intellectual limitations and genetic disorders can cause deficiency in their development, chronic diseases and various eating disorders (DANIEL et. al, 2021).

Researchers have observed a higher prevalence rate of overweight in people with Down Syndrome, Intellectual Disability and Autism; these conditions are associated with genetic, behavioral, environmental factors and physical limitations that can increase the risk of excessive weight gain (LOPES, 2017).

In their study, with children with Down Syndrome, Giaretta and Ghiorzi (2009) demonstrated that through the playful activities of food and nutrition education it was possible to identify the desires, thoughts and food preferences of people with Down Syndrome. Most participants demonstrated a strong desire for high-calorie foods high in fat and sugars. This food preference is in line with the current reality of these people, since many of them are overweight or obese.

NAS actions, which seek to combat obesity in children with disabilities, are necessary and efficient when relevant variables of these individuals are considered that can influence the results of actions such as age, type of disability and participation of parents and caregivers. These variables may play a relevant role in the effectiveness of the strategies adopted (MAGAGNIN, 2021).

This current panorama of overweight and obesity brings the need to develop strategies of food and nutrition education directed to such a public in the search for awareness of the factors that lead to obesity. To work with strategies of food and nutrition education, the educator or professional needs to be didactic and should arouse the interest of students to the content addressed, facilitating their participation in the teaching processes through playful techniques, which facilitate learning, and increase the performance of students in the acquisition of new knowledge (LANG; CIACCHI, 2021).

3 METHODOLOGIES

The Food and Nutrition Education Action was developed and carried out by students of the Nutrition course of the Federal Institute of Goiano-Campus Urutaí, addressing the theme of obesity and overweight. The study involved 10 participants, aged 5 to 40 years, among them the practitioners of hippotherapy with special needs, auxiliaries and employees of the Integrated Center of Equine Therapy (CIEU) of the Federal Institute of Education, Science and Technology Goiano – Campus Urutaí.

Three stages were carried out: the first was the making of a colored box that aroused the curiosity of the individuals and the elaboration of a poster with the following phrase "WHAT DO YOU THINK LEADS PEOPLE TO BECOME OVERWEIGHT" (figure 1).

The second step involved the movement of the students to the hippotherapy site to fix the poster and box, in which the individuals present at the site were approached and instructed to answer the highlighted question and deposit it in the box, in which it was exposed in the place for 10 days.

The third stage consisted of the analysis of the results in which a word cloud was elaborated using the online program WordArt (https://wordart.com/nwl5dq0aletg/nuvem-de-palavras). In this tool, the words that appear most prominently show the terms that were most frequently mentioned by the individuals (figure 2).

In order to preserve the identity of the participants, the answers were not identified with name, for the action the individuals gave consent by filling out the Term of Free and Informed Consent (ICF), in order to contemplate all the necessary ethical precepts.

Figure 1: Box and poster of the Food and Nutrition Education intervention.



Source: Authors, 2023.

4 RESULTS AND DISCUSSION

Individuals who attend the Integrated Equine Therapy Center of IF Goiano - Campus Urutaí participated in this Food and Nutrition Education Action. The result of the information collection was organized in a word cloud, after the box was opened, the answers were read and systematized into keywords to facilitate the presentation of the answers (figure 2).

Figura 2. Nuvem de palavras da coleta de informações.



The words described in larger letters were the ones that appeared most frequently, according to the opinion of the participants, an "Inadequate Diet" is one of the most relevant factors for the maintenance of an adequate body weight. This described factor was already expected, since studies point to lifestyle, which includes eating habits and physical exercise, as the main causes of obesity (JIA, LIU, 2021; DE CASTRO, DE LIMA, BELFORT, 2021). However, it should be noted that obesity has been declared as a disease of multifactorial etiology and the associated factors are already addressed and disclosed by the Brazilian Association for the Study of Obesity and Metabolic Syndrome (2016), in its Brazilian obesity guidelines.

The aspect "lack of physical activity" was also mentioned by the participants. It is known that this is an environmental factor that along with caloric intake are determinants in weight gain (BRAZIL, 2016). Therefore, there is a significant increase in the prevalence of obesity in various populations

around the world, including Brazil, which is often limited by issues of access and educational level (BRASIL, 2016).

The term "genetics" was pointed out as a possible factor associated with the appearance of obesity and overweight. Regarding this, common obesity is characterized by a polygenic inheritance, therefore, not all individuals gain weight in the same proportion when exposed to hypercaloric diets (NICOLAIDIS et al., 2019). The risk of developing obesity is higher when there is a family history of morbid obesity, with a Body Mass Index (BMI) equal to or greater than 40 kg/m², or even in cases of obesity at more moderate levels, determined by BMI.

In this study, the number of factors related to mental health cited by the individuals is highlighted, the words "anxiety" and "depression" were highlighted and the terms "emotional" and "relationship with food" also appeared as important for an individual to be overweight or obese. Thus, these findings evidence the importance of a multidisciplinary team for the integral health care of individuals considering the consequences that emocial eating can entail and implications in dysgnostic and treatment (KONTTINEN, 2020; DA SILVA, BY ANDRADE, 2023).). Individuals with depression tend to have an increase in inflammation (BREMNER et al., 2020).

Finally, a diversity of causal factors was observed that lead the individual to a poor control of their own body weight. Diet and obesity can influence mood through direct effects, while stress-related mental disorders can lead to changes in eating habits that affect body weight, in addition, stress or genetic predisposition can contribute to both obesity and stress-related mental disorders such as depression and post-traumatic stress disorder (PTSD) (ABIRI et al., 2022).

5 CONCLUSIONS

The results of the action of diagnostic food and nutrition education applied to the attendees of the Integrated Center for Equine Therapy (CIEU) of the Federal Institute of Education, Science and Technology of Goiás – Campus Urutaí demonstrated that individuals related environmental factors in the development of obesity, such as the built environment, sedentary habits and inadequate eating patterns. In addition, it was notorious that individuals have correct and satisfactory perceptions about the causal multifactoriality of obesity.

The results also underscore the importance of mental health in the context of obesity, such as anxiety, depression and emotional relationships with food mentioned by the participants. These findings emphasize the need for a multidisciplinary approach to comprehensive health care, especially in people with special needs, thus considering psychological and emotional implications associated with obesity and the diet of these individuals.

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Interprofessionality in Health Care

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ABSTRACT
Introduction: Interprofessional education in health has been revealed as an important strategy of professional training, in which professionals are able to develop teamwork that seeks to achieve integrality in health care. Objective: Tounderstand interprofessional education in health from the perspective of health education. Method: A bibliographic review with a reflective approach was carried out published between 2011 and 2021 in the SciElo, Pubmed and CAPS databases, using specific descriptors, in Portuguese and English languages, in February 2022. The titles and abstracts were analyzed, followed by the selection of articles that related to the theme, and 7 articles were included in the final sample. Subsequently, the reflection on the theme was carried out. Results and Discussions: From the selection of the articles, it was possible to understand that there is a long trajectory in the implementation of changes in teaching in the context of health education, and there is a need to improve the teaching-service-community integration, as well as to prioritize interdisciplinarity and interprofessionality, enabling cooperation for the exercise of transformative practices. Final considerations: this study revealed the urgent need for the implementation, strengthening and support of interinstitutional partnerships, the promotion of public policies that qualify the faculty for the development of interprofessional education and the strengthening of relations between the university, health institutions and the community. In addition, it pointed out the need to promote a culture of collaboration and teamwork among health professionals, valuing the diversity of knowledge and skills in order to achieve more comprehensive results to improve the results and quality of health care.

Keywords: Interprofessional education, interdisciplinarity, professional training in health, teamwork, health care.

1 INTRODUCTION

Interdisciplinarity is the set of different axes with the objective of building a new knowledge. In the health field, the intersection of knowledge promotes greater health education, stimulating autonomy, training of patients and professionals in the health-disease process (BISPO; TAVARES; TOMAZ, 2014).

In the principles that govern the Unified Health System (SUS), it is perceived the valorization of health promotion and the right to equity and integrality within the system. In this sense, multidisciplinary health teams are essential in the health education process, since they act as an integrative factor in health care, promotion and prevention (TAUCHEN; FAVERUS; ALVARENGA, 2017).

In addition, according to Almeida and Afonso (2020), interdisciplinarity is considered an expansion of science, as well as a dynamic process that enhances the articulation between scientific knowledge and public policies. It seeks to break with the traditional perspective of the transmission of knowledge, with medicine centered only on the disease and the doctor as the only protagonist.

It is worth mentioning that there are obstacles to the implementation of interdisciplinarity, such as the lack of permanent education and academic training of the teams. It is also noticed the disparity between existing public policies among Brazilian municipalities, scarcity of resources and insufficient integrality in the health network (ALMEIDA; AFONSO, 2020).

This study is justified by the need to analyze the perspective of health education in interprofessional education, critically examining the practice of interdisciplinarity in the Brazilian context and its impact on health promotion and the quality of services provided. Understanding the historical evolution of the interdisciplinarity process in Brazil and its relationship with health education will provide valuable insights to improve training strategies and interprofessional practice, contributing to the effectiveness of health interventions and the strengthening of the health system as a whole.

In this sense, the present study seeks to understand interprofessional education in health from the perspective of health education and, as well as to discuss the practice of interdisciplinarity in prevention, promotion and health education, seeking to analyze historically the process of interdisciplinarity in Brazil and health education.

2 METHODOLOGIES

This study aims to understand interprofessional education in health from the perspective of health education. It consists of a bibliographic review with a reflective approach, elaborated based on the searches carried out in February 2022 in the Scientific Electronic Library Online (SciELO), Pubmed and CAPS databases. The search used specific descriptors, including "interprofessional education", "professional training", "teamwork" and "health", crossed by the Boolean operators "AND" and "OR", who seek to respond to the objectives of the study.

In the initial search, we used the inclusion criterion of full text, in the Portuguese and English languages, free, published between the years 2011 to 2021, which had the following profile: theoretical and conceptual studies that provide a solid conceptual basis, systematic reviews and meta-analyses

that synthesize and analyze the results of multiple primary studies, qualitative empirical studies that explore the subjective perspective of individuals, quantitative empirical studies that provide numerical evidence on associations or effects of interventions, and narrative review studies that present a descriptive overview of existing studies. As exclusion criteria for the selection of researches, we considered studies that were case reports, observational studies and poster presentations.

Through the analysis of the titles and abstracts and having as a criterion their relationship with the theme addressed for the bibliographic review, 07 articles were selected to read in full and included in this study.

Based on the information obtained on the theme, a comprehensive systematic and reflective analysis was conducted with the objective of exploring and deepening the understanding of the proposed theme

3 RESULTS AND DISCUSSIONS

From the reading and analysis of the articles, it was noted that interprofessional education in health has been revealed as an important strategy of professional training, in which professionals are able to develop teamwork. This practice is essential to achieve integrality in health care (BATISTA, 2012). By resuming important aspects related to the concepts of health education, it is understood that this is transformed over time, that society educates itself, in one way or another, and education, shapes man, and can also be used as a form of domination or liberation (SOUZA, 2018).

Thus, education in a dialogical and critical perspective, is committed to the construction of knowledge and as an instrument of social transformation, in which the teacher and the student act in interactive situations of teaching and learning. In this course of transformations, the process of teaching learning must be attuned to reality, with the problems of society, with the political and social reality and with the different cultures providing skills and competencies that make it critical and reflective (BATISTA, 2012).

In this perspective, it is perceived that the concern with health education in Brazil had a greater emphasis from the movement of the Sanitary Reform, in 1986, with the realization of the VIII National Health Conference, an important historical milestone in the consolidation of the SUS. With the promulgation of the Federal Constitution of Brazil, in 1988, it was established that the managing bodies of the SUS must structure mechanisms of educational action, which take into account to ensure the development of educational actions for the qualification of personnel and investigative actions of research and innovation (XIMENES NETO, 2020)

In 1990, with the creation of the SUS (Law 8.080/90), it was ensured that the public health services that integrate the SUS constitute a field of practice for teaching and research, through the norms elaborated jointly with the educational system (BRASIL, 1990). In this sense, health in a socio-

historical-cultural conception emphasizes the integrality of care, with the health team acting in an interdisciplinary and multidisciplinary perspective. This perspective advances in relation to the biopsychosocial conception by considering the health-disease process and recognizing the importance of multiprofessionality in care, breaking with the purely biomedical conception of health, centered on the disease, in which the physician is considered a central figure in health care (BATISTA, 2012).

It is important to highlight that in 2002, the CNE/CES Opinion 1.133/2001 was approved, in which the proposals for National Curricular Guidelines (DCN) of the Undergraduate Courses in the area of Health were analyzed and, among other important points, the Commission reinforced the articulation between higher education and health aiming at a contemporary profile of the graduates/professionals with emphasis on promotion, prevention, recovery and rehabilitation of health, indicating the general common competencies (BRASIL, 1996).

Aligning this perspective with the context of training in the health area, there is a long process of implementing changes in education to reduce the distance to training and the reality of health services. It was with this purpose that the need for changes in the training of professionals emerged to meet the health needs of the population and culminated with the DCNs, although still in the process of consolidation, despite its twenty years, as there are numerous challenges (ARAÚJO et al., 2019).

Currently, the logic and structure of higher education in Brazil are obstacles to interprofessional education, since the courses work in their own structures, legitimizing and strengthening the separation and hindering the interaction between other courses in the health area (BATISTA, 2012; COSTA, 2016). Added to this, the cultural barrier is shown as an even more challenging element, considering that the logic of specific training is very strong and exerts an important influence on the construction of professional identities. Thus, the training process is very content-oriented and hinders the adoption of strategies capable of forming attitudes, skills and values based on collaboration (COSTA, 2016).

Among these and other challenges, there is a discussion about the need to expand university education beyond specific professionalization. The growing problematization in the teaching proposal, with consequent changes in the attitude of teachers and students and the integration and interdisciplinarity as drivers of the training proposal. The need for integration is evidenced while it is understood from the point of view of new interactions in interprofessional teamwork, exchange of experiences and knowledge and position of respect for diversity. It enables cooperation for the exercise of transformative educational practices (BATISTA, 2012).

It is in this perspective that health has become increasingly complex and interconnected, bringing together more professionals from different backgrounds every day. Thus, requiring these professionals to collaborate to achieve high levels of quality in health care, as well as learn to work in teams, giving meaning to interprofessional education (SCHMUTZ, 2021).

Interprofessional education, as a training proposal, has already been discussed in Europe and the United States for more than three decades and is applied both in the graduation of the different health professions and in the permanent education of professionals who already work in a team. They have as central characteristics teamwork, discussion of professional roles, commitment to problem solving and negotiation in decision-making (BARR, 2015).

It also values the history of the different professional areas considering the other as a legitimate partner in the construction of knowledge, with respect for the differences seeking dialogue, challenge, commitment and responsibility in health care. In this movement, it is committed to the development of three competencies - competencies common to all professions, specific competencies of each professional area and collaborative competencies (BATISTA, 2012).

This study provides a relevant reflection for the health area, highlighting the importance of interprofessional education and the practice of interdisciplinarity in prevention, promotion and health education. We emphasize here the need to overcome fragmented and uniprofessional approaches in health care, seeking a closer collaboration between professionals from different areas and knowledge. This implies valuing the diversity of knowledge and skills, promoting a more holistic understanding of health problems and a more integrated action to improve the results and quality of health care.

In addition, the importance of a historical and contextualized approach to understand the evolution of interdisciplinarity and health education in the Brazilian context is highlighted. By looking to the past, it is possible to identify challenges, successes and opportunities that have shaped the way health is approached in the country. This historical reflection can provide valuable insights to address current and future health issues, contributing to the development of more effective policies, innovative training strategies, and evidence-based interventions.

However, this study presents important contributions to health science. By discussing the practice of interdisciplinarity in health prevention, promotion and education, the study contributes to the integration of diverse knowledge and approaches, facing complex health challenges and enabling significant advances in the understanding of diseases and the development of more effective interventions. In addition, it provides a deeper understanding of the factors that have influenced the interdisciplinary approach in the country, informing future policies and practices to address the specific challenges of Brazilian health.

Regarding the limitations of this study, although it has significant contributions, it is important to recognize some limitations. First, the literature review may be subject to selection bias, since it depends on the studies available in the databases consulted. In addition, the quality and representativeness of the included studies may vary, which may affect the generalization of the results.

However, the reflective approach may involve a subjective interpretation of the data, which may introduce a certain degree of bias in the analysis and conclusions, and it is relevant to interpret

the results with caution and consider these limitations when assessing the relevance and applicability of the study findings.

4 FINAL CONSIDERATIONS

As traditional health education practices change, the possibility of teaching in a more participatory, creative and interactive way emerges. Thus, enabling the involvement of the teacher in an innovative pedagogical project, making him co-responsible in the formative process.

In this sense, it is essential to promote a culture of collaboration and teamwork among health professionals, valuing the diversity of knowledge and skills. Interprofessional education emerges as a fundamental strategy to prepare professionals for collaborative practice and multidisciplinary understanding of health problems. Investments in interprofessional training, the development of integrated curricula and the creation of joint learning opportunities are necessary to promote this interprofessional approach.

In addition, it is necessary to foster the practice of interdisciplinarity in prevention, promotion and health education. This implies overcoming barriers and challenges, such as the fragmentation of health services and the lack of effective communication among professionals. The adoption of interdisciplinary approaches requires a paradigm shift, encouraging knowledge exchange, collaboration and teamwork to achieve more comprehensive and sustainable health outcomes.

Finally, it is necessary to implement, strengthen and support interinstitutional partnerships, promote public policies that qualify the faculty for the development of interprofessional education, strengthen relations between the university, health institutions and the community (teaching, service and community integration). It is also necessary to join efforts to promote a change in the interprofessional and interpersonal relationships of the different actors involved in health education and production in the various services.

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Importance of public awareness of hand hygiene and the spread of hand-foot-mouth disease

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ABSTRACT
It is known that hygiene is a determining factor for the health area, becoming an important marker of social inequality and its habit is responsible for the prevention of infectious diseases such as hand-foot-mouth disease, caused especially in children, but may also affect adults. Therefore, this article aims to discuss the relationship of hand hygiene against the contamination of hand-foot-mouth disease in children and the importance of raising public awareness to prevent its spread. The methodology was based on a Literature Review, where a bibliographic search was performed in the Google Scholar and SciELO databases, where the following descriptors were used: "hand-foot-mouth"; "spread of disease"; "personal hygiene", "child health" and "hand hygiene". In view of the selected descriptors, 30 studies were identified, which went through a screening process where 20 articles were selected, according to the eligibility criteria, for the accomplishment of the present study. It was observed that with prevention and control measures it can reduce the numbers of infected people, as well as prevent the disease from getting worse, so it is extremely relevant to discuss the subject, both by health professionals and academics as well as by the entire local community, in order to prevent this disease from causing greater damage to the individuals present.

Keywords: hand, foot and mouth, spread of disease, personal hygiene, child health, hand hygiene.

1 INTRODUCTION

Hand hygiene (HH) is a globally recognized practice as a primary measure and is extremely important in the control of healthcare-related infections. For this reason, it has been considered as one of the several pillars of infections in health services, and the safety of patients during these services depends, however, on the frequent careful hand hygiene of multiple health professionals. (ANVISA, 2020)

"Hand hygiene" is a universal term, which refers to any action of sanitizing hands to prevent the transmission of microorganisms and consequently prevent the population and health professionals from acquiring HAI. According to the National Health Surveillance Agency – Anvisa, the term

comprises simple hygiene, antiseptic hygiene, antiseptic rubbing 2 of the hands with alcoholic preparation. (MINISTRY OF HEALTH, 2013)

Throughout the periods of the history of society, religious beliefs and practices came to cleanliness and religiosity. In each historical epoch it is feasible to relate the definition of hygiene with the present sociocultural and philosophical context, as, for example, in certain societies people kept themselves clean to present themselves pure in the eyes of the gods, and not for hygienic reasons, as the modern conception of this concept. (LAROCCA, MARQUE, 2005)

It is necessary to guide the population about the hand-foot-mouth disease, which is a contagious viral infection where its transmission unfolds precisely because of the lack of hygiene, very common during the summer period, which mainly affects children, although it can also manifest itself in adults, it is more common during childhood and there may be complications if not treated correctly. (WHO, 2022)

Thus, this article aims to discuss the importance of raising the awareness of the population regarding hygiene and the dissemination of the hand-foot-mouth disease in children, in order to promote the control of the disease and avoid its possible aggravation.

2 METHODOLOGIES

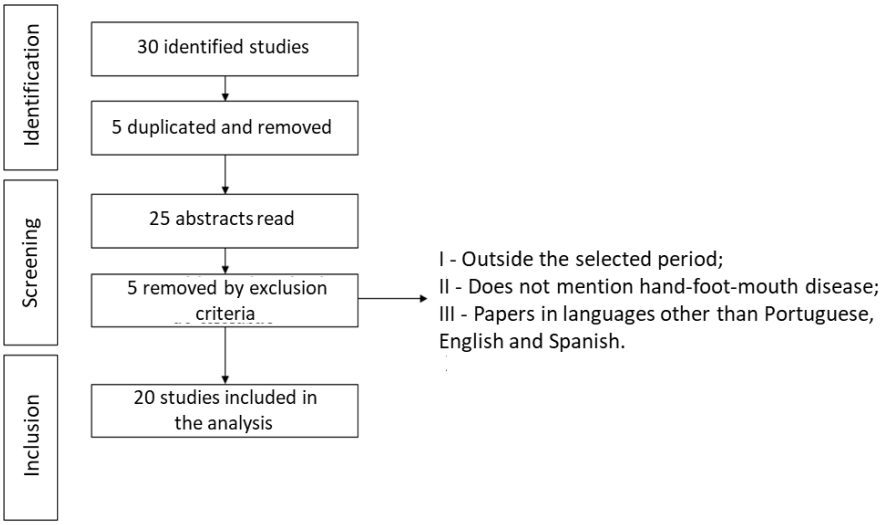
The present study refers to a literature review with a qualitative approach to the proposed theme. A bibliographic survey was carried out in the following databases: Google Scholar, SciELO, PUBMED and websites of the Ministry of Health, where the selection was made from the descriptors: "hand, foot and mouth"; "spread of disease"; "personal hygiene"; "child health".

The inclusion criteria were: to be a study published in the period from 1999 to 2022, to target children up to twelve years of age and who have already had the hand-foot-mouth disease, the importance of the Unified Health System in this hygiene scenario and texts that addressed the importance of hygiene in the control of this disease, which may be publications in English and Portuguese. On the other hand, the exclusion criteria were: articles outside the stipulated period, scientific papers that are not related to the proposed theme and in other languages.

3 RESULTS AND DISCUSSIONS

Taking into account the inclusion and exclusion criteria proposed for the present study, 30 articles were selected. The stages of evaluation and obtaining the works used are illustrated in Figure 1. Table 1.0 describes the articles used in the article, according to author, country, year, type of study and objective.

Figure 1



Source: prepared by the authors

Table 1.0

AUTHOR/YEAR/COUNTRY	TYPES OF STUDY	GOAL
Santos, Goncalves. 2021, Brazil	Qualitative literature review	The objective is to improve the training of the student who can work with the students with instructional pedagogical material with technical demonstrations of the procedures proposed here.
Markus. 2020, Brazil.	Case report	the objective of drawing attention to more severe pictures of the disease and the need for greater attention by the pediatrician of signs of severity that can even lead to death.
Mortari, et al. 2018, Brazil	Literature review	This document provides guidance on the etiology, epidemiology, clinical picture, diagnosis, treatment, control measures and management of BPD outbreaks, in order to support the actions of health care professionals and epidemiological surveillance in the state of São Paulo.
Nakao, et al. 2020, Brazil	Literature review	The objective of this article is to present the aspects of this viral disease that is present nowadays describing the etiology, epidemiology, outbreaks, symptoms and comorbidities, diagnosis, prevention and treatment of the clinical entity known as hand-foot-mouth disease.
Larocca. Select. 2005, Brazil	Literature review	The objective of this work is to analyze the formation of the first concepts about Hygiene as a form of health planning by the public sector and the use of this conception as an instrument for structuring society.
Dos Santos. 2022, Brazil	Literature review	Hand hygiene is considered the single most important action in the control of infections in health services. However, the lack of adherence of health professionals to this practice is a reality that has been observed over the years

		and has been the object of studies in various parts of the world.
Almeida. 2013, Portugal	Book	The main objective of this investigation is to analyze how scientific knowledge reached the common citizen, using the generalist press as the main source and vehicle for the dissemination of the cognitive repertoire of the time.
WHO. 2022, Brazil	Site	Hand-foot-mouth disease is a contagious disease caused by the Coxsackie virus of the enterovirus family that normally inhabits the digestive system and can cause stomatitis (a kind of canker sores that affects the mucous membrane of the mouth).
ANVISA. 2020, Brazil	Site	The hands are considered the main tools of the professionals who work in the health services, because it is through them that they perform their activities. The safety of patients in these services depends, therefore, on the careful and frequent hand hygiene of these professionals.
Lacen. 2018, Brazil	Epidemiological surveillance	The epidemiology center, through the Division of Surveillance of Communicable Diseases of the Paraná State Department of Health, emphasizes guidelines and conducts in the face of outbreaks of Hand-foot-mouth Syndrome (SMPB).
Usihealth. 2020, Brazil	Site	The hands are the main routes of transmission of viruses and bacteria and therefore the main gateway of diseases into our body. Correct and frequent hand hygiene is essential to prevent the development of various diseases.
Fiocruz. 2022, Brazil	Site	Universality is one of the fundamental principles of the Unified Health System (SUS) and determines that all Brazilian citizens, without any type of discrimination, have the right to access health actions and services.
Calegari. 2017, Brazil	Site	The SUS is much larger and more comprehensive than one imagines and, in some respects, quite different from the image of a giant and inefficient program.
Calili. et al. 2021, Brazil	Systematic Review	The hand-foot-mouth syndrome is considered a highly contagious disease that affects children under five years of age, because at birth, babies do not have antibodies.
Lugo and Krogstad. 2016, USA	Literature review	Enteroviruses cause a wide variety of diseases with neurological, respiratory, skin and gastrointestinal findings. The purpose of this review is to clarify changes in the classification of enteroviruses, provide information on recent outbreaks of the disease, and summarize progress in the treatment and prevention of these infections.

World Health Organization. 2011	Book	Hand-foot-mouth is a common infectious disease caused by a group of enteroviruses, including Coxsackievirus A16 (CA16) and Enterovirus 71 (EV71). Infection with EV71 is of particular concern as it can cause severe illness in children, sometimes resulting in death.
Bernier et. al. 2001, Belgium	Literature review	Onychomadesis and/or onycholysis is a newly recognized complication in the course of viral infections that present clinically as hand, foot, and mouth disease, and because of mild forms, is probably underestimated.
Lementz and Mancini. 2000, USA	Literature review	Foot-and-mouth disease (HFMD) is a contagious enteroviral infection that occurs mainly in children and is characterized by a vesicular palmoplantar eruption and erosive stomatitis.
Mendonça. 2018, Brazil	Site	Spaces shared by many children and the lack of hygiene habits are essential factors for the spread of viruses. The disease known as hand-foot-mouth is a contagious disease, caused mainly by the Coxsackie virus of the enterovirus family.
Estrada and Lazcano. 1999, Mexico	Literature review	Avoid inappropriate treatments, especially with antibiotics and primarily due to the history of respiratory conditions and/or abdominal pain, as well as the presentation of fever, considering the etiology.

4 HYGIENE AND BASIC HEALTH

Hand hygiene is considered the single most important action in the control of infections in health services. However, the lack of adherence of health professionals to this practice is a reality that has been noticed over the years and has been the object of studies in various parts of the world. The simple use of soap and water can reduce much of the microbial population present on the hands and, in most cases, end the chain of disease transmission. The application of antiseptic products can limit the risks of transmission, by intensifying microbial reduction or by benefiting an increase in the frequency of hand hygiene. (APARECIDA and SANTOS, 2002)

The importance of hand hygiene in preventing the transmission of nosocomial infections is based on the ability of the skin to host microorganisms and transfer them from one surface to another, by direct contact, skin to skin, or indirect, by means of objects. The normal skin microbiota is divided into resident and transient and this classification is paramount for understanding the transmission current of infectious agents. (APARECIDA and SANTOS, 2002)

Technological innovations were developed to be used by an amplified number of people, without which they would lose their meaning and practical application. With regard to Medicine and Public Health, the dissemination of information, especially in epidemic periods, was a matter of

survival. Throughout the nineteenth century awareness was created, by the traumatic experience of successive pandemics, that prevention and increasingly hygiene were the most efficient ways to deal with health crises in most cases and diseases in particular.

Without this resource the doctors and the health authorities would have lost the consecutive struggles against the diseases in which the whole world was involved, at least they would have had many greater obstacles. (MARIA ANTÓNIA ALMEIDA, 2013)

Therefore, Hand-Foot-Mouth Disease (BMD) is an acute, often self-limiting, viral exanthematous condition caused by non-polio human enteroviruses. Several factors such as environmental, socioeconomic and immunological factors allow the circulation of enteroviruses in a seasonal way. Outbreaks of these agents have been recorded worldwide since the 1960s. During the flow of non-polio EV, children under five years of age are the most affected. (MORTARI et al, 2022)

It is a fact that all Brazilian citizens, without any type of discrimination, have the right to access health actions and services, according to the principle of universality, in this scenario, the National Health Surveillance Agency (Anvisa) is also part of the SUS, and it is responsible for quality control and food hygiene, cosmetics, cleaning products, vaccines, transplants, cigarettes and medicines in Brazil. Anvisa's purpose is to identify the potential risks to health and the environment of several of the products and services marketed in the country. (FIOCRUZ, 2022)

The SUS is responsible for planning basic sanitation actions in the small municipalities of the country, with up to 50 thousand inhabitants (except in metropolitan regions). The activities are carried out by Funasa, the National Health Foundation, associated with the Ministry of Health. The scope of the foundation includes the construction of wells, distribution networks, water treatment plants and reservoirs, as well as garbage disposal programs to prevent the contamination of diseases in these areas. (CALEGARI, 2017)

There are several actions that can be done to make a group of people aware of hygiene and diseases that are caused by it, such as:

→ Prevention and Control Measures in the care in the residence, daycare centers and schools: Guide social isolation of cases, while the acute phase of the disease lasts, the child should not attend the daycare center for about seven days or until the absence of skin lesions, subject to medical reevaluation. When the child returns to the activities in the daycare, certify compliance with personal hygiene measures and the environment by caregivers and collaborators, since the viral excretion by feces in convalescence remains for weeks, being able to perpetuate the outbreak and observe hand washing in diaper changes. Warn the institutions involved, encourage the clarification of parents, train service providers on measures to prevent transmission.

In addition, carry out socio-educational activities to maintain the high standard of hygiene, such as:

- → Hand hygiene with soap and water, especially if dirt is apparent, or alcoholic products;
- → Avoid nail biting and finger sucking;
- → Hygiene of personal objects;
- → Cleaning disinfection of the environment with 70% ethyl alcohol solution. In the case of visible dirt, opt for cleaning followed by disinfection with high-concentration chlorinated solution (15ml of concentrated bleach 5 to 6% or 30ml of bleach at 2% for a liter of water), let it dry. Personal items should be rinsed after 10 minutes, before using again;
- → Avoid the flow of children under five years of age in agglomerations, during periods of outbreak;
- → Care for pregnant and postpartum women, where pregnant women need to distance themselves from people with BPDM, it is recommended that they seek their doctor reporting the exposure for specific guidance. Nursing mothers of infected infants are encouraged to remain breastfeeding, needing to wear a surgical mask, sanitize their hands and nipples after breastfeeding. Symptomatic infected nursing mothers need to pause lactation until symptoms are resolved, as they can transmit EV through milk.
- → Care in the care of patients in health settings the dispersion of respiratory secretions, vomiting and fecal contamination of surfaces are capable of causing outbreaks in health services. The Hospital Infection Control Service should emphasize the routine cleaning and disinfection measures already determined in the institution, as well as strengthen the standard precautionary methods and/or appropriate contact for patient care.

Standard considerations: to increase adherence to the components of this precaution, with specific attention to hand hygiene, use of personal protection instruments during the management of secretions and care of infected materials and utensils.

The transport of the patient should be restricted to the minimum possible and, when performed, the hygiene of the regions that had contact with the patient's secretions should be strengthened.

Contact precautions need to be maintained throughout the event in the following episodes:

- Children in diapers;
- Children with incontinent diarrhea;
- Occurrence of outbreak in health units. Although there is evidence of viral excretion in respiratory tissues, there is no formal warning for the adoption of droplet precautions for enteroviruses in health units.

Cleaning and disinfection procedures should be performed because in the case of an unenveloped virus, similar to polioviruses, the level of disinfection should be intermediate. The indicated solution should be sodium hypochlorite in standard commercial concentration (concentrated bleach at 5-6%), in its dilutions of 1:10 to 1:100, ensuring the contact time of the sanitizer. Soon after cleaning and disinfection, objects and surfaces should be rinsed in running water and if possible, employ ethyl alcohol in the concentration 60-80%. (CALEGARI, 2017)

Epidemiological surveillance is the part of the SUS that identifies and controls disease epidemics in Brazil. Professionals in this area supervise the emergence and spread of communicable and non-communicable diseases and their risk factors, in addition to carrying out environmental health surveillance. Prevention actions against the Aedes aegypti mosquito are an example of epidemiological surveillance actions. (CALEGARI, 2017)

In Brazil, including the State of São Paulo, isolated cases of hand-foot-mouth disease are not compulsorily notifiable, but outbreaks of the disease must be reported by SINAM (National System of Medical Care). Thus, it is possible to be aware of the magnitude of the disease and to establish the appropriate prevention and control measures. (MORTARI et al,2022)

5 HAND, FOOT AND MOUTH SYNDROME

Hand-foot-mouth disease was first described in 1958 by Robinson et. al, where symptoms included the presence of fever, ulcerative lesions of the face and mouth, macula and after, blisters and ulcers, where Group A Coxsackie virus was found in 71% of patients. And in 1960 Birmingham, Alsop, suggested the name "hand-foot-and-mouth-disease". (NAKAO et al., 2020)

Certain studies have observed that the etiologic agents of BMDM have undergone some changes over time with circulation of several serotypes in several locations. Climate change has a major influence on the occurrence of BMD outbreaks in some Asian countries. However, government measures and surveillance actions are extremely important and necessary in Brazil, to collect more information about the syndrome in relation to outbreaks and evolution of its complications. (CALILI et al., 2021)

Enteroviruses are prevalent worldwide and have relevant potential for emerging diseases due to their adaptive and evolutionary genetic variability. BMD has a versatile geographic distribution; it is endemic to Southeast Asian and Western Pacific countries. It has a temporal variation, with seasonality related to summer and the rainy season and its infectivity can be compared to that of diseases such as diphtheria, mumps, polio. (MORTARI et. Al, 2018)

Lugo et al., (2016) characterizes Hand, Foot and Mouth Disease in 3 phases:

1. Prodome: from two to four days before the appearance of the rash it is possible to notice the appearance of fever, adynamia (intense muscle weakness), prostration, diarrhea, odynophagia (pain in swallowing food) and vomiting.
2. Acute Phase: the appearance of erythematous macules on the hands and feet with small, non-pruritic vesicles of 2 to 5 millimeters is observed. Very painful aphtoid lesions still appear on the oral mucosa. The vesicles tend to persist for 7 to 10 days, cause difficulty in feeding and fluid intake, leading to dehydration.
3. Convalescent phase: the infected individual shows signs of prostration. Not infrequently, another symptom that can happen up to two months after the onset of the disease, is onychomadesis, painless displacement of the nail from its matrix. (CLEMENTZ & MANCINI, 2000; BERNIER et al., 2001).

According to the severity of the disease, the World Health Organization categorizes Hand, Foot and Mouth Disease into: Hand, Foot and Mouth Disease without major complications. Self-limiting disease; Hand, Foot and Mouth Disease with Involuntary Central Nervous System involvement; DMPB that presents dysregulation of the Autonomic Nervous System and DMPB with cardiopulmonary failure. (WHO, 2011)

The most common clinical manifestations are fevers associated with a papulovesicular eruption on the palms and plants (Figure 2), usually more oval in the shape of a "grain of rice" and ulcerated lesions in the oral cavity (Figure 3) that may not be present in all cases. One of the main concerns in the vast majority of cases is dehydration, however in recent years, it has been observed in epidemics in Asia that this disease can be fatal, mainly related to enteroviruses, and may cover the central nervous system and even the autonomic, causing changes in circulation, heart and even pulmonary edema. In addition, clinical pictures with disseminated lesions that cause pain and are quite debilitating have been described, and it is common in these cases to require hospitalization and management of the hospitalized condition. (JANDREI et al., 2020)



Figure 2



Figure 3

Source: Estrada e Lazcano

Around the 13th day the symptoms subside. From the appearance of the first signs to the healing of the lesions on the skin are, at most, 17 days. In rare circumstances, this can develop into viral meningitis, milder than bacterial meningitis. However, the disease is limited. Between the second and sixth day after infection occurs the incubation period in which the symptoms are similar to a flu. (MENDONCA, 2018)

The diagnosis is made only clinically. The characteristic history, complete physical examination of the patient with fever, sore throat, skin lesions in typical regions and asthenia will provide sufficient information to make the diagnosis. In this case, laboratory confirmation is not required. If the presentation is atypical or behaves like another disease, it may be advantageous to test for diagnostic confirmation. Tests for rapid diagnosis are available, if necessary, by PCR or indirect immunofluorescence. As a differential diagnosis of classic viral exanthems we have that of measles, rubella, and scarlet fever that are well known. Other types of viral rashes that can also occur in the pediatric population are erythema infectiosum caused by Human Parvovirus B19, sudden rash caused by human herpes viruses HHV-6 and HHV-7, and exanthema by Epstein-Barr virus (EBV), of the family herpesviridae. (CHEN, [n.d.])

The management of hand-foot-mouth disease is carried out through supportive measures and measures for infection control. There is still no specific therapy for the disease, analgesics, such as paracetamol, and anti-inflammatory drugs, such as ibuprofen, are used to relieve pain and discomfort caused by fever and oral lesions have a good therapeutic response. The use of oral topical medications containing lidocaine and other anesthetic agents is not advisable due to the lack of evidence of benefit, the risk of systemic toxicity and allergic reaction, and the difficulty of application in young children. It should be noted that children with the inability to maintain adequate hydration through fluid intake should be hospitalized. (BRAZIL, 2018).

6 CONCLUSIONS

Given this, it is extremely important to identify and recognize early symptoms of the disease hand, foot and mouth, in order to avoid the proliferation of it, in the same way that it is necessary to implement preventive measures, among other various care aimed at the school area, children's hygiene, adequate cleaning protocols for the efficient control of this disease and subsequent that may arise from the lack of hygiene of children.

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Bibliometric study of chemical compounds based on medicinal plants anti-Alzheimer

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ABSTRACT
Alzheimer's disease is a chronic neurodegenerative condition that affects mainly memory and other cognitive functions. Interest in finding treatments effective for this disease has increased in recent years, leading to the investigation of the use of medicinal plants and isolated compounds as possible therapeutic treatments. This study aims to identify research on plants and isolated compounds that demonstrate efficacy in the treatment of markers of Alzheimer's pathology over the years. To achieve this goal, we performed a literature review using methods quantitative, which allows us to identify trends, authors, journals and research areas most relevant to the topic. We collect data and submit them to quantitative analyzes to get an overview of the state of the art in this particular field. The methodology employed included the use of bibliometric software for surveys quantitative surveys and the Rayyan platform for qualitative surveys. The quantitative analysis covered the leadership of the studies, the power analysis used in the articles and the identification of predominant themes. While in the qualitative analysis, we focused on the experimented plants that cause anti-Alzheimer's effects, with a focus on the isolated chemical compounds responsible by pharmacological action. As a result of the quantitative analysis, we found a growing interest in research on plants and Alzheimer's disease. Since the first publications at the beginning of the 2000s to the present day, there has been a steady increase in the number of studies, reflecting a significant progress has been made in understanding the possible benefits of plants in the treatment and in preventing this debilitating disease. Our findings highlight the continuing importance of research in this area, which may provide promising therapeutic alternatives to face the challenges posed by the disease of Alzheimer's. Through this bibliographic research, we hope to contribute to the advancement of scientific knowledge and for the development of more effective therapeutic approaches and accessible for this complex condition.

Keywords: Alzheimer's disease, isolated compound, medicinal plants, technology.

1 INTRODUCTION

Alzheimer's disease (AD) is a neurogenerative pathology discovered in 1906 by the German physician Alois Alzheimer. And as the number of elderly people in the world grows, there is a proportion of new cases of this pathology, due to physiological and immunological factors that

decrease in old age. The main symptom of AD is memory loss, worsening of daily habits, difficulty in understanding, discouragement and mental confusion (Jamshidi-Kia et al., 2018).

For many years human beings have always been in contact with nature and have taken advantage of the environment to obtain tools, supplies and medicines. The ability to use plants as food and to treat diseases was conducted over several failures over time, and progressively man was able to use the flora for his activities. The use of medicinal plants is passed from generation and gradually the understanding of the effectiveness has been increased the reliability of the use of species around the world, due to the potential in the development of drugs favoring public health for the treatment of current and future neurological diseases (Breijyeh & Karaman, 2020).

Medicinal plants are a world wealth of importance in food and in the production of new medicines, only in Europe there are about 1300 species of wild plants for use in medicine and in the United Studies around 118 to 150 of the main existing and prescribed drugs are of natural bases and 80% of developing countries are dependent on herbal drugs. And 25% of developed countries the drugs prescribed are of wild plant origin, this growing consumption by herbal drugs from plants is expanding rapidly around the world in primary health (S.-L. Chen et al., 2016)

According to the Declaration of Alma Ata (1978), primary health care is care based on methodologies, technologies, practices that are reliable and accepted by society, disposed in the community at a cost that everyone can perpetuate from its use and the phases of its development. The declaration of Alma Ata also manifests the primordiality of the incorporation of medicinal plants and phytotherapy in the public health of countries, justifying that 80% of the world population uses plants or preparations from them in primary health (Akram & Nawaz, 2017)

Plant species are made up of healing properties due to the existence of chemical substances called secondary metabolites contained in parts of the plant that have as their purpose self-defense or sustainability in the environment. These metabolites are chemically classified within groups with biological activities flavonoids, alkaloids, anthraquinones, glycosides, tannins, saponins among others and may be present in several species, whether they are land plants, marine plants, lichens and / or fungi capable of assisting in the cure and / or treatment of neurological diseases including Alzheimer's (Panda & Jhanji, 2020)

One of the most important methods employed in the therapy for Alzheimer's disease is the management of normal levels of the enzyme acetylcholine in the synaptic cleft, but these drugs that provide this action have some side and adverse effects to those who consume, so the search for new more efficient drugs is of paramount importance, currently numerous active constituents of plants are explored and experimented in studies as possible drugs in the therapy of neurodegenerative diseases, Due to the availability, lower cost, low toxicological feats of herbal medicines in relation to synthetic drugs make them a better choice. (This approach called ethnopharmacological uses health system and

pathologies and the inclusion of plants with their traditional knowledge, chemical and pharmacological studies in the discovery of new drugs based on the screening of plant extracts or isolated compounds (Tuzimski; Petruczynik, 2022) Pyou; Jhanji, 2020).

The pathology causes increased oxidative damage, neurofibrillary entanglements, decline of the enzyme acetylcholine among other serious problems in the brain that require medications to assist in the health of the person carrying the disease, although there are synthetic and semisynthetic drugs used for AD plants including here those with action on the CNS, especially those with direct or indirect action on the pathology, acting on the mechanism, or in the prevention of disease have importance in health (Panda & Jhanji, 2020).

The review presents studies of medicinal plants and their isolated compounds in the Scopus database effective for Alzheimer's in two methodological stages: qualitative and quantitative, focusing on the production of studies over the years and on the species studied. This study also aims to highlight the most commonly used families and isolated compounds of Anti-Alzheimer's interest.

2 ETHNOPHARMACOLOGY AND ALZHEIMER'S DISEASE

The origins of ethnopharmacology go back to ancient times, when communities depended exclusively on nature to meet their health needs. Over the centuries, these cultures have accumulated a vast knowledge about the medicinal properties of the plants present in their ecosystems. This knowledge was transmitted orally from generation to generation, constituting a true treasure of traditional wisdom and with the advancement of modern science, there was a tendency to devalue this ancestral knowledge. Fortunately, ethnopharmacology has emerged as a discipline to rescue and elevate this knowledge, recognizing its potential in the development of new treatments and therapies (Pirintsos et al., 2022).

One of the main characteristics of ethnopharmacology is its multidisciplinary approach. This area of study combines elements of ethnobotany, ethnology, anthropology, botany, pharmacology and chemistry, among other disciplines. This holistic approach allows for a deeper understanding of traditional practices of medicinal plant use, incorporating cultural, social and scientific aspects (Reyes-Garcia, 2010).

This approach highlights the importance of biodiversity conservation. By investigating medicinal plants valued by local communities, ethnopharmacologists have succeeded in identifying and preserving key species in their natural habitats. This promotes sustainability and conservation of natural resources, ensuring the continued availability of medicinal plants for future generations (Rodrigues et al., 2022) .

One of the main objectives is the discovery of new therapeutics based on traditional knowledge. Many modern medicines have their origins in compounds found in plants used in

ethnopharmacological practices. Research in this area can lead to the identification of new bioactive compounds, providing knowledge for the development of more effective treatments with fewer side effects (Turpin et al., 2022).

This approach has shown promise in the context of Alzheimer's disease, as many cultures possess ancestral knowledge about using plants to promote cognitive health and improve brain function. Understanding the ethnopharmacological practices related to Alzheimer's disease is critical to identifying plants with potential neuroprotective or cognitive-enhancing properties. Several cultures around the world have used medicinal plants as part of their traditional treatments for impaired memory and brain function problems (Gregory et al., 2021).

Through scientific research, it is possible to investigate the chemical properties of plants and identify bioactive compounds that can act in the brain, protecting nerve cells and accepting the neuroinflammatory processes associated with Alzheimer's disease. In addition, ethnopharmacology values the traditional knowledge and ancestral wisdom of indigenous communities. This information is valuable for the discovery of new therapies and may open avenues for the development of drugs for neurological diseases that are more effective and have fewer side effects (Grodzicki & Dziendzikowska, 2020).

A notable example is the Ginkgo biloba plant, widely used in traditional Chinese medicine and other Asian cultures. Ethnopharmacological and scientific studies have shown that Ginkgo biloba extract has antioxidant and anti-inflammatory properties, which can improve cognitive function and slow the progression of Alzheimer's disease (Tewari et al., 2018a).

Another plant that arouses interest in ethnopharmacology is turmeric (Curcuma longa), known for its anti-inflammatory and antioxidant action. Turmeric's main active compound, curcumin, has been the subject of research for the treatment and prevention of Alzheimer's disease due to its neuroprotective properties and its ability to inhibit the formation of beta-amyloid protein plaques in the brain, a hallmark of the disease (Mishra & Palanivelu, 2008; Sharifi-Rad et al., 2020).

Ethnopharmacology also contributes to the discovery of new therapeutic targets. Through the investigation of ethnopharmacological practices, it is possible to identify plants and substances that operate in different molecular pathways related to Alzheimer's disease, such as the regulation of beta-amyloid metabolism, the fight against oxidative stress and the modulation of brain inflammation (Tewari et al., 2018b).

Although ethnopharmacology has guarantees for Alzheimer's disease research, it is important to note that studies in this area are still ongoing. Scientific validation of these medicinal plants and natural substances as effective treatments requires rigorous investigation and further clinical studies (Akram & Nawaz, 2017)

In short, ethnopharmacology plays a key role in Alzheimer's disease research, exploring the traditional knowledge of different cultures and identifying medicinal plants with therapeutic potential. This multidisciplinary approach offers new perspectives and could lead to the development of innovative and more effective treatments for this neurodegenerative condition that affects millions of people around the world (Tyler & Tyler, 2023).

3 METHODOLOGIES

In order to analyze the production of scientific studies on plants and isolated compounds for Alzheimer's disease, we opted for bibliometric research by analysis of the Software-RStudio through the tool Bibliometrix and Scopus. (Aria & Cuccurullo, 2017).

Bibliometrics is an area that addresses quantitative research, analysis of several studies detailed as year of publication, countries, journals, most cited authors, funders among others, this series of evidence shows the importance of scientific production in various areas such as health, humanities, education, technologies among others. Through statistical data, bibliometrics makes it possible to evaluate and monitor the evolution of the field of study through the classification of citations and cooperation through keywords and themes. As a result, one can know about the area (GUIMARAES; MOREIRA; BEZERRA, 2021).

For the synthesis of the first data, the date of collection on February 14, 2023 of the documents was chosen; choice of key terms by applying the Boolean operators TITLE-ABS-KEY (isolated AND compound AND alzheimer's AND plants); collection of bibliometric data in the Scopus database in which there was no exclusion of language or temporal design, having 530 records, then imported the documents in "BibTeX" format. Then, installed the RStudio Software - Applying the codes ("BIBLIOMETRIX", "LIBRARY (bibliometrix)", "BIBLIOSHINY ()"), in order to access the bibliometrix package and insert the documents in "BibTeX" format. To evaluate the quantitative analysis of research carried out over time, analysis of terminologies among authors and thematic evaluation among authors.

In the second step of data extraction applying the same key terms and filter in the Scopus database, articles from reviews, book chapters, short researches, conferences, books, editorials, letters and observations were excluded. There are 399 documents left for analysis that were inserted in the tool (Rayyan) - AI Powered Tool for Systematic Literature Reviews that enables the qualitative development of studies.

Of 399 documents 212 were included. And for the insertion of these 212 researches was read the abstracts and only the isolated active compounds with positive results in which the terms mentioned by the authors such as "first report", "potent inhibition", "more potent", "more active", "significantly", "strong inhibitor", "potently", "higher activity", "more effective activity", "more promising".

The 187 excluded articles had isolated substances with moderate and weak effect, studies that included seaweed, activity in neuropathological diseases that did not exclusively encompass Alzheimer's disease, inhibition by extract, did not mention the plant, studies of fungi, bacteria, review articles, no anti-Alzheimer's action or anti-Alzheimer's activity.

4 OUTCOME AND DISCUSSION

4.1 PRODUCTIVITY ANALYSIS

The first work produced regarding the keywords inserted in the Scopus database is authored by researchers Jin-Hui Kim, Sang-In Kim and Kyung-Sik Song, published in 2001. Under the title *Prolyl Endopeptidase inhibitors from green tea,* research conducted by methanolic extract of green tea leaves succeeded in isolating three compounds gallate from (-)-epigallocatechin, gallate from (-)-epicatechin and gallate from (+)-gallocatechin. From 2003 to 2006 had a continuous growth, the other years until the realization of this research it is possible to verify several oscillations. Relating to the measures taken worldwide of social isolation that have driven many researchers away from their face-to-face studies due to Covid-19, the year 2020 presented a satisfactory rate of documents with 62 publications compared to 2022 which obtained 69.

The most productive author according to Scopus' metric analysis is Choi, J. S. has 17 announced papers addressing studies of plants, Alzheimer's disease, cholinergic inhibition and neuroprotection. The first research conducted by the author entitled *Cholinesterase and BACE1 inhibitory diterpenoids from Aralia cordata* in the year 2009. The researcher has as first author 6 articles published in the *Archives of Pharmacal Research*; the others divided among other sources as co-author.

In analysis of publication of the documents by funding institution highlighted by Scopus China has (127 articles) and in second place South Korea (86 articles) until the date of this research, countries such as India, Japan, Spain, Saudi Arabia, Egypt, Pakistan, United States and Brazil do not appear as major producers by funding foundation, however by country / territory all other countries mentioned above, are the 10 largest producers of articles published on the plant over the years, where each one presents more than 20 indexed documents. Looking at the time frame from 2011 to 2017, the small difference between the two largest producers: China with 48 articles and South Korea presenting 40 plant research articles.

This number of studies involving plants and Alzheimer's disease may be related to the number of elderly people living in this country. China is the second most populous country in the world second only to India and according to China's seventh national census in 2020, there are 264,018,766 and 190,635,280 elderly people aged 60 and 65, if you buy with census conducted in 2010 the country's elderly population has aged rapidly and the number of incidences, mortality and problems related to

aging gradually increases. The existence and incidence of the increase in Alzheimer's disease presents several problems in public health and in the urban and rural society of China, this recent census points out that there are 15.07 million elderly people with dementia and of this totality 9.83 million are with Alzheimer's. A study also showed that China spent US$ 167.74 billion on treatment for people with Alzheimer's in the year 2015 and points out that by the year 2050 the costs of this pathology may reach 1.8 trillion (R. Ren et al., 2022)

4.2 ANALYSIS OF VOCABULARIES

In the evaluation of the keywords used by all the researchers, inserted in the Bibliometrix tool, it was found 2758 sets of words where the term "Alzheimer's disease" was the most assiduous, with 404 appearances, in second place, word "plant extract", which repeats twice, as shown in Table 1. This denotes the importance of plant studies and a network of occurrence of this term during the passage of time as shown in Figure 3.

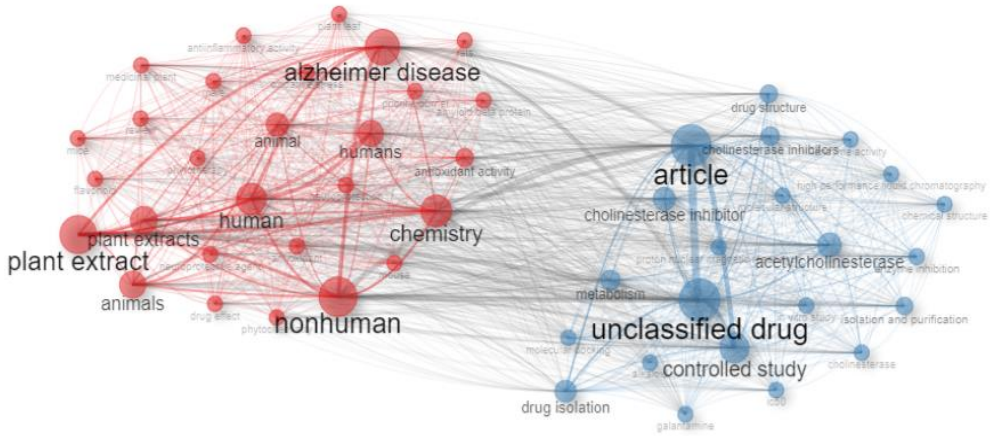
Table 1. Frequency, keywords and consistencies

Words	Occurrences
Alzheimer's disease	404
Plant Extract	325
Unclassified drugs	308
Articles	304
Non-Human	287
Acetilccolinesterase	266
Human	244
Quimíca	224
Control Study	202
Plant extract	194

Source: Adapted Bibliometrix (2023)

Figure 3 represents a set of ideas between authors and co-authors of related studies. The lines show a link between the keywords mentioned by the authors. On the red side, the featured keywords are "Alzheimer's disease," "plant extract," "human," "animal," "chemical," and "non-human," indicating a research collaboration over time among researchers in these areas. On the blue side, there are two featured terms, "articles" and "unclassified drug," which appear to be related to observational research studies and data collection. This figure can represent the interconnection of ideas and collaboration between researchers in different areas of study, as well as the collection of data through observational studies.

Figure 3. Co-occurrence Network

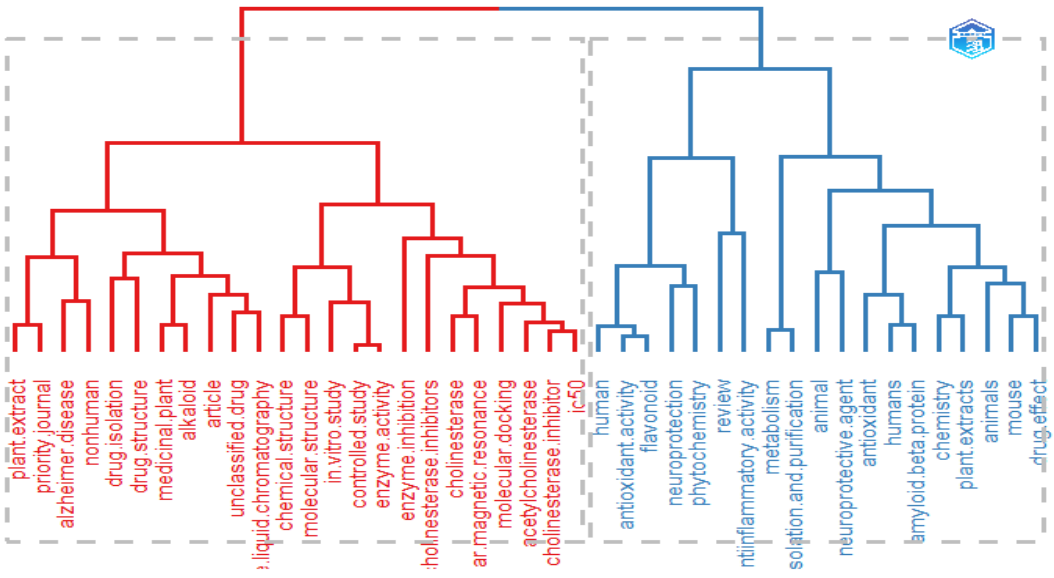


Source: Bibliometrix

4.3 EVALUATION BY THEME

In the analysis of the themes more in accordance with (Figure 4), it is possible to observe that the most recurrent themes in the research of plants and alzheimer are formed by 2 clusters in blue and red color.

Figure 4. Dendrogram



Source: Bibliometrix (2023)

Figure 4 shows two clusters, one in blue and the other in red, which represent the most recurrent themes in plant and Alzheimer's research. Through the analysis of the dendrogram, it is possible to observe the order and connections between these most frequent themes.

In total, 24 central themes with a high degree of development are identified, which are related to phytochemical studies of plants, isolation of chemical compounds and neurological inhibitory biological activities, both in humans and in non-humans.

The themes highlighted in blue are related to 19 central themes and represent studies in humans, isolation of compounds, antioxidant potential and control studies. In the dendrogram, it is possible to observe that the use of plants is related to all areas, from the tolerance and isolation of active substances to the performance of tests to verify the effects of drugs.

This analysis suggests a strong connection between plant phytochemical studies and Alzheimer's disease research, with a wide range of related topics and a comprehensive approach from administration to evaluation of the therapeutic effects of isolated compounds.

4.4 MEDICINAL PLANTS INHIBITING THE ENZYMES ACETYLCHOLINESTASIS (ACHE) AND BUTYRYLCHOLINESTERASE (BUCHE)

One of the most widely used methods for detecting enzymatic inhibitory activity is the Ellman technique. This test is performed by means of photometry that has the ability to cause action of the enzyme through tissue extracts, homogenized fractions, isolated compounds among others. In this test the enzymatic activity is observed by the growth of the yellow color that is formed due to thiocholine, this occurs at the moment that thiocholine comes into contact with the reagent of 5,5'-dithiobis-(2-nitrobenzoic acid) or DTNB) the production of anions of yellowish color. This same enzymatic method written by Ellman et al, is also used with alteration by. That includes the thin-layer chromatography (CCD) technique. The studies by Thin Layer Chromatography are performed to trace plant extracts prepared in an amount of 10mg/mL added in a certain chromatographic plate in a thin layer of silica gel (Ellman et al., 1961) (Rhee et al., 2003) (Castro and Silva et al., 2020)

In addition to this enzymatic study several researchers use in *vivo method by the* tissue of the frontal cortex, in the cerebellum even in the area of memory, this method has the objective of observing improvements in memorization, inhibitory protection induced by oxidative stress among others (Farias et al., 2022)

Existing treatments for Alzheimer's disease use drugs to increase acetylcholine (ACh) levels, causing inhibition of acetylcholinesterase and butyrylcholinesterase that are in charge of hydrolyzing ACh into acetate and choline, act only in the progressive relief of Alzheimer's (Masondo et al., 2019)

In the brains of people diagnosed with Alzheimer's, the enzyme acetylcholinesterase is found in large proportion more than butyrylcholinesterase, this increase causes the rapid hydrolysis of acetylcholine prevented the action of the neurotransmitter (Marucci et al., 2021)

The importance of compounds presents in plants called secondary metabolites in addition to helping in the survival and protection of plants, has become fundamental for humans in the

development of medicines. And these chemicals extracted from plants that have an affinity to act on the central nervous system (CNS) are of interest for the development of new pharmaceutical drugs as shown in (table 2) studies that obtained inhibitory activity of enzymes for Alzheimer's disease carried out over the years.

Tables 2. Medicinal plants with anticholinesterase and anti-butyrylcholinesteratic activity

Plants and Families	Anti-Alzheimer's Compounds	Author
Piper nigrum L. (Piperaceae)	Piperine (derivative)	(Jaipea et al., 2023)
Cassia timoriensis DC. (Fabaceae) Cassia grandis Lf (Fabaceae)	luteolin, cinnamic acid, 4-hydroxycinnamic acid	(Alhawarri et al., 2023)
Grewia tiliaefolia Vahl (Malvaceae)	propyl 3-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta [a]phenanthreno-17-carboxylato	(Rajput et al., 2023)
Fragaria ananassa Duchesne (Rosaceae)	4,22-cholestadien-3-one, stigmast-4-en-3-one	(Mahnashi & Alshehri, 2022)
Andrographis paniculata (Burm.f.) Wall. (Acanthaceae)	desoxy-Andrographolide (Derivative)	(Jatav et al., 2022)
Fritillaria taipaiensis P.Y.Li *(Liliaceae)*	taipainin (Derivative)	(A.-W. Wang et al., 2022)
Talguenea quinquenervia (Gillies & Hook.) I.M. Johnst., (Rhamnaceae)	Zizibberenalic acid, zizibberanalic acid, ceanotic acid, ceanotenic acid, ceanotannolic acid, 3-oxo-oceanic acid, 3-O-acetyl-oceanic acid	(Muñoz-Nuñez et al., 2022)
Notholirion thomsonianum (Royle) Stapf *(Liliaceae)*	2-(3,4-dimethoxifenyl) -3,7-dihidroxi-4H-cromen-4-one	(Mahnashi, Alshahrani, et al., 2022)
Plantago subulata L. (Plantaginaceae)	acteoside, isoacteoside, echinacoside, and arenarioside	(Özaslan et al., 2022)
Polygonum aviculare L. *(Polygonaceae)*	hydroxy succinimide	(Mahnashi, Alyami, et al., 2022)
Pongamia pinnata (L.) Pierre (Fabaceae)	pongapine, ovalichromene B, gamatin and pongaglabrone	(Nguyen et al., 2022)
Vincetoxicum funebre Boiss. & KotschyName (Apocynaceae)	daucosterol	(Abbas-Mohammadi et al., 2022a)
Conocarpus lancifolius Engl (Combretaceae)	lancifolamide	(Saadullah et al., 2022)
Berberis parkeriana CKSenvy. (Berberidaceae)	3-O-(p-Bromobenzoyl)jatrorrhizine	(R. Ali et al., 2022)
Caragana balchaschensis (Kasn. ex Kom.) Pojark. (Fabaceae)	quercetin (derivatives)	(Zhumanova et al., 2021)
Castanopsis cuspidata var. sieboldii (Makino) Nakai (Fabaceae)	4'-O-(α-L-rhamnopyranosyl) -3,3',4-tri-O-methylillagic acid and 3,3',4-tri-O-methylillagic acid	(Oh et al., 2021)

Spiranthes sinensis (Pers.) Ames (Orchidaceae)	quercetin, kaempferol, 3-(4-tolyloxy)-propanolic acid, ethyl ferulate	(Zou et al., 2021)
Mitragyna speciosa Korth. (Rubiaceae)	mitragynine	(Innok et al., 2021)
Vanda roxburghii R.Br. (Orchidaceae)	Gigantol, syringaldehyde	(Ahammed et al., 2021)
Grewia optiva J.R. Drumm. ex Burret (Malvaceae)	2,2'-(1,4-phenylene) bis (3-methylbutanoic acid)	(Ul Bari et al., 2021)
Lawsonia inermis var. spinosa (L.) Pers. (Lythraceae)	3-O-β-acetyloleanolic acid, oleanolic acid	(Balaei-Kahnamoei et al., 2021)
Astragalus membranaceus fish. ex Bunge (Fabaceae)	calycosin-7-O-β-d-glucoside, pratensein-7-O-β-d-glucoside, formononetin-7-O-β-d-glucoside, calycosin, genistein and formononetin	(S. Li et al., 2021)
Cremastra appendiculata (D. Don) Makino (Orchidaceae)	cremaphenanthrene	(L. Liu et al., 2021)
Amaryllis belladonna E. Mey. ex Steud. (Amaryllidaceae)	Acetylcarnosine	(Sibanyoni et al., 2020)
Rauvolfia vomitoria Wennberg (Apocynaceae)	vobasenal	(Zhan et al., 2020)
Acacia auriculiformis A. CUNN Ex. Benth *(Fabaceae)*	α-spinasterol	(Lawal et al., 2020)
Carissa carandas L. (Apocynaceae)	1-Heneicosanol; N-nonadecanol-1; cholesta-4,6-dien-3-ol, (3beta); di-n-octyl phthalate; 7,9-di-tert-butyl-1-oxaspiro (4,5) deca-6,9-diene-2,8-dione; 6-undecyl-5,6-di-hydro-2H-pyran-2-one e phenol, 2,4-di-t-butyl-6-nitro	(Kareti & Pharm, 2020)
Narcissus tazetta var. orientalis (L.) hört. (Amaryllidaceae)	11-Hydroxygalanthin and narcissidin	(Karakoyun et al., 2020)
Piper longum L. (Piperaceae)	piperine	(Khatami et al., 2020)
Hedyotis spread Spreng. (Rubiaceae)	6-O-E-pcoumaroyl scandoside methyl esterr, quercetin-3-O-[2″-O-(6‴-O-O-E-feruloyl) -β-d-glucopyranosyl] -β-d-glucopyranoside, E-6-O-feruloyl scandoside methyl ester, 6-O-methyldeacetylasperulosidic acid methyl ester, asperulosidic acid, deacetylasperulosidic acid methyl ester, scandoside methyl ester, 6-O-methylscandoside methyl ester.	(J. H. Park & Whang, 2020)
Hippeastrum reticulatum Herb (Amaryllidaceae)	N-chloromethylnarcissidinium, narciprimine, N-methyltyramine, 3β,11α-dihydroxy-1,2-dehydrocrinane	(Hoang et al., 2020)
Tinospora cordifolia (Willd.) Miers ex Hook.f. & Thomson (Menispermaceae)	Oxoglaucine, liriodenine, N-formylanonein	(Onoja et al., 2020)
Erythrina caffra White (Fabaceae)	Erythralin, erythrinin, cristanin A	(Nassief et al., 2020)
Zanthoxylum rigidum Humb. & Bonpl. ex Willd. (Rutaceae)	avicin	(Gonzalez et al., 2020)
Leucophyllum ambiguum Bonpl. (Scrophulariaceae)	furofuranone (derivatives)	(Rios et al., 2020)

Anarrhinum pubescens Loudon (Plantaginaceae)	iridoids (derivatives)	(Mahran et al., 2020)
Narcissus pseudonarcissus subsp. bicolor (L.) Baker (Amaryllidaceae)	carltonin	(Al Mamun et al., 2020)
Geophila repens (L.) I.M. Johnst (Rubiaceae)	pentylcurcumene	(Dash et al., 2019)
Andrographis paniculata (Burm.f.) Wall. (Acanthaceae)	3,4-di-di-o-caffeoylquinic acid, apigenin and 7-o-methylwogonin	(Benche et al., 2019)
Anthocleista vogelii Planch. (Gentianaceae)	swertisine	(Ajayi et al., 2019)
Dioscorea communis (L.) Caddick & Wilkin (Dioscoreaceae)	2,4,8-Trimethoxy-3,7-phenanthenediol	(Boudjada et al., 2019)
Zanthoxylum bungeanum Maxim. (Rutaceae)	3,4-Dihydroxyphenylethanol	(C.-H. Li et al., 2019)
Solenostemma argel (Delile) Hayne (Apocynaceae)	kaempferol	(Demmak et al., 2019)
Atalantia monophylla (L.) DC (Rutaceae)	lupalbigenin	(Posri et al., 2019)
Elsholtzia ciliata (Thunb.) Hyl. (Lamiaceae)	acacetin (derivatives)	(Nugroho et al., 2019)
Berberis vulgaris L. (Berberidaceae)	aromoline	(Hostalkova et al., 2019)
Artocarpus lakoocha Roxb. (Moracea)	2-Arylbenzofurans (derivatives)	(Namdaung et al., 2018)
Artabotrys spinosus Craib (Annonaceae)	O-Methylmoschatoline, artacinatine C	(Sichaem et al., 2018)
Narcissus poeticus L. (Amaryllidaceae)	narcipavine	(Šafratová et al., 2018)
Cassia obtusifolia L. (Fabaceae)	rubrofusarin 6-O-β-D-gentiobioside, nor-rubrofusarin 6-O-β-D-glycoside	(Shrestha et al., 2018)
Tephrosia purpurea (L.) Pers. (Fabaceae)	trans-tefrostacin	(Pitchai et al., 2018)
Delphinium denudatum Wall. (Ranunculaceae)	Norditerpenoid	(H. Ahmad et al., 2018)
Hieronymiella marginata (Pax) Hunz. (Amaryllidaceae)	sanguinine	(Ortiz et al., 2018)
Stachys japonica Miq. (Lamiaceae)	4'-O-methylisoscutellarein 7-O-(6'''-O-acetyl)-β-D-allopyranosyl (1→2)-β-D-glucopyranoside	(Nugroho et al., 2018)
Polygonum limbatum Meisn. (Polygonaceae) Dorstenia barteri Bureau (Moraceae)	(-) pinostrobin, 2',4'-dihydroxy-3',6'-dimethoxychalcone, 6-8-diprenyleriodictyol, isobavachalcone, 4-hydroxylonchocarpine e 6-prenylapigenin	(Dzoyem et al., 2017)
Leonurus japonicus Miq. (Lamiaceae)	caffeic acid, quercetin, p-coumaric acid, kaempferol and hydroxytyrosol.	(Nugroho et al., 2017)

Rosmarinus officinalis (l). (Lamiaceae)	Nepitrin	(Karim et al., 2017)
Cornus officinalis Siebold & Zucc. (Cornaceae)	telimagrandin II, 1,2,3,6-tetra-O-galloyl-β-d-glucose	(Bhakta et al., 2017)
Morinda officinalis F.C. How (Rubiaceae)	anthraquinones, coumarin (derivatives)	(Y. K. Lee et al., 2017)
Pueraria lobata (Fabaceae)	Lupeol	(Koirala et al., 2017)
Kaempferia parviflora Wall. ex Baker (Zingiberaceae)	3,5,7,3′,4′-pentamethoxyflavone	(Seo et al., 2017)
Argemone platyceras Link & Otto (Papaveraceae)	(-)-munitagin	(Grid et al., 2017)
Rhodiola crenulata (Hook.f. & Thomson) H. Ohba (Crassulaceae)	(-)-Epicatechin gallate ((-)-ECG), rhodionin, herbacetin, rhodiosin	(F.-J. Li et al., 2017)
Carthamus tinctorius L.(Asteraceae)	carthatins	(Peng et al., 2017)
Juncus acutus L. (Juncaceae)	Juncunol	(M. J. Rodrigues et al., 2017)
Mutellina purpurea (Poir.) Reduron, Charpin & Pimenov (Apiaceae)	Pteryxin	(Orhan, Senol, et al., 2017)
Fritillaria walujewii Regel (Liliaceae)	tortifolin, Walujewine C, Sinpeinine A, Walujewine E, Walujewine A,	(Y.-M. Liu et al., 2017)
Crataegus oxyacantha Walter (Rosaceae)	β-Sitosterol-3-O-β-D-Glucopyranoside	(M. Ali et al., 2017)
Salsola grandis Freitag, Vural & Adigüzel (Amaranthaceae)	N-acetyltryptophan	(Orhan, Kucukboyaci, et al., 2017)
Valeriana officinalis var. latifolia Briq. (Caprifoliaceae)	volvalerenic acid K	(H.-W. Chen et al., 2016)
Mesua congestiflora (Clusiaceae)	α-mangostin, congestiflorone acetate	(Teh et al., 2016)
Pycnanthus angolensis (Welw.) Campaigned. (Myristicaceae)	pongaflavone, (2R,3R)-3-hydroxy-5-methoxy-2″,2″-dimethylpyrano [7,8:5″,6″]-flavanone	(Elufioye et al., 2016)
Xylia xylocarpa (Roxb.) W. Theob. (Fabaceae	(3b)-hopan-3-ol-28,22-olide , lupeol, betulin, 28-norlup-20(29)-ene-3β-hydroxy-17β-hydroperoxide, betulinic acid, oleanolic acid, 3β-formyloxy-l8α-oleanane-28,19β-lactone, 2,6-dimethoxy-p-benzoquinone	(Lam et al., 2016)
Cryptocarya infectoria Miq. (Lauraceae)	2-Methoxy-atherosperminine	(Wan Othman et al., 2016)
Hoppea fastigiata (Griseb.) C.B. Clarke in Hook.f. (Gentianaceae)	1,5,7-tri-hydroxy-3-methoxyxyanthione, 1,5-di-hydroxy-3,7-dimethoxyxyanthone, 1,3,5-tri-hydroxy-8-methoxyxyanthione	(Moon et al., 2015)
Ampelopsis brevipedunculata	santin, 7-O-α-rhamnoside Luteolin, 7-O-β-glucuronide Apigenin	(Rashed et al., 2015)

(Maxim.) Trautv. (Vitaceae)		
Artemisia maderaspatana L. (Asteraceae)	maderaspatana	(Jyotshna et al., 2015)
Angelica decursiva Franch. & Sav. (Apiaceae)	hydroxybenzoic acid	(Yousof Ali et al., 2015)
Piper bavinum C.DC. (Piperaceae)	Bavinol A	(Dung et al., 2015)
Garcinia hombroniana Pierre (Clusiaceae)	garcihombronan N	(Jamila et al., 2015)
Nelumbo nucifera Gaertn. (Nelumbonaceae)	liensinine	(Jung et al., 2010)
Evodia lepta Merr. (Rutaceae)	kokusaginin, melineurin	(Sichaem et al., 2015)
Achillea biebersteinii Hub. -Mor. (Asteraceae)	Quercetin-7-O-β-D-glucoside, patuletin-7-O-β-D-glucoside	(Sevindik et al., 2015)
Harpagophytum procumbens DC. ex Meisn. (Pedaliaceae)	verbascosides (derivatives)	(Bae et al., 2014)
Myristica fragrans Houtt. (Myristicaceae)	(7S)-8′-(4′-hydroxy-3′-methoxyphenyl)-7-hydroxypropyl]benzene-2,4-diol, (8R,8′S)-7′-(3′,4′-methylenedioxyphenyl)-8,8′-dimethyl-7-(3,4-di-hydroxyphenyl)-butane, malabaricone C	(Cuong et al., 2014)
Ipomoea aquatica var. aquatica (Convolvulaceae)	quercetin, phenolic acid, chlorogenic acid, chlorogenic acid	(Sivaraman et al., 2014)
Maytenus imbricata Mart. ex Reissek (Celastraceae)	3-oxo-11α-hydroxylup-20(29)-ene, 3-oxo-29-hydroxyfriedelane, 3,7-dioxofriedelane	(V. G. Rodrigues et al., 2014)
Acanthopanax henryi Harms (Araliaceae)	5-caffeoylquinic acid	(X. D. Zhang et al., 2014)
Stemona sessilifolia (Friends.) Friends. (Stemonaceae)	stenin B	(Lai et al., 2013)
Amberboa ramosa (Roxb.) Jafri (Asteraceae)	Amberbin	(Ibrahim et al., 2013)
Murraya paniculata Kaneh. (Rutaceae)	eucrestifolin	(Rehman et al., 2013)
Boesenbergia rotunda (L.) Mansf. (Zingiberaceae)	Boesenbergine A	(Abdelwahab, 2013)
Holarrhena antidysenterica Wall. ex A.DC. (Apocynaceae)	conessine, conessimine, conarrimine, conarrimine and conimine	(Z. Yang et al., 2012)
Abuta grandifolia (Mart.) Sandwith (Menispermaceae)	R,S)-2 N-norberbamunin, (S-S)-O4″-methyl, Nb-nor-O6'-demethyl-(+)-curine, (S-S)-O4″-methyl, O6'-demethyl-(+)-curine	(Cometa et al., 2012)
Semecarpus anacardium Blume (Anacardiaceae)	1',2'-dihydroxy-3'-pentadec-8-enylbenzene (A) e 1',2'-dihydroxy-3'-pentadeca-8,11-dienylbenzene (B)	(Adhami et al., 2012)
Corydalis cava (L.) Schweigg. & Körte (Papaveraceae)	(+)-Canadalin, (+)-Canadin, (+/-)-corycavidin, (+)-bulbocapnin	(Chlebek et al., 2011)

Cyrtanthus contractus N.E.Br. (Amaryllidaceae)	narciprimine	(Nair et al., 2011)
Buxus sempervirens L. (Buxaceae)	(+)-buxabenzamidienin	(Orhan et al., 2011)
Morus lhou Koidz. (Moraceae)	5'-geranyl-4'-methoxy-5,7,2'-trihydroxyflavone	(J. Y. Kim et al., 2011)
Hippeastrum papilio (Ravenna) Van Scheepen (Amaryllidaceae)	11β-hydroxygalanthamine	(De Andrade et al., 2011)
Alpiniae officinarum (Zingiberaceae)	Galangin	(Guo et al., 2010)
Esenbeckia leiocarpa Engl. (Rutaceae)	leptomerin	(Cardoso-Lopes et al., 2010)
Ferulago campestris (Better) Grecescu (Apiaceae)	siol anisoate, epielmanticin	(Dall'Acqua et al., 2010)
Cleistocalyx operculatus (Roxb.) Merr. & L.M. Perry (Myrtaceae)	myricetin-3′-methylether 3-O-β-d-galactopyranoside, myricetin-3′,5′-dimethylether 3-O-β-d-galactopyranoside, quercetin, kaempferol and tamarixetin.	(Min et al., 2010)
Eschscholzia californica Cham. (Papaveraceae)	1-(3-hydroxy-4-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetra-hydroisoquinoline, reticulin	(Cahlíková et al., 2010)
Aralia cordata Thunb. (Araliaceae)	17-hydroxy-ent-kaur-15-en-19-oic acid, ent-pimar-15-en-8α,19-diol	(Jung et al., 2009)
Kaempferia parviflora Wall. ex Baker (Zingiberaceae)	5,7-Dimethoxyflavone	(Sawasdee et al., 2009)
Iris pseudopumila Tineo (Iridaceae)	Isoorientin, isovitexin	(Conforti et al., 2009)
Peganum nigellastrum Bunge (Nitrariaceae)	vasicinone, vasicine, harmine, deoxyasicinone, deoxivasicinone, deoxivasicine, harmaline, harmol, harman, nigelastrin I, nigelastrin II	(C.-H. Wang et al., 2009)
Magnolia officinalis Rehder & E.H.Wilson (Magnoliaceae)	4-O-methylhonokiol	(Y. K. Lee et al., 2009)
Ginger rhizomes (Zingiberaceae)	6-Gingerol	(Ghayur et al., 2008)
Salvia sclareoides bread. (Lamiaceae)	(1beta,3beta)-lup-20(29)-ene-1,3,30-triol, nepetidine, nepeticin, lupendiol, (1beta,11alpha)-dihydroxy-lup-20(29)-en-3-one , ursolic acid, sumaresinolic acid, hederagenin	(Rauter et al., 2007)
Hosta plantaginea (Lamb.) Asch. (Asparagaceae)	8-Demethoxy-10-O-methylhostasine	(Y.-H. Wang et al., 2007)
Skimmia laureola (DC.) Siebold & Zucc. ex Walp. (Rutaceae)	quinoline 5-one, ribalinin, methyl isoplatodesmine	(Rahman et al., 2006)
Detarium microcarpum Guill. & Perr. (Fabaceae)	3,4-epoxyclerodan-13E-en-15-oic acid, 5α,8α(2-oxokolavênico acid), 3,4-dihydroxyclerodan-13Z-en-15-oic acid	(Cavin et al., 2006)
Stephania Venous (Blume) Spreng. (Menispermaceae)	stearanine, cyclanoline, N-methyl stepholidine	(Ingkaninan et al., 2006)
Sarcococca saligna Müll.Arg. (Buxaceae)	2-hydroxysalignarin-E (=(2′E,20S)-20-(dimethylamino)-2β-hydroxy-3β-(tigloylamino)pregn-4-ene; 1), 5,6-dihydrosarconidine (=(20S)-20-(dimethylamino)-	(Atta-your-Rahman et al., 2004)

	3β-(methylamino)-5α-pregn-16-ene; 2), salignamine (=(20S)-20-(methylamino)-3β-methoxypregn-5,16-diene; 3), 2-hydroxysalignamine (=(20S)-20-(dimethylamino)-2β-hydroxy-3β-methoxypregn-5,16-diene; 4), salignarin-F (=(2′E, 20S)-20-(dimethylamino)-4β-hydroxy-3β-(tigloylamino)pregn-5-ene; 5), salonin-C (=(2′E, 20S)-20-(dimethylamino)-3β-(tigloylamino)pregnna-4,14-diene; 6) e N-[formyl(methyl)amino]salonin-B (=(20S)-20-[formyl(methyl)amino]-3β-methoxypregna-5,16-diene; 7) were isolated from the MeOH extract of Sarcococca saligna, together with the six known alkaloids dictyoflebin (8), epipacisamine-D (9), saracosine (10), iso-N-formylchonemorphine (11), sarcodinine (12) and alkaloid-C (13).	
Ballota limbata Benth. (Lamiaceae)	diterpenoids (derivatives)	(V. U. Ahmad et al., 2004))
Salvia miltiorrhiza Bunge (Lamiaceae)	diterpenoids (derivatives)	(Y. Ren et al., 2004)
Murraya paniculata Kaneh. (Rutaceae)	murranganone, paniculatin	(Choudhary et al., 2002)
Fatoua villosa Nakai (Moraceae)	zeatin	(Heo et al., 2002)

Source: Author (2023)

Inhibition of the enzyme acetylcholinesterase and butyrylcholinesterase causes increased acetylcholine in the synaptic cleft, this causes AD progression to slow. AChE is responsible for the transmission of nerve impulses in vertebrates and invertebrates and hydrolysis of ACh (Tuzimski & Petruczynik, 2022) . Butyrylcholinesterase has a role in cholinergic hydrolysis (ACh) and hydrolysis of organic compounds such as choline esters, butyrylcholine and succinylcholine, among others, such as the alkaloid cocaine and heroin and acetylsalicylic acid (ASA). In the study it is possible to see in (Table 2) studies d (Stefanello, 2003) the plants that have a double inhibitory action of AChE and BChE can be seen of great therapeutic interest for pharmaceutical industries and researchers, their isolated compounds are able to benefit public health and several people with Alzheimer's disease, totaling 121 documents collected in the Scopus database.

It is possible to observe the percentage of studies in relation to the botanical families and the authors, there are a total of 51 families mentioned in table 2, and using the percentage of studies dividing the number of families individually by the total document it is possible to observe that 1% of the researches are related to the families *Annonaceae, Asparagaceae, Amaranthaceae, Anacardiaceae, Combrateceae, Cornaceae, Crassulaceae, Caprifoliaceae, Convolvulaceae, Celastraceae, Dioscoreaceae, Iradaceae, Juncaceae, Lythraceae, Lauraceae, magnoliaceae, Myrtaceae, Nelumbonaceae, Nitrariaceae, Polygonaceae, Pedaliaceae, Rhamnaceae, Ranunculaceae, Scrophulariaceae, Stemonaceae, Vitaceae* with 1 survey each.

The researches carried out in the families Asteraceae, Apiaceae, Acanthaceae, Araliaceae, Berberidaceae, Buxaceae, Clusiaceae, Gentianaceae, Liliaceae, Malvaceae, Menispermaceae, Myristicaceae, Orchidaceae, Pireraceas, Plantaginaceae, Papaveraceae and Rosaceae, totaled 2%, - 2 to 3 files each. 3% contains the families *Moraceae, rubiaceae with* 3 articles

Apocynaceae, Zingiberaceae comprise 4% with 5 documents, *6%* Lamiaceae *with 7 articles, 7% Rutaceae* with 8 articles*, and with the* highest rate of appearance we have the family *Fabaceae* with *11%* totaling 13 documents presented.

The *Fabaceae was named for the first time 1789 commonly known as leguminosae is a characteristic family with the presence of flowers distributed in different geographical regions, cultivated for economic interest in the world is considered the third largest existing terrestrial family surpassed only by* the families Asteraceae *and* Orchidaceae *According to* (Christenhusz & Byng, 2016) World Flora Online *(2023) the families* Fabaceae It has about 70,898 synonyms and 789 genera.

This family has a specific chemical particularity, for example, the isoflavonoid pterocarpans discovered in *Fabaceae;* and many of the compounds present are toxic and others are strongly found such as kaempferol, quercetin and myricetin (or myricetin). The subclass papilionoideae makes up the largest subfamily of the *Fabaceae*, isoflavonoids being found in a large proportion of them (Machado et al., 2020)

For a long time the use of herbal medicines has always been used pharmacological and plant studies for treatment related to the central nervous system (CNS), has been studied and raised for example Tettevi et al (2022) prepared a review on African plants and foods related to the treatment of Alzheimer's disease listing several plants with benefits for memory, anticholinesterase and neuroprotective inhibition, in which he addressed phenotypes related to Alzheimer's and the family *Fabaceae* among others. The author in the intention of showing applications in the study of plants for Alzheimer's listed the benefits of vegetables and the possible neuroprotectors exposing extracts and compounds isolated from plants with Anti-Alzheimer's activities, boasted the species Cheng, Lin e Lane (2021) *Glycyrrhiza inflata* B. *(Fabaceae)* and its benefits for Alzheimer's in aqueous extract and its isolated compounds.

The study carried out by the authors by the plant Alhawarri et al (2023) *Cássia timoriensis DC, Cássia grandis Lf* both belonging to (*Fabaceae)* isolated three compounds luteolin, cinnamic acid, 4-hydroxycinnamic acid with promising activities for Alzheimer's, *in addition to these plants' other important plants of the Fabaceae family such as* Pongamia pinnata (*L.) Pierre,* Caragana balchaschensis *(*Kasn. ex Kom.) Pojark, *Castanopsis cuspidata var. sieboldii* (Makino) Nakai, *Astragalus membranaceus* Fisch. ex Bunge, *Acacia auriculiformis A.* CUNN Ex. Benth., *Erythrina caffra Blanco, Cassia obtusifolia L., Tephrosia purpurea (L.) Pers., Pueraria Lobata, Xylia Xylocarpa*

(Roxb.) W. Theob., Detarium Microcarpum Guill. & Perr. They obtained admirable results for the treatment of AD.

The pharmacological treatments currently used are substances whose action is to increase the levels of acetylcholine in the brain is these plants that act on the central nervous system in cholinergic action are expressly relevant for medicine. In particular plants produce two types of substances called primary metabolites responsible for plant and secondary development that include essential oils (OE) (terpenes) being entirely of plant origin, these substances make available interests to pharmaceutical, cosmetic and food industries (Akman, et al 2023). These terpenes have the ability to cross biological barriers through interactivity with endogenous molecules (Ali et al., 2017)

EOs are mostly found in flowers, leaves, seeds and are usually isolated by hydrodistillation method where the extract is in direct interaction with water at the time it goes into boiling transports volatile compounds such as oil. (Ali et al., 2017) OE as examples of *ducosterol, alpha-spinasterol* among others presented in table 2- contains inhibition activity of the enzyme acetylcholinesterase ensuring new target molecules for the treatment of Alzheimer's. (Abbas-MOHAMMADI et al., 2022)

The therapy for Alzheimer's as well as the pathology itself has several unknowns as over the years the progression of the pathology causes numerous physiological processes such as lipid peroxidations which is a chain reaction caused by organic substances called fatty acid (hydrocarbons) that cause changes in the cell membrane influencing the permeability, fluidity and activity of the cell that can be coated by antioxidant drugs that make peroxidation impossible (BUTTERFIELD, 2020 ; YIN et al., 2016).

Several researchers demonstrate that the use of plants with antioxidant activity containing substances such as vitamin C, vitamin E, beta-carotene can benefit memory loss, these antioxidant compounds have the ability to neutralize free radicals inhibiting health problems. But free radicals do not only cause harm to the human being their normal production is important for cellular respiration and our survival, only their development can cause diseases to be human (LAUER et al., 2022).

The instability in antioxidant defense and increase of free radicals present in the brain produces *stress* oxidative which is another factor associated with Alzheimer's, as well as the occurrence of senile plaques formed by the abnormal metabolization of the amyloid beta protein, neurofibrillary tangles formed by the excess of Tau proteins that arose due to the action of hyperphosphorylation. All these events cause complications in the brain producing symptoms prevalent in various neurological pathologies (Griñán-Ferré et al., 2021) .

These insertions lead to severe brain atrophy, neurodegeneration and neuroinflammation mediated by innate cells present in the brain mentioned in thes authors: neuroinflammation comes from tissue damage caused by neurotoxic substances, which produces several complex chemical actions and because Alzheimer's is quite hermetic and multifactorial, the

initial state of neuroinflammation is not yet known, it is only known that Machado et al (2020) Astrocytes and microglia found near senile plaques can trigger the process of the participation of immune system compounds.

Considering the pathophysiology of the disease, biochemical research with the intention of discovering treatment, it was possible to contact in the brain variations of the enzyme MAO-A and B in high amounts, indicating that the activity of MAOs may also be the reason for AD progression. MAOs have the ability to activate beta-secretase and gamma-secretase action by amplifying the disordered generation of amyloid plaques. (Behl et al., 2021)

A study carried out by on the plant (Mahnashi et al., 2021) *Notholirion thomsnianum* (Royale) Stapf, isolating the flavone 2-(3,4-dimethoxyphenyl)-3,7-dihydroxy-4H-cromen-4-one, in its tests showed that the flavone exhibited excellent inhibition of the enzymes AChE and BChE, also contacted the inhibition of the inflammation signaling pathways COX-1 and COX-2, which may contribute to neuroinflammation and in the antioxidant test the authors denoted a relevant increase in antioxidant enzymes caused by the isolated. Similar results can be found in several studies as shown in table 3. Plant species with antioxidant, anti-inflammatory and neuroprotective activity.

Table 3. Plants with antioxidant, anti-inflammatory and neuroprotective activity in Alzheimer's disease

Plants and Families	**Anti-Alzheimer's Compounds**	**Author**
Nardostachys jatamansi (D. Don) DC. *(Caprifoliaceae)*	actinidine, glaziovine	(Krishnan et al., 2022)
Rubus chingii Hu. (Rosaceae)	ellagic acid, tiliroside and kaempferol-3-o-rutoside	(Wu et al., 2022)
Prangos uechtritzii Boiss. & Hausskn. (Apiaceae)	(+) -Falcarindiol and imperatorin	(Albayrak et al., 2022)
Atractylodes macrocephala Koidz. (Asteraceae)	Biatractylolide	(Q. Hu et al., 2022)
Agathophora alopecuroides (Delile) Fenzl ex Bunge, Bassia indica (Wight) AJScott (Amaranthaceae)	N-trans-feruloyl-3-methoxytyramine, N-trans-feruloyltyramine, S-(−) -3-(4-hydroxy-3-methoxyphenyl) -N-[2-(4-hydroxyphenyl) -methoxyethyl] acrylamide, N-trans-caffeoyltyramine	(Othman et al., 2022)
Ocimum basilicum var. basilicum album (L.) Benth. (Lamiaceae)	5,7-dihydroxy-3′,4′,5′-trimethoxyflavone and 3-hydroxy-3′,4′,5′-trimethoxyflavone	(Singh et al., 2022)
Nelumbo nucifera Gaertn. (Nelumbonaceae)	Neferine	(Tang et al., 2022)
Bacopa occultans (Hiern) Hutch. & Dalziel (Plantaginaceae)	bacoside-A3	(Q.-K. Bai & Zhao, 2022)
Geophila repens (L.) IM Johnst (Rubiaceae)	genistin, quercetin-3-D-galactoside, 9,12,15-octadecatrienoic-acid methyl-ester, phytol, retinal,	(Dash et al., 2019)

	stigmasterol, n-hexadecanoic acid, β-sitosterol	
Acorus calamus L. (Acoraceae)	α-asarone	(Venkatesan, 2022)
Rhinacanthus nasutus (L.) Kurz (Acanthaceae)	Rhinacanthin-C	(Rakkhittawattana et al., 2022)
Munronia henryi Harms (Meliaceae)	Munronin V	(Yan et al., 2022)
Myrsine seguinii H.Lév. (Primulaceae)	(2R,3S)-4''-O-galloylisoastilbin, (2R,3R)-4''-O-(4''-Hydroxybenzoyl)astilbin, (2R,3R)-3''-O-E-Feruloylastilbin	(H.-J. Lee et al., 2021)
Xysmalobium undulaum (Apocynaceae)	acetylated glycosydated crotoxogenin, xysmalogenin-3, β-d-glucopyranoside	(Thakur et al., 2021)
Eucommia ulmoides Olive. (Eucommiaceae)	ulmoidol	(Han et al., 2021)
Litchi chinensis Sonn. (Sapindaceae)	Jasmonates, terpenes (derivatives)	(X. Zhang et al., 2021)
Silybum marianum (L.) Gaertn. (Asteraceae)	silibinin A	(Esselun et al., 2021)
Erythrina corallodendron var. orientalis L. (Fabaceae)	10,11-Dioxo-6,7a-erythraline epoxide	(Aboelmagd et al., 2021)
Murraya koenigii (L.) Spreng. (Rutaceae)	9-Benzyl-9H-carbazol-4-ol	(Yano, Nakashima, Kasa, et al., 2020)
Nelumbo nucifera Gaertn. (Nelumbonaceae)	Asimilobine, N-methylasimilobine	(Yano, Nakashima, Oda, et al., 2020)
Quercus serrata Thunb. (Fabaceae)	triterpenóides (derivatives)	(May et al., 2020)
Elaeagnus glabra f. oxyphylla (Elaeagnaceae)	procyanidin B3, procyanidin B4 and helichrysoside (13)	(Y. J. Kim et al., 2020)
Xanthoceras sorbifolia Bunge (Sapindaceae)	barrigenol (derivatives)	(W. Li et al., 2020)
Corydalis tomentella Franch. (Papaveraceae)	isoquinolines	(Y.-M. Wang et al., 2020)
Ceiba pentandra (L.) Gaertn. (Bombacaceae)	cinchonain	(Abouelela et al., 2020)
Garcinia mangostana (Clusiaceae)	α-mangostin	(Pole et al., 2020)
Zingiber officinale Roscoe(Zingiberaceae)	[6] -gingerol, [8]-gingerol and [6]-shogaol	(Simon et al., 2020)
Xanthoceras sorbifolium bunge (Sapindaceae)	3-*O*-[*β*-D-glucopyranosyl (1→6)] -(2'-angeloyl)-*β*-D-glucopyranosyl-28-*O*-*β*-D-glucopyranosyl(1→6)[*α*-L-rhamnopyranosyl(1→2)-*β*-D-glucopyranosyl]-21-*O*-acetyl-16-deoxybarringtogenol C	(Thing et al., 2020)
Isodon japonicus (Burm.f.) H.Hara (Lamiaceae)	Rosmarinic Acid	(Sun et al., 2019)
Abronia nana S.Watson (Nyctaginaceae)	boeravinone x	(E.-J. Yang et al., 2019)
Lawsonia inermis L.(Lythraceae)	1,2,4-Trihydroxynaphthalene-2-O-β-D-glucopyranoside	(Dhouafli et al., 2019)
Sophora tonkinensis (Fabaceae)	sophotokin	(Xia et al., 2019)
Cirsium maackii Maxim. (Asteraceae)	luteolin	(Wagle et al., 2019)

Schinus polygamus var. chilensis F.A. Barkley (Anacardiaceae)	Agathisflavone	(Dumitru et al., 2019)
Lycoris ×chejuensis Kurita & P.S. Hsu (Amaryllidaceae)	7-deoxy-trans-dihydronarciclasine	(D. Zhao et al., 2019)
Pithecellobium Clypearia (Jack) Benth. (Fabaceae)	(2 R ,3 R)-7,8,3 ′,4′-tetrahidroxidihidro-flavonol	(Y.-X. Wang et al., 2017)
Reynoutria sachalinensis Nakai (Polygonaceae)	1-Decanol, campesterol, ergosterol peroxide, quercetin and isoquercitrin	(Eom et al., 2017)
Pyrola decorate H. Andr (Pyrolaceae)	Betulin, ursolic acid , monotropein	(X. Yang et al., 2017)
Angelica gigas var. minor Momiy. (Apiaceae) Scutellaria baicalensis Georgi (Lamiaceae)	decursin, Wogonin	(H. W. Lee et al., 2017)
Aframomum melegueta var. violaceum (Ridl.) K. Schum. (Zingiberaceae)	Gingerol	(El Halawany et al., 2017)
Monsonia angustifolia E. Mey. (Geraniaceae)	justicidin A	(Chun et al., 2017)
Akebia quinata (Thunb. ex Houtt.) Decne. (Lardizabalaceae)	akequintoside F, collinsonidin, akebonic acid, hederagenin, asperosaponin C	(Chowdhury et al., 2017)
Pteris multifida Poir (Pteridaceae)	2b,15α-dihydroxy-ent-kaur-16-ene, pterokaurane P1	(J. W. Kim et al., 2017)
Fumaria officinalis (Papaveracea)	Parfumidine, sinactine	(Chlebek, Novák, et al., 2016)
Sophora flavescens Aiton (Fabaceae)	maackiain	(H. W. Lee et al., 2016)
Siegesbeckia pubescens (Asteraceae)	5,3′-dihydroxy-3,7,4′-trimethoxyflavone	(D.-S. Lee et al., 2016)
Valeriana amurensis P.A. Smirn. ex Kom. (Caprifoliaceae)	(+)-medioresinol-4,4'-di-O-β-D-glucopyranoside, (+)-syringaresinol-4,4'-di-O-β-D-glucopyranoside, prinsepiol-4-O-β-D-glucopyranoside , (+)-8,8'-dihydroxy-pinoresinol-4,4'-di-O-β-D-glucopyranoside, prinsepiol, and 6 iridoids of jatamanin A, 7-hydroxy-8-(hydroxymethyl)-4-methylenehexahydrocyclopenta[c] pyran-1(3H)-one , 4-hydroxymethyl-cyclopenta[c] pyran-7-carboxaldehyde , patriscabroside III , jatamanin E, patrinoside .	(Wan et al., 2016)
Sophora flavescens Aiton (Fabaceae)	Maackiain	(H. W. Lee et al., 2016)
Uncaria rhynchophylla Miq. (Rubiaceae)	Uncarinic Acid C	(Yoshioka et al., 2016)
Prunus persica (L.) Batsch (Rosaceae)	methyl amygdalinate	(X. Zhao et al., 2016)
Corydalis cava (L.) Schweigg. & Körte (Papaveraceae)	(-) -corycavamine, (+) -corynoline	(Chlebek, De Simone, et al., 2016)
Corydalis cava (Fumariaceae)	(-) -corycavamine, (+) -corynoline	(Chlebek et al., 2011)
Zelkova serrata Makino (Ulmaceae)	7-Hydroxycalamenene	(Yen et al., 2016)

Lycium barbarum Mill. (solanaceae)	dicaffeoylspermidine (derivatives)	(Zhou et al., 2016)
Garcinia mangostana L.(Clusiaceae)	α-Mangostin, Gartanin, Garcinone C, C-Mangostin	(S.-N. Wang et al., 2016)
Serjania erecta Radlk. (Sapindaceae)	vitexin	(Guimarães et al., 2015)
Angelica shikokiana Makino ex Y. Yabe (Apiaceae)	quercetin, hyuganin E, isoepoxyterixin.	(Mira et al., 2015)
Vitis thunbergii var. taiwaniana F.Y. Lu (Vitaceae)	miyabenol C	(J. Hu et al., 2015)
Acer nikoense (Miq.) Maxim. (Sapindaceae)	Acerogenin A	(D.-S. Lee et al., 2015)
Origanum glandulosum Desf. (Lamiaceae)	Rosmarinic acid, globoidnan A	(Bash et al., 2014)
Disporum viridescens (Maxim.) Nakai (Colchicaceae)	(+) -dihydrodehydrodiconiferyl alcohol-9-O-β-d-glucopyranoside, (−) -9′-hydroxypinoresinol	(Cho et al., 2014)
Jatropha multifida L. (Euphorbiaceae)	Apocynin	('T Hart et al., 2014)
Torreya yunnanensis WCCheng & LKFu (Taxaceae)	(±) -Torreyunlignans (derivatives)	(Z.-B. Cheng et al., 2014)
Celastrus orbiculatus Thunb. (Celastraceae)	(M)-bicelaphanol A	(X. J. Wang et al., 2013)
Orobanche minor Sm. (Orobanchaceae)	acteoside (1a)	(Kurisu et al., 2013)
Lycoris radiata (L'Hér.) Herb. (Amaryllidaceae)	1,2-Di-O-acetyllycorine, 1-O-acetyllycorine	(Xin et al., 2013)
Perilla frutescens (L.) Britton (Lamiaceae)	Luteolin	(G. Zhao et al., 2012)
Uncaria rhynchophylla Miq. (Rubiaceae)	hynchophylline, isorhynchophylline	(Xian et al., 2012)
Valeriana amurensis P.A. Smirn. ex Kom. (Caprifoliaceae)	sesquiterpenoids (derivatives) lignans(derivatives)	(Q. Wang et al., 2012)
Ginkgo biloba L. (Ginkgoaceae)	Isorhamnetin	(Xu et al., 2012)
Itoa orientalis Hemsl. (Salicaceae)	Xylocoside G	(Yu et al., 2012)
Erigeron annuus Sessé & Moc. (Asteraceae)	Caffeic acid	(Jeong et al., 2011)
Eleutherococcus senticosus Maxim. (Araliaceae)	eleutheroside B, eleutheroside E, isofraxidin	(Y. Bai et al., 2011; Jeong et al., 2011)
Euclea crispa subsp. Crispa (Ebenaceae) Crinum macowanii Baker (Amaryllidaceae)	3-oxo-oleanolic acid, natalenone, lycorine, hamayne	(Kwon et al., 2011)
Iris tenuifolia Pall. (Iridaceae)	3′-hydroxy-5,7-dimethoxy-4-O-2′-cycloflavan, 3′-hydroxy-5-methoxy-6,7- methylenedioxy-4-O-2′-cycloflavan	(Cui et al., 2011)
Siegesbeckia glabrescens (Asteraceae)	3, 4'-dimethylquercetin, 3, 7-dimethylquercetin, 3-methylquercetin and 3, 7, 4'-trimethylquercetin	(Lim et al., 2011)
Pueraria lobata (Willd.) Ohwi (Fabaceae)	genistein, biochanin A	(Choi et al., 2010)

Rhodiola rosea L. (Crassulaceae)	salidroside	(Na et al., 2010; L. Zhang et al., 2010)
Eragrostis ferruginea P. Beauv. (Poaceae)	Tricin	(Na et al., 2010)
Hypericum perforatum L. (Hypericaceae)	hyperforin	(Denmark et al., 2006)
Uncaria rhynchophylla (Miq.) Jacks. (Rubiaceae)	(+) -catechin, (-) -epicatechin	(Hou et al., 2005)
Flemingia macrophylla (Willd.) Kuntze ex Merr. (Fabaceae)	flemingichromone, osajin, 5,7,4'-trihydroxy-6,8-diprenylisoflavone, 5,7,4'-trihydroxy-6,3'-diprenylisoflavone, aureole	(Shiao et al., 2005)
Turmeric longa L. (Zingiberacea)	calebin-A, curcumin, bisdemethoxycurcumin, 1,7-bis(4-hydroxyphenyl)-1-heptene-3,5-dione	(S.-Y. Park & Kim, 2002)

Table 3 shows the total of 50 botanical families. Applying the percentage, it is found that 1% of the families have anti-Alzheimer's activity, such as Acoraceae, Acanthaceae, Apocynaceae, Araliaceae, Anacardiaceae, Bombacaceae, Brassicaceae, Celastraceae, Colchicaceae, Crassulaceae, Eucammiaceae, Elaeagnaceae, Euphorbiaceae, Ebenaceae, Fumariaceae, Ginkgoaceae, Hypericaceae, Iridaceae, Lythraceae, Lardizabalaceae, Meliaceae, Nyctaginaceae, Orobanchaceae, Polygonaceae, Pyrolaceae, Pteridaceae, Plantaginaceae, Primulaceae, Poaceae, Rutaceae, Solanaceae, Salicaceae, Taxaceae and Ulmaceae, each with 1 document.

The families Clusiaceae, Geramiaceae, Nelumbonaceae and Rosaceae represent 2% of the plants mentioned in table 3, each containing 2 documents.

Apiaceae, Amaryllidaceae, Caprifoliaceae, Papaveraceae and Zingiberaceae exhibit 3% of the studies collected. 4% correspond only to the Rubiaceae family, which presented 4 articles. 6% correspond to the Lamiaceae family. The family Sapindaceae has 5 studies, representing 5% of the studies. 7% correspond to the Asteraceae family, with 6 published articles.

The most studied family, shown in the table, was the Fabaceae, with 11% of the research and 10 documents presented.

The medicinal plants mentioned in Table 3 in turn presented by families, species, isolated compound responsible for the pharmacological activity include antioxidant mechanism in the direct elimination of reactive oxygen species (ROS), in the activation of enzymes that have antioxidant activity, activity of metal chelating agent, reinforcement of the amount of α-tocopherol radicals, blocking of NAPDH, relief of oxidative stress caused by nitric oxide, addition of uric acid levels and increase of substances with antioxidant characteristics and antioxidant molecules of low molecular weight (Kurutas, 2016)

The antioxidant activity may be present in several chemical compounds isolated from plants, called natural antioxidant, used in several groups of secondary metabolites, such as flavonoids (catechins) and tannins (proanthocyanidins), among others. Catechins are formidable antioxidants

thanks to the group of hydroxyls present in their molecules, the elimination of free radicals present in the body can also be generated by molecules that contain double bond in the phenolic ring, hydroxyl side chain molecules, anthocyanidin glycosylation among others, can also be classified as synthetic antioxidant widely used in the food industry (Collins et al., 2022)

The use of plant antioxidants has many contradictions by some researchers plus studies that point out that antioxidant supplementation by external means is one of the most favorable methods in progression in the development of therapies for neurological diseases caused by radicals' books. (Kasote et al., 2015)

5 CONCLUSIONS

Based on the analysis carried out, it can be concluded that there has been a significant development in the number of publications of studies related to plants, isolated compounds and Alzheimer's diseases over the years. Although there have been fluctuations, especially in the period of the COVID-19 pandemic, the number of publications has increased substantially, indicating a growing interest in this field of research.

The most productive author identified was Choi, JS, who contributed 17 papers addressing studies of plants, Alzheimer's disease, cholinergic disease, and neuroprotection. China and South Korea stood out as the main producers of articles on the subject, with a significant number of publications.

The high incidence of Alzheimer's disease in China may be a factor driving interest and research in this area. The rapid aging of the Chinese population and the increase in age-related problems, including appearance, pose challenges to public health and society as a whole. The costs associated with treating Alzheimer's disease are also long-lasting and likely to increase in the future.

The analysis of the advanced and themes revealed the importance of the keywords "Alzheimer's disease" and "plant extract" in the studies carried out. The collaboration between the researcher, evidenced by the network of co-occurrence of the keywords, demonstrates the construction of knowledge over time.

Studies on medicinal plants that inhibit the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) have been highlighted as relevant to the development of drugs in the treatment of Alzheimer's disease. Methods such as Ellman's technique and thin layer chromatography were used to detect enzymatic inhibitory activity and track plant extracts.

In summary, productivity analysis has revealed a growing interest in research on plants, isolated compounds, and Alzheimer's disease. These studies aim to find therapeutic solutions for Alzheimer's disease, which pose a significant public health challenge in several countries, including China. The

development of new medicines based on medicinal plants and the search for compounds that inhibit disease-related enzymes are promising areas of research.

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The discrepancy between patient expectations and realistic outcomes in aesthetic plastic surgery: A comparative analysis

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ABSTRACT

Cosmetic plastic surgery has become increasingly popular in recent years, with individuals seeking various procedures to improve their physical appearance. However, an important issue that arises in this field is the discrepancy between patient expectations and the realistic outcomes of these surgeries. In addition, strategies to improve communication between patients and surgeons and manage patient expectations will be discussed. To begin with, it is essential to understand the fundamentals of cosmetic plastic surgery. This overview will cover the definition of cosmetic plastic surgery, the different types of procedures available, and the common motivations for individuals to undergo such surgeries.

1 INTRODUCTION

Cosmetic plastic surgery has become increasingly popular in recent years, with individuals seeking various procedures to improve their physical appearance. However, an important issue that arises in this field is the discrepancy between patient expectations and the realistic outcomes of these surgeries. In addition, strategies to improve communication between patients and surgeons and manage patient expectations will be discussed. To begin with, it is essential to understand the fundamentals of cosmetic plastic surgery. This overview will cover the definition of cosmetic plastic surgery, the different types of procedures available, and the common motivations for individuals to undergo such surgeries. By establishing this foundation, we can delve into the expectations of patients who choose to undergo cosmetic plastic surgery and how these expectations compare to actual outcomes. Factors that contribute to the discrepancy between patient expectations and realistic outcomes will also be explored. To quantify and compare this discrepancy, several methods can be employed. This research will examine the advantages and disadvantages of different comparison methods and provide insight into how the discrepancy between patient expectations and realistic outcomes can be measured effectively. Understanding the impact of this discrepancy is crucial, as it can significantly affect patient satisfaction and overall outcomes. Therefore, an analysis of the consequences of this discrepancy will be carried out. To mitigate the impact of the discrepancy between patient expectations and realistic outcomes, strategies to improve communication between patients and surgeons will be discussed. This includes exploring effective communication techniques, avoiding misunderstandings, and managing patient expectations. In addition, the responsibilities of surgeons in ensuring that patients have realistic expectations will be highlighted. In conclusion, this research paper aims to clarify the discrepancy between patient expectations and realistic results in aesthetic plastic surgery. By examining the factors that influence this discrepancy, quantifying and comparing the differences, and understanding their impact, this study seeks to contribute to improving patient satisfaction and outcomes in this area. Ultimately, the results of this research will provide valuable information and recommendations for patients and surgeons to ensure a more accurate understanding of the possible outcomes of cosmetic plastic surgery procedures.

2 OBJECTIVE

This research paper aims to explore the comparative analysis of patient expectations and realistic outcomes in cosmetic plastic surgery, examining the factors that influence this discrepancy and its impact on patient satisfaction and outcomes.

3 METHODOLOGY

3.1 DISCUSSION

3.1.1 Overview of aesthetic plastic surgery

3.1.1.1 What is cosmetic plastic surgery?

Aesthetic plastic surgery is a clinical specialty within facial plastic surgery, which has significant overlap with general plastic surgery, maxillofacial surgery, ophthalmology and dermatology [1]. This field of surgery focuses on procedures and operations that involve the anatomy from the neck up, with examples such as rhinoplasty, eyebrow lifts, blepharoplasty, and facelifts [1]. Facial plastic surgeons in the United States focus primarily on cosmetic procedures, while utilizing injectable fillers, neural modulators, lasers, and other devices for skin rejuvenation [1]. Surgeons specialized in facial plastic surgery complete residency training in otorhinolaryngology and a facial plastic surgery fellowship, since facial plastic surgery is a subspecialty of otorhinolaryngological head and neck surgery [1]. Several preoperative screening techniques are discussed, and different types of psychopathology are considered in relation to cosmetic surgery, with the typical candidate for cosmetic surgery considered psychologically stable [2]. The psychological impact of cosmetic surgery and the patient's motivations and expectations for surgery in the context of self-image are discussed [2]. The perception of psychopathology in the plastic surgery population has evolved over time, and screening for psychopathology during the preoperative interview is essential [2]. In addition, the relevance of psychological issues in plastic surgery has been established in the literature, and the article reviews the current literature on the psychology of plastic surgery [2]. Jacques Joseph is considered the founding father of modern facial plastic surgery, while Sir Harold Gillies standardized rhinoplasty, skin grafts and facial reconstruction and is often considered the founding father of plastic surgery [1]. Facial plastic surgery societies have expanded globally and modern facial plastic surgery began more than 100 years ago as a subspecialty of otolaryngology [1]. The endoscopic approach produces less dramatic results and is preferred by younger patients seeking more natural and subtle changes, while the midbrowlift is an option for men, where an incision is made in a deep furrow of the eyebrow and a fusiform ellipse of skin is resected [1]. The classic approach to forehead lifting involves resecting excess skin and repositioning the forehead skin superiorly, while different types of incisions are used based on the patient's hairline [1]. Middle and direct frontal lifts can leave visible scars and are most commonly used for functional eyebrow surgery in patients with eyebrow ptosis, while direct frontal lifting, performed on the upper margin of the eyebrows, is rarely done [1]. Endoscopic surgery is a newer approach to forehead lifts, involving small incisions behind the hairline and the use of an endoscope for visualization [1]. The motivation for surgery can be external or internal [3], and psychological complications may arise

What are the different types of cosmetic plastic surgery available? appearance. Some of the most popular plastic surgery procedures include rhinoplasty, blepharoplasty, breast augmentation, and facelifts [4]. These surgeries can help individuals achieve a more aesthetically pleasing appearance and boost their confidence. In addition, there are many other types of cosmetic plastic surgery available, such as liposuction, tummy tuck, Botox injections, and forehead lifting [4]. To gain a better understanding of the various types of plastic surgery available, researchers conducted a study where they collected data from YouTube videos related to plastic surgery [4]. The videos were classified according to the type of content, authorship, number of views and number of likes [4]. Through the analysis of the 20 most viewed videos, the researchers were able to know the different types of plastic surgeries available and how they are perceived by the public. Ultimately, this research provides valuable information about the various types of plastic surgery available to individuals who wish to improve their physical appearance.

What are the common motivations for undergoing cosmetic plastic surgery? they can be external or internal [5]. External motivations may include the desire to please a romantic partner or the perception that the procedure will save a relationship [5][6]. Internal motivations may include the desire to improve self-esteem, correct perceived flaws, or address body image dissatisfaction [6][5]. Unrealistic expectations of the outcome can also be a motivation to undergo cosmetic plastic surgery [6]. Studies have shown that individuals motivated to please a romantic partner are more likely to have a poor outcome after surgery [5]. In contrast, internally motivated patients are more likely to achieve their goals for surgery [5]. In addition, individuals with a history of depression, anxiety, or personality disorder may also be more likely to undergo cosmetic plastic surgery [6]. Overall, plastic and cosmetic surgeons report high satisfaction rates among their patients [6]. It is assumed that a successful cosmetic procedure will result in improved self-confidence, self-esteem and psychosocial functioning [6]. However, more research is needed to determine if this is indeed the case [6]. In addition, patients may be dissatisfied with plastic surgery even when the result is objectively successful, which may indicate a possible body dysmorphic disorder [6]. Thus, it is important to evaluate the motivations for surgery during the initial consultation [5], as this can help identify patients who may have a poor outcome in terms of psychological adjustment and psychosocial functioning [6].

3.2 PATIENT EXPECTATIONS AND REALISTIC OUTCOMES

3.2.1 What are the expectations of patients undergoing cosmetic plastic surgery?

Patients undergoing cosmetic plastic surgery have some expectations that should be addressed preoperatively, such as improved health-related quality of life, self-confidence and body image. One team developed an expectation scale specifically for cosmetic plastic surgery patients [7] that asks about the changes they expect to see in their appearance and life after the procedure. In addition, a

PRO scale can be used to measure patient expectations [7]. Surgeons must ensure that they accurately inform patients about the risks, benefits, limitations, and expected outcomes of the procedure, as well as the psychological and social problems they can expect to overcome [8]. It is also important to assess the patient's motivation for surgery and their understanding of the procedure [9] to determine if they are able to be satisfied with the results. Many patients feel that the level of information they receive before surgery is inadequate [8], while others are surprised to find that they have achieved a new body shape and size [7]. However, some participants expressed disappointment at seeing their scars for the first time, or had unmet expectations [7]. Surgeons have a responsibility to legally protect themselves from medical malpractice lawsuits by providing accurate and informative information to their patients [8]. They should also ensure that patients have realistic and appropriate expectations about the outcomes of cosmetic plastic surgery, as well as expectations about the recovery process [7].

How do patient expectations compare to realistic outcomes? procedure are often not complied with [10]. This is especially true for minimally invasive surgery (MIS), which has a high expectation rate among patients [11]. There is a clear discrepancy between patient expectations and actual outcomes, and this may play a greater role in patient satisfaction after MIS compared to open surgeries [11]. It is important to understand the patient's expectations before surgery, so that they can be aligned with the realistic results of a given procedure [12]. To this end, the EXPECT intervention was developed, which focuses on developing realistic expectations and providing guidance on how to positively influence the course of the disease after surgery [13]. The patient's expectations of control are enhanced by discussing ways in which they can cope with unpleasant symptoms or sensations [13]. In addition, the importance of meeting previous expectations is fundamental [14], because higher preoperative expectations of the patient are associated with greater satisfaction [15], better quality of life (QoL) and decreased disability [16]. However, some studies suggest that it is the actual improvement in symptom status that governs the outcome, regardless of previous expectations [14]. This is evident by the fact that higher preoperative patient expectations are not associated with greater satisfaction, but are associated with greater improvement in patient-reported outcomes (PROs) [15]. In addition, the impact of patient expectations on outcomes and satisfaction may vary depending on the specific disease process and interventions being studied [16]. It is observed that unrealistically high expectations can have a negative impact on the results reported by the patient in orthopedic surgery [12], because the actual result itself may be the most important indicator of patient satisfaction after surgery [11]. Additional studies are needed to determine the impact of preoperative expectations on patient satisfaction after lumbar fusion surgery MIS of the spine, since the expectation-reality discrepancy and postoperative improvement do not show strong correlations for all outcome measures reported by the patient [11].

3.2.2 What factors influence the discrepancy between patient expectations and realistic outcomes?

The discrepancy between patient expectations and realistic outcomes is an important factor influencing patient satisfaction. A systematic review of the literature was performed to understand the patient's expectations and identify the main factors that determine these expectations [17]. It was found that patients' expectations regarding orthodontic treatments were generally overly optimistic [18]. This discrepancy can be influenced by a number of factors, such as personal experiences, other people's information, and social media [17]. In addition, the degree of improvement of symptoms and function, as well as the presence of other joint problems, can affect patient satisfaction with the result [18]. For example, one study [18] examined the importance of expectations in predicting outcomes after total joint arthroplasty. It was found that the unique variation represented by expectations in predicting outcomes was relatively low and that expectations about pain had a significant predictive value in relation to pain and functional outcomes [18]. However, the study did not investigate whether the discrepancy between patient expectations and realistic outcomes influenced their satisfaction with treatment [18]. It also did not examine how well the reality of the outcome met patients' previous expectations or expectations about overall success and the likelihood of complications [18]. On the other hand, another study [18] found that patients underestimated total recovery time and were overly optimistic about the likelihood of not feeling pain. This discrepancy between patient expectations and realistic outcomes was considered an important factor influencing patient satisfaction. Therefore, it is important for surgeons to combine education programs and discussions with orthopedic surgeons preoperatively to develop realistic and achievable expectations [19]. This will help reduce the discrepancy between patient expectations and actual outcomes and improve patient satisfaction.

3.3 COMPARATIVE DISCREPANCY ANALYSIS

3.3.1 How to quantify the discrepancy between patient expectations and realistic outcomes?

Quantifying the discrepancy between patient expectations and realistic outcomes has been an ongoing task of concern in the orthopedic field. Comprehensive patient data, including information on lifestyle activities, can help accurately assess this discrepancy [20]. Predictive models based on objective data can also be used to measure the gap between patient expectations and realistic outcomes [20]. In addition, informing patients about the outcome of orthopedic procedures can lead to greater alignment of expectations and greater patient satisfaction [20]. This process of informing patients can also contribute to quantifying the mismatch between patient expectations and realistic outcomes [20]. The gap of understanding between patients and surgeons about the limitations of orthopedic procedures is one of the main sources of discrepancies in patient expectations and dissatisfaction [20]. Generally, patients are less satisfied than surgeons with the results of orthopedic procedures [20]. In addition,

patients may not always be aware that some of their expectations cannot be met by current orthopedic procedures [20]. Surgeons wish to fulfill the goals of their patients, but are aware that this cannot always be achieved [20]. Lastly, patients have expectations of long-term symptom-free functioning, particularly in activities that are personally important to them [20].

3.3.2 What methods can be used to compare the discrepancy between patient expectations and realistic outcomes?

One of the most important issues in facial plastic surgery is the comparison between patient expectations and realistic outcomes [21]. A retrospective study suggested that patient expectations about the outcome after a medical intervention may influence the outcome of the intervention [21]. In the study, pre-transplant expectations were described based on patients' memories [21]. There are longitudinal studies on the evolution of quality of life before and after the intervention, however, there is limited prospective longitudinal evidence on patients' expectations regarding future quality of life before the intervention and their actual quality of life after the intervention [21]. The study also showed that liver transplant patients with unmet optimistic expectations after transplantation had lower quality of life scores compared to patients with less optimistic expectations [21]. This discrepancy between patient expectations and realistic outcomes can have important clinical and economic consequences for the healthcare sector [21]. Therefore, the clinical importance of high pre-transplant expectations needs to be examined to understand the discrepancy between patient expectations and realistic outcomes [21]. To obtain more information about this phenomenon, it is necessary the long-term follow-up of renal transplant patients [21]. In addition, if expectations are not met, patients may change their behavior, such as failing to comply with their therapeutic regimen [21]. In addition, there is a discrepancy between the quality of life judgments of health professionals and the quality of life reported by patients [21]. A study was conducted to evaluate this discrepancy in the kidney transplant population, however, no relevant evidence was found [21]. It was also found that nurses tend to overestimate patients' feelings of anxiety, depression and distress [21]. However, aspects of life beyond the physical dimension are more important to patients than physicians anticipate, and physicians tend to underestimate the intensity of patients' pain [21]. In addition, health professionals tend to underestimate the quality of life of patients, although some researchers have found close correspondences between the quality of life judgments of health professionals and the quality of life reported by patients [21]. The agreement between health professionals and patients is higher for the most visible, concrete and objective dimensions of health-related quality of life [21]. Inconsistencies in patients' assessments of expected and actual health status after transplantation may contribute to discrepancies between patient expectations and realistic outcomes [21]. In the study, the inconsistency in the answers was not a reason for exclusion and all the patients' answers were accepted as a valid

reflection of their personal feelings at that moment [21]. Some patients gave inconsistent assessments for expected and actual quality of life after transplantation, classifying a state that was logically better or worse than another inferior or superior, respectively [21]. In three patients, consistency could not be established because there was no logical classification between the two states [21]. 4 transplant patients felt better than expected 14 days after discharge, 2 patients felt better than expected 12 months after transplantation, 7 patients felt worse than expected 12 months after transplantation [21], 16 transplant patients experienced un

3.3.3 What are the advantages and disadvantages of different comparison methods?

The analysis was performed according to the STROBE criteria to evaluate the quality of non-randomized studies [22]. The objective of the analysis was to determine the strengths and weaknesses of different comparison methods based on the results obtained. The study used three broad groups of methods: analytical, empirical quality, and empirical discrepancy [23]. Each group of methods was described in detail and comparative discussions were held to compare them [23]. The study also discussed special methods in addition to the three main groups [23]. The authors aim to provide guidelines for the proper use of existing evaluation methods and improve their performance [23]. An experimental comparison was performed for some empirical methods of quality and discrepancy commonly used to determine their assessment abilities [23]. However, the study presented some limitations, such as the lack of evaluation and three-dimensional analysis [24], which may have resulted in the loss of information during the evaluation. Despite these limitations, the authors still consider the evaluation of accuracy using different printing techniques as a simple and perceptual means [24]. The authors also mentioned the ongoing data analysis of a clinical trial, suggesting that future research may provide more information about the advantages and disadvantages of different comparison methods [24]. Finally, the authors highlighted the need to carefully evaluate potential treatment effect modifiers, even in high-quality non-randomized trials, and the use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework to assess the quality of evidence from non-randomized trials in the context of network meta-analysis [22].

3.4 IMPACT OF THE DISCREPANCY

3.4.1 What is the impact of the discrepancy between patient expectations and realistic outcomes?

The discrepancy between patient expectations and realistic outcomes is an important factor to consider when assessing patient satisfaction. Studies have revealed that preoperative expectations are associated with greater satisfaction and better results after surgery [25]. However, the discrepancy between expectations and actual outcomes can lead to dissatisfaction, as patients may have unrealistic expectations of outcomes [25]. One study found that preoperative expectations, improvements in

disability and pain, and meeting expectations are positively associated with greater satisfaction with surgery [25]. The expectation-reality discrepancy measure (E-AD) can be used to measure the impact of the discrepancy between patient expectations and realistic outcomes [25]. This measure categorizes the fulfillment of expectations in different levels [25], being especially important in the first 6 months after surgery [19]. Other studies have found that actual preoperative functional status is more predictive of satisfaction than outcome expectations [25]. In addition, patients with higher preoperative expectations were more likely to report improvements in disability and pain, and also less likely to have their expectations met [25]. Of course, the discrepancy between patient expectations and realistic outcomes can have a significant impact on patient satisfaction after surgery [19]. To improve patient satisfaction, it is important for surgeons to provide education programs and have discussions with patients preoperatively to develop realistic and achievable expectations [19].

3.4.2 How does the discrepancy affect patient satisfaction and outcomes?

The discrepancy between patient satisfaction and outcomes has been extensively studied in the literature, particularly in the area of low back pain rehabilitation (LBP) [26]. In one study, patients with acute low back pain were given a questionnaire assessing their satisfaction with symptoms, which was compared with symptom reduction [26]. This was different from previous studies that focused on inpatient or chronic pain patient populations [26]. Interestingly, the item that assesses patient satisfaction with symptoms showed no discrepancy between satisfaction assessments and symptom reduction [26]. However, patient satisfaction with symptoms was considerably lower than other patient satisfaction items, such as satisfaction with treatment [26]. This suggests that patients are able to differentiate between satisfaction with the effect of treatment and satisfaction with treatment administration [26]. In addition, it was found that the degree of discomfort caused by the symptoms significantly influences patient satisfaction [26]. In addition, patient satisfaction with symptoms was considered responsive to measures of treatment effect [26]. Despite this, it has been found that the discrepancy between the effect of treatment and treatment administration does not affect patient satisfaction [26]. In addition, the overall improvement in pain and function may explain only part of the variation in patient satisfaction [26]. This highlights the need to further explore the factors that influence patient satisfaction, such as expectations and attitudes [26]. That said, the relevance of patient satisfaction as an outcome assessment has been questioned due to the existence of this discrepancy [26].

3.4.3 How can the impact of the discrepancy be minimized?

The impact of the discrepancy can be reduced in several ways. For example, effective self-regulation can help control biased responses, thereby minimizing the impact of the discrepancy [27].

Individuals with low bias are better able to inhibit prejudiced responses when discrepancies are activated [27]. This is further exacerbated by the compunction and self-reflective thoughts that prejudice-related discrepancies can lead to [27]. This cycle of self-regulation is activated in individuals with low prejudice when confronted with bias-related discrepancies [27]. They tend to pay more attention to information relevant to discrepancies than those with greater bias [27]. In addition, the extent of the discrepancy between the opinions of a communicator and a recipient is an important factor in determining the conformity of the opinion [28]. Thus, minimizing the impact of the discrepancy can help reduce the level of compliance [28]. Involving the recipient more in the process can also lead to a greater change of mind [28]. In addition, longer read times are associated with greater scrutiny of post-event information, resulting in a greater likelihood that discrepancies will be detected and misinformation will be resisted [29]. Subjects who naturally read a post-event narrative more slowly are also more likely to detect a discrepancy between what they were reading and what was stored in their memory, and those who were instructed to read slowly were also more likely to detect a discrepancy than those who were instructed to read quickly [29]. In addition, studies have shown that low-income women who preferred lean-bodied silhouettes had an increased risk of inadequate weight gain, while women with less education who preferred lean-bodied silhouettes were at risk for excessive weight gain [30]. Identifying factors that affect whether certain women are at higher risk of gaining weight outside of guidelines can improve our ability to decrease pregnancy-related health problems [30]. Women who preferred to be thinner had a reduced risk of excessive weight gain if they were overweight or obese, and an increased risk of excessive weight gain if they began pregnancy with a BMI ≤26 kg/m2 [30].

3.5 STRATEGIES TO IMPROVE COMMUNICATION

3.5.1 What strategies can be used to improve communication between patients and surgeons?

Effective communication between physicians and patients is an important factor in achieving successful treatment outcomes. Communication failures are common in the operating room, leading to increased complications [31]. To address this problem, the World Health Organization created the Surgical Safety Checklist, which has been shown to reduce morbidity and mortality [31]. Compliance with the checklist is essential to improve patient safety [31]. The checklist serves as a scaffold to improve attitudes toward teamwork and communication and can help prevent miscommunication and decrease complications [31]. To identify strategies to improve communication between patients and surgeons, the researchers conducted a literature search using specific keywords, including the Cochrane Database of Abstracts of Reviews of Effectiveness (DARE) for relevant information [32]. The research included databases such as Embase, PsycINFO and Medline, covering the last 10 years of research [32]. Original research studies have been used to explore the relationship between key

consultation skills and the performance of specific tasks in doctor-patient communication [32]. The aim of the research was to identify methods that can be used to improve communication between patients and surgeons [32]. Key findings included the fact that patients are more likely to adhere to treatment when there is effective communication with their doctors [32]. Improving communication skills can also benefit the well-being of physicians [32]. Effective communication between physicians and patients can decrease patients' distress and lead to greater patient satisfaction and better understanding of their problems, investigations, and treatment options [32]. In addition, physicians who use effective communication skills can identify their patients' problems more accurately [32].

How to avoid misunderstandings and manage expectations? of communication strategies [33]. Reflective listening is an effective tool for managing expectations and avoiding misunderstandings [34]. It involves summarizing what another person says and checking the understanding [34]. In the veterinary setting, this is especially important when discussing complicated diagnoses and treatment plans [34]. Price transparency is also important for building customer trust [34]. Openly discussing the costs of different treatment plans and offering inclusive packages with fixed prices can help manage expectations and simplify the estimation of rates [34]. In addition, it is important to discuss the family's goals when caring for your pet [34]. Asking questions about concerns, tolerance, ability to return for reappraisal exams, and budgeting for care can help manage expectations and avoid misunderstandings [34]. Using a conversation guide can provide structure for difficult conversations [34]. Checking with owners to ensure they are ready to continue a difficult conversation and allowing them to process the information are sensitive tactics for managing expectations [34]. In addition, being transparent about the cost of basic services, such as the initial exam fee, can help set expectations and alleviate anxiety [34]. In addition, involving owners in the decision-making process and considering the individual characteristics of their pets can help avoid misunderstandings and manage expectations [34]. Ultimately, incorporating basic communication skills into veterinary school curricula and continuing education can help veterinarians learn how to avoid misunderstandings and manage client expectations [34].

3.5.2 How can surgeons ensure that patients have realistic expectations?

Surgeons must take responsibility for ensuring that patients have realistic expectations before surgery [35]. This is particularly important for elderly patients and their surrogates, as communication between surgeons, patients, and surrogates plays a key role in determining the interventions that elderly patients receive for severe illness and acute surgical conditions [36]. Surgeons should be aware of the pitfalls and communication challenges that may arise during discussions about treatment goals with elderly patients and their surrogates [36]. In addition, surgeons should recognize reduced capabilities and options after surgery and prepare patients appropriately to go home within hours of surgery [37].

This can help protect the safety of your patients and avoid unrealistic expectations. In addition, surgeons need to ensure that patients have realistic expectations about the ongoing need for supervised physical therapy and achievable outcomes [35]. To that end, surgeons should focus on ensuring clear and realistic patient expectations before surgery [35]. Inconsistent counseling can lead to premature discontinuation of therapy and suboptimal outcomes [35]. It is also beneficial to involve other health professionals, such as physical therapists, in the follow-up [35]. This can contribute to realistic expectations and play a complementary role in assessing patient outcomes. In conclusion, surgeons must ensure that patient expectations are clearly communicated and realistic before surgery [35].

4 CONCLUSION

The discussion section of this research paper focuses on the discrepancy between patient expectations and realistic outcomes in aesthetic plastic surgery. He highlights the importance of surgeons ensuring that patients have clear and realistic expectations before undergoing surgery. Unrealistic expectations can lead to dissatisfaction and disappointment with the outcome of the procedure. The article emphasizes the need for effective communication between surgeons and patients to manage expectations and avoid misunderstandings. It also suggests that the use of patient-reported outcome scales can help measure and meet patient expectations. The discussion recognizes that the field of aesthetic plastic surgery has evolved over time, with advances in techniques and procedures. However, it also recognizes the psychological impact of plastic surgery and the role of the patient's motivations and expectations in the context of self-image. The paper suggests that more research is needed to better understand the factors that influence patient satisfaction and develop strategies to reduce the discrepancy between patient expectations and actual outcomes. In addition, the discussion highlights the importance of considering the psychological well-being of patients before undergoing cosmetic surgery and the need for preoperative screening for psychopathology. Overall, this research paper underscores the importance of managing patient expectations in cosmetic plastic surgery to ensure the best outcomes and patient satisfaction.

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Global Well-being Scale: Analysis of their psychometric characteristics

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ABSTRACT
Interest in the study of well-being remains relevant. Seligman (2011/2012) presents a theory of well-being based on five elements: positive emotions, engagement, meaning, positive relationships and personal accomplishment. On this basis, a global well-being scale (EBeG) was constructed and validated for the Portuguese population. Through the exploratory and confirmatory factorial analysis, a structural model with a well-adjusted component and 9 items was obtained, with a good level of internal consistency.

Keywords: Global well-being scale, Scale validation, Theory of well-being.

1 INTRODUCTION

The question of well-being, of what is the good living has been a central theme in Western civilization since the Greek philosophers (Barros & Moreira, 2014), having constituted a problematic of scientific research and social and clinical intervention at the end of the twentieth century (Diener, 1984; New, 2005; Ryan Deci, 2001; Ryff, 1989; Ryff & Singer, 2008). Well-being is a complex and multifaceted concept that can be investigated from different levels of analysis, in diverse dimensions.

The study of well-being has come to be defined from two dominant theoretical perspectives, the *hedonic and* the *eudemic*, which intertwine with the Greek conceptions of pleasure and happiness. The *hedonic perspective* (Diener, 1984; Diener & Biswas-Diener, 2004) is based on the principle of accumulation of pleasure and avoidance of pain and suffering. Thus, according to this approach, the goal of life is to experience well-being that consists of the "subjective evaluation of happiness and concerns the experiences of pleasure and suffering, broadly situated in the judgments about the good and bad elements of life" (Fernandes, Vasconcelos-Raposo, Bertelli & Almeida, 2011, p. 157). Subjective well-being is based on this *hedonic conception of* well-being arising from the satisfaction of desires, the pursuit of pleasure, avoiding displeasure. On the other hand, the notion of psychological well-being (Ryff, 1989; Ryff & Singer, 2008) is grounded in the classical thought, developed by Aristotle, regarding *eudaimonia*. This concept, often translated as happiness is, however, richer, so it implies the connotations of self-realization, in the sense of the conquest of a virtuous life (*aretê),* ethical

and wise (*phronêsis*), a life in the sense of human flourishing that allows to grow the full potential of each person. Well-being or happiness, in the Aristotelian line, is an activity of the soul in conformity with excellence or virtue. Thus, a good life is one in which we develop our capacities, realize our potential and become what it is in our nature to become (Haidt, 2006/2006).

The approach of well-being (and happiness) in the scope of positive psychology, namely in the perspective of Seligman (2011/2012), embodies an integrating dimension of the two previous approaches, overcoming those constraints. For Seligman (2011/2012) well-being is "at its core a theory of uncoerced choice, and its five elements comprise what free people choose for their *intrinsic value*" (p. 30). In this sense, well-being is not a real thing, but rather a *construct* that "contains several measurable elements, each of which is a real thing that contributes to well-being, *although none of them defines it*" (Seligman, 2011/2012, p. 29). And each of these elements of well-being has in itself three properties: (i) to contribute to well-being, (ii) to be desired by many people for its intrinsic value, not only to obtain one of the other elements, and (iii) to be defined and measured independently of the other elements, that is, being subject to the principle of exclusivity.

The theory of well-being is thus constituted by five elements: positive emotion, involvement, meaning, positive relationships and personal fulfillment that Seligman (2011/2012) designates ***PERMA,*** an acronym, functioning as a mnemonic, derived from the initials in English of these five elements: ***Positive*** *emotion,* Engagement***, positive*** Relationships*, Meaning* **,** ***Achievements***. Let us characterize each of these elements.

Positive *emotion*, pleasant life, is the first element of the theory of well-being, encompassing the subjective variables of well-being, such as pleasure, ecstasy, comfort, warm affection and the like. It refers to what the individual feels and thinks is their level of satisfaction with life, which leads them to experience positive emotions associated with the present (joy, emotion, pleasure, love), the future (optimism, hope, faith, trust), and the past (satisfaction, pride, serenity, forgiveness).

Involvement *is* the emotional bond that people establish with work, being marked by the experience of flow – a state in which we feel that we control what we do, that we do it effortlessly and in which we are able to give our best. In this type of experience, thought and feeling are absent, implying attraction, absorption, enthusiasm, commitment, and in which a union with the execution of the task is felt. It is a subjective state of which we are only retrospectively aware, that is, only later, when we remember it, do we have the notion of how fun and wonderful it was.

Meaning consists in the understanding of belonging and serving something greater than oneself */ self and* that provides a reason or meaning for life and work; it has two components: a subjective one, which is experienced by the individual in an idiosyncratic way, and another objective, which seeks a dimension of rigor and logical coherence.

Personal *fulfillment* is realized in a successful life. It is based on the realization that people desire success for success, victory, success, and mastery simply for the pleasure of achieving them. This aspect is affirmed in opposition to the theory of impulse reduction, based on the theory of the motivation of competence, according to which the goal of animals and people is to exercise dominion over the environment.

Positive *relationships* refer to the quality of interpersonal relationships. These are characterized by the presence and abundance of closeness, support, protection, affection, empathy and recognition in interaction with other people. In fact, people, others are the high points of life, being the best antidote to when one is in life at the "bottom millstone" and allow us to rise again. The human being is a group being. Biologists D. Wilson and E. Wilson (2007) have gathered evidence that the group is a primal unit of natural selection, being the most successful form of superior adaptation known, as it has allowed the development of the capacity for cooperation. We are beings who, inevitably, seek positive relationships with other peers, even as a way of survival and also of development.

The elements of *PERMA* can be understood as the different ways to increase well-being, that is, the pathways to *flourishing*, and there are people who experience well-being emphasizing some elements more than others. Flourishing presupposes that a person simultaneously experiences high levels of life satisfaction, high engagement with work, high level of positive relationships, high levels of meaning, and outstanding results in personal fulfillment. Thus, flourishing, more than the absence of disease, malaise or any other type of emotional suffering, is defined by the presence of positive signs of life: it is the combination of feeling good and effectively functioning well, and people who flourish are healthier, have longer life expectancy, contribute more in the communities where they live and are actually more productive (Helliwell, Layard & Sacchs, 2013; Lyubomirsky, 2008/2011; Seligman, 2011/2012).

With a view to assessing well-being, both subjective (Lyubomirsky & Lepper, 1999) and psychological (Ryff, 1989) and well-being/PERMA (Butller & Kern, 2015; Gouveia & Caracol, 2016; Huppert & So, 2009; Ibáñez Sepulveda, 2013), several scales have been elaborated. However, there is not, for the context Portuguese, a brief scale that evaluates the five elements of PERMA globally. Therefore, we built and validated for the Portuguese population a scale of well-being/PERMA in order to evaluate the five constitutive elements of well-being/PERMA (Seligman, 2011/2012) as a whole.

The objective of this article is, then, to present the psychometric characteristics of this global well-being scale (EBeG).

2 METHOD

2.1 PARTICIPANTS

Participated in this study 476 subjects from all Portuguese districts, with the exception of the district of Beja and the autonomous region of the Azores, in a non-probabilistic sampling of geometric propagation, *snowball*. Of the respondents, 65 (13.6%) are aged between 18-39 years, 298 (62.3%) are between 40-59 years and 113 (23.8%) are 60 years or older, being of both sexes, although the frequency of female cases is higher (Fem= 72.3%, Masc= 27.7%). Around 85% of the participants have tertiary education. Of the subjects in this sample, 56.5% are married, 24.4% are single, 12.8% are divorced, 2.3% are widowed and 4% are included in other situations.

2.2 INSTRUMENT

The measure used was a Global Well-being Scale (EBeG) and sociodemographic variables. This questionnaire was constructed by the authors of this article taking into account the five elements of the theory of well-being (positive emotion, involvement, meaning, positive relationships and personal fulfillment). This construction was based on the well-being module of the *European Social Survey (ESS)* of Huppert and So (2009) in order to assess flourishing in general and also the well-being/PERMA module, included in the Happiness Barometer, carried out in 2012 in Chile (Ibáñez Sepulveda, 2013).

It is a self-administered questionnaire, consisting of 9 items, distributed over a single dimension. Participants are asked to choose the answer that most accurately describes them. The items are evaluated on a 5-point Likert scale, ranging from 1 = strongly disagree to 5 = strongly agree. All items are positively formulated and the result is obtained by the sum of the answers obtained in each item, which can range between 9 and 45 points Higher values correspond to higher levels of well-being.

2.3 PROCEDURE

Inspired by the items of the scales of Huppert and So (2009) and Ibáñez Sepulveda (2013) we adapted and constructed the items of this scale. The formal process of data collection was carried out with the publication in *Google Drive,* having been assured the informed consent and guaranteed the confidentiality of the data. Data analysis was performed using the *statistical* software SPSS 20.0 *and* Amos 20.0.

3 FINDINGS

In order to validate the Global Well-being scale, an exploratory factor analysis was performed using the technique of principal component analysis with *Varimax* rotation, reliability analysis according to Cronbach's alpha, as well as confirmatory factor analysis.

Table 1 presents the descriptive data of the scores of each of the items of the scale. Item 3 - «I love learning new things» - was the item that presented the highest average (M=4.63, SD=0.69). Items 5 to 8 also presented mean scores higher than 4. Item 2 - "the conditions of my life could not be better" - recorded the lowest average score compared to the other items.

Table 1. Scores (Means and Standard Deviation) of the Global Well-being Scale Items

Item	*Average*	*DP*
1 - I feel satisfied with my life.	3,66	0,94
2 - The conditions of my life could not be better.	2,79	1,07
3 - I love learning new things.	4,63	0,69
4 - I like the work I do and it is one of the most important things in my life.	3,89	0,92
5 - There are people in my life who are important to me and who really care about me.	4,62	0,62
6 - I feel, generally, that what I do in my life is valid and worth doing.	4,22	0,75
7 - I feel that I belong and contribute to something bigger than myself.	4,08	0,82
8 - I face the obstacles and challenges of life, believing I am able to overcome them.	4,07	1,03
9 - I usually achieve my goals.	3,94	0,64

As it was conceived with the intention of a global well-being assessment scale, a single dimension was tested through factor analysis. The *Kaiser-Meyer-Olkin* test (KMO) showed a value of 0.82 ($p<0.001$), thus indicating an adequacy of the sampling to the scale data (Table 2). Next, we analyzed the commonalities presented in Table 2, which ranged from 0.30 to 0.60. The factor explains 40.6% of the variance and all factor loadings described in Table 2 were higher than 50%.

Table 2. Commonalities and Saturation Values in the Items of the Well-being/PERMA Scale

Item	Comunalidades	Saturation values
1 - I feel satisfied with my life.	0,44	0,80
2 - The conditions of my life could not be better.	0,28	0,73
3 - I love learning new things.	0,26	0,69
4 - I like the work I do and it is one of the most important things in my life.	0,48	0,67
5 - There are people in my life who are important to me and who really care about me.	0,28	0,66
6 - I feel, generally, that what I do in my life is valid and worth doing.	0,64	0,56
7 - I feel that I belong and contribute to something bigger than myself.	0,53	0,53
8 - I face the obstacles and challenges of life, believing I am able to overcome them.	0,31	0,52
9 - I usually achieve my goals.	0,44	0,51
SME *P*	0,820 <0,001 *KMO*	

Therefore, the factor analysis in principal components revealed the emergence of a single factor, a result that suggests a great coherence for the concept (Huppert & So, 2009; Ibáñez Sepulveda, 2013).

Next, the reliability of the scale was analyzed using *Cronbach*'s alpha values for each of the items that compose it and for its totality (Table 3). Individually, the alphas obtained were all higher than 0.76 and lower than 0.80. The alpha for the 9 items was 0.801, showing a high internal consistency of the present scale.

Table 3. Reliability of the Global Well-Being Scale

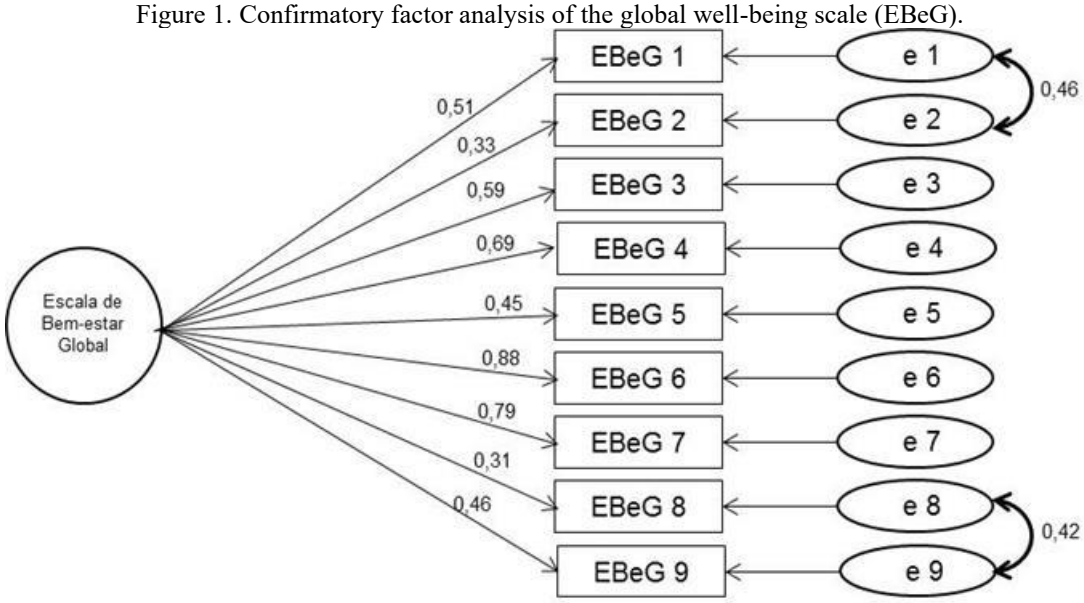
Item	*Alfa de Cronbach*
1 - I feel satisfied with my life.	0,771
2 - The conditions of my life could not be better.	0,796
3 - I love learning new things.	0,794
4 - I like the work I do and it is one of the most important things in my life.	0,773
5 - There are people in my life who are important to me and who really care about me.	0,793
6 - I feel, generally, that what I do in my life is valid and worth doing.	0,761
7 - I feel that I belong and contribute to something bigger than myself.	0,770
8 - I face the obstacles and challenges of life, believing I am able to overcome them.	0,795
9 - I usually achieve my goals.	0,777
Total	0,801

Subsequently, confirmatory factor analysis was performed at the same scale. The analysis of the structure resulting from the exploratory factor analysis revealed adequate indices of adjustment to the tested model: ratio $\chi 2$ to degrees of freedom ($\chi 2$/df)= 1.705, RMSEA index (root mean square error of approximation)= 0.057, CFI (comparative fit index)= 0.971; GFI (goodness-of-fit index)= 0.961, NFI (normed fit index)= 0.936, IFI (incremental fit index)= 0.971, TLI (Tucker- Lewis index)= 0.958,

RFI (relative fit index)= 0.908, PGFI (parsimony goodness-of-fit index)= 0.534, PCFI (parsimony comparative fit index)= 0.674, and the PNFI index (parsimony normed fit index)= 0.650.

Figure 1 systematizes the confirmatory factor analysis of EBeG.

Figure 1. Confirmatory factor analysis of the global well-being scale (EBeG).



4 DISCUSSION

The objectives of the work of this chapter were the construction and validation of the global well-being scale (EBeG). These objectives were developed through different statistical procedures to determine the most appropriate factor structure for the study population. The statistical procedures were initially based on principal component analysis in order to explore the factor structure, followed by internal consistency analysis and confirmatory factor analysis of the final solution. The initial version of the scale included nine items.

By the exploratory analysis in principal components to the factorial structure of the original scale, it was found that the most appropriate solution was maintained through a unifactorial structure. The data showed that the one-factor solution indicated an adequacy of the sampling to the scale data with an explained variance level of 40.2%. The reliability analysis also demonstrated a satisfactory value of consistency for the present scale.

The factor analysis confirmatory to the structure resulting from the exploratory factor analysis revealed adequate indices of adjustment to the model tested, so that the number of initial items was maintained in the final version of the present scale.

The fact that this scale was confirmed and validated was in the expected direction, since the construction of this scale was based on both the well-being/flourishing module of Huppert and So (2009), widely applied in several European countries, and the well-being/PERMA module, included

in the happiness barometer, carried out in 2012 in Chile (Ibáñez Sepulveda, 2013), countries that, although culturally different, maintain many affinities and idiosyncrasies with each other.

In this validation study, no other concurrent scales were applied, and therefore it is not possible to test the concurrent validity, constituting, therefore, a limitation to this validation work.

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Hyperglycemic emergencies: Clinical features and diagnostic criteria. A systematic literature review

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ABSTRACT
Diabetes Mellitus is a chronic condition in which the manifestation occurs when blood glucose levels are elevated due to the inability of the body to produce insulin in adequate quantity or efficiently use the insulin produced. This metabolic dysfunction can be attributed to several mechanisms, varying according to the specific type of diabetes. Methodology: This is a systematic literature review constructed by searching the PUBMED, VHL and CAPES Periodicals Portal, using the terms "Diabetic Ketoacidosis", "Hyperglycemic Hyperosmolar State", "Hypoglycemia", "Diabetic Emergencies" in Portuguese, English, Spanish and German. Results: Of the 229 articles found, only 10 were selected according to the guiding question and the eligibility criteria. Conclusion: The study conducted on hyperglycemic emergencies brought a wide range of fundamental information to understand and manage these conditions. Through the analysis of the selected studies, it was possible to obtain insights into the complications and possible sequelae associated with these emergencies. In short, research on diabetic emergencies establishes a solid knowledge base for health professionals and researchers, contributing to improve the early identification, appropriate treatment and prevention of these complications, aiming to improve the quality of life of individuals living with diabetes.

Keywords: Diabetic ketoacidosis, Hyperosmolar State, Hyperglycemic, Hypoglycemia, Diabetic Emergencies.

1 INTRODUCTION

Diabetes Mellitus (DM) is a condition characterized by the manifestation of several signs and symptoms, which involve the impairment of the metabolism of fats, proteins and carbohydrates. This metabolic dysfunction occurs due to different mechanisms, depending on the specific type of DM. As a result, there is an increase in blood glucose levels and a reduction in the ability of cells to properly utilize glucose. Consequently, there is a significant increase in the use of proteins and fats as alternative energy sources, which leads to weight loss (GUYTON; HALL, 2002 apud LADEIA et al, 2020).

It can be characterized as a chronic condition that manifests itself when blood glucose levels are elevated due to the body's inability to produce insulin in adequate quantity or to effectively utilize the insulin produced. This dysfunction can be classified according to its pathophysiology, that is, the underlying mechanisms involved.

Type 1 Diabetes Mellitus (T1DM) is an autoimmune and polygenic disease that results in the destruction of the β cells of the pancreas, leading to deficiency in insulin production. This condition mainly affects children and adolescents, and about 88,000 Brazilians are diagnosed with T1D, representing about 10% of diabetes cases. Importantly, people with T1D need to make use of insulin throughout their lives to control blood glucose levels (BRAZILIAN DIABETES SOCIETY, 2019-2020).

The development of T1DM is thought to be triggered by the presentation of peptides from the β cells of the pancreas by antigen-presenting cells (APCs). These APCs, carriers of these autoantigens, migrate to the pancreatic lymph nodes, where they interact with self-reactive CD4+ T lymphocytes. This interaction triggers the activation of self-reactive CD8+ T cells. After activation, these CD8+ T cells return to the pancreatic islets and destroy β cells expressing immunogenic autoantigens on the surface of the class I molecules of the major histocompatibility complex. The destruction of β cells is further aggravated by the release of pro-inflammatory cytokines and reactive oxygen species by innate immune cells. These inflammatory processes contribute to a cycle of continuous destruction of β cells and the progression of the disease (DIMEGLIO; EVANS-MOLINA; ORAM, 2018).

Type 2 Diabetes Mellitus (DM2) has a multifactorial etiology, which involves genetic and environmental factors, with inadequate diet, sedentary lifestyle, lifestyle and lack of physical exercise being the main triggering elements. T2DM has a higher incidence in middle-aged people, usually from the age of 40, and corresponds to approximately 90 to 95% of all cases of diabetes. Importantly, in T2DM, there is a combination of insulin resistance (when the body's cells do not respond adequately to the action of insulin) and deficiency in insulin secretion by the pancreas. This condition results in high blood glucose levels. The adoption of a healthy lifestyle, with a balanced diet and regular practice of physical exercises, is essential for the control of DM2 (FERREIRA et al. 2020).

The pathophysiology of type 2 diabetes mellitus (T2DM) is largely driven by the induction of insulin resistance in skeletal muscle, liver and adipose tissues. Insulin resistance in skeletal muscle is particularly relevant, since this tissue is responsible for the efficient removal of glucose after meals. In T2DM, insulin resistance in skeletal muscle significantly limits the ability to clear glucose from the blood. At the cellular level, insulin resistance in skeletal muscle manifests itself through several mechanisms. This includes a deficit in the recruitment of GLUT-4 glucose transporter proteins to the plasma membrane, which is mediated by the action of insulin. In addition, there is a reduced glycogen storage capacity, a decrease in glucose oxidation and impaired mitochondrial function (JAVEED and MATVEYENKO, 2018 apud MAGNUSSON et al. 1992).

These changes impair glucose metabolism, resulting in elevated blood glucose levels in T2D. In addition, the liver also plays an important role in the pathophysiology of T2DM, since insulin resistance in this organ leads to an excessive production of glucose by the liver, further contributing to the hyperglycemia observed in this condition (JAVEED and MATVEYENKO, 2018 apud MAGNUSSON et al. 1992).

Pregnancy can also be a diabetogenic catalyst, causing the emergence of Gestational Diabetes Mellitus through the activity of the placenta, which produces hyperglycemic hormones and placental enzymes that degrade insulin, and triggers an increase in insulin production and resistance, which may evolve with dysfunction of pancreatic β cells. This condition can be temporary, existing only during some periods of pregnancy, most often in the second and third trimesters, or persist even after childbirth being an important risk factor for the development of DM2, requiring immediate intervention of the multidisciplinary health team (SOCIEDADE BRASILEIRA DE DIABETES, 2019-2020).

DM leads to acute and chronic complications, including Diabetic Ketoacidosis (DKA), Hyperosmolar Hyperglycemic Syndrome (HHS), and hyper- and hypoglycemia during treatment. DKA is the most common acute or hyperglycemic emergency complication of T1DM, but it also occurs in T2DM, happens as a result of peripheral resistance, partial or absolute insulin deficiency, and is commonly associated with triggering clinical conditions. (MÉNDEZ et al., 2018).

That said, the following question arises: what are the main characteristics, symptoms, causes and diagnostic criteria related to diabetic emergencies?

2 GENERAL OBJECTIVE

Identify and describe the main clinical features of diabetic emergencies.

2.1 SPECIFIC OBJECTIVES

- Understand the underlying causes of diabetic emergencies;
- Explore the diagnostic criteria used to identify and differentiate diabetic emergencies;

- Recognize the warning signs of diabetic emergencies.

3 METHODOLOGY

This is a systematic literature review. To answer the guiding question, a search was conducted in the following databases: National Library of Medicine (PubMed), Virtual Health Library (VHL), CAPES Periodicals Portal between January 2022 and March 2022, always using the Boolean operator AND for the pairing of the following Health Sciences Descriptors (DeCS): "Diabetic Ketoacidosis", "Hyperglycemic Hyperosmolar State", "Hypoglycemia", "Diabetic Emergencies" for the databases described above.

As inclusion criteria for the studies, we opted for articles available in full and free of charge, in the languages Portuguese, English, Spanish and German, published from 2017 to 2022. The exclusion criteria were: articles that did not address the research theme or that did not answer the guiding question, studies in editorial format and duplicate articles in more than one database **(Table 1).**

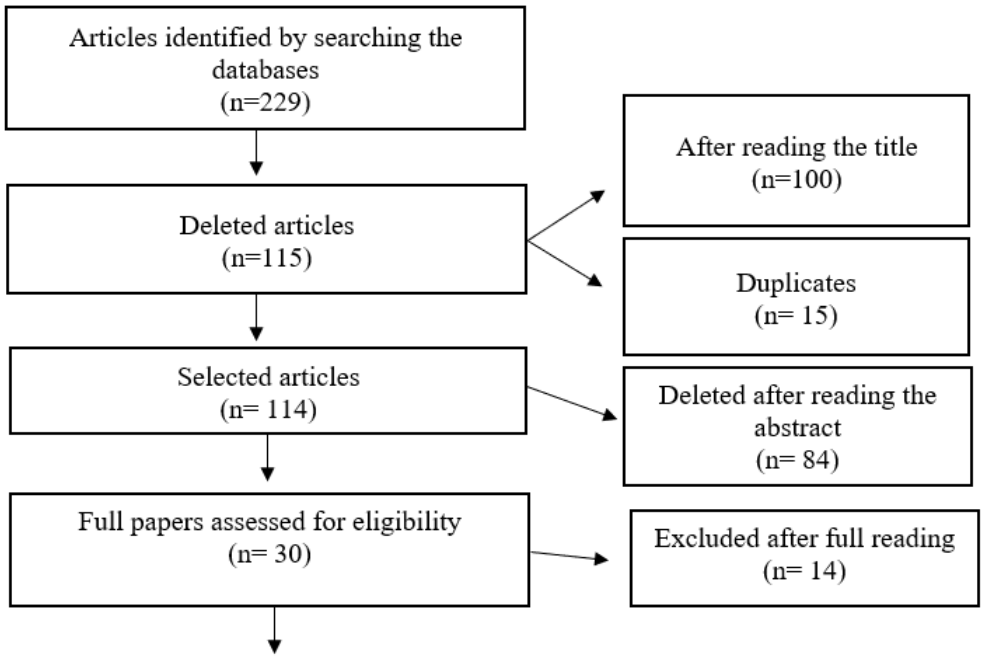
Table 1. Publications found between the years 2017 to 2022 according to the PUBMED, VHL and CAPES databases.

DESCRIPTORS	PUBMED	VHL	CAPES
Diabetic Ketoacidosis AND Hyperglycemic Hyperosmolar State **AND Hyperglycemic Hyperosmolar State AND Hypoglycemia AND Diabetic Emergencies**	08	13	198

After performing the electronic search, the publications were submitted to an initial pre-selection by reading the titles and, subsequently, based on the abstracts. Then, the previously selected articles were read in full, allowing the identification of the studies that composed the final sample of this review. A total of 229 studies were found and 10 articles were selected from the following databases:

Figure 1 shows the flowchart referring to the selection process of the articles that were part of the final sample of this selection.

Figure 1. Flowchart representative of the article selection process.



For data collection, the analysis of the full article occurred descriptively, in order to gather knowledge about the theme addressed in the review, for this a data collection form was filled out according to the previously validated model, which includes the identification of the article and methodological characteristics (SOUZA et al, 2010).

4 FINDINGS

Chart 1 presents the characterization of the 10 included productions, highlighting the predominance of studies published in the period from 2017 to 2022, covering several scenarios in the international context.

Table 1 - Presentation of the characteristics of the articles included in the Integrative Review.

N	Authors (year)	Main findings
1	FORTOFOIU M, et al. (2022)	New diagnostic strategies and therapeutic approach to emergencies in the evolution of patients with diabetes mellitus (Review)
2	SANTOMAURO, et al. (2022)	Euglycemic diabetic ketoacidosis (E-CAD) is an uncommon but potentially life-threatening condition and an emergency that can occur in people with T1D, T2D.
3	MODI, et al. (2017)	Euglycemic DKA represents a challenge for physicians, as patients who have normal BG levels in ketoacidosis may be neglected, leading to a delay in appropriate treatment strategies.
4	Mendéz R, et al. (2018)	Acute complications of Diabetes Mellitus, practical vision for the physician in emergencies: Diabetic Ketoacidosis, Hyperosmolar State and Hypoglycemia.
5	DHATARIYA K, et al. (2017)	Treatment of Diabetic Ketoacidosis (DKA)/Hyperglycemia Hyperosmolar State (HHS): Advances in Hyperglycemic Crisis Management (UK vs. US)

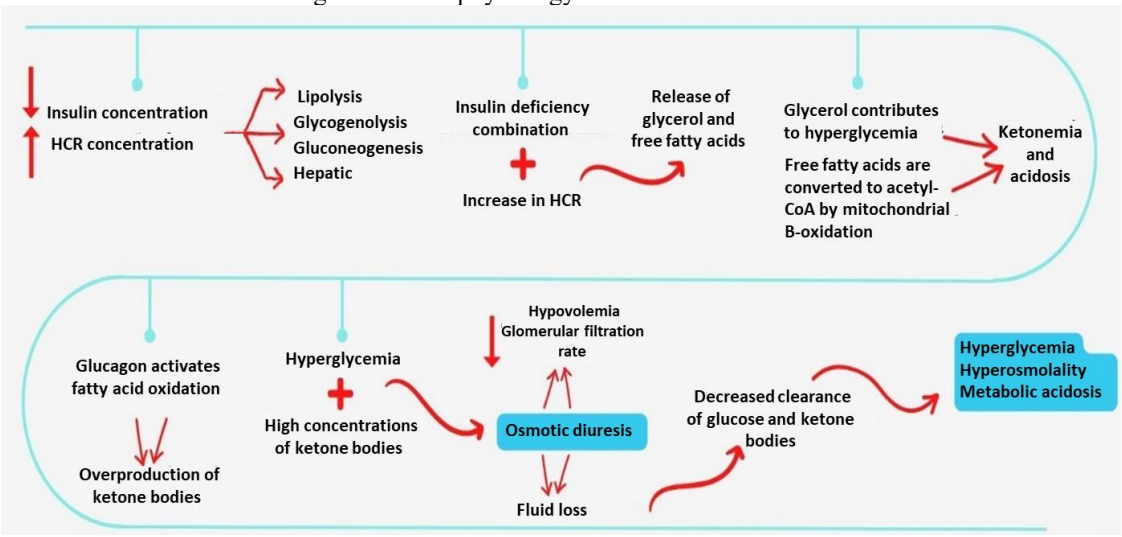
6	KARSLIOGLU F, et al. (2019)	Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome: review of acute decompensated diabetes in adult patients
7	ROMÁN-GONZALEZ, et al. (2018)	Inpatient management of patients with T2DM can become very difficult and complex if there are no clear guidelines for insulin initiation and titration.
8	KUTZ, et al. (2017)	In this large cohort of emergency medical department patients, admission hyperglycemia was strongly associated with adverse clinical course in people without diabetes
9	ALGHAMDI M, et al. (2021)	Administration of hyperosmolar hyperglycemic state in the emergency department; Literature review
10	JACOBI J (2019)	Management of endocrine emergencies in the ICU

5 DISCUSSION

5.1 METABOLIC EMERGENCIES ARISING FROM DIABETES

5.1.1 Diabetic Ketoacidosis

Figure 1- Pathophysiology of Diabetic Ketoacidosis



Source: Author's compilation

*The pathophysiology of DKA begins when low levels of insulin concentration associated with high concentrations of counterregulatory hormones, such as catecholamines, cortisol, glucagon, and growth hormone (GH) promote insulin-opposed metabolic pathways in both the liver and peripheral tissues. The increase in gluconeogenesis at the hepatic level due to the high availability of gluconeogenic precursors such as the amino acids alanine and glutamine (a result of accelerated proteolysis and decreased protein synthesis), lactate (due to increased muscle glycogenolysis) and glycerol (a result of increased lipolysis). Increased glycogenolysis and decreased utilization of glucose by peripheral tissues (MÉNDEZ et al, 2018, apud HIRSCH; EMMETT et al. 2017). *

According to Dhatariya et al (2016), the combination of insulin deficiency and increased counterregulatory hormones in DKA leads to uncontrolled release of glycerol and free fatty acids into the circulation from adipose tissue by increased lipolysis. Glycerol is used for gluconeogenesis, thus contributing to the maintenance of hyperglycemia, while free fatty acids are converted to acetyl-CoA by β-oxidation in mitochondria. In addition, hyperglycemia and DKA are also the result of an inflammatory state characterized by elevated pro-inflammatory cytokines, markers of oxidative stress (TNF-α, IL-6, IL-8, CRP), reactive oxygen species, lipid peroxidation, plasminogen-1 activator

inhibitor, and free fatty acids (MÉNDEZ et al, 2018, apud KENKATESH; PILCHER; PRINS et al. 2017).

In diabetic patients, the precipitating events for DKA are lack of exogenous insulin due to poor adherence to treatment or subtherapeutic doses; infections such as urinary tract infections (UTIs), pneumonia, dental or skin abscesses, sepsis, viral syndromes, pelvic inflammatory disease and malignant otitis externa, and underlying medical conditions that cause release of hormones against regulators, such as appendicitis, pancreatitis, abdominal inflammation, trauma, pregnancy, cerebrovascular disease or acute myocardial infarction (AMI), as well as the use of some drugs and substances that cause metabolic decompensation, pancreatitis, abdominal inflammation, trauma, pregnancy, cerebrovascular disease or acute myocardial infarction), as well as the use of some drugs and substances that cause metabolic decompensation, such as cocaine, alcohol, sympathomimetic drugs, atypical antipsychotics, corticosteroids and thiazide diuretics, etc. (MÉNDEZ et al, 2018, apud UMPIERREZ; Korytkowski. 2016).

Euglycemic Diabetic Ketoacidosis (E-CAD) is an uncommon but potentially life-threatening condition and an emergency that can occur in people with T1D, T2D, or even in people without diabetes. It presents a diagnostic challenge because, as blood glucose is not very high, there may be delays in recognizing the diagnosis and initiating treatment. The E-DKA is defined by the presence of glycemia < 200 mg/dL, with pH < 7.3, bicarbonate < 18 mEq/L, anion gap 10-12 mEq/L and high concentrations of ketonemia. The measurement of ketonemia is preferred over ketonuria. Ketonemia indicates the serum level of β-hydroxybutyrate, which rises earlier and more markedly than aceto acetate, measured in the urine. Measurement of ketonemia is especially important if the patient is on SGLT2 inhibitors. In this situation, there may be a reduction in ketonuria by increased tubular reabsorption of aceto acetate, despite the increase in ketonemia (SANTOMAURO et al. 2022).

CAD-E results from absolute or relative insulin deficiency, associated with an increase in counterregulatory hormones (glucagon, cortisol, catecholamine, and growth hormone). In E-DKA, insulin deficiency and insulin resistance are milder, so glucose overproduction and underutilization are lower than in DKA, limiting the increase in blood glucose levels. The mechanism of ECAD-is due to the decrease in hepatic glucose production during the fasted state, and the urinary increase in glucose excretion induced by an excess of counterregulatory hormones, the former being the most common reason. In ISGLT2-induced E-CAD, renal glycosuria contributes to even lower plasma glucose levels (SANTOMAURO et al. 2022).

The American Diabetes Association (ADA) adopts, as a diagnostic criterion for DKA in adults, blood glucose > 250 mg/dL, pH < 7.3, bicarbonate (HCO3) < 18 and ketone bodies present in the urine. The clinical presentation of DKA begins with some or all of the following symptoms: polyuria, polydipsia, nausea, vomiting, abdominal pain, visual disturbances, lethargy, sensory alteration,

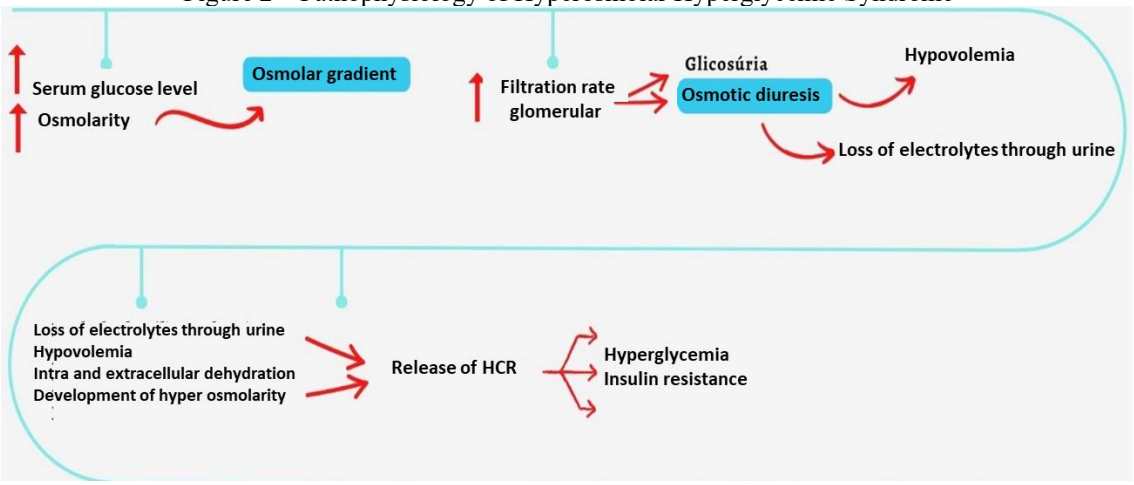
tachycardia, tachypnea, and Kussmaul breathing, with a fruity odor on the breath. Patients usually present with severe volume depletion with orthostatic hypotension. Patients with E-CAD secondary to treatment with an SGLT2 inhibitor may have less polyuria and polydipsia due to the milder degree of hyperglycemia and may present with malaise, anorexia, tachycardia, or tachypnea with or without fever (MODI; AGRAWAL; MORGAN. 2017).

The criteria for the diagnosis of DKA begin on physical examination, when in the presence of acidosis, hyperpnea can be observed and, in more severe situations, Kussmaul's breathing. Dehydration with dry and cold skin, dry tongue, hypotonia of the eyeballs, cold extremities, agitation, hyperemic face, muscle hypotonia, rapid pulse, and blood pressure ranging from normal to hypovolemic shock may occur. Initial laboratory evaluation of patients with DKA should include determination of plasma glucose, phosphorus, urea, creatinine, ketonemia, electrolytes, including anion-gap calculation, urinary analysis, ketonuria, blood gas analysis, blood count, and electrocardiogram. When necessary, chest X-rays and blood and urine cultures are ordered. The last ADA recommendation, dated 2009, adopts, as a diagnostic criterion for DKA, blood glucose ≥ 250 mg/dL,1 but some patients have smaller increases in blood glucose concentration values after retention or decrease of insulin dose in the presence of diseases that decrease food intake (SOCIEDADE BRASILEIRA DE DIABETES, 2019-2020).

5.2 HYPEROSMOLAR HYPERGLYCEMIC SYNDROME

HHS is defined by severe hyperglycemia, elevated serum osmolarity and dehydration, the pathogenesis of HHS differs from DKA in that a more severe degree of dehydration is present due to osmotic diuresis and an absence of significant ketosis/ketone.

Figure 2 – Pathophysiology of Hyperosmolar Hyperglycemic Syndrome



Source: Author's compilation

* The pathophysiology of SHH begins when there is an extreme elevation in serum glucose level and hyperosmolarity with significant absence of ketosis. After an increase in the level of serum glucose and extracellular osmolarity, an osmolar gradient is formed, which draws water from the cells. Initially, the glomerular filtration rate (GFR) increases, which leads to glycosuria and osmotic diuresis, consequently, this glycosuria prevents the progression of severe hyperglycemia,

provided that the GFR is normal. Eventually, when osmotic diuresis continues and hypovolemia develops, it results in a progressive decline in GFR and worsening of hyperglycemia (KARSLIOGLU et al. 2019; ALGHAMDI et al. 2021). *

Unlike what occurs in DKA, in HHS there is a higher concentration of hepatic and circulating insulin with low levels of glucagon, preventing the development of ketogenesis and ketoacidosis, especially because patients with HHS have some functional pancreatic β cells. The passage of intracellular to extracellular fluid resulting from osmotic gradients can cause hyponatremia (reduction in plasma sodium concentration) in the early stage of HHS. Osmotic diuresis can lead to the loss of potassium, sodium, magnesium, and phosphate through the urine. The consequences of the loss of electrolytes in the urine, hypovolemia, intra and extracellular dehydration and the development of hyper osmolarity, leads to the release of counterregulatory hormones, which exacerbates hyperglycemia and contributes to insulin resistance. The total body water deficit is estimated at 7 to 12L in the SHH, representing a loss of 10% to 10% of the total body weight. Elderly patients with HHS usually have enough insulin to protect them from lipolysis and the consequent abundance of ketoacidosis, but do not have enough insulin to protect them from hyperglycemia (ALGHAMDI et al. 2021).

The laboratory diagnoses for HHS according to the ADA are blood glucose greater than 600 mg/dL, effective serum osmolarity greater than 320 mOsm/L, and absence of ketoacidosis (pH > 7.3 and bicarbonate > 18 mEq/L). HHS has an insidious onset, the clinical picture is related to hyperglycemia and increased serum osmolarity, causing signs and symptoms of dehydration and changes in the level of consciousness. In general, patients report a history of polyuria, polydipsia, weakness, blurred vision, and progressive decline in the level of consciousness. In more severe cases, there may be focal neurological symptoms, seizures, hypotension, shock, and/or acute renal failure. Nausea and vomiting are uncommon in HHS. Infection can occur without the presence of fever due to peripheral vasodilation (BRAZILIAN DIABETES SOCIETY, 2019-2020).

5.3 HYPOGLYCEMIA

Acute hypoglycemia is a common consequence of treatment with insulin or oral hypoglycemic agent with reduced glucose intake, but may arise from errors in insulin dosing, liver failure (reduced gluconeogenesis), decreased insulin levels, or changes in corticosteroid therapy without changes in insulin regimen. Severe hypoglycemia can lead to seizures, brain or heart injuries, early recognition of signs and symptoms (sympathetic stimulation, sweating, anxiety, confusion of visual changes, aphasia, etc.) leads to earlier therapy. However, recognition of hypoglycemia may be difficult in patients who are sedated or who have a blunted hypoglycemic response with chronic diabetes and autonomic failure or with concurrent therapy with β-blockers. Hypoglycemia can be classified as mild 55 to 69 mg/dL, moderate 50 to 54 mg/dL, or severe (less than 40 mg/dL), and all are associated with a mortality in the

Intensive Care Unit (ICU) 2 to 3 times higher than normoglycemia, and any value lower than 70 mg/dL should be a warning value for the treatment of the patient and evaluation of the insulin and nutritional regimen (JACOBI, 2019).

According to Román-Gonzalez et al 2018, hypoglycemia is a complication with a wide spectrum of manifestations, as it can be asymptomatic or can be accompanied by autonomic symptoms, pallor, blurred vision, sweating, dizziness, asthenia, adynamia, tachycardia and nervousness, asthenia, adynamia, tachycardia and nervousness; it can also manifest with loss of consciousness, and even death if it is not identified in time. The main risk factors for the development of hypoglycemia are advanced age, chronic kidney disease, malnutrition, medication and diabetes without adequate control. The annual prevalence of severe hypoglycemia is approximately 30% in individuals with T1DM. It is higher in those with risk factors, including strict glycemic control, impaired awareness of hypoglycemia, and increased duration of DM. It is also common during sleep, i.e. nocturnal hypoglycemia. The diagnosis of hypoglycemia is based on three criteria (Whipple's triad): symptoms and signs suggestive of hypoglycemia (feeling faint, dizzy and sweating); low blood sugar levels during seizures (<70 mg/dl); and resolution of symptoms after glucose administration (FORTOFOIU M, et al. 2022).

5.4 HYPERGLYCEMIA

Hyperglycemia is considered as a condition that has an important prognosis, since it affects normal physiology in multiple systems; It is also an independent risk factor for mortality in both diabetics and non-diabetics, especially in acute coronary patients with acute coronary syndrome of any kind. The acute effects of hyperglycemia are not so decisive for the establishment of the hospitalization of diabetics, unless the cause of hospitalization is the acute decompensation of diabetics due to hyperosmolar hyperglycemia, that is, HHS or DKA, conditions in which dehydration is an important factor (ROMÁN-GONZALEZ et al. 2018).

Hyperglycemia leads to certain chronic metabolic changes, such as direct involvement of the entire endothelium, procoagulant tendency, peripheral axonal damage, loss of self-regulation of autonomic functions over time and activation of pro-inflammatory signaling pathways, among the latter are increased oxidative stress, deficiency of platelets and erythrocytes, protein glycation, debilitated phagocytosis, change to the polyol pathway, increased TNF alpha and other cytokines. Taking into account all this, it is to be expected that diabetic patients are prone to infections, which affect them much more markedly, and that, management is sometimes more difficult due to hypoperfusion, endothelial involvement and immune dysfunction (ROMÁN-GONZALEZ et al. 2018).

Hyperglycemia leads to impaired performance of the polymorphonuclear neutrophil cell, a key factor in innate immunity. Reduced levels of neutrophilic degranulation and exaggerated coagulation

were also found during human hyperglycemia, with decreased lipopolysaccharide-stimulated messenger ribonucleic acid (mRNA) of different pro-inflammatory cytokines compared to normoglycemic people. Diabetes also affects the adaptive immune system, with decreased T-cell function and decreased antibody production (KUTZ et al. 2017). Insocomial hyperglycemia is defined by blood glucose values greater than 140 mg/dL.

6 CONCLUSION

The present study on hyperglycemic emergencies revealed a wide range of information essential for the understanding and management of these conditions. The literature review addressed the main characteristics, causes and diagnostic criteria related to diabetic ketoacidosis, hyperosmolar state syndrome and hyperhypoglycemia.

Through the analysis of the selected studies, it was possible to understand the complications and potential sequelae of these conditions. In addition, recent advances in the diagnosis and treatment of these conditions were discussed, aiming to improve clinical outcomes and quality of life of patients.

In short, research on diabetic emergencies provides a solid knowledge base for health professionals and researchers, contributing to improve the early identification, appropriate treatment and prevention of these complications, aiming to improve the quality of life of individuals with DM.

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Nurses' performance in the face of oncological emergencies: An integrative review

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ABSTRACT

Objective: to identify, in the scientific production, the role of nurses in the face of oncological emergencies. Method: Descriptive study, qualitative approach, of the Integrative Literature Review type. PubMed/Medline, LILACS, SciELO, CINAHL, Google Scholar and Web of Science were used as a database and library. For the categorization and lexical analysis of the selected data, the software IRaMuTeQ was used. Results: The formation of 5 correlated classes emerged. There was a limited amount of materials aimed at nursing care, with a small number of articles published in the last 5 years. Conclusion: The role of nurses in oncological emergencies, supported by scientific knowledge, makes a significant difference in the early detection of oncological emergencies, preventing complications and improving quality of life. The limitations of this review refer to the scarcity of current studies that address the role of nurses in oncological emergencies.

Keywords: Oncology Nursing, Emergency Nursing, Nursing care.

1 INTRODUCTION

Neoplasms are defined as a disease that has the great potential for multiplication and disordered differentiation of cells, which can invade adjacent tissues or distant organs (INCA, 2019/1). Currently, cancer is considered a serious public health problem due to its high incidence and also its social and economic importance (SOUZA, 2021/2).

In Brazil, estimates indicate that for each year of the triennium (2020-2022) there will be 625 thousand new cases of neoplasms, which is responsible for more than 230 thousand deaths in the year 2019 (INCA, 2019/1). Thus, cancer should be considered an emergency, considering that it is a condition of aggravation to health that puts at risk of complications, permanent serious damage and death of affected users, requiring specific, fast and efficient actions of professionals (Barbosa, 2020/ 3).

Oncological emergencies are acute conditions of sudden or late onset related to antineoplastic treatment or also to complications resulting from the disease, since they can be classified as hematological, structural, metabolic and secondary to treatment emergencies. Thus, it is necessary that

nursing care in oncological emergencies be performed quickly in order to provide immediate control of neoplastic changes and assist in the stabilization of the organism (Vieira, 2020/4).

Nursing care comprises the physiological and psychological perspectives of the disease in which the psychological aspect of the patient is related to cognitive function, degree of anxiety and emotional state. In this way, nursing professionals should not only identify an oncological emergency situation, but also proceed in a technical, competent and reassuring way in situations at the psychological level (Kesbakhi, 2020/5).

In relation to the physiological aspects, it is essential to evaluate the main complaint, physical examination, clinical reasoning of health professionals and analysis of the results of laboratory reports (Silva, 2019/6). In view of the above, this study aimed to identify the nurse's performance in the face of oncological emergencies described in the literature.

2 METHODOLOGY

This is a descriptive study, with a qualitative approach, of the Integrative Literature Review type. The review aims to synthesize and critically analyze the identified studies, being developed from six stages: Elaboration and definition of the guiding question, organization and determination of the inclusion and exclusion criteria, (3) definition of the selected studies, categorization of the selected data, analysis and interpretation and presentation of the review (SOUZA; SILVA; CARVALHO, 2010).

The guiding question of the review was elaborated from the PICo strategy (P: Patient- "Users with cancer", I: Interest- "Nursing Care" and Co: Context- "Oncological Emergencies") (GUIMARÃES *et al*., 2019). Thus, it obtained as a guiding question: How is the nursing care provided to patients in situations of oncological emergencies?

The search for the studies obtained was carried out in September 2022 by consulting the databases and electronic databases being: National Library of Medicine and National Institutes of Health/ Medical Literature Analysi Sand Retrieval System (*PubMed/ Medline*), Latin American and Caribbean Literature in Health Sciences (*LILACS),* Scientific Electronic Library Online (*SciELO*), Google Scholar, BDENF, CINAHL and Science Citation Index Expanded (*Web of Science*). The strategy used in the research was through the combination of the descriptors controlled and registered in the DeCS / MeSH (Descriptors in Health Sciences/Medical SubjectHeading) in Portuguese and English being: "Oncological Nursing" AND "Emergency Nursing" AND "Nursing Care".

This review included complete studies contained in the gray literature, published from 2012 to 2022, articles available in journals with online and free access in Portuguese, Spanish and English, and that had relevance to the theme. Out-of-period studies, incomplete studies, reflective studies, letters to the editor, paid studies, editorials and those that were not related to the guiding question were excluded.

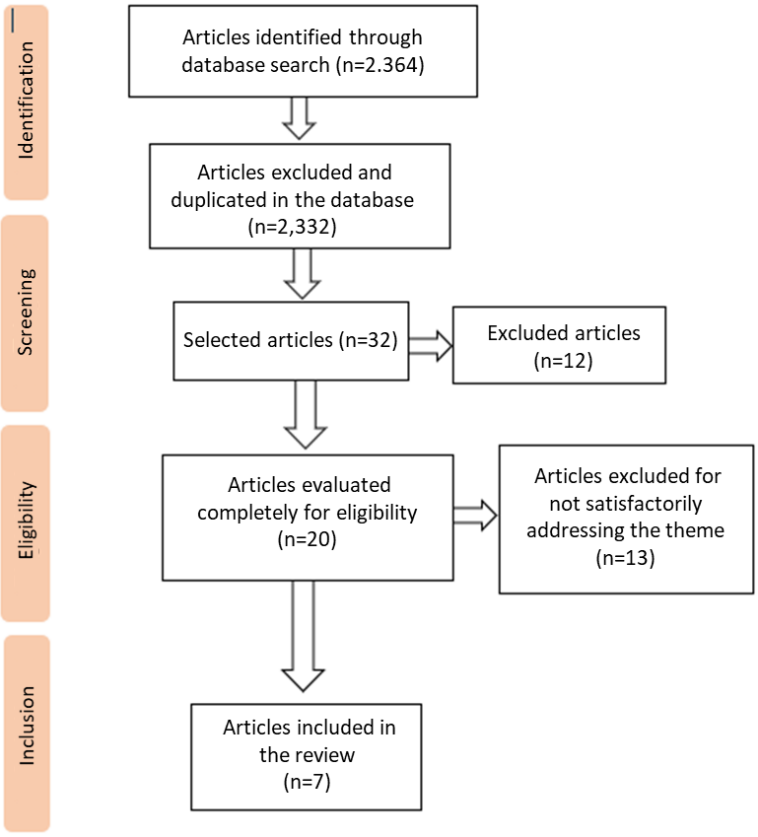
To elaborate the data collection, based on the inclusion and exclusion criteria, the form adapted from Ursi was used in order to remove pertinent data, minimize errors in transcription and ensure the information contained in the selected studies. This instrument contains article code/database, title/author/year, type of study/level of evidence, objective and synthesis of the main results (URSI; GALVÃO**,** 2005).

The content analysis was performed from the content proposed by Lawrence Bardin which is subdivided into three stages in which are: pre-analysis, exploration of the material and the approach of the results found. The objective of this method is to enable the critical appreciation of content analyses in quantitative and qualitative research (BARDIN, 2016). To establish the quality and reliability of the information of the studies, the degree of evidence was determined (GALVÃO, 2006).

Subsequently, for the categorization and lexical analysis of the selected data, the software *IRaMuTeQ (Interface de R pour lês Analyses Multidimensionnelles de Textes et de 101 Questionnaires)* was used, which was developed in France by Pierre Ratinaud (2009). The software is anchored in the statistical program R which generates data from texts (textual corpus). This program groups the words and offers several possibilities of analysis (KLAMT; SAINTS, 2021). The type of analysis used in the *IRaMuTeQ* tool was the Descending Hierarchical Classification (CHD), which is important to correlate the terms of the same corpus.

The process of presentation and selection of the studies found was carried out through the flowchart adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as shown in **Figure 1:**

Figure 1: Detailed flowchart of studies adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009)



Source: Research Authors, 2022

3 FINDINGS

In this review, a total of 2,364 studies were obtained in the databases and databases. After this phase, the inclusion criteria were applied, and 2,332 duplicate studies and those that did not fit the delimited criteria were eliminated, leaving only 32 studies to be read in full. After reading, 25 articles were excluded. The final sample was the inclusion of 7 studies in this review, as shown in Chart 1.

Table 1: Studies included in the review

Item Code/ Database	Title/ Authors/ Year	Type of study and Level of evidence	Goal	Summary of the main results
E1/ BDENF	Nursing Care in Oncological Emergency Care: an integrative review Ramos LGA, Savoy VM, Fortini RG. (2018)	Integrative review study Tier 6	To highlight the knowledge about nursing care in the care of people living with neoplasms and are in an oncological emergency situation.	Most nursing studies related to oncological emergencies were limited to describing the specific interventions for each situation.
E2/ LILACS	Oncological emergency: nurses' role in the extravasation of antineoplastic	Cross-sectional study Level 5	To investigate the role of nurses in the extravasation of antineoplastic chemotherapy.	Nurses show sufficient knowledge about risk factors, prevention and recognition of signs and symptoms.

	chemotherapy drugs Souza NR, Bushatsky M, Figueiredo EG, Melo JTS *et al.* (2017)			
E3/ SciELO	Prevention and management in the face of extravasation of antineoplastic agents: scoping review Melo JMA, Oliveira PP, Souza RS *et al.* (2020)	Scope review study Tier 6	Identify and synthesize the scientific evidence on prevention and management of extravasation of antineoplastic agents in adult patients performed by nurses	Most of the studies dealt with prevention and management of chemotherapy extravasation in adult patients
E4/Google Scholar	Extravasation of chemotherapy drugs: the role of the nurse in the oncological emergency Faria LP, Fagundes TR. (2020)	Integrative literature review study Tier 6	To review the scientific production focused on the role of nurses in the management and prevention of extravasation of chemotherapy drugs	Nurses have limited information about the risks involved in handling, administration and disposal of antineoplastic drugs, as well as the conducts after extravasation.
E5/Google Scholar	Nursing care in oncological emergencies: an integrative review Lopes GMJ, Simino GPR, Rocha PRS *et al.* (2022)	Integrative literature review study Tier 6	To identify the nursing care described in the literature for the management of oncological emergencies	Nursing care involves physiological and psychological aspects.
E6/Google Scholar	Nursing care in oncological emergencies: an integrative literature review from 2008 to 2016 Junior SRAM, Matos SSMS. (2018)	Integrative literature review study Tier 6	To identify the performance of nursing care in oncological emergencies, in the period from 2008 to 2016	The nurse is responsible for providing adequate care in the care of cancer patients in clinical, surgical and hematological diseases throughout the life cycle.
E7/Google Scholar	Nursing care for neutropenic cancer patients: scoping review Oliveira PP, Freitas ATS, Maia PA *et al.* (2019)	Integrative literature review study Tier 6	Identify nursing care related to risk factors for febrile neutropenia; prevention of infection and neutropenic sepsis; protocols for the use of colony-stimulating factors and the introduction of antibiotic therapy for neutropenic cancer patients	The main nursing care found were: standard precautions, evaluation of risk factors for febrile neutropenia; education about self-care, among others;

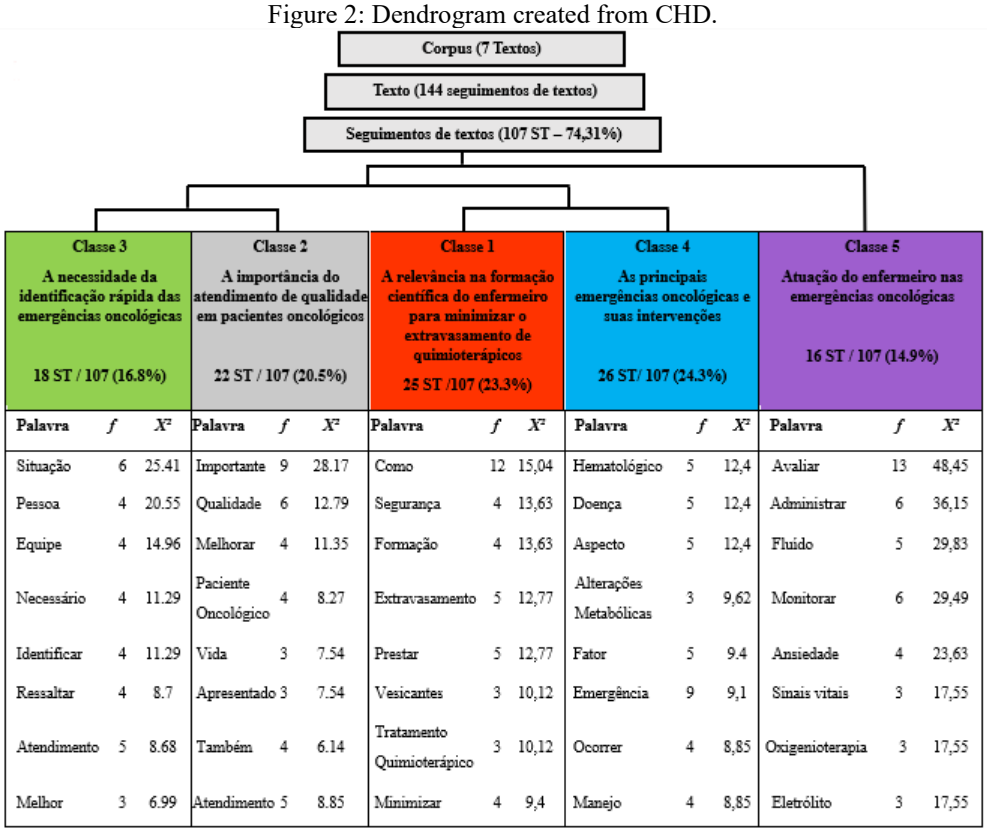
Source: Adapted from Ursi, 2022

In the search for scientific studies, a limited amount of materials focused on nursing care was found, and there was also a small number of articles published in the last 5 years. Among the studies

included in this review, 6 of them were integrative reviews, 1 of which was a scope review, with the level of evidence being 6 (E1, E3-E7). The risk of bias is high for the 6 studies and only 1 study has the risk of moderate bias (E2).

Moreover, through the CHD, the formation of 5 classes was emerged, which evidenced the correlation of the words and the representation on the theme studied, having the frequency and chi-square of the words described in the dendrogram **(figure 2).**

Figure 2: Dendrogram created from CHD.



Palavra	f	X²	Palavra	f	X²	Palavra	f	X²	Palavra	f	X²	Palavra	f	X²
Situação	6	25.41	Importante	9	28.17	Como	12	15,04	Hematológico	5	12,4	Avaliar	13	48,45
Pessoa	4	20.55	Qualidade	6	12.79	Segurança	4	13,63	Doença	5	12,4	Administrar	6	36,15
Equipe	4	14.96	Melhorar	4	11.35	Formação	4	13,63	Aspecto	5	12,4	Fluido	5	29,83
Necessário	4	11.29	Paciente Oncológico	4	8.27	Extravasamento	5	12,77	Alterações Metabólicas	3	9,62	Monitorar	6	29,49
Identificar	4	11.29	Vida	3	7.54	Prestar	5	12,77	Fator	5	9.4	Ansiedade	4	23,63
Ressaltar	4	8.7	Apresentado	3	7.54	Vesicantes	3	10,12	Emergência	9	9,1	Sinais vitais	3	17,55
Atendimento	5	8.68	Também	4	6.14	Tratamento Quimioterápico	3	10,12	Ocorrer	4	8,85	Oxigenioterapia	3	17,55
Melhor	3	6.99	Atendimento	5	8.85	Minimizar	4	9,4	Manejo	4	8,85	Eletrólito	3	17,55

Source: Dendrogram created in word from *IRaMuTeQ software*, 2022.

In summary, the formation of the classes is verified through the reading of the fragments of texts, studies included, more characteristic of each class (corpus in color) generated by *the IRaMuTeQ software* and the main findings according to table 2. In addition, it is important to emphasize that the classes correlate with each other, observing the relationship lines in the dendrogram.

Table 2: Presentation of class titles and their main findings

Class 1: The relevance in the scientific education of nurses to minimize the extravasation of chemotherapy drugs. It is of great relevance to seek new knowledge and strategies that assist in nursing care in oncological emergencies	E1, E2,
Lack of studies with a higher level of evidence that address the problem of extravasation of antineoplastic drugs	E3
The limited knowledge of oncology nurses through the conducts and management of extravasation of chemotherapy	E4

Class 2: The importance of quality care in cancer patients. Provide patient comfort and control of the evolution of the clinical picture	E1
Assists in the identification of intercurrences, reducing the harm to the patient and favoring safety	E2, E5
The nurse offers the first care and needs to be able to recognize oncological emergencies	E6
Class 3: The need for rapid identification of oncological emergencies Recognize oncological emergencies and the various warning signs for each situation	E1
Rapid intervention of oncological emergencies prevents death and permanent injury to the patient	E1
Class 4: The main oncological emergencies and their interventions The prevalent oncological emergencies found in the studies were: Superior vena cava syndrome, tumor lysis syndrome, spinal cord compression syndrome, hypercalcemia, hyponatremia, febrile neutropenia and extravasation of antineoplastic drugs (tissue changes)	E1, E2, E7
The interventions related to oncological emergencies, according to the specificity of each emergency, are: respiratory rate assessment, headboard elevation, attention to hydration, electrolyte replacement, venous access monitoring, lower limb elevation, among others	E1, E4, E5, E7
Class 5: Nurses' performance in oncological emergencies Act in the execution of the physical examination to identify infectious foci in patients with febrile neutropenia	E1,
Manage the anxiety of patients and families, monitor laboratory tests and the implementation of protocols	E5, E7

Source: Research Authors, 2022

4 DISCUSSION

The proposed review is pertinent to the investigation of the nurse's performance in relation to oncological emergencies and also to the identification of the main oncological emergencies discussed in the literature. It is observed that the professional training of the nurse is important to avoid complications to the patient, thus it was identified in a study found in the literature that nurses were attentive to the care provided at the time of extravasation or shedding of chemotherapy (COSTA, 2019).

However, it was found in a cross-sectional study that the knowledge of nursing professionals regarding the management of adverse events related to neutropenia and extravasation of chemotherapy drugs was insufficient, given that some answers of the interviewees were limited to the request of the doctor (GOZZO, 2015). The literature highlights febrile neutropenia as the most frequent problem in oncological emergency care, since it is the main cause of infections, being responsible for the mortality and morbidity of cancer patients (CASTRO, 2018).

Thus, it is of great relevance to seek new knowledge and strategies that help in the identification of manifestations related to oncological emergencies. In this way, establishing systematized and individualized strategies will provide the recovery of health or the improvement of the well-being of cancer patients. The nurse, as a strategy, can make use of the nursing process, as it is addressed in the literature (BOAVENTURA 2015).

Despite this, it was observed that few studies address the systematization of nursing care (NCS) in oncological emergencies, with only one study that addressed that the main difficulties encountered by nurses in performing the NCS is the lack of knowledge, lack of time and lack of encouragement from the organization, since organizations are increasingly reducing the number of nurses (CASTRO, 2018).

Another point that we had as a result is that the nurse is the professional who offers the first care to the patient, so he needs to be able to recognize the oncological emergencies, but the care to these patients must be carried out in a multiprofessional way, since the harmonious relationship between the functions developed by the different professionals will provide the best results (SILVA, 2021).

For example, the nurse who is responsible for the overall planning of care and for recognizing the signs and symptoms of the patient, intervenes quickly with competence to avoid complications as well as offering support and adequate information to patients and caregivers. In this way, this information should about the main signs and symptoms and also the numbers and places that can request assistance (PIRSCHEL, 2018).

It was observed that among the oncological emergencies most discussed in the scientific literature were the Medullary Compression Syndrome (MCS), Superior Vena Cava Syndrome (SVCS), Tumor Lysis Syndrome (TLS) and febrile neutropenia (NF) having a quantitative of studies that address the concepts, management and clinical signs. In addition, the main nursing interventions were highlighted (MANZI, 2012; Smith, 2019).

SCM is determined by compression of the spinal cord and its nerves by tumor cells. The syndrome is one of the main causes of paralysis in a patient with bone metastasis, being able to become irreversible if treatment is not carried out immediately. For this reason, it is necessary to carry out the rapid identification of signs and symptoms and consequently early diagnosis (KAMENO, 2018).

The main signs and symptoms of MCS are related to hypersensitivity in the region of the injury, pain and motor dysfunction that is evidenced through symptoms of bilateral asthenia in the legs and motor difficulties (THANTA, 2020). The synthesis of nursing interventions described according to scientific studies are: Continuous evaluation of pain, elaboration of care plan according to individual needs, skin care during radiotherapy, monitoring of breathing pattern, offering guidance and emotional support to the user and family members and detecting signs of infection (MANZI, 2012; CASTRO, 2018).

SVCS is a set of symptoms that occurs due to direct compression or obstruction of the superior vena cava, a vein that transfers blood from the head, neck, chest to the myocardium. Therefore, it is verified in the literature that the most common signs and symptoms of the syndrome are: edema of the face, neck and upper extremities, cough and dyspnea (SHAIKH, 2013).

According to the study of Lopes (2022) the obstruction of blood flow can provide increased intracranial pressure and impairment of respiratory flow. Thus, the nursing interventions will be elaborated from the complications, being necessary to monitor and maintain the breathing pattern: to evaluate signs of respiratory distress, to maintain supplemental oxygen and to keep the headboard elevated in the Fowler position, to perform fluid and electrolyte balance, to look for signs of facial edema, to evaluate the neurological system and to calm the patient and minimize anxiety.

With regard to research focused on oncological emergencies, TLS is part of the emergencies classified as metabolic, in which it is characterized as a severe electrolyte disturbance resulting from the destruction of neoplastic cells, which may arise spontaneously or after the beginning of treatment. The most common complication of TLS is acute kidney injury (GANDA, 2017). The clinical signs of TLS are nonspecific and edema, lethargy, nausea, vomiting, pain in the lumbar region of the colic type, arrhythmias can be identified (SILVA, 2019).

The important nursing interventions highlighted for TLS include monitoring biochemical parameters (serum levels of potassium, phosphate, calcium and creatinine, uric acid, arterial blood gas and urine pH, arterial blood gas analysis), performing hydration, evaluating renal function , and preventing the user from ingesting potassium-rich foods and being aware of other drugs administered that may cause renal impairment (MANZI, 2012; LOPES).

Neutropenia is also highlighted, which is defined as an absolute neutrophil count and may occur due to the effects of treatment. Febrile neutropenia is characterized as the presence of a fever of ≥38.0°C sustained during 30-minute intervals in a neutropenic user. Fever indicates a sign of infection, which if left untreated can be fatal, however even if there is no occurrence of fever the presence of sore throat, diarrhea, swelling and cough can be signs of infection and need to be treated immediately (CAMPOS, 2017).

Thus, the nurse is responsible for the orientations and care related to the prevention of infection, evaluation of laboratory tests (blood culture, urine culture and chest X-ray) and monitoring of the patient in the time elapsed between the application of the medications and the picture of lower value of the hematological count (FERREIRA, 2017). In addition, it was contacted in the study by Oliveira (2019) that the implementation of protocols for the introduction of antibiotic therapy in neuropenic patients are effective and safe, as they improve quality of life and enable a better clinical outcome.

5 CONCLUSION

The review, when analyzing the importance of recognizing the main oncological emergencies and their clinical manifestations, showed that despite the need for early identification of these manifestations, some nursing professionals are not qualified for this function. Thus, the need for training of nursing professionals is highlighted, in order to provide better care to these patients.

Thus, it is evident that the nurse's performance in oncological emergencies, supported by scientific knowledge, makes a significant difference in the early detection of oncological emergencies, prevention of complications and consequently in the improvement of the quality of life and comfort of cancer patients.

The limitations of this review refer to the scarcity of current studies that address the role of nurses in oncological emergencies and also the realization of new studies that bring reliable scientific evidence to have a better foundation of nursing practices.

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Leadership competencies: Tools for the promotion of quality in health care

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ABSTRACT

At this moment 'shared leadership' is in discussion. This means to delegate more autonomy to those who work on all levels of organizations as well as to give them the chance to become individuals and also citizens capable of changing things and assuming reponsibilities in order to direct their actions in search of the already planned objectivities. The structure of the old administration has to make room to new ones which should be more flexible, wider and more decentralized, thus creating autonomy, pro-activity, and conditions for every single one to assume leadership. The hospital is not an outsider in this process and goes also through a renewed form of thinking and planning. In this sense, both Medicine and the other multidisciplinary areas of health has assumed different roles within its care activities linked to the patient until health management, thinking not only about managing with leadership skills, but also interacting with new times and methods, becoming audacious from mechanisms like a lot of attention and emotion, intelligence and self-development to break paradigms of a professional profile. This study sought to analyze the Leadership Competencies as tools for the promotion of quality in health care, based on Explanatory Research and

meta-analysis in a hospital, with 37 graduated and specialized health professionals.

Keywords: Shared Leadership, Competence in Leadership, Quality.

1 INTRODUCTION

Much is said and written about what a successful leader should do and how to be respected by the team. However, little is said about how to achieve competencies in a fast-changing and globalized world. What is indispensable for leader training? This question is largely responsible for the quality and scope of vision of leaders.

Enterprises and businesses linked to the health sector need vision and precise strategies, since the focus is linked to the treatment of people who need special attention to their basic needs.

The exercise of leadership requires from this professional analytical skills, management skills, empathy, whose strength attributed to a leader is in his "inner life", revealed in his way of being and acting, in his passions, security, creative vision, determination for an idea, a cause or project, objectivity to innovate and change, withstand pressure frustrations, persuade, captivate, seduce and demand, among other personal attributes.

It is necessary for leaders to have exceptional and differentiated training, since their mission is also accomplished through human relations. Thus, the priority in the formation of a leader is his degree of self-knowledge and his level of psychological maturity.

It is suggested that leaders must have the humanistic societal value, without which no one can realize themselves.

Leaders must know how to love, not contrast. "Knowing how to love" means knowing how to give something where the other increases his identity, knowing how to serve the other. Therefore, no one can be great, fully realize himself, if he does not pass through the function of serving society.

The worst crime is the murder of the inner core of the individual. Whoever kills his own light or allows the light of another to be killed is also against himself, against his brothers, against life.

Currently, shared leadership and its competencies are the subject of debate. For Warren, Gretchen & Thomas (2001) research results suggest that this will be the leadership model of the future, as it is the one that seems to respond best to the needs of organizations that have undergone mergers, acquisitions or joint ventures.

Within its approach, the study of leadership has always dealt with contradictory aspects, making it evident that what is coherent at a given moment may not be able to explain reality later on (BERGAMINI, 1994).

This work aimed to analyze the Leadership Competencies as tools for promoting quality in health care.

2 METHODOLOGY

The methodological procedure used in the Research was Meta-analysis, raising the objectivity of literature reviews, with research synthesis, research review or systematic review. It was specially developed to integrate the results on the same research question in a systematic literature review.

Representative sample with thirty-seven (n=37) Nurses Graduated, Specialists, who occupy different positions, directly admitted to the Intensive Care Center (ICU), working in the morning, afternoon and evening shifts and who consented to participate in the study after the researcher's orientation and signing the Informed Consent.

For data collection, a form was used to fill in information obtained from the study population and response items to a closed questionnaire structured by interview by agenda, composed of four objective questions, two of them based on the Likert scale.

3 RESULTS AND DISCUSSION

For the analysis of the results, the "on-site leadership competencies" were considered as a reference, through comparison with the answers obtained in the closed questionnaire by interviewing the nurses.

The Nursing philosophy of the Institution, supported by the theoretical framework of Jane Watson's philosophy and science of caring (BORK, 2003), derived from a humanistic vision, aims at promoting health and not only curing diseases.

In order to achieve these prepositions, the Nursing care model adopted is presented, which is the Shared Practice described by Marie Manthay (BORK, 2003).

The Nursing system of the Hospital under study believes in the scientific foundation as a foundation for clinical and professional development, and it is hoped to contribute to the enhancement of nursing practice.

A nursing theory is a relatively specific and concrete set of concepts and propositions that explain or characterize phenomena of interest to nursing science - people, their environment, their health and nursing itself.

For Ferraz (1995), caring is the essence of nursing practice and involves human acts in the process of assisting the individual, group or community, characterized by interconnected actions, endowed with feelings. The inherent objective of nursing care is comfort, essential in nursing care and complementary to the therapeutic component of hospital care.

Therefore, it is imperative to adopt tools that are supported by scientific knowledge and promote nursing care, based on an institutional philosophy and a theoretical model.

This philosophy presupposes the development of interpersonal and individual care, supported by a Shared Nursing Decision Management Structure, decentralized, open and based on scientific evidence and undisciplinary work.

It bases its activities on the patient, highlighting him first, and basing its decisions on clinical judgment, on the one that best meets his needs, seeking his active participation in decisions about his treatment. In shared nursing practice, the patient is integrated into decision-making and participates in the planning and implementation of care.

Shared Practice organizes the provision of nursing care developed by nurses, technicians or nursing assistants, actions are planned, performed or delegated according to levels of knowledge and competence. In this model, the need for care is assessed, a care plan is drawn up, implemented and considered with regard to the patient to the nurses' interventions.

The provision of care in Shared Practice is characterized by the application of skills of several professionals, in a model where the nurse identifies, coordinates and monitors the implementation of all the care necessary to meet the needs of each patient under his/her responsibility, within a given period.

Undoubtedly, the adoption of a philosophy and a model of care necessarily involves the construction of the identity of the nurse in an institution. It is not an easy task, on the contrary, its complexity requires the participation and involvement of all the members that make up the team of nurses.

They also require the questioning and reflection of these professionals on their aspirations, roles and objectives as a professional body. Table 1 shows the list of nurses by work shift, length of employment, time in the institution, position, gender and participation in a nursing support group.

Table 1- List of nurses by work shift, time in profession, time in the institution, position, gender and participation in a nursing support group.

	Shift of Work	Time of Profession	Time in Institution	Position	Sex	Participation in group of Nursing support
1	M/T	16 years	16 years	Manager of Nursing	F	NO
2	M/T	09 years	08 years	Coordinator of Nursing	F	YES
3	M	13 years	05 years	Assistance	F	YES
4	M	13 years	11 years	Assistance	F	YES
5	M/T	19 years	10 years	Supervisor of Practice	F	YES
6	T	21 years	9 years	Assistance	F	YES
7	N	12 years	8 years	Assistance	F	NO
8	M	15 years	8 years	Assistance	F	YES
9	M	17 years	7 years	Assistance	F	YES
10	N	10 years	7 years	Assistance	M	YES
11	M	14 years	6 years	Assistance	F	YES

12	N	11 years	5 years	Assistance	F	YES
13	N	10 years	5 years	Assistance	F	YES
14	M	26 years	15 years	Assistance	F	YES
15	T	10 years	4 years	Assistance	M	YES
16	M	10 years	4 years	Assistance	F	YES
17	T	1 year	4 years	Assistance	F	YES
18	N	7 years	3 years	Assistance	F	NO
19	M	18 years	4 years	Assistance	F	YES
20	N	7 years	3 years	Assistance	F	YES
21	T	7 years	3 years	Assistance	F	YES
22	M	4 years	2 years	Assistance	F	YES
23	T	8 years	2 years	Assistance	F	YES
24	N	4 years	2 years	Assistance	F	YES
25	M	4 years	2 years	Assistance	F	YES
26	N	16 years	2 years	Assistance	M	NO
27	N	8 years	2 years	Assistance	F	YES
28	M	6 years	2 years	Assistance	F	YES
29	T	10 years	1 year	Assistance	F	YES
30	N	6 years	1 year	Assistance	F	YES
31	N	7 years	1 year	Assistance	F	YES
32	M	4 years	7 months	Assistance	F	NO
33	M	3 years	7 months	Assistance	F	YES
34	T	1 year	7 months	Assistance	F	NO
35	N	3 years	6 months	Assistance	F	NO
36	N	8 years	6 months	Assistance	F	NO
37	M	3 years	6 months	Assistance	F	NO

Source: Prepared by the author, Veloso (2020).

Descriptive statistics - Table 1

f1: time <= 5years f1:time<=5years f2: 5< time <= 10years f2:time>5years f3: time>10years

Table 2- Descriptive statistics -Table 1

Ttempprof	Count	Percent	tempinst	Count	Percent
f1	9	24,32	f1	20	54,05
f2	15	40,54	f2	17	45,95
f3	13	35,14	N=	37	
N=	37				

Source: Prepared by the author, Veloso (2020).

Table 3- Descriptive statistics -Table 1

bandwidth	Count	Percent	Nursing	Count	Percent
Assistance	34	91,89	No	9	24,32
Other	3	8,11	Yes	28	75,68
N=	37		N=	37	

Source: Prepared by the author, Veloso (2020).

Table 4- Descriptive statistics - Table 1

Sex	Count	Percent	Position	Count	Percent	Shift	Count	Percent
F	34	91,89	Assistance	34	91,89	M	14	37,84

M	3	8,11	Coordinator	1	2,7	M/T	3	8,11
N=	37		Manager	1	2,7	N	13	35,14
			Supervisor	1	2,7	T	7	18,92
			N=	37		N=	37	

Source: Prepared by the author, Veloso (2020).

Table 5- Descriptive statistics - Table 1

Variable	N	N*	Mean	StDev	Minimum	Q1	Median	Q3
tempprof	37	0	9,757	5,866	1,000	5,000	9,000	13,500
timeinst	37	0	5,435	3,61	1,000	5,000	5,000	7,000

Source: Prepared by the author, Veloso (2020).

Variable Maximum	Mean=average	Q1= first quartile
Tempoprof 26,000	Median=median	Q2=third quartile
timeinst 16,000		

Prof. time is a variable with a Normal (Gaussian) distribution.

Time institution is a continuous variable with approximately Normal distribution.

Analyzing Table 1, 37 (thirty-seven) nurses from different positions participated in the research - Management, Nursing Coordination and Supervision and Nursing Assistance; institutional time - ranging from 06 (six) months to 16 (sixteen) years in the Company: time of profession - between 03 (three) months and 16 years; gender; participation in Nursing support groups.

The clarity that all change comes with challenges and perspectives permeates all planning of the new structure from the beginning. Research reports that Participatory Management is an organizational model that can be adapted to nursing services, having already been implemented in American, Canadian and English hospitals (BORK, 2003).

In the survey 37.8% of the nurses work in the morning; 35.1%, in the evening; 18.9%, in the afternoon 8.1% work as off-duty coverage in the morning and afternoon shifts, as needed by the duty roster.

The nurses interviewed, nine nurses have up to five years of profession; fifteen, between six and ten years of profession; thirteen, above ten years of profession.

This means that 75.68% of these nurses have extensive professional experience in Nursing, having already experienced some experience with different types of leadership. Regarding the time in the institution under study, 54.0% of the nurses have up to five years; 46.0%, above five years in the hospital in question.

Assuming that the Shared Decision Structure has only been implemented for a short period of time - less than five years, it is inferred that a large proportion of the interviewees have a greater knowledge of the new structure, since they participated in its implementation, and have been following its development, analyzing its results and sensitizing those newly hired nurses.

The vast majority of the nurses interviewed (91.9%) assume the care function, managing their immediate peers in their rental unit. Only 8.1% of the total number of nurses in the survey occupy a management position. This favors a better parameter of the results of the evaluation of the Shared Decision Structure, since it does not infer an ideological character of "positions of trust".

The great prevalence in the survey is women, reaching 91.9% of respondents, as pointed out in the survey, This also portrays the predominance of the female figure in the health area.

Of all respondents, 75.7% actively participate in some nursing support group. This reinforces the nurses' engagement in the Shared Decision Model, since from these groups, the current organizational structure improves the identification and daily exercise of successes and deviations, in order to redesign processes, minimize conflicts, involve professionals in the adoption of practical improvements in Nursing, according to Table 6.

For example, in the hospital under study, there are teams and small assistance groups divided by specialties, whose purpose is to research, improve, apply proposals to improve health care through scientific studies. With this, their results become a reference in the hospital area at the national level, with dissemination of their methods and procedures through courses, symposia, congresses.

The survey describes that 83.8 of the respondents agree and strongly agree with the first leadership competency (Applied knowledge in organizational theories) as a determinant in building the Shared Nursing Decision Model. None of the nurses strongly disagreed.

It is important to highlight the equity of responses between indifferent (13.5%) and strongly agree (13.5%) among nurses, which suggests a certain difficulty in understanding this competence in the organizational model under study.

In the second leadership competency (Applied knowledge in systems, values and social relationships), 86.5% of nurses agree and strongly agree with the statement that this competency determines the construction of the Shared Nursing Decision Model.

In this third leadership competency, (Knowledge applied in ethical foundations and social responsibility), none of the interviewees disagreed with the statement that this competency contributes to the construction of the Shared Nursing Decision Model.

Of the respondents for this leadership competency, (Applied knowledge in economic and cultural globalization), 75.7% with the statement that this competency determines the construction of the Shared Nursing Decision Model. None of the nurses disagreed.

The percentage of responses for indifferent, as shown in the graph above, was high in relation to the other leadership competencies, 24.3%. It seems, at first glance, that the vision of nurses in large hospitals is restricted in relation to what happens around them. Hence the high This fifth leadership competency, (Skills in planning and implementing public relations activities) points out, among the

interviewees, 78.4% agreement that this competency determines the construction of the Shared Nursing Decision Model. None of the nurses disagreed.

In the competency of Skills in organizational development, according to Graph 14, 89.2% agree and strongly agree that this competency determines the construction of the Shared Nursing Decision Model. Of all the nurses in the survey, only 2.7% strongly disagree with the assertion.

The seventh leadership competency, was accepted by 82.9% of nurses as a determinant in building the Shared Nursing Decision Model. Of the respondents, 5.4% strongly disagreed above.

Regarding the eighth leadership competency, Graph 16 (Skills in allocating material and financial resources), 75.7% confirm the statement that this competency determines the construction of the Shared Nursing Decision Model, against the opinion of 5.4% of the interviewees, who disagree and strongly disagree with this statement.

The survey pointed out that the ninth leadership competency (Skills in human development), 94.6% approve the statement that this competency determines the construction of the Shared Nursing Decision Model. None of the interviewees disagreed with this statement.

The survey indicated that 91.9% of nurses approve the statement that this competence, (Skills in various learning strategies) determines the construction of the Shared Nursing Decision Model.

In the competency of Skills in problem solving and decision making, Graph 19, 94.6% of the nurses in the survey approve the statement that this competency determines the construction of the Shared Nursing Decision Model. Of the respondents, 5.4% disagreed with this statement.

The competency of Knowledge applied in small group work shows that 81.1% of respondents approve the statement that this competency determines the construction of the Shared Nursing Decision Model. Of the total number of nurses, 2.7% disagreed with this statement.

This result demonstrates the reality of their professional routine, since multi- and interdisciplinary teamwork is indispensable for successful patient care.

The fourteenth leadership competency, (Applied knowledge in interpretation of laws, regulations and policies) is confirmed by 73.0% of nurses as a determinant in the construction of the Shared Nursing Decision Model.

This research showed that 70.0% of nurses agree with all Nursing activities as fundamental to the exercise of leadership.

It is observed, specifically in political activity, that 59.5% of respondents are indifferent to this factor as important for the leader to play his role with the team.

Of the respondents, 100.0% agree and strongly agree with the statement that activities such as concern for staff development and rapid decision making in nursing care are important to ensure the success of the Shared Decision Model.

Of all nurses, 8.1% disagreed with the statement that activities such as participation in administrative services and political activities, computer knowledge is important to ensure the success of the Shared Decision Model.

Of the respondents, 86.5% agree and strongly agree with the statement that activities such as performing nursing procedures are important to ensure the success of the Shared Decision Model. Of the total nurses, 5.4% disagree with this statement.

In the survey, 86.5% of nurses agree and strongly agree with the statement that activities such as receiving and passing on duty are important to ensure the success of the Shared Decision Model. Of those respondents, 8.1% disagree and strongly disagree with this statement.

None of the interviewees disagreed with the statement that developing and/or enforcing standards and routines are important to ensure the success of the Shared Decision Model.

None of the interviewees disagreed with this statement. Nursing, in particular, is concerned with the professional profile and, through knowledge of its Code of Ethics, guides all its actions.

4 CONCLUSION

Participatory management is based on humanism, as it is based on respect and integration of human values, the needs of people and work. It considers the worker as an active being in the organization, with the capacity to develop his role with autonomy and to participate effectively in decision-making related to the work processes of the services.

The organizational structure is flexible and adaptable, there is greater reliability in informal interactions and decisions are decentralized. This proposal fosters personal and professional growth, contributing to the worker feeling more motivated and recognized.

One of the rights is the autonomy of the user, considering that for him to make decisions or participate in decisions regarding his treatment and well-being, two conditions are necessary: freedom and competence to decide.

Competence means having the necessary clarification for decision making; freedom presupposes having the possibility of choice. Thus, in parallel with Participatory Management, it means that there should be a socialization of knowledge and a redistribution of power, because in order to be able to decide, the professional will have to have the opportunity of choice and competence, covering knowledge, skills and attitudes.

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Epidemiological analysis of tuberculosis in Brazil

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ABSTRACT
INTRODUCTION: Tuberculosis (TB) is still a major public health problem worldwide. It is estimated that in 2019, worldwide, about ten million people evolved with TB and 1.2 million died due to the disease. As for treatment outcomes, in 2018, the percentage of treatment success was 85% among new cases. OBJECTIVES: To conduct an epidemiological analysis of tuberculosis in Brazil from 2012 to 2022. METHODOLOGY: This is a bibliographic and theoretical-descriptive research, based on studies and theoretical research, seeks to identify elements to describe characteristics related to information, usability and visualization of platforms that provide open data. Data collection was performed in the following sources: Database of the Unified Health System - DATASUS and official documents of the Ministry of Health. Descriptors used for the search were tuberculosis, epidemiology, incidence, vulnerability. The time frame determined 2012- 2022. RESULTS: In the stratification by Federated Unit, there is evidence of an important heterogeneity in the country, with the highest incidence coefficients of TB in the Southeast. Men between 25 and 40 years old are the most affected by TB, a fact that may be related to the man's lifestyle. Indigenous, black and brown populations appear to be more vulnerable to tuberculosis. The prevalence of TB higher in individuals who have not completed elementary school. FINAL CONSIDERATIONS: It is concluded that the greatest representativeness of populations are the most vulnerable to TB, among new cases, which indicates that intersectoral actions will be necessary to serve vulnerable populations, in addition to articulated actions between the three spheres of management of the Unified Health System (SUS).

Keywords: Tuberculosis, Epidemiology, Incidence, Vulnerability.

1 INTRODUCTION

Tuberculosis (TB) is still a major public health problem worldwide. It is estimated that in 2019, worldwide, about ten million people evolved with TB and 1.2 million died due to the disease. As for treatment outcomes, in 2018, the percentage of treatment success was 85% among new cases1. Brazil is among the 30 countries with a high burden of TB and TB-HIV co-infection, considered a priority for the control of the disease in the world by the World Health Organization (WHO) 1,2.

The planning of tuberculosis control actions depends on the epidemiological indicators of the disease. Facing the new coronavirus has worsened the epidemiological situation of TB in the country and in the world3. TB mainly affects people who have compromised immune systems to some degree,

such as patients with HIV. However, historically, TB represents a panorama of class inequality, people who suffer a process of marginalization by society, people in a situation of vulnerability, among others, that is, according to the state in which the individual is in becomes more susceptible to exposure to Koch's bacillus2,3.

The disease is cured through effective treatment, which is carried out with the use of various anti-TB drugs. According to the PNCT (National Program for Tuberculosis Control), of the Ministry of Health, there are four drugs used in the basic regimen for the treatment of tuberculosis, in combination, in adults and adolescents: Rifampicin 150 mg, Isoniazid 75mg, Pyrazinamide 400mg and Ethambutol 275mg. In the case of the disease in children, Ethambutol 275mg is removed from the regimen, using only the first three4.

In Brazil, the diagnosis of TB is performed as recommended in the Manual of Recommendations for the Control of Tuberculosis in Brazil being subdivided into clinical, differential, bacteriological, imaging, histopathological diagnosis and other diagnostic tests. In addition to laboratory diagnosis, clinical evaluation is of paramount importance for the diagnosis of TB and chest X-ray is indicated as a complementary method for this diagnosis4.

According to the recommendations of the Ministry of Health there is a group of people who are more susceptible to becoming infected by tuberculosis, it is called "populations more vulnerable to tuberculosis" that includes indigenous people, the population deprived of liberty, people living with HIV/AIDS and homeless people. This population demands specific care. For the Information System of Diseases and Notifications (SINAN), there is a "special group" in which health professionals are considered vulnerable along with the population mentioned above3.

Considering that TB is a serious disease that affects the most vulnerable population, the study aims to perform an epidemiological analysis of tuberculosis in Brazil between 2012 and 2022.

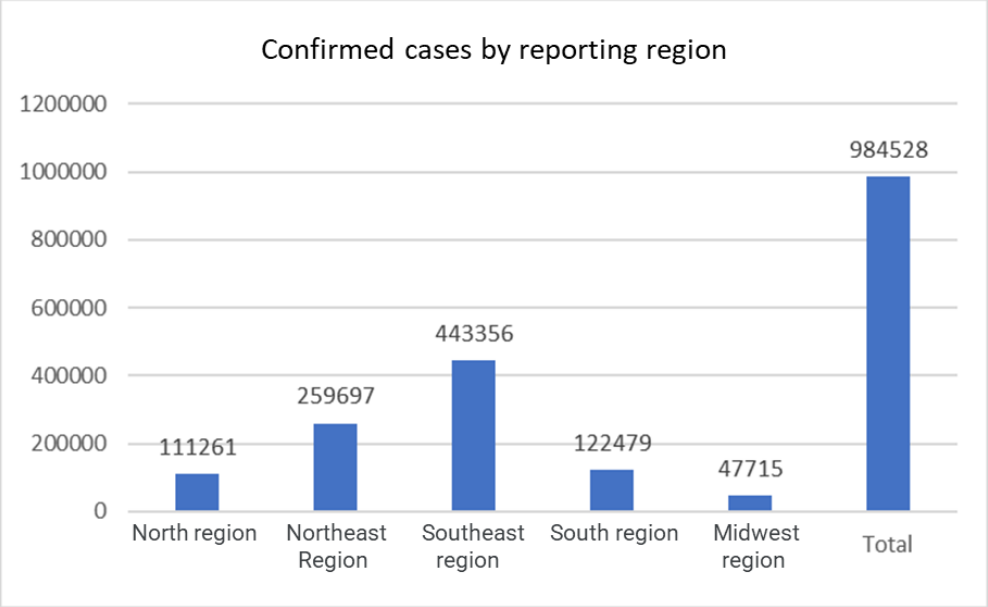
2 METHODOLOGY

It is a bibliographic and theoretical-descriptive research, based on studies and theoretical research, seeks to identify elements to describe characteristics related to information, usability and visualization of platforms that provide open data. It is also an exploratory research, whose objective is to provide an overview of a certain fact and enable increased familiarity with the problem from concepts related to the theme makes an exploratory research. Data collection was performed in the following sources: Database of the Unified Health System - DATASUS and official documents of the Ministry of Health. Descriptors used for the search were tuberculosis, epidemiology, incidence, vulnerability. The time frame determined 2012-2022.

3 FINDINGS

In the stratification by Federated Unit (UF), there is evidence of an important heterogeneity in the country, with the highest incidence coefficients of TB in the Southeast, as shown in Graph 1.

Graph 1 – Confirmed cases of TB according to Region of notification in the Period: 2012-2022



Sources: Ministry of Health/SVS - Information System of Notifiable Diseases - Sinan Net, 2022.

Brazil covers approximately 50% of South America and is subdivided into five administrative/geographical regions (North, Northeast, Southeast, South and Midwest). These five regions show different climatic patterns, socioeconomic characteristics, political dynamics and administrative structures, although the organization of health services is also different between regions, the majority (71%) of the population depends on the public health services provided by the Unified Health System. The primary health care (PHC) system should be the first point of contact for people who interact with the health system6.

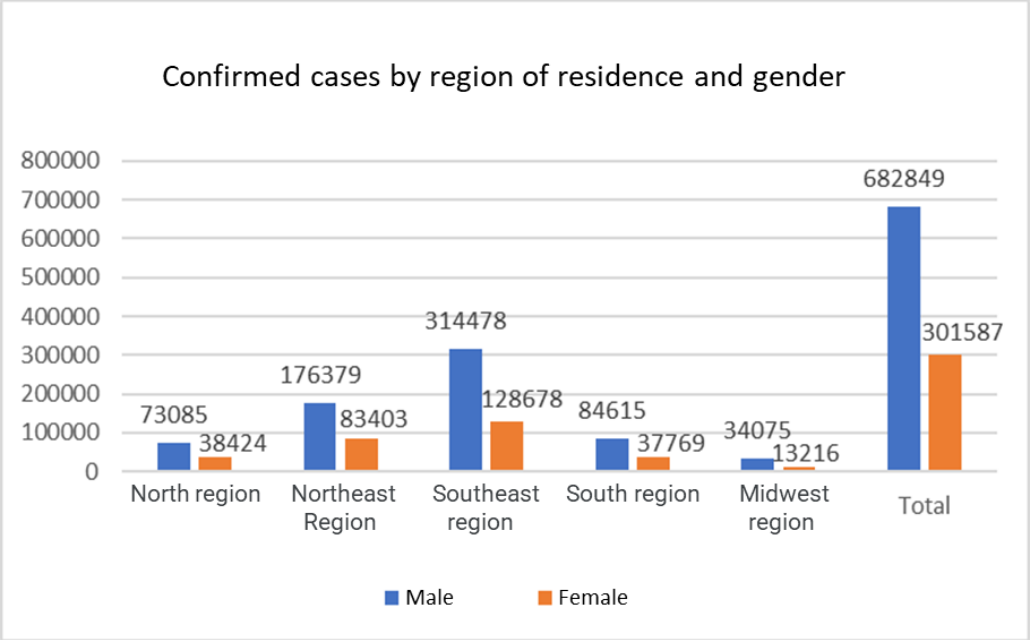
The Northeast region with an increase in notification cases in the year 2021, but there is a data conflict when compared to the table above, which highlights the Southeast region with a high number of notifications of 183,659 cases above the Northeast region, these data can be justified by the lack of notification of the region. The two regions have individual characteristics, such as economic and economic conditions.

Development, in the Northeast region there is a need to supervise and monitor the notifications made, to ensure greater reliability of the data and already in the Southeast region has a larger population, with greater development of the region with a greater number of penitentiaries, and people who perform the treatment for access to health service. According to the MS, in 2022 were notified 84,1 cases of the disease for each group of 100 thousand people in the Amazon. Rio emerges in second place with 75.9, and Roraima in third place with 68.8 cases. Data from the information system indicate

that, in general numbers, 3,826 cases and 214 deaths from the disease were recorded in 2022, throughout the state7.

Men between 25 and 40 years of age are the most affected by TB, a fact that may be related to the man's lifestyle (Graph 2) According to studies, men are more likely to suffer from cases of silicosis, drug use, alcohol abuse, chronic obstructive pulmonary disease, human immunodeficiency virus (HIV) infection and lung cancer, factors that can interfere with the body's defenses when fighting the bacterium Mycobacterium tuberculosis6.

Graph 2 - Confirmed Cases by Region of Residence and Sex in the period of 2012-2022

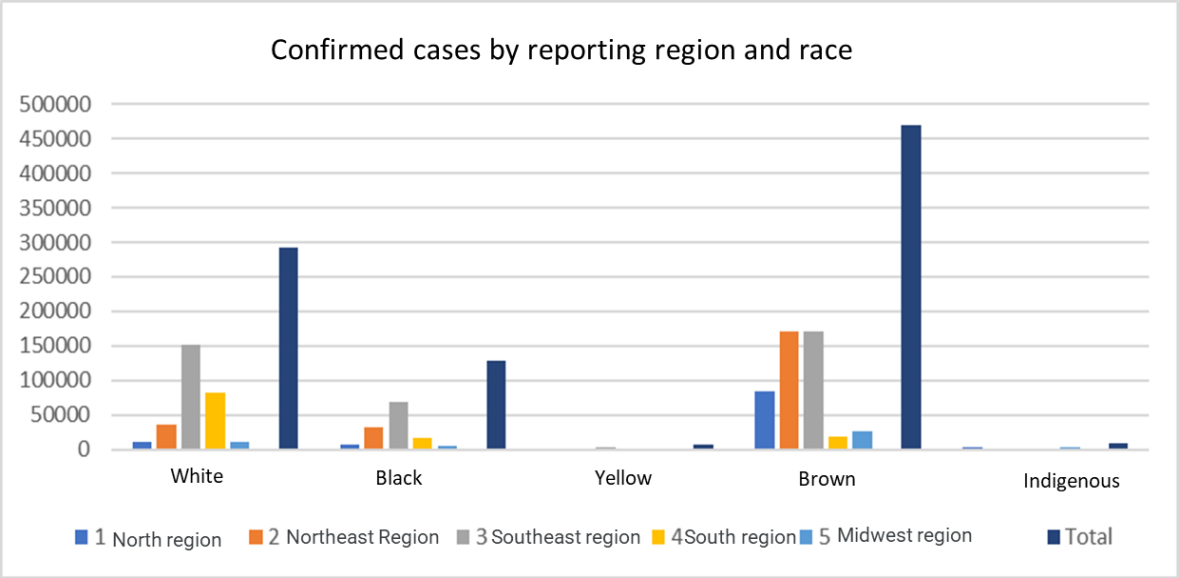


Sources: Ministry of Health/SVS - Information System of Notifiable Diseases - Sinan Net, 2022.

After the analysis of the table highlights some factors that predispose each sex to the bacillus, the male sex is more vulnerable. Men had a lower schooling rate than women, worked and had more time dedicated to activities outside the home. The female participants had higher schooling, worked and dedicated more time to activities at home, these exposure factors have high relevance in terms of sex and exposure to TB. Male genders stand out in exposure to the agent, due to individual gender factors such as: type of work, not seeking health services, low level of education, neglect of the disease, among other factors7,8. In all regions of the country according to TABNET data, the male sex stands out in the cases of notification of the disease reaching twice as much as the female sex, The region where there are higher notifications of the disease in males and the Southeast region, in this same region there are less than half in females, reaching 128,678 cases of notification, and the region that remains in second place in cases of notification is the Northeast region1,5,6.

Indigenous, black and brown populations are considered more vulnerable to tuberculosis.

Graph 3 - Confirmed Cases by Region of Residence and Race in the period of 20122022

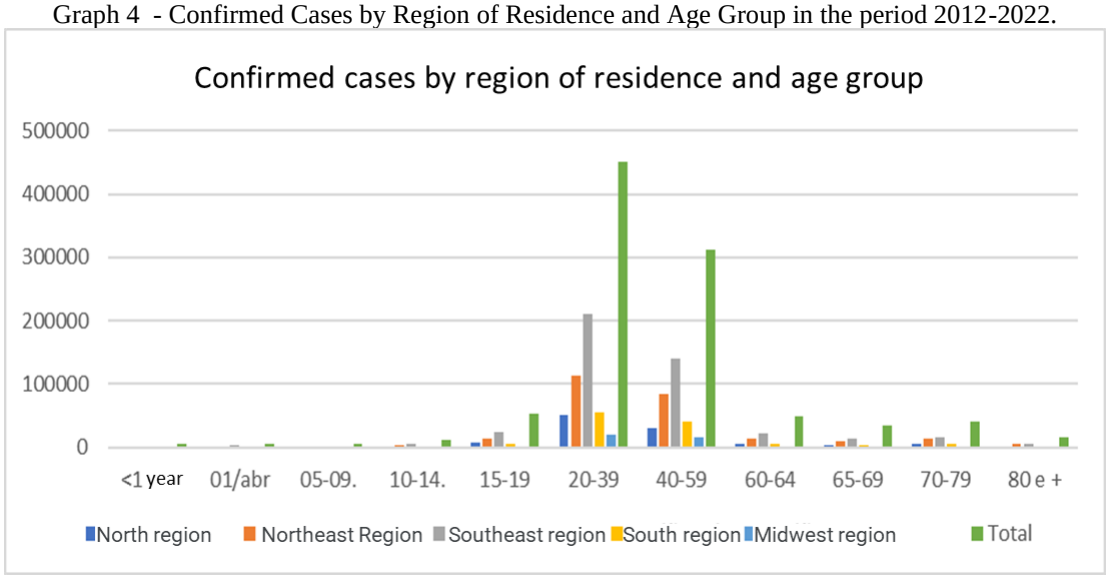


Sources: Ministry of Health/SVS - Information System of Notifiable Diseases - Sinan Net, 20225.

In view of the data collection shown in the table, we analyze that people of the brown race are being more infected by tuberculosis because they are a population in a greater situation of economic and social vulnerability.

However, the increased incidence of tuberculosis in vulnerable populations reflects the need for collaborative behaviors, since only popular participation and the rights provided for by law will, in fact, be granted equally among individuals. Note the importance of priority in developing projects and actions with repercussions in the fight and eradication of the disease, which pays attention to the most vulnerable groups with regard to reducing the incidence of TB.

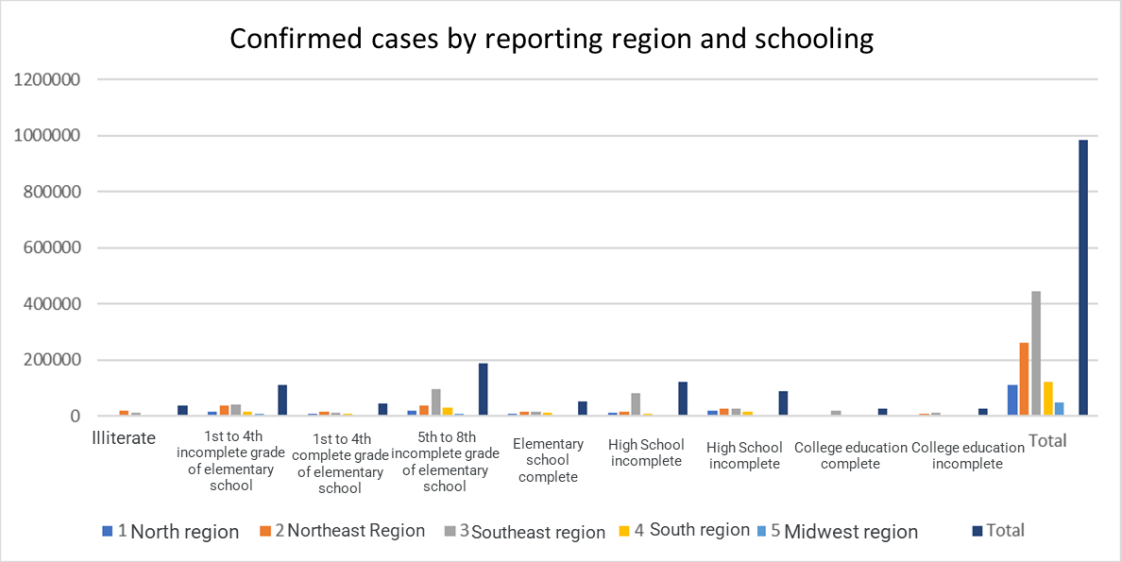
Graph 4 - Confirmed Cases by Region of Residence and Age Group in the period 2012-2022.



Sources: Ministry of Health/SVS - Information System of Notifiable Diseases - Sinan Net. 20225.

The Southeast region has 31,600 cases reported for those over 20 years of age, followed by the Northeast region with 18,122 cases reported in 2018 for those over 20 years of age, demonstrating that from adolescence entering adulthood and where the confirmed and notified cases of TB stand out, due to social factors of exposure. The age group that showed the lowest rate of contagion was in the Midwest region with 20 cases was less than 1 year in 2018. After the analysis of the data collected and the table we observed a relationship between both, with the data obtained from the tabnet in the year 2023, having relations in the age groups with higher and lower index of contagion and notification, demonstrating that from the adult phase of 20 to 59 years and where there are greater cases of notification, manifesting the most severe forms of the disease. And children under 1 year and where there are the lowest cases of notification in all regions of the country.

Graph 5 - Confirmed cases by Region of notification and Education in the period 2012-2022



Sources: Ministry of Health/SVS - Information System of Notifiable Diseases - Sinan Net, 2022.

After the analysis of the table, it is noticed that there is a greater number of confirmed cases of tuberculosis in individuals with incomplete elementary education. Low schooling may influence the lack of understanding of tuberculosis treatment, consequently causing non-continuity of therapy. This can generate difficulties for the effective control of tuberculosis, also contributing to the triggering of drug resistance. It is known that for treatment efficacy, patient adherence to the adopted regimen is fundamental, since the current therapeutic regimen is highly effective and provided free of charge with the capacity to cure practically all cases8,9.

As a consequence, the lack of accessibility to information for these individuals is low, reflecting the level of education of the majority of the population and leading to increased vulnerability to tuberculosis, being responsible for the higher incidence of the disease, which favors lower adherence to the respective treatment in Brazil 9,10.

However, it is necessary to make greater efforts by health teams, established governments, to improve the level of education, as well as continued actions to the population, especially those at risk of contracting and developing the disease, and adoption of strategies that enable communication, access to information, knowledge of the therapy used and monitoring of confirmed cases10.

4 FINAL CONSIDERATIONS

Tuberculosis is one of the infectious diseases of great importance for public health and significantly affects the most vulnerable populations. The epidemiological data of tuberculosis cases in Brazil were analyzed in the period 2012 to 2022; by the Information System of Notifiable Diseases (SINAN) and the results indicated a linear increase in cases in recent years that may be mainly related to the increase in poverty. Another factor that may contribute to TB control is linked to social determination, along with an important economic crisis that Brazil has been going through in recent years. The result of the research shows greater representativeness of populations more vulnerable to TB, among the new cases, which indicates that intersectoral actions will be necessary to serve vulnerable populations, in addition to articulated actions between the three spheres of management of the Unified Health System (SUS).

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Sweet potato: Nutritional aspects of roots and leaves

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ABSTRACT
Sweet potato is an important source of nutrients. This systematic review of scientific research aimed to synthesize data on the nutritional composition of sweet potato roots and leaves and health benefits. The roots are an important source of carbohydrates, minerals and bioactive compounds. The leaves are rich in fiber, minerals and polyphenols. Dietary intake of sweet potato can be strongly recommended for its undeniable health-promoting properties.

Keywords: Ipomoea batatas, Roots, Leaves, Nutritional composition.

1 INTRODUCTION

Sweet potato is a vegetable of world importance for food and nutrition security, and is ranked among the six most important food crops, behind rice, wheat, potatoes, corn and cassava. Originated in Latin America, this culture stands out for its social and economic importance in various regions of the world, especially in Asian and African countries. There is great varietal diversification in different growing regions (Shekhar et al., 2015; Lee et al., 2012), which together with climatic factors, soil, cultivation practices, and post-harvest conservation lead to variations in chemical composition of the roots and leaves.

Sweet potatoes are becoming the focus of several researches due to their unique nutritional and functional properties. Almost all parts of the sweet potato plant (stem, leaf and root) can be consumed as food, and these parts can vary in terms of nutrients, non-nutrients and anti-nutrients (Alam, 2021).

Bioactive carbohydrates, proteins, lipids, carotenoids, anthocyanins, phenolic acids and minerals are present in different parts of the sweet potato plant. This composition makes sweet potato a plant capable of providing several health benefits, such as antioxidant, hepatoprotective, anti-inflammatory, antitumor, anti-diabetic, antimicrobial, anti-obesity action (Mohanraj & Sivasanka,

2014; Wu et al., 2015; Wang, Nie & Zhu, 2016; Wang et al., 2017; Albuquerque, Sampaio & Souza, 2019).

However, despite the important nutrients and bioactive compounds, sweet potato and leaves, contains antinutrients such as phytic acid, cyanide, tannins, oxalates and anthraquinones (Islam, 2006; Mitiku & Teka, 2017; Abong et al., 2020; Oloniyo, Omoba & Awolu, 2021; Alam, 2021).

2 SWEET POTATO ROOTS

The roots of many varieties of sweet potato have an outer skin of different colors, yellow, white, purple (Alam, 2021), and are generally classified by size, flesh and skin color, leaf and flower color, and agronomic parameters such as resistance to pests and diseases and precocity.

Sweet potato roots show a great variation in dry matter content, which is due to not only growing conditions and harvest time, but is intrinsically linked to the genotype. Oboh, Ologhobo & Tewe (1989), analyzing forty-nine sweet potato genotypes, observed a variation of 17.8 to 36.8 g $100g^{-1}$ of dry matter in the roots.

Roots are important energy sources due to their considerable carbohydrate contents, with starch as the main component (42.5 to 64.9% of dry matter) (Wang, Nie & Zhu, 2016).

The sweet taste of sweet potato is due to the presence of sucrose, glucose and fructose. During storage and cooking, maltose is observed resulting from the hydrolysis of starch by α- and β-amylases (Wang, Nie & Zhu, 2016). Adu-Kwarteng et al. (2014), evaluating the sugar profile of sweet potatoes, observed variation in the total sugar content from 4.10 to 10.82 g $100g^{-1}$ of dry matter, with the highest levels at the end of the growing season (five months). According to these authors, sucrose is the main sugar in cultivars with high dry matter content.

Glucose and fructose are the most abundant reducing sugars in sweet potato roots, with contents of 2.7 to 4.7 mg/g of glucose and 1.4 to 4 mg/g of fructose in dry weight of roots (Mei et al., 2010). Wu et al. (2015) analyzing non-starch polysaccharides in purple-fleshed sweet potatoes report that polysaccharides extracted from roots comprised residues of rhamnose, xylose, glucose and galactose.

The relationship between the carbohydrate contents in sweet potato roots and the size/weight of the roots showed that with the increase of tuberization there is an increase in the starch and sucrose contents and a decrease in the glucose and fructose contents (Wang et al., 2016).

In addition to the nutritious aspects, high levels of reducing sugars lead to browning of products subjected to high temperatures, which in most cases is undesirable in sweet potato processing. On the other hand, sugars can be used as substrates for fermentation, having softening effects on bakery products such as bread and cake, positively affecting their texture.

The protein contents in sweet potato roots vary widely (1.3 to 9.5% of dry matter) (Wang, Nie & Zhu, 2016), and sporamines (A and B) are the main proteins in the roots of the sweet potato (60% -

80% of total protein) (Chen et al., 2006). Sporamines play important roles in the physiology of the sweet potato plant, as a defense, nitrogen source and stress tolerance (Senthilkumar & Yeh, 2012).

Some studies have shown beneficial effects of sweet potato protein isolates for cancer treatments. Zhang & Mu (2018) reported that in human colon cancer cell HT-29, sweet potato protein hydrolysates, treated by 6 proteases, exhibited some antiproliferation effect with IC_{50} values ranging from 119.72 to 422.05 μg/mL. As a type of mucoprotein, sweet potato glycoprotein (SPG) is an important biological active constituent. Li et al. (2019), evaluating the effect of SPG-56 glycoprotein in the treatment of breast cancer, observed that oral administration (240 mg/kg/d) was able to inhibit breast cancer metastasis in mice with MCF-7 and 4T1.

Dietary fiber is present in food components and is resistant to digestion and absorption in the small intestine. According to water solubility, dietary fiber can be classified into insoluble fiber and soluble fiber, with insoluble fiber being assigned the volume property, while soluble fiber has the function of promoting or suppressing the growth of distinct bacterial groups in the competitive environment of the intestine and colon (Liu et al., 2020).

Mullin, Rosa & Reynolds (1994) analyzing the dietary fiber contents in roots of five sweet potato cultivars observed contents of 18.04, 19.04, 17.88, 21.99 and 19.86% of dry matter in the roots of Georgia Jet, Jewel, Beauregard, Resisto and Southern Delite cultivars. The soluble and insoluble fiber contents in the dry basis were respectively 5.58 and 5.77% for 'Georgia Jet', 6.06 and 5.95% for 'Jewel', 4.47 and 4.60% for ' Beauregard', 5.91 and 5.12% for 'Resisto' and 5.07 and 4.86% for the Southern Delite cultivar.

Liu et al. (2020) analyzing the effects of sweet potato dietary fibers on the intestinal microbiota, with an assay simulating the human intestine, observed that sweet potato fibers provided a significant increase in the concentrations of *Bifidobacterium* and *Lactobacillus* and a significant decrease in *Enterobacillus*, *Clostridium perfringens* and *Bacteroides*. The prebiotic index and the value of *Bifidobacterium/Enterobacillus* also increased significantly compared to results from the control group, suggesting prebiotic effects for isolated sweet potato fibers.

Vitamins and minerals are essential for the vast majority of biochemical processes in the human body, and sufficient intake of these nutrients can prevent the development of hidden hunger.

Sweet potato roots contain significant amounts of essential minerals for health. Fresh roots of sweet potato harvested at various locations have contents ranging from 34 to 101 mg 100 g^{-1} for calcium, 15 to 37 mg 100 g^{-1} for magnesium, 28 to 58 mg 100 g^{-1} for phosphorus, 191 to 334 mg 100 g^{-1} for potassium, 0.62 to 1.26 mg 100 g^{-1} for iron, 0.37 to 0.69 mg 100 g^{-1} for zinc, 0.38 mg 100 g^{-1} for manganese and 0 .12 mg 100 g^{-1} for copper (Laurie et al., 2015).

Alam et al. (2020) studying the mineral content of roots of nine orange-fleshed sweet potato cultivars observed for the microminerals iron (Fe), copper (Cu) and zinc (Zn) in dry basis contents

ranging from 0.91 to 1, 40 mg 100 g^{-1} Fe, 0.25 to 0.67 mg 100 g^{-1} Cu and 2.85 to 4.25 mg 100 g^{-1} Zn. The authors also reported different levels of macrominerals, calcium (Ca), potassium (K), magnesium (Mg) and phosphorus (P) for the cultivars, with variations from 21.98 to 27.35 mg 100 g^{-1} Ca, 310.04 to 368.35 mg 100 g $^{-1}$ K, 21.28 to 25.40 mg 100 g $^{-1}$ Mg and 41.98 to 45.29 mg 100 g $^{-1}$ P.

These studies show that sweet potato consumption can contribute to the recommended intake of minerals. According to FAO / WHO (2001) the daily mineral intake required for a normal adult male are: 10-15 mg iron, 12-15 mg zinc, 2-3 mg copper 1000-1300 mg calcium and 220-260 mg of magnesium.

For vitamins in sweet potatoes, Ishida et al. (2000) reported that the highest levels are found in the leaves, but the authors observed in the fresh pulp of the cultivars Koganesengan and Beniazuma 8 and 23 µg 100g^{-1} of β-carotene, 52 and 126 µg 100g^{-1} of vitamin B1, 37 and 52 µg 100g^{-1} of vit. B2, 36 and 105 µg 100g^{-1} of vit. B6, 627 and 913 µg 100g^{-1} of niacin, 335 and 695 µg 100g^{-1} of vit. B5, 32.3 and 35 mg 100g^{-1} of vit. C and 0.34 and 0.18 mg 100g^{-1} of vit. E., respectively.

Sweet potato roots have gained recognition as a functional food due to the various bioactive compounds in different parts of the plant, which provide a variety of health-promoting benefits.

Carotenoids are natural pigments in foods and some act as precursors of vitamin A, have a regulatory function and high antioxidant capacity. Thus, they have been associated with the prevention of neoplasms, increased activity of the immune system, in addition to being related to the prevention of most non-communicable chronic diseases (Fernández-Garcia et al., 2011).

Sweet potatoes with orange, yellow, cream and white pulps differ in the composition of carotenoids. The carotenoid content of eleven sweet potato varieties of different flesh colors ranged from 0.4 to 72.5 µg g^{-1} fresh weight (Tomlins et al., 2011). The trans-β-carotene content of four orange pulp varieties ranged from 79.1 to 128.5 mg 100 g $^{-1}$on a dry basis and lutein and zeaxanthin ranged from 0.1–0.4 and 0.1– 0.2 mg 100 g^{-1}, respectively (Donado-Pestana et al., 2012).

The relationship between flesh color of sweet potato varieties and levels of bioactive compounds has been observed. Park et al. (2016) analyzing bioactive compounds in sweet potato roots with different flesh colors reported higher levels of carotenoids in orange-fleshed sweet potatoes, with high levels of β-carotene, and anthocyanins were detected only in sweet potatoes from purple pulp. The levels of phenolic acids and flavonoids were relatively higher in the purple-fleshed sweet potato than in the other two varieties.

Antioxidant activities have been attributed to sweet potato roots. This is due to the bioactive compounds present, but the cultivation and processing conditions can interfere with this characteristic. Rautenbach et al. (2010) studied the effect of different water regimes in sweet potato cultivation and thermal processing on antioxidant content (β-carotene, chlorogenic acid and vitamin C) and antioxidant capacity and observed that orange pulp varieties had more β- carotene, chlorogenic acid

and vitamin C than cream pulp varieties. The authors also observed that water stress increased the levels of β-carotene, vitamin C and chlorogenic acid, as well as the antioxidant capacity of some varieties and that thermal processing decreased the content of carotenoids and vitamin C in all varieties, but increased the chlorogenic acid content and antioxidant capacity.

3 SWEET POTATO LEAVES

Sweet potato leaves have been used as a fresh vegetable in some parts of the world. They can be harvested before the end of the sweet potato growing cycle, representing an important source of nutrients beneficial to health.

Different levels of nutrients are observed in sweet potato leaves, which vary between cultivars with contents in g/100g of dry matter of moisture from 84.09 to 88.92, crude fiber from 9.15 to 13.59, crude fat from 2.37 to 5.28, carbohydrates from 42.03 to 61.36 and ash from 7.83 to 14.66 (Sun et al., 2014).

Sweet potato leaves are important sources of fiber and the interference of the moment of harvesting the leaves on their nutritional composition was highlighted by Suárez et al. (2020). The authors observed variations in g/100g of dry matter from 49.8 to 51.8 for total dietary fiber, 42.8 to 45.1 for insoluble fiber and 7.3 to 8.1 for soluble fiber.

Minerals play important roles in the human body and the consumption of sweet potato leaves can contribute to the necessary daily intake. According to their daily requirements, minerals are classified into macrominerals (Ca, P, K, Na, S, Cl, Mg) (daily requirements of >100 mg in adults) and microminerals which are divided into trace elements (Fe, Zn, Mn , Cu, F) (daily requirements between 1 and 100 mg in adults) and ultra-trace elements (Se, Mo, I, Cr, B, Co) (daily requirements of <1 m in adults).

The mineral profile of sweet potato leaves is strongly influenced by genotype, growing conditions (soil, fertilizers, water management, pests, diseases) and plant age at harvest. A study of forty sweet potato cultivars grown in China shows variation in macromineral contents between genotypes, with calcium contents ranging from 229.7 to 1958 mg/100g DW, potassium ranging from 479.3 to 4280 mg/100g DW, phosphorus from 131.1 to 2639.8 mg/100g DW, magnesium from 220.2 to 910.5 mg/100g DW and sodium from 8.06 to 832.31 mg/100g DW (Sun et al., 2014). This study shows the unexplored potential of sweet potato leaves as a source of minerals.

Antioxidants play important roles in preventing of aging and age-related diseases. Encouraging the consumption of fruits and vegetables as natural sources of antioxidant compounds is justified by the safety concerns associated with supplemental forms of antioxidants.

In vitro antioxidant and free radical scavenging activities, as determined by various chemical assays. Suárez et al (2020), studying the harvest of sweet potato leaves in three periods of the crop

cycle, reported variations in their composition, concluding that leaves harvested at the end of the cycle had the highest total polyphenol content (9.1 ± 0. 3 g/100 g dw) and antioxidant activity (DPPH: 7.4 ± 0.1 g VcE/100 g dw; ABTS: 10.6 ± 0.7 g VcE/100 g dw; FRAP: 0.617 ±0.005 µmol TroloxE /100 g dw).

According to Alam et al. (2021), compared to the main commercial vegetables such as spinach, broccoli, cabbage and lettuce, sweet potato leaves contain high concentrations of polyphenolics and these compounds are claimed to have antioxidants, anti-cancer, anti-diabetic, cardioprotective, antimicrobial, stimulants of immune system, in addition to having hepatoprotective properties.

4 CONCLUSION

An adequate and healthy diet is the best alternative for the quality of life of humanity. The valorization of sweet potato not only as an energy base, but also as a food rich in nutrients beneficial to health, can increase the worldwide consumption of this vegetable and its benefit value, contributing to social and economic advances in the main producing regions.

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Tobacco control by public pharmaceutical assistance policies

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ABSTRACT
Smoking is responsible for several diseases and millions of deaths every year, being one of the major causes of preventable death in the world. Defined as the chemical dependence on nicotine in cigarettes, its main associated diseases are lung cancer (about 90%), cardiovascular diseases (about 25%), chronic respiratory diseases such as bronchitis and emphysema, and a higher risk of stroke and respiratory infections. The most effective policies to combat this addiction include increasing taxes on tobacco products, banning tobacco advertising, creating smoke-free environments, clearly labeling tobacco products, and offering smoking cessation services. In Brazil, the National Tobacco Control Program (PNCT), created in 1986, and the Anti-Smoking Law (Federal Law No. 9,294/1996), are milestones for pharmaceutical assistance, which assists policies in the treatment of smoking. In the pandemic, this dependence was one of the main comorbidities associated with severe cases of COVID-19, which were better controlled by updated health professionals and acting together to guarantee access to essential treatments and support therapies for smokers. Currently, public policies are needed to raise awareness among the population about the risks of smoking and e-cigarettes, avoiding their indiscriminate and uncontrolled trade, among other measures. In this sense, the 2030 Sustainable Development Goals (SDGs) impose coordinated efforts on countries to implement effective tobacco control policies in an integrated, sustainable and democratic manner, with the participation of civil society and health professionals.

Keywords: Pharmaceutical assistance, Public policies, Smoking.

1 INTRODUCTION

Tobacco control in the face of pharmaceutical services and public policies is a topic of great importance in the health area, since smoking is considered a public health problem, where cigarette consumption is responsible for several diseases and deaths worldwide (RIBEIRO, 2022).

Smoking is defined as the chemical dependence of nicotine present in cigarettes, being monitored among chronic non-communicable diseases in Brazil since 2006 (PAHO/WHO, website). Its history of control is marked by certain government actions, such as the creation of laws that prohibit smoking in public places, awareness actions about the harms of smoking and the availability of treatments to help smokers quit smoking (MOCCIO, 2022).

Initially, tobacco control in Brazil began in 1986, with the creation of the National Program

for Tobacco Control (PNCT), whose main objective was to reduce tobacco consumption in the country. Since then, several measures have been taken to combat smoking, such as the prohibition of cigarette advertising on television and other media, the creation of smoke-free environments, the implementation of health warnings on cigarette packages and the increase in the price of the product (TEIXEIRA, 2011).

Only ten years later, when the Anti-Smoking Law (Law No. 9,294/1996) emerged, the consumption of cigarettes began to be prohibited indoors, such as bars, restaurants and nightclubs. For Buteri (2022), the law was an important milestone in the fight against smoking in Brazil, and since then, the country has been internationally recognized for its tobacco control policies. But despite the advances, smoking is still a public health problem in Brazil.

Thus, pharmaceutical assistance is fundamental in this process, as it offers drugs and therapies that help in the treatment of nicotine chemical dependence, in addition to public policies have an important role, as they encourage the adoption of healthy habits and the prevention of smoking-related diseases, since tobacco control is a constant challenge, but it is fundamental for the promotion of health and quality of life of the population (BARRETO, 2022).

According to Fianco *et al*., (2021) smoking is one of the leading causes of preventable death in the world, accounting for about 6 million deaths per year. The problems that smoking can cause are numerous and affect not only the smoker, but also those who are exposed to cigarette smoke.

Among the diseases associated with smoking, lung cancer, cardiovascular diseases, chronic respiratory diseases such as bronchitis and emphysema stand out, in addition to increasing the risk of stroke and respiratory infections (SMITH *et al.,* 2022).

A study by Muakad (2014) points out that smoking is a risk factor for sexual impotence, infertility and pregnancy complications and it is estimated that smoking is responsible for about 90% of lung cancer cases and 25% of cardiovascular diseases.

It is important to emphasize that the effects of smoking are not limited only to physical health, but also affect the quality of life, work capacity and self-esteem of smokers, making it essential to adopt measures to prevent and combat smoking, such as the implementation of public policies for tobacco control, the promotion of awareness campaigns and the treatment of smoking (ALCANTARA, 2022).

In view of this, pharmaceutical assistance is a crucial aspect in the fight against smoking, since the role of the pharmacist is fundamental in the follow-up of the patient who wishes to stop smoking, since he is able to guide and prescribe medications that help reduce withdrawal symptoms and reduce the desire to smoke. In addition, the pharmacist can advise on the importance of a healthy diet and physical activities for the maintenance of health and for the success of treatment (CHENCHI, 2021).

Pharmaceutical assistance is essential for the success of smoking treatment, because the

pharmacist is able to offer adequate support and guidance so that the patient can achieve his goal of quitting smoking and improving his quality of life, it is also important in monitoring the side effects of prescribed drugs and in identifying possible drug interactions (FERREIRA, 2022).

It is also worth noting that the COVID-19 pandemic has posed many challenges for healthcare, including the relationship with tobacco consumption and the challenges faced by pharmaceutical care and to deal with these issues professionally and effectively. Since the beginning of the pandemic, much has been said about the relationship between COVID-19 and tobacco, because tobacco consumption is one of the main risk factors for several diseases, including respiratory, cardiovascular and cancer problems (TOMIM *et al*., 2022).

It is important to note that the pandemic has brought a number of changes in people's routines. Social isolation, anxiety and stress are some of the factors that may have led many smokers to increase their cigarette consumption. In addition, the pandemic may have hindered access to treatments to quit smoking, which may have aggravated tobacco dependence (LIMA *et al.,* 2021).

According to Ferreira *et al.,* (2020) smoking was one of the main comorbidities associated with severe cases of COVID-19. This is because tobacco consumption affects the function of the lungs and immune system, increasing susceptibility to infections and compromising the body's responsiveness.

In addition, smoking can also increase the risk of transmission of the coronavirus, since the act of smoking can facilitate the spread of the virus by touching the mouth and nose with hands contaminated by the cigarette (PEIXER *et al*., 2022). It was essential that professionals were updated on information and recommendations and adopted protective measures to prevent transmission and worked together with other areas of health to ensure access to essential treatments (CALEJON, 2021).

The impacts caused by the pandemic on smokers are numerous and worrying, where this global health crisis has brought with it a series of changes in people's routine, which may have directly affected the health of smokers, having also increased the use of electronic cigarettes, among other devices (CHATKIN; GODOY, 2020). E-cigarettes are seen by many as a less harmful alternative to conventional cigarettes, but the truth is that there are still many uncertainties about the long-term effects of using these products (BARUFALDI, 2021).

The use of e-cigarettes can lead many young people to become addicted to nicotine, which is extremely concerning and it is critical that public health authorities intensify awareness campaigns about the risks of smoking and e-cigarette use and warn the population about the dangers of these habits, especially during the pandemic, when health became an even more crucial issue (CAVALCANTE *et al.,* 2020).

Concomitantly, it became important that public health policies include measures to help smokers quit, such as the provision of treatments and supportive therapies. It has also become necessary to establish stricter regulations on the use of electronic cigarettes, to prevent these products

from being marketed indiscriminately and without control (MELO, 2020).

The impacts caused by the pandemic on smokers are worrisome and required urgent measures by public health authorities and raising awareness of the risks of smoking and e-cigarette use and offering support to those who wish to quit smoking has become essential to ensure a healthier life free from the harm caused by tobacco (CASTEDO, 2021).

In this sense, public policies and the Sustainable Development Goals (SDGs) 2030 are closely linked to the smoking program. After all, smoking is one of the main risk factors for public health and, therefore, must be addressed with effective public policies (ACHELUS, 2022).

According to Miranda (2023) SDG 3, which deals with health and well-being, has as one of its goals to reduce the number of premature deaths caused by non-communicable diseases, such as lung cancer, which is directly related to smoking. In addition, SDG 12, which deals with sustainable production and consumption, is also linked to tobacco control, since the production and consumption of cigarettes have negative impacts on the environment.

Thus, it is important that public policies aimed at tobacco control are effective and comprehensive, including measures such as increasing taxes on cigarettes, prohibiting tobacco advertising, expanding smoke-free spaces, among others (SANTOS, 2022).

The program aimed at tobacco control, in turn, should offer support so that smokers can quit the addiction, through appropriate treatments and therapies. It is important that this program is aligned with public policies and the 2030 SDGs, in order to contribute to the improvement of public health and the promotion of sustainability (ANDREIS, 2021).

Tobacco control is a global challenge that affects public and individual health, the economy and the environment and to address this problem, a joint effort is needed between society, governments and health professionals together with pharmaceutical assistance being one of the tools available to help smokers quit addiction in the aid of information on smoking cessation drugs, such as nicotine replacement therapy and non-nicotinic medications, which may increase the chances of success in trying to quit smoking (RIBEIRO, 2022).

However, pharmaceutical assistance alone is not enough to control smoking, making it necessary a set of public policies that address the problem on several fronts, such as education, supervision, regulation and health promotion (RECH *et al.,* 2022).

Public policies should also take into account the social and economic inequalities that affect the prevalence of smoking in different population groups and with regard to the 2030 Sustainable Development Goals includes the goal of reducing premature mortality from non-communicable diseases such as tobacco-related diseases by one third and to achieve this goal, a coordinated effort is needed among countries to implement effective public policies for tobacco control (CORDEIRO, 2022).

Some of the public policies that have been shown to be effective in controlling tobacco include increasing taxes on tobacco products, banning tobacco advertising and promotion, creating smoke-free environments, clearly labeling tobacco products, and offering smoking cessation services, where these policies should be implemented in an integrated and sustainable manner, with the participation of civil society and health professionals (MIODOWNIK, 2022).

Tobacco control is a complex challenge that requires a multidisciplinary and integrated approach. Pharmaceutical care is one of the tools available to help smokers quit, but a set of effective public policies is needed to reduce the prevalence of smoking and its impacts on public and individual health. SDG 2030 sets an ambitious target for reducing premature mortality from non-communicable diseases, including tobacco-related diseases. To achieve this goal, a joint effort among countries is needed to implement effective public policies for tobacco control (BESSA, 2023).

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Relationship between SARS-CoV2 infection and the development of chronic non-communicable diseases

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ABSTRACT
COVID-19, a disease triggered by the SARS-CoV-2 coronavirus, emerged in Wahuan and became a global pandemic abruptly, causing great tensions around the world. The composition of the virus is based on a single-stranded RNA viral structure that uses the spike protein (S-spike) to bind to the ECA2 receptor in human cells. Symptoms can range from mild, moderate or severe symptoms and infection can lead to systemic complications and chronic sequelae. In addition, the disease can be classified into asymptomatic, acute, subacute, and post-covid syndrome when symptoms persist for more than 12 weeks. Sequelae can include heart, lung, neurological and renal problems, which can affect the quality of life of infected patients. The prognosis is motivated by the severity of the infection and the pre-existing health status. Preventive measures such as strict hygiene, social distancing, mask-wearing and vaccination are of utmost importance to mitigate the spread of the virus. However, long-term medical follow-up is necessary to monitor and treat complications arising from the infection.

Keywords: Sequelae, COVID-19, Inflammation, Exacerbated, Comorbidities, Chronic non-communicable diseases.

1 INTRODUCTION

COVID-19 is a disease caused by the SARS-CoV-2 coronavirus, which can lead to mild, moderate or severe symptoms. In addition, SARS-CoV-2 infection can lead to various sequelae, such as heart, lung, neurological and renal problems, which can affect the quality of life of infected patients (FORTUNATO et al., 2021).

The advance in the disease was alarming. The number of cases computed in Brazil, until 03/25/2023, was 37,258,663 cases with a number of deaths of 700,229 (BRASIL, 2023).

Individuals who have contracted the virus can present the disease in different forms such as mild, moderate and severe. The latter is related to sequelae of the disease. In addition, the disease can be classified into asymptomatic, acute, subacute, and post-covid syndrome when symptoms persist for more than 12 weeks. Patients have some more common symptoms such as cough, sore throat, pyrexia, rhinorrhea, anosmia, ageusia, nausea, vomiting, diarrhea, fatigue, hyporexia, dyspnea, among others (SOARES et al., 2021).

The pathophysiology of COVID-19 occurs mainly by two mechanisms: direct, which is the entry by the ECA-2 receptor that is present in many organs and systems such as blood, endothelium, eyes, kidneys, gastrointestinal system, vascular system, heart and airways, mainly of type II alveolar cells; and indirect by the systemic inflammation that activates the immune system leading to a "cytokine storm" (ALMEIDA et al., 2021).

According to the World Health Organization (WHO), there is still much to be discovered about COVID-19 and the best forms of prevention and treatment. The WHO states that ongoing research is needed to fully understand the disease and develop effective solutions. It is crucial that patients recovered from COVID-19 are monitored long-term by healthcare professionals in order to identify and treat any future complications. As stated by the WHO, COVID-19 is a new disease and we are still learning about the long-term effects of infection. Those who have recovered from COVID-19 should be closely monitored to assess possible long-term sequelae and provide appropriate treatment (WHO, 2021).

2 COVID-19 AND ITS AFTERMATH

2.1 THE HISTORY OF COVID-19

The year 2019 brought as a milestone a huge change to the lives of human beings. Since the start of the pandemic in Wuhan, China, with the pandemic signaling in March 2020, a new era of isolation and social distancing from family and friends began. In December 2020, the first vaccination campaigns began in some countries. However, social distancing and general hygiene measures continue to be used by some people to this day (MARINO *et al.,* 2021).

In February 2003, 305 cases of Severe Acute Respiratory Syndrome (SARS) were recorded. However, the first reports of the severe disease occurred in 2002 in southern China in Guangdong. The Chinese Ministry of Health came to the conclusion that it was an outbreak of unknown and atypical pneumonia that spread mainly among health personnel, who transmitted it in their homes. This syndrome has also affected other countries such as Canada, Vietnam, Hong Kong, and Singapore (XAVIER *et al.,* 2020).

Due to its spread, an international mobilization began to find the etiological agent of this infection. In 2003 in the United States of America (USA) and Hong Kong had already observed a new

virus, different from the other organisms of the group that causes diseases in humans. In April of that same year, the WHO proposed a global surveillance system to prevent international spread. The tests used in the identification of this new causal agent were: polymerase chain reaction (PCR) studies, cell culture and electron microscopy (XAVIER *et al.,* 2020).

In 2019, China reported the appearance of new cases of pneumonia of unknown etiology in the city of Wuhan in Hubei province. However, it was not until January 2020 that a new coronavirus was identified in China, which was later named SARS-CoV-2. Theories are that the first cases of COVID-19 appeared at a seafood market in Wuhan, where several people buying goods were infected. The infection is zoonotic, but the spread of cases was due to human interactions, and this transmission can occur even in asymptomatic individuals (XAVIER *et al.,* 2020; MARTIN *et al.,* 2020).

The novel coronavirus falls into the order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae. It received the designation of severe acute respiratory syndrome – coronavirus-2 (SARS-CoV-2) by the *International Committee on Taxonomy of Viruses* (ICTV), because it is very similar to another species of coronavirus that almost became a pandemic in 2002, SARS-CoV. It was declared as COVID-19 (coronavirus disease) in February 2020 by the World Health Organization (WHO) (XAVIER *et al.,* ., 2020).

In short, the first symptoms reported to WHO were in December 2019. In March 2020, a global pandemic state was decreed and until December 2020 vaccination and social isolation campaigns began. The disease has spread worldwide. In Brazil, reports of the first case of the disease were confirmed on February 26, 2020 and the first death occurred on March 16 of the same year (MARTIN *et al.,* 2020; Marino *et al.,* 2021). As of March 28, 2023, 13,331,975,343 vaccine doses have been administered (WHO, 2023).

2.2 STRUCTURE AND VIRAL REPLICATION

Since the 60s, a recombination of coronavirus that only reached animals has resulted in outbreaks of infection in humans. It is known, so far, that there are 7 (seven) different strains known. All human coronaviruses are of animal origin, and this recombination probably occurred in bats (CARVALHO *et al.,* 2021).

According to Carvalho et al. (2021), SARS-CoV-2 has a much higher rate of spread than SARS-CoV and MERS-CoV, these three strains are the ones that cause most severe cases of the disease. Coronaviruses (CoVs) contain a positive-sense single-stranded RNA genome, with an extension that can reach 32 kilobases (Kb). They are enveloped viruses and can have pleomorphic capsids and have radial surface projections that look like a corona, hence the name coronavirus (ZHU *et al.,* 2020).

The viruses responsible for the diseases need the cellular machinery to produce their new viral particles. In this way, they need viral replication to survive. These viruses have developed proteins that make them capable of infecting other beings (MARTIN *et al.,* 2020).

The process of viral replication is summarized in the transcription and initial translation of genomic RNA, dependent on the RNA of the host, an enzyme replicasse viral follows completely transcribing a strand of negative simple RNA that will serve as a model for the transcription of subgenomic messenger RNA. The latter will be used to encode new proteins. COVID-19 is a pathology caused by the SARS-CoV-2 virus, which can have mild to moderate or severe symptoms and can affect the quality of life of infected individuals. Consequently, there are several sequelae that can occur (ALMEIDA *et al.,* 2020).

SARS-CoV-2 has unique characteristics that set it apart from its ancestors. These characteristics are in the most diverse post-replication nucleotypes. This is a specific feature of RNA viruses. With each replication, they have the chance to slightly modify its structure and virulence, arriving at the result and characteristic of this virus of having a unique and complex infection capacity (ALMEIDA *et al.,* 2020).

2.3 EPIDEMIOLOGY

The pandemic is a spread of a new disease, on an international scale, attacking almost all individuals from different regions, being related to geographical affect and not related to clinical severity (ÁVILA; 2020).

In just six months, 216 countries have been hit. The most affected was the United States, surpassing the numbers of infected and deaths. On 06/22/2020, there were 119,923 deaths and 2,275,645 contaminated. Worldwide, on the same date, there were 8,860,331 cases and 465,740 deaths (MARTIN *et al.,* 2020).

According to the World Health Organization (WHO, 2023), data as of March 29, 2023, record 761,402,282 confirmed cases of COVID-19 and 6,887,000 deaths reported to WHO. As of March 28, 2023, 13,331,975,343 doses of vaccine have been administered.

The computed number of cases in Brazil, until 03/25/2023, was 37,258,663 cases with a number of deaths of 700,229, reaching, at that moment, a mortality rate of 333.2 per 100 thousand inhabitants (BRASIL, 2023).

According to the study by Malta *et al.* (2021), during the pandemic there was a reduction in the practice of physical activity and the consumption of vegetables; increase in the time of use of television and computer/tablet; increased consumption of frozen, snacks and chocolate; people with at least one CNCD had a smaller increase in alcohol consumption compared to those who do not have NCDs.

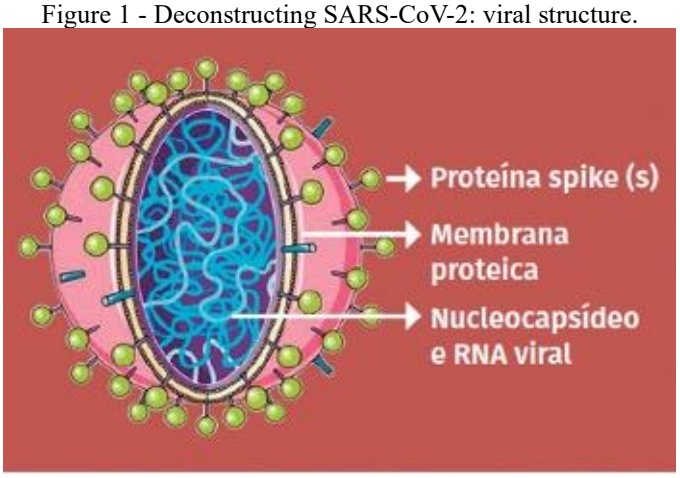
High mortality rates and the lower number of recovered individuals were associated with low schooling, black/brown class and residents of municipalities with lower MHDI (Human Development Index of the municipality) (BRASIL, 2023). However, mortality is also directly related to the clinical picture of the patient and the pathophysiological mechanism of the disease.

2.4 PATHOPHYSIOLOGY

SARS-CoV-2 infection in the host cell occurs through the spike protein (*S-spike*) as we can see in Figure 01, which has two subunits S1 and S2 present in the viral membrane, which binds to the angiotensin-converting enzyme II (ACE-2) being bound to the membrane of the target cell. Thus, its soluble portion in the blood is very low and is present in various tissues such as endothelium, eyes, kidneys, gastrointestinal system, vasculature, heart and airways, mainly of type II alveolar cells (CARVALHO *et al.,* 2021; CARNAÚBA, 2021).

The onset of this viral replication can be by two mechanisms: cleavage of the spike protein in the membrane or endocytosis. After this initial contact, viral replication begins in the infected cell. The pathogenesis of the coronavirus depends on which tissue will be affected by the virus (CARNAÚBA, 2021).

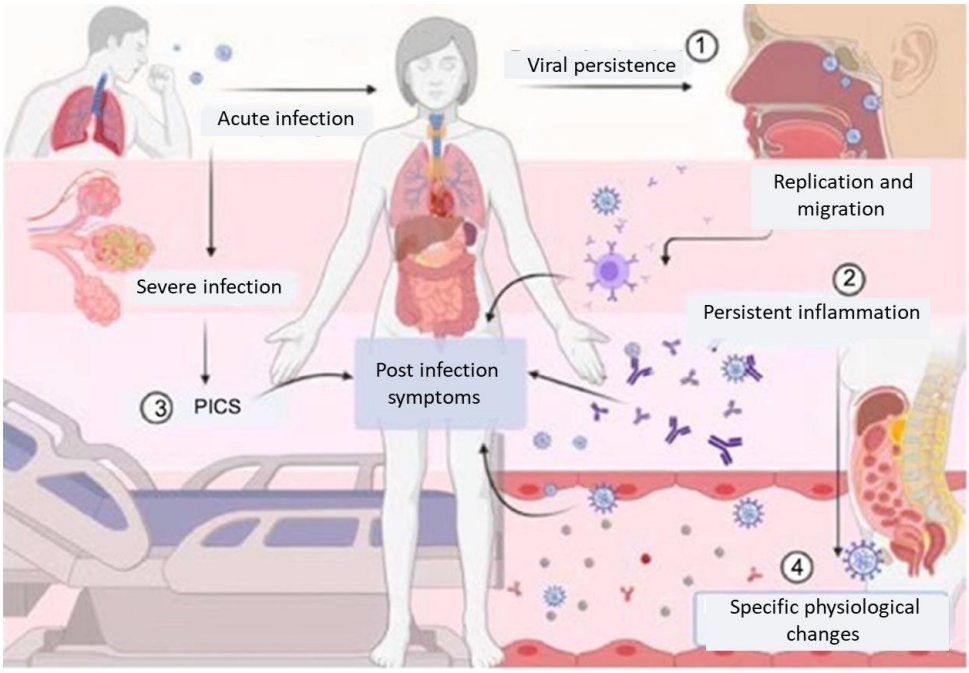
Figure 1 - Deconstructing SARS-CoV-2: viral structure.



Source: Bonjorno *et al.* (2020, p. 07)

The ECA-2 enzyme has many functions, being mainly related to the renin-angiotensin system (RAS), which is a hormonal mechanism, which converts angiotensin I to angiotensin II. The ACE-2, within this system, converts from angiotensin II, a vasoconstrictor peptide, to angiotensin, a vasodilator peptide, whose effect leads to antagonize angiotensin II. enzyme ECA-2, result of an increase in the effect of angiotensin II, thus occurs greater vasoconstriction, production of aldosterone, oxidative stress, inflammation, thrombogenesis and arteriogenesis (AGONDI; AUN; GIAVINA-BIANCHI, 2020; SALHA, 2022). As can be seen in Figure 02 the pathophysiology of COVID-19, which is directly related to the chronic consequences of the disease.

Figure 2 - Pathophysiological mechanisms for the development of post-COVID-19 symptoms. Pathophysiological mechanisms for the development of post-COVID symptoms. 1. The viral persistence found in PCR tests indicates viral replication, which can generate a persistent inflammatory response, promoting the development of symptoms. 2. High levels of inflammatory and angiogenic cytokines have been found, potentially causing post-COVID symptoms. 3. The pathophysiological changes caused by COVID-19 cause structural changes that can lead to system-specific post-COVID symptoms and persistence of the inflammatory response. 4. Severe COVID-19 as an initial disease implies the use of invasive supportive measures, which can lead to the development of PICS, with persistence of symptoms beyond critical illness.



Adapted: Gutiérrez *et al.* (2021, p. 425).

2.5 CLINICAL ASPECTS

COVID-19 has many signs and symptoms varying in infected individuals, and may be asymptomatic and transmit the disease, or have mild, moderate or severe symptoms. Most common symptoms are cough, sore throat, rhinorrhea, pyrexia, rhinorrhea, anosmia, ageusia, disorders, nausea, vomiting, diarrhea, fatigue, hyporexia, and dyspnea (SOARES *et al.,* 2021).

According to the Ministry of Health (2020), patients with severe disease usually have signs and symptoms of viral pneumonia and can progress to situations of Acute Respiratory Distress Syndrome (ARDS), acute heart failure, acute kidney injury, about infection, sepsis or shock.

According to Gutiérrez *et al.* (2021), infection can be classified by the persistence of signs and symptoms in acute: up to 4 weeks; subacute 4-12 weeks; and post-COVID-19 syndrome more than 12 weeks.

Treatment of post-COVID-19 syndrome is multifaceted and should address each patient's individual symptoms. Some treatments may include medications, occupational therapy, and physical therapy to help restore lung and cardiovascular function, as well as relieve symptoms of fatigue and pain. It is important for people who experience these symptoms after recovering from COVID-19 to consult a healthcare professional to get an accurate diagnosis and a proper treatment plan (SIVAN *et al.,* 2021).

According to Melo *et al.* (2019), we can cite five diseases as being the main NCDs: Cardiovascular Diseases (Such as Systemic Arterial Hypertension), Neurovascular Diseases, Chronic Lung Diseases, Diabetes Mellitus and Cancer.

2.6 PROGNOSIS

Lung damage and sequelae will depend on the severity of the disease. They present more frequently in the elderly, but the rate of young people has been increasing due to pneumonia associated with low immunity (LIMA *et al.,* 2021).

In the study by Franco *et al.* (2021), a digital survey was conducted in which 95 participants were counted. The sequelae recorded in this study were found mainly in patients with some comorbidity (61% of the sample).

Several authors have mentioned in their works cases of sequelae and morbidity and mortality after COVID-19 linked to patients who have some comorbidity (diabetes and hypertension, for example) or to cases of hospitalization and complications of the disease (BRAZÃO; NOBREGA, 2021; CARVALHO *et al.,* 2021; CASTRO *et al.,* 2021; ESTRELA *et al.,* 2021; LIMA *et al.,* 2021).

In Brazil, the prognosis remains disproportionate with a mortality rate of around 333.2 per 100,000 inhabitants. Higher mortality rates are observed in patients with low socioeconomic factors and low education (BRASIL, 2023).

2.7 PREVENTION

Contamination by the virus occurs through droplets breathed in close contact. It is very important to note that asymptomatic person is able to transmit the virus. To avoid contamination, some actions should be taken such as asepsis of the hands with soap or alcohol 70% frequently, avoid bringing the hands to the face, use of disposable and non-handmade masks, social isolation when sick. When sneezing or coughing, cover mouth and nose (SOARES *et al.,* 2021).

In addition, pandemic control measures, such as social distancing, can lead to a more sedentary lifestyle and a less healthy diet, which can further increase the risk of developing chronic non-communicable diseases (MORAIS *et al.,* 2022).

The risk depends on factors such as the severity of the infection, the age and previous health conditions of the individual. It is important that patients recovering from COVID-19 are regularly followed up by a healthcare professional to monitor and treat any possible long-term complications (GRAÇA *et al.,* 2020).

2.8 CHRONIC SEQUELAE OF COVID-19

2.8.1 COVID-19 and its relationship to nervous system damage

To better understand the sequelae of COVID-19, it is of fundamental importance to understand how SARS-CoV-2 causes neurological pathology and manifestations.

According to Costa and Silva-Pinto (2020), it is not yet known for sure the mechanism by which this virus reaches the central nervous system (CNS). Theories that stand out are that the virus is transmitted through hematogenous and transsynaptic pathways by infected neurons (olfactory bulb, for example).

Regarding the body's responses to COVID, Gomes, Medeiros Filho and Sousa (2020) state that "[...] In severe forms the resulting inflammatory response can lead to a 'cytokine storm', in which increased serum cytokine levels occur."

Regarding what the same authors expose, we arrive at one of the causes of central nervous system injury. Endothelial cells can be destroyed by inflammatory cytokines, and this can result in hypercoagulation and vascular problems in the brain. Meningitis, encephalitis, encephalopathy, and stroke are neurological diseases that have been linked to infection.

Neuroinflammation, due to inflammatory cytokines, can lead to several modifications in the central nervous system: activation of microglia (CNS immune cells that also release cytokines); changes in neuroplasticity; changes in neurotransmitter metabolism; dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis; and structural and functional changes in the brain. These effects may later lead to neurodegenerative diseases (ACCORSI *et al.,* 2020).

Neuronal pathogenicity is directly linked to the neuroinvasive properties of the virus. ECA-2 enzymes were found in the central nervous system. It is known that SARS-CoV-2 has the ability to bind to ACE-2, which shows us that the pathogenicity in this case is due to this binding in the CNS (GOMES; MEDEIROS FILHO; SOUSA, 2020).

The main neurological symptoms presented by patients affected by COVID-19 are headache, disturbances of consciousness, paresthesia, anosmia and dysgeusia (SILVA *et al.,* 2020). The manifestations found in the studies by Nunes *et al.* (2020) include dizziness, headache, myalgias, hypogeusia, hyposmia, and less common disorders including polyneuropathy, myositis, cerebrovascular diseases, and encephalitis.

Even though the neurological sequelae are still in the study phase, scientists point out that these problems stem from physical damage caused to the neurons themselves and from psychological damage brought on by social distancing and the pandemic. Changes in taste and smell, for example, may be irreversible and are related to the injury caused directly to the primary sensory neurons (LOPES; ABREU, 2021).

People reported feeling exhausted or fatigued, with concentration problems ("brain fog"), anosmia or ageusia, dizziness, tachycardia, palpitations, dyspnea, cough, mood disorders such as depression and/or anxiety, and other sequelae unrelated to the nervous system. What explains these sequelae would be the sum of aggravating factors in the affected patients. Studies report that this post-COVID-19 picture resembles immune system and autonomic nervous system dysregulation syndromes, in addition to aggravating factors found, such as malnutrition found in some post-COVID-19 patients (CASTRO et al., *2021).*

Also according to Castro *et al.* (2021)., the presence of dysregulation of beta-2 receptors and the acetylcholine M3 receptor was identified. This is due to autoantibodies against these receptors. This explains the reported mental fatigue and difficulty concentrating. May result from reduced cerebral blood flow due to excessive sympathetic vasoconstriction in the presence of dysfunctional beta-2 receptors.

2.8.2 COVID-19 and its relationship with damage to the Cardiac System

It is widely known that COVID-19 infection can cause changes in the cardiovascular system. The virus can directly affect myocardial cells and indirectly increase the inflammatory response, which can lead to activation of the immune system and elevated concentrations of lymphocytes and cytokines. These changes can result in significant impacts on the cardiovascular system (COSTA, 2020).

The enzyme ECA-2 is found in the cardiac system and plays a key role in regulating hormonal balance. According to Pecho-Silva *et al.* (2020), ACE-2 is involved in the renin angiotensin aldosterone system, which can lead to a hormonal imbalance. Normally, ACE-2 helps decrease the renin angiotensin aldosterone system by converting angiotensin II to angiotensin I, which is a vasodilator. However, when infected, this balance is affected, leading to increased angiotensin II and, consequently, vasoconstriction. This imbalance can also lead to decreased fibrinogen, increasing the chances of flat ruptures.

All this inflammation leads to a greater oxidative stress and increased metabolism, hindering the gas exchange of cells, having a difficulty pumping in the carotion (GUTIÉRREZ *et al.,* 2021).

Patients who have cardiovascular comorbidities, such as coronary vascular disease (CVD) and high blood pressure, have worse prognoses when infected with COVID-19, as these patients have higher levels of ACE-2. In addition, individuals belonging to other risk groups, such as those of advanced age, carriers of diabetes and cancer, also have worse prognoses when infected by the virus (MELO and MELO, 2023).

2.8.3 COVID-19 and its relationship to damage to the respiratory system

The main function of the respiratory system is the proper gas exchange of oxygen and carbon dioxide between the body and the external environment. When it comes into contact with SARS-CoV-2, an inflammatory process begins in the lung, which can reach other areas of the body, causing numerous problems and subsequent sequelae after infection (LIMA *et al.,* 2021).

Lung injury is the result of the inflammatory process (which begins in the lung). This inflammatory process leads to lung destruction and results in pulmonary remodeling with fibrosis. Fibrosis is a chronic and aggressive process (SILVA, 2021).

What should happen is a recovery of this lung infected by pneumocyte type 2 (PNC2) cells. These cells are the ones that give rise to type 1 pneumocytes (PNC1), which produce surfactant and prevent lung collapse. What happens is that these PNC2 have a higher amount of ACE-2, and are then attacked in greater numbers (LIMA *et al.,* 2021).

It is common for several of the pulmonary symptoms to linger for weeks. This is due to severe hypoxemia, lung injury and respiratory muscle dysfunction as a consequence of cardiopulmonary dysfunctions. Thus, decreasing the tolerance of patients to perform their activities of daily living (SILVA *et al.,* 2022).

2.8.4 COVID-19 and its relationship with damage to the gastrointestinal and hepatobiliary systems

The virus has the ability to infect the gut microbiota. There are receptors of ACE-2 in intestinal epithelial cells and lymphocytes, that is, the virus infiltrates and generates intestinal dysbiosis, which can generate some of the symptoms, anorexia, nausea, dyspepsia, abdominal pain and diarrhea (GUTIÉRREZ *et al.,* 2021).

The gut microbiota is strongly linked to the immune system, generating an immune response by releasing high amounts of inflammatory factors, triggering injury to the gastrointestinal system. Patients with COVID-19 may present hypoxia, resulting in an imbalance in oxygen supply, thus occurring an alteration of intestinal homeostasis, causing loss of integrity of the intestinal epithelium barrier (MORAIS *et al.,* 2021).

There is a gut-lung axis, the virus attacks the pulmonary ECA-2 receptors being then released and through the mucociliary movement goes to the gastrointestinal system, there changes the absorption of some essential amino acids such as tryptophan generating an intestinal dysbiosis (OLIVEIRA *et al.,* 2022).

Another important point to be addressed is that during the infection in most patients was used antibiotics and steroids indiscriminately as a consequence occurs an alteration of the intestinal microbiota (NECOCHEA, 2022).

The hepatic system has high expression of ACE-2, occurring the entry of SARS-CoV-2 in the cells, but the lesion of the hepatic system has not yet been very well elucidated, believed to be multifactorial, such as use of medications, cytokine storm and the entry of the virus into the cells, occurring a metabolic increase and damaging the system (LIMA, 2020).

2.8.5 COVID-19 and its relationship with Rheumatic Diseases

COVID-19 infection generates a large systemic inflammation activating the immune system. The first line of defense is the innate immune system, which generates the so-called cytokine storm, which helps fight the antigen/virus. The main cytokines and chemokines involved are IL-1β, IL-2, IL-6, IL-7, IL-10, TNF and interferon gamma. This high amount of immune response can cause damage to the body's cells. In this sense, the activation of the complement system occurs, mediating dendritic cells, neutrophils and monocytes until there is the collaboration of the adaptive immune system (BONJORNO *et al.,* 2020; FIGUEIREDO *et al.,* 2021).

When activated, adaptive immunity triggers the production of B lymphocytes, which in turn give rise to plasma cells, cells responsible for producing specific antibodies against antigens. However, in some situations, this response can be misdirected, leading to the emergence of autoimmune diseases (CICHELERO and FRAPORTI, 2022).

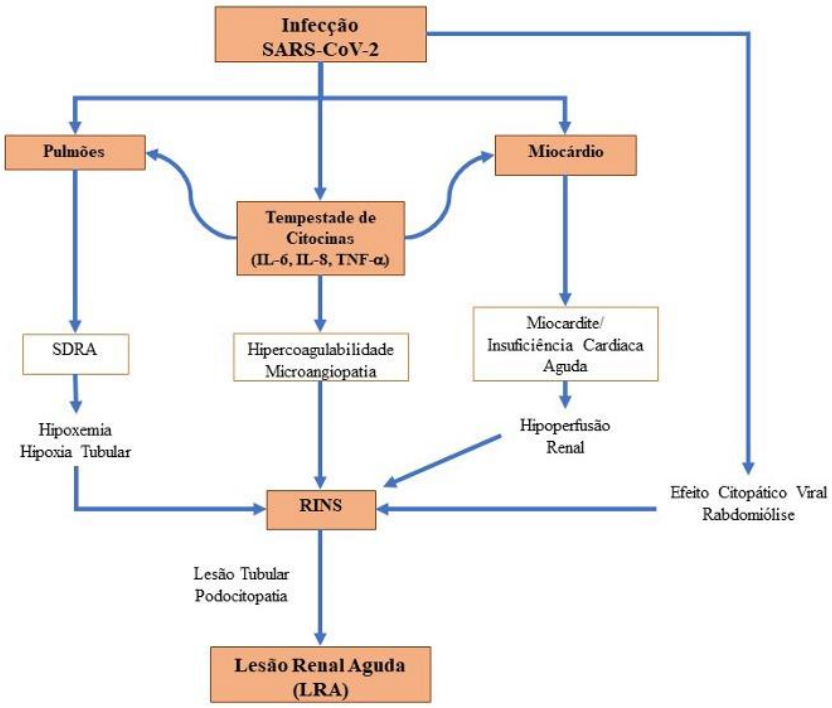
According to Benites, Bagio and Filho (2023), the following diseases were found in descending order: reactive arthritis, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Adult Still's Disease (ASD), dermatomyositis, large cell arteritis, microscopic polyangiitis, systemic sclerosis and acute gout crisis.

2.8.6 COVID-19 and its relationship with damage to the Renal System

According to a study by Hirsch et al. (2020), patients with COVID-19 are at a high risk of developing kidney complications, including acute kidney injury and proteinuria, even in the absence of pre-existing kidney disease.

SARS-CoV-2 infection can result in acute kidney injury as shown in Figure 03, affecting podocytes, proximal tubular cells, and endothelial cells. This lesion can occur by direct mechanisms in the renal cells, as well as by deposits of immune complexes, as well as indirect mechanisms, such as the cytokine storm generated by the immune system, which can lead to renal hypoperfusion. Additionally, pharmacological neurotoxicity may also contribute to the development of kidney injury in patients with COVID-19. Therefore, it is possible to perceive that kidney injury in patients with COVID-19 is multifactorial and complex, involving several pathophysiological mechanisms, as can be seen in Figure 03 (PECLY et al., 2020).

Figure 3 - Pathophysiology of acute kidney injury in SARS-CoV-2 infection. Brief schematization and summary of the main aspects related to the pathophysiology of AKI in patients with COVID-19.



Source: Pecly et al. (2021, p. 558).

2.8.7 COVID-19 and its relationship to endocrine damage

Several factors may be involved in the complications of the endocrine system, such as direct damage to the beta cells of the pancreas due to the expression of ACE-2, resulting in diabetes mellitus, or the possibility of bone demineralization in individuals who have made prolonged use of corticosteroids (BRAZÃO; NOBREGA, 2021; SERNA et al., 2023).

Subacute thyroiditis with thyrotoxicosis, bone demineralization and the onset of diabetes mellitus have been reported as endocrinological consequences. Systemic inflammation, prolonged immobilization, corticosteroid exposure, or vitamin D deficiency may lead to bone demineralization (BREASON; NOBREGA, 2021).

According to D'caminha *et al.* (2022), COVID-19 has directly impacted the decrease in hospitalizations for NCDs in all Brazilian states and in other countries. This was a result of the overload of the Unified Health System in Brazil due to hospitalizations for infected people and social isolation itself. So those pandemic years have been bad for public health control of chronic diseases.

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The performance of the physical education professional in public health in Santa Catarina

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ABSTRACT
This study aimed to analyze the performance of the Physical Education Professional (PEF) and identify which actions they develop in public health in Santa Catarina, as well as what are the difficulties and facilities of the performance. The present research is characterized as a mixed (QUAL>QUAN) and exploratory research model. Participated in the research 35 PEF that work in public health in the State of Santa Catarina. The research instrument used was a questionnaire developed by the researchers and made available via Google Forms®. This instrument is composed of 9 questions, of which 2 are open and 7 are mixed, forming two broad categories of analysis: "aspects of professional performance" (questions 1 to 6) and "training" (questions 7 to 9). The collected data were analyzed through descriptive statistics, organized in a Microsoft Excel® for Windows® spreadsheet. The statistical treatment was performed through the MAXQDA® software, version 2022, for qualitative data analysis. The results show that there is a predominance of performance in exercise programs with the population (FA-33/FR-94.28%), with the main difficulty being the lack of adequate environment for practice (FA-27/FR77.14%) and the main ease the respect and interaction between the professionals of the multidisciplinary team (FA-26/FR 74.28%), it was also possible to verify the understanding of the role of the PEF, characterized by health promotion based on prevention with the practice of physical activity (Figure 3). The findings also show that the professionals consider their incipient training for the work (FA-27/FR-77.14%), as well as presenting the undergraduate disciplines that most contributed to the performance in the context of public health (figure 4). It is concluded that the PEF inserted in public health in Santa Catarina work by developing physical exercise programs in health prevention, being able to identify their facilities, being mainly the respect and rapport between the professionals of the team, and also the difficulties, characterized by the lack of adequate environments for the performance.

Keywords: Public health, Physical Education Professional (PEF), Unified Health System.

1 INTRODUCTION

The insertion of the physical education professional (PEF) in public health was facilitated and regulated after the creation of the Family Health Support Center (NASF) in 2008.[1] It underwent a structural and financing modification in 2017,2 being called the Extended Center for Family Health-Primary Care (NASF-AB). However, the objective of expanding the scope and scope of primary care actions was maintained, seeking the full integrality of the physical and mental care of the population.

Although the PEF was recognized as a health professional in 1997,3 its insertion within this vast field of action is still considered incipient today.

The PEF is responsible for stimulating a new lifestyle of the population, aiming at improving health. Since it is the responsibility of the PEF to carry out activities that generate positive changes in the physiological, psychological and social spheres of the population.[4] The performance of the PEF in the NASF is restricted only to conducting incentive programs and practice of physical activities and exercises, this practice is essential in public health, since staying physically active brings several health benefits.[5]

On the other hand, the PEF could contribute with other innovative actions and practices, which can favor the needs of the population. Such as health education that concerns to promote knowledge of ways to acquire healthy habits, for the improvement of health and quality of life, making the user (population) an active participant in the health-disease process.[6]

This scarcity of PEF in public health is still common today, even though we are aware of its importance in health promotion. The southern regions of Brazil are considered one of the regions with the highest rate of PEF working in public health, with an average of only 3.30 professionals per 100,000 inhabitants.[7]

The role of the PEF in public health, even though the insertion is still recent, is very well grounded in theory, but in practice there is still not much knowledge, both by the population and by the academics of the health area themselves. In view of the above, the objective of this study is to analyze the performance of the PEF and identify the actions developed in public health in Santa Catarina, as well as the difficulties and facilities of the action.

2 METHODOLOGY

This study is characterized as a mixed (QUAL>QUAN) and exploratory research model. Participated in the study 35 professionals of Physical Education inserted in public health.

The research instrument was developed by the researchers themselves and made available via *Google Forms*®. This instrument is composed of 9 questions, of which 2 are open and 7 are mixed, forming two broad categories of analysis: "aspects of professional performance" (questions 1 to 6) and "training" (questions 7 to 9), according to the supplementary material. In order to verify and consolidate the process of interaction between the interlocutors, in order to improve this tool, a pilot test was applied with 25 health professionals (physical education, nutrition, nursing, pharmacy and biological sciences) teachers.

As a distribution vehicle, the virtual medium was used through social networking applications such as *Whatsapp*®, Instagram® *and* Facebook®, as well as e-mail. For this, a search was carried out through the health departments of each city of the State (via e-mail and/or telephone contact), in

order to identify and contact the population investigated. Each secretariat acquired a different approach to reach the professionals, some sent directly to the study population and others granted a list of names and contacts for the authors to send the research instrument.

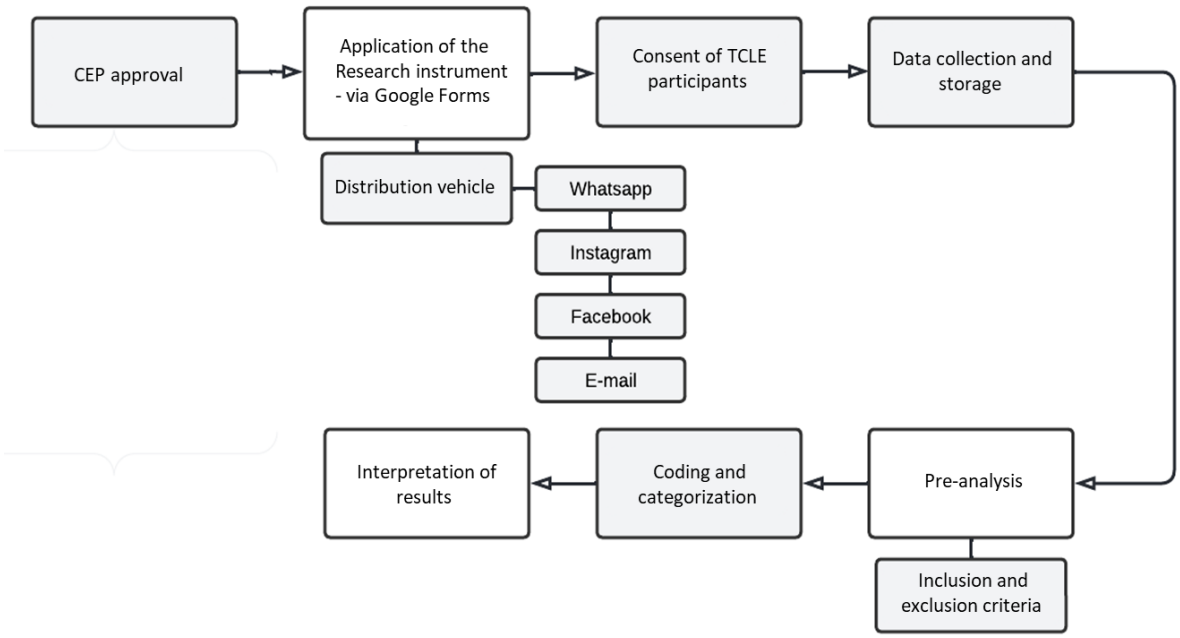
The tool began with an invitation to participate voluntarily, then the Term of Free and Informed Consent - ICF, preceding the research questions, which for access, it was necessary to consent to participation, that is, only after agreement with the ICF. The average response time was approximately 10 minutes, being of rapid reading and comprehension. Only the data from the questionnaires that were answered adequately, in a complete way, were used, and the others were excluded.

Data were collected from May to August 2022, and stored in a database using *Microsoft Excel® for Windows®10*.

Descriptive statistics were used with measures of central tendency (mean), measures of dispersion (standard deviation) and frequency (absolute and relative). The statistical treatment was performed through the *MAXQDA® software*, version 2022, for qualitative data analysis. The inference technique is based on the content analysis proposed by Laurence Bardin,8 comprising the stages of pre-analysis, coding and categorization, and interpretation of the results. Figure 1 briefly presents the methodological planning of the present study.

This research was submitted to and approved by the Research Ethics Committee of the Universidade da Região de Joinville/SC - UNIVILLE - CEP, according to the Resolution of the National Health Council for research with human beings, obtaining a favorable opinion for its execution, under opinion number 5,147,667.

Figure 1: Methodological Planning Flowchart



Source: Prepared by the author.

3 FINDINGS

The study sample was composed of 35 physical education professionals working in public health, 21 (60%) women and 14 (40%) men. Table 1 shows the characteristics of the study population.

Table 1 - Characteristics of the study population

Tabela 1 - Características da população de estudo.

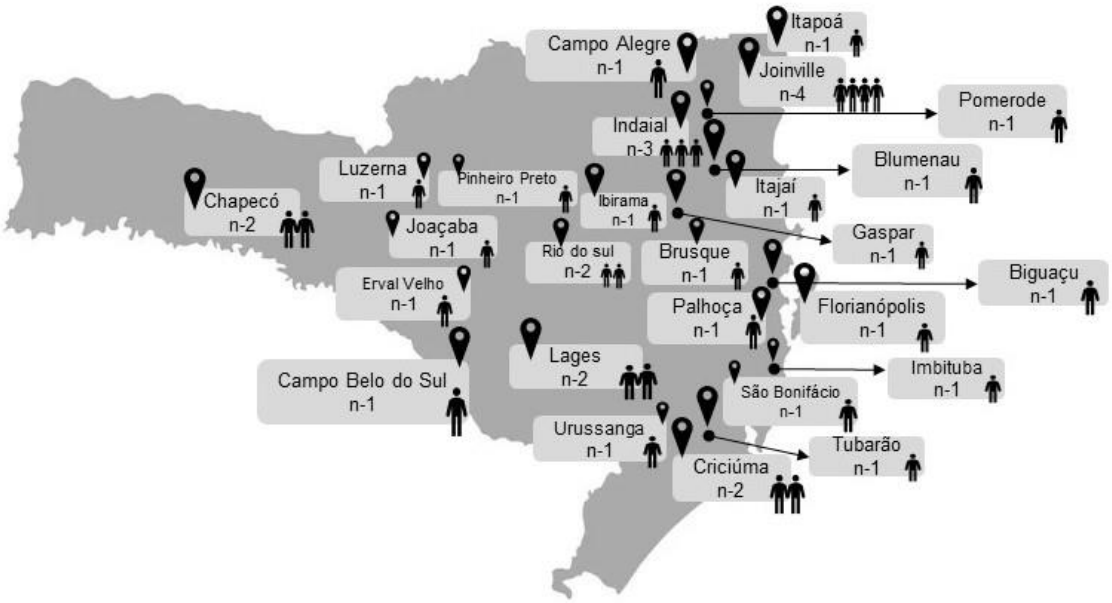
Variáveis		
Amostra (n-35)		
Masculino	14(FA)	40(FR)
Feminino	21(FA)	60(FR)
Idade (anos)	38,37(X̄)	8,55(SD)
CH Semanal	38,11(X̄)	6,12(SD)
Tempo de Atuação		
Menos de 1 ano	3(FA)	8,57(FR)
Entre 1 e 5 anos	14(FA)	40(FR)
Entre 5 e 10 anos	9(FA)	25,71(FR)
Mais de 10 anos	9(FA)	25,71(FR)
Formação		
ES Completo	8(FA)	22,85(FR)
Especialização	24(FA)	68,57(FR)
Mestrado	3(FA)	8,57(FR)

Legenda: FA-frequência absoluta; FR-frequência relativa%; X̄-média; SD-desvio padrão; CH Semanal- carga horaria semanal; ES Completo- ensino superior completo;

Legend: AF- absolute frequency; FR- relative frequency %: X-mean; SD-standard deviation; CH-Weekly-weekly workload; ES-Complete higher education;

Figure 2 shows the scope of the present study in the state of Santa Catarina, identifying the number of respondents by region and city. Thus, it is possible to verify the predominance of participations in the region of Vale do Itajaí with 30.8% of the population investigated, followed by the West region with 19.2%, just after the South and East regions both with 15.4%, the North region with 11.5% and finally the region of Planalto Serrano with 7.7%.

Figure 2: Perimeter of coverage of the study population.



Source: Prepared by the author. (2022)

The results from the content analysis were organized with reference to the categories ("aspects of professional performance" and "training"), as well as the format of the questions (open or mixed). Starting with the data obtained with the open questions (questions 1 and 8), it is possible to verify in question 1 (after the coding process) referring to the category of "aspects of professional performance", the prevalence of four words in the answers of the participants, evidenced by the absolute frequency (AF) and relative frequency (RF), considering the number of occurrences. Figure 3 summarizes this finding through the technique - Word Cloud, highlighting the most frequent word in proportion, followed by the others: "Health" FA-18/FR-51.43%; "Prevention" FA-9/FR-25.71%; "Activity" FA-9/FR-25.71%; and "Physics" FA-7/FR-20%.

Figure 3: Analysis of question 1 through the word cloud technique.



Source: *MAXQDA® Software*, version 2022.

Figure 4 presents the results of question 8 related to the category "training", presenting the predominance of the words: "Physiology" FA-12/FR-34.28%; "Special Groups" FA-8/FR-22.85%; "Anatomy" FA-5/FR-14.28%; and "Gymnastics" FA-5/FR-14.28%; according to the number of occurrences in the responses of the research participants.

Figure 4: Analysis of question 8 through the word cloud technique.



Source: *MAXQDA® Software*, version 2022.

In relation to the data obtained with the mixed questions, we can highlight in the category "aspects of professional performance", the predominance of the interest of professionals in public health (FA-26/FR-74.28%, question 2); the prevalence of responses aimed at the application of

physical exercise programs with the population (FA-33/FR-94.28%, question 3); the higher occurrence of responses to the lack of adequate environments (FA-27/FR-77.14%, question 4); the predominance of respect and interaction with the professionals of the multidisciplinary team (FA-26/FR-74.28%, question 5); and the prevalence of lack of opportunity (FA-19/FR-54.28%, question 6). For the category "training", the data show the predominance of responses to the incipient training provided by the graduation (FA-27/FR-77.14%, question 7); and the unanimity of the answers to the agreement of the importance of continuing education for the performance in public health (FA-35/FR-100%, question 9).

4 DISCUSSION

The present study aimed to analyze the performance of the PEF and identify the actions developed in public health in Santa Catarina, as well as the difficulties and facilities of the action.

Thus, through the analysis of the results, it is possible to observe that the PEF that participated in this research are inserted in public health throughout the State of Santa Catarina, so the study reached at least two PEF from each region of the State, allowing to have an overview of the performance of these professionals throughout the territorial perimeter.

However, even with the historical dissociation of Physical Education and public health [policies,9] making it very difficult to introduce this field of action, Bandeira et al.,[10] point out that there has been an exponential increase in the insertion of PEF in public health since 2013. This fact corroborates one of the characteristics of the respondents of the present study, because it is a predominantly experienced sample group in their area of expertise.

When the aspects of professional performance were analyzed, the words that most represent the role of the PEF within public health were identified, Figure 3 shows that professionals understand as their responsibility the promotion of health from prevention with the practice of physical activity. The study by Valle et al.,[11] corroborates the findings of the present study, where the authors were able to analyze that the PEF in their sphere of attributions in public health, perform various physical activities with the population, such as gymnastics, dance, recreational activities and games. However, over the years it is seen an evolution of the performance and responsibility of the PEF within public health, with this the Ministry of Health published an ordinance No. 15 12 with new attributions to the PEF, which makes it responsible to perform various activities, beyond only the practice of physical activity. In this context, Ferreira; Kirk and [Drigo,13] show that the performance of the PEF goes beyond just the promotion of physical activity, overcoming the biomedical model of care, where it is centered only on the disease and its treatment, it is necessary that the PEF act in a more humanized way, contributing to the construction of new healthy lifestyle habits.

In relation to the difficulties and the ease of action, with the analysis of the results it was evidenced that the lack of adequate environments is the main difficulty. In agreement, Oliveira et al.,[14] show that the lack of infrastructure and material is cited in several studies as the greatest obstacle to professional performance. Valle et al.,[11] also highlight that the greatest difficulty found in public health work is in the infrastructure and lack of materials to develop the activities. As the main ease of action, they mentioned respect and interaction with the professionals of the multidisciplinary team. In contrast, Castro et al.[15] cites the commitment of the population with the activities and therapies performed as the main facility, the authors bring the team as a difficulty due to the paradigms regarding the possibilities of action. Melo et al.[16] highlights that multidisciplinary teamwork can be considered an ease and at the same time a difficulty, because it favors care by articulating knowledge and sharing actions among professionals, as well as there is still a difficulty in recognizing the capacities of certain professions to work in public health.

Some Universities/colleges are directing and inserting the academic of physical education in public health, but it is still very inefficient, due to the lack of recognition of the importance of the performance of this professional in this area.[17] Even with new internship and residency programs in the area of public health, Dutra and Knuth18 highlight that the trainee and/or resident of physical education still needs to fight for their space, creating strategies of action, investigating new perspectives and, mainly, knowing the context that relates physical education with the field of public health. This fact solidifies the findings of this research in relation to the reasons for the insufficient presence of this professional in public health (question 6), in which the respondents predominantly opted for the lack of opportunity.

In the training category, when asked about graduation, most of the PEF answered that the training was incipient to work in public health, given the gaps that still exist today. According to Souza Filho et al.,[19] the weakened formation of the PEF can generate limitations in health care, due to insufficient knowledge. Barboni and Carvalho,[20] mention that the formation of the PEF should be adapted to the needs of action in public health, the theoretical-practical training should include interdisciplinary actions, together with the other courses in the health area, focused on collective health.

Figure 4 shows the disciplines that most contributed to public health activities according to the sample of the present study. Thus, it is possible to observe that they are basic and common disciplines of the health area, without a proximity to public health specifically. In this sense, Souza Filho et al.[19] emphasize that the formation of the PEF should contain themes such as health policy and program, primary care, collective health, among other themes aimed at consolidating the performance of this professional in public health.

Regarding continuing education, the responses of the participants were unanimous for the importance of improving to work in public health. With this, permanent and continuing education in

health should be present in the career of the PEF who work in public health, given the assumption that their training is still shallow in this area, these professionals should increasingly seek knowledge so that their performance turns to a caregiving practice, directed to integral care from the broad concept of health. [21st]

The present study presents limitations in the representativeness of the sample, considering that the research reached only 26 (8.8%) municipalities in the State of Santa Catarina, considering that the state has 295 municipalities in its totality. In view of this, the results obtained in this research represent only the referred group investigated.

The difficulty of access to professionals, as well as their engagement in dedicating a small portion of their time to contribute to the objective of this study, reflects the difficulty imposed by the research model.

And as a strong point, we can highlight the methodological rigor, with the application of a pilot test for the detailed collection of information that reflects the outcome investigated.

5 CONCLUSION

Therefore, it was possible to conclude that the PEF inserted in public health in Santa Catarina act in a multidisciplinary way together with the population developing physical exercise programs in health prevention, being able to identify their facilities, being mainly the respect and rapport between the professionals of the team, and also the difficulties, characterized by the lack of adequate environments for the performance.

As well, this study evidenced the importance and need to strengthen the training of this professional so that it is possible to meet the new demands of this field of action, enabling the approximation of physical education with the context of public health.

As a suggestion, it is necessary that new studies on the subject be carried out with more professionals, also bringing other aspects of insertion and performance in this field. The development of new research can facilitate interest, knowledge and even reduce the existing distance between physical education and public health.

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The importance of blood evaluation before donation

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ABSTRACT
The article is a bibliographic review with the title of: The Importance of Blood Evaluation Before Donation, aiming to show the whole process and how safe it is, showing the need for donor collaboration. Because it is a bibliographic review, it was not done in a practical way, but the research part of articles, magazine and books, always verifying the veracity and reliability of the materials used in its preparation. Development: it has the history of blood donation, all stages of the processes, questionnaires, screening, serological tests, importance of screening, the importance of training professionals, and the resolutions that control that helps ensure that this blood is safe for the patient who will receive and the process is also safe for the donor. In addition to the importance of blood donation, the loyalty and awareness of those who donate when going through the screening, also having classification for the types of donors. Concluding that it is a procedure in which it needs the collaboration of all, ethical and of paramount importance, besides that all the analysis is done with great care to ensure the safety of both what is donating and what will receive.

Keywords: Blood Donation, Triage, Serological examination.

1 INTRODUCTION

The evaluation of the blood before the donation is extremely important to avoid the possibility of diseases, contamination, protecting the patient who had received that is already debilitated and also what is donating that often did not even know about the disease and ends up discovering. Being thus made a screening before donating and even after the donation is made an analysis so that only after the analysis the blood is donated.

Before checking weight, height, blood glucose, pressure, beats, to check if it is ok, then it is passed to the social service where questionnaires are made about vaccines, sex life, health and only then passes donate the blood, even after taking the blood is delivered the paper in which you confirm or deny if it was true with the answers or missing with the truth, And it is also done blood tests to only after going through all these steps reach the patient who needs it.

In addition to having the problem that happens many people omit or lie information out of shame or think or unnecessary thus harming the fidelity of the result, at the stage of the questionnaire is impaired, running the risk of the donated blood not being able to donate, seeing this see necessary to also analyze the blood. So that it sees ensuring total safety and zero risk of transmitting a disease when performing the transfusion, in addition to that the donor may have been contaminated with some disease and not know.

Seeing all this, it is necessary to clearly show the importance of this analysis, resolving all doubts, passes awareness also about the security that existed and also reduce the fears and myths about the blood that is donated and received, also showing in a summarized and clear way the process of advancement, in the process of blood donation, bringing more and more security, with its technologies, scientific advances and always making it clear that it is a process in which it is constantly evolving, thus always seeking the best to ensure the optimization and reduction of risks.

Having as motivation for the study to show how safe the process is and how important the collaboration to facilitate. Having as central objective to show the importance of the analysis of the donated blood, being necessary knowledge in the area of analysis, hematology and immunology for the construction of this article, besides showing the whole process. And it also shows some resolutions that I enforce to ensure a rigorous and reliable process.

2 DEVELOPMENT

The history of blood transfusion in the world is divided into two phases: one, empirical, which goes until 1900, and another, scientific that begins from then on, with the discovery of the ABO system, by Landsteiner, in 1900, transfusions were made with more success. In Brazil, the first blood transfusion was performed, using the Agote device, improvised by Garcez Fróes, transfusing the donor's blood to a patient operated on for uterine polyp with significant metrorrhagia. (7)

After several decades after the discovery of the ABO system, the Rh factor was discovered, followed by other findings of anticoagulants, by scientists such as Loitt and Mollison, establishing a milestone in the creation of blood banks. And among the factors that helped the enormous development of transfusion medicine in the twentieth century stand out the two great world wars, the wars of Korea and Vietnam, and the post-epidemic of Acquired Immunodeficiency Syndrome. In the beginning, donors were paid and highly selected, which is one of the causes of low blood donation; Another problem was the lack of donors, leading public services to require blood donation to admit patients or to perform blood collections in prisons. Private blood banks, in turn, resorted to paid donation in capitals and medium-sized cities, thus creating a profession - that of the gratified donor(7).

The clinical and epidemiological distinction of blood donors means the beginner, and supposedly the primordial, stage in the scope of transfusion safety. Seeking voluntary, benevolent, altruistic and habitual donors is a task for hemotherapy services around the world. Studies have shown that improvements in the profile of blood donors interfered precisely in the quality and safety of the units collected. It is identified, as an indicator of the quality of the blood units collected, the impediment of paid blood donation from the 80's onwards. (10)

With the origin of the Screening and Counseling Centers (CTA), the demand in research the donation as a way to have results of examinations is inclined disappears. As for the motivation for

blood donation, the donor can be identified as: spontaneous, replacement, summoned and autologous. No form of restraint should be used to influence bestowal. The spontaneous and habitual donor is the most coveted and, consequently, the one with the highest probability of promoting better transfusion safety. Serological screening The serological tests to be enjoyed for the screening of the collected units should have high sensitivity and, when appropriate, high specificity. By identifying the lack of introduction of a new test in serological screening, it should have ensured the vacancy of acquisition in the market, registration in the Ministry of Health, equipment and essential training. There is still no available serological test with 100% sensitivity and specificity in the world market. (12)

One of the difficulties of health institutions is to conserve blood collection, since donors represent only 1.8% of the Brazilian population. It is of paramount importance the role of the nursing professional in the awareness, capture and screening of voluntary donors (1). A problem of worldwide interest, even today, is the granting of blood, since this is an element of extreme relevance to the human body. Blood centers face problems in preserving the ideal collection of this substance, which can endanger the life and health of patients who need the donation(2). This lack of donors and high rates of clinical and serological unfitness for donation can end up in a deficit in blood stocks, causing adverse consequences for individuals and public health. Therefore, it is of fundamental importance to stimulate blood donation in various ways, either by the loyalty of donors or by the permanent mobilization of the population (3).

All candidates for donation are submitted to an individual, confidential and confidential interview, with the use of accessible language and understandable terms, under medical supervision, in order to evaluate the clinical history and the current state of health, so that the blood collection is carried out in those candidates considered fit, without the procedure causing harm to donors or those awaiting blood transfusion. The candidates approved in the clinical screening, who understood the explanations provided by the triagist and who are in agreement with the performance of the procedure from the signing of a Term of Free and Informed Consent (ICF), confirming this understanding, agreement and commitment to the truth of the answers of the questionnaire, are sent to the hematological screening and, then to blood donation. Records of interviews are kept on file according to specific legislation. (5)

It is also up to the triagist to check the candidate for his general appearance, behavior and reactions; regarding the existence of cutaneous and mucosal pallor, suggestive of anemia, yellowish skin and sclera, indicative of jaundice; hyperemic conjunctivae, uncertain walking, disjointed or meaningless speech and characteristic breath, which may indicate consumption of alcohol or other drugs; swollen facies, suggestive of chronic alcoholism; unconvincing speech, which may indicate omission of information or embarrassment in giving the requested answers. After the interview and the clinical examination, carried out in sequence, the candidate for blood donation is informed of the

result of the selection process – fit or unfit – so that those who are considered unfit receive clear information of the reason for the refusal and the time they must wait for return. It is noteworthy that in the situations informed, the candidates are referred for specialized medical evaluation, when necessary. (5)

Therefore, it is essential for the triagist physician to place, with the candidates, a relationship of empathy that contributes to an environment of trust and credibility, without the existence of prejudices and/or biased judgments. In addition, the donor receives additional information regarding the care to be followed during and after the donation, being informed of possible adverse reactions, as well as being instructed about the possibility of self-exclusion from the donation process in situations where he does not consider the use of his blood safe. (5)

Self-exclusion occurs from the donor's information, by filling out the confidential vote after blood donation, requesting that their blood not be used. In this way, the collected bag is discarded. Unfit candidates are oriented, according to their ineptitude, as to the period they should wait for return, as to the clinical guidelines to be followed and, when necessary, referred to specialized follow-up in the reference services. (5)

The lack of medical knowledge in hemotherapy can reduce transfusion safety and cause significant harm to the patient. Thus, competent action becomes an essential requirement in transfusion medicine, avoiding possible damages and transfusion reactions Given that transfusions are becoming increasingly important as a therapy today and are not risk-free procedures, it is necessary to take a close look not only at transfusion safety. (4)

The circumstances of the transfused blood, whose extraction begins from the apprehensions of candidates for blood donation, as well as understanding the origin and destination of the blood collected, in order to increase security. The following sectors constitute the blood cycle: donor capture and awareness, clinical screening, hematological screening, blood collection, fractionation and distribution. Also part of the blood center are the apheresis sector, which performs the individualized collection of blood components, the donor medical care service (SAMD), which assists the unfit serological donor, and the outpatient clinic, where blood transfusions and specialized monitoring of patients with sickle cell anemia and coagulation disorders are performed. (4)

To achieve safety of blood products to be used in transfusions, strict quality parameters must be used. Transfusion safety is understood as the set of quantitative and qualitative measures followed that seek a lower danger to blood donors and recipients, in addition to ensuring that strategic blood stocks are organized to meet the transfusion need. Despite all the growth in the search for transfusion safety, "there is no transfusion without risks." (8) Hence the hardness of faithfully complying with the hemotherapy cycle whose development begins with the reach and selection of donors, followed by

serological and immunohematological screening, processing and fractionation of the units collected, dispensing, transfusion and post-transfusion evaluation. (9)

The transfer of infectious-contagious agents, through blood transfusion, in blood components and blood products, points to the late opposite reaction of greater periogo to the blood receptor. Synthesize the rates of disease transmission by transfusion in a precise way that can ensure the credibility of the blood that will be transfused. However suspension of doing justice, society becomes tolerant without bothering to argue these problems. Ethics are suppressed by forgetting discussion. Donating blood is an ethical act, taking into question that the donor should be free to choose and have the notion of the consequences in relation to him and the recipient. For this, the health professional must have all the necessary information to the donor; therefore, the SD is an artifice that violates the ethical principles of the human being. (6)

The Brazilian guidelines that control that every donation is a rigorous clinical-epidemiological screening of candidates for donation. Through trained professionals, clinical screening is done by tracking the recognition of signs and symptoms of diseases in candidates for donation that may cause danger to themselves or to the recipient. Once the reaction to the screened diseases is proven, the donor is directed to the referral services for specific care in each pathology. The main characteristic of donors with reactive serology is to be affected by chronic and asymptomatic disease, often making it impossible to exclude them in the clinical screening phase. Another key factor in the epidemiological analysis of candidates for donation is the exclusion, in clinical screening, of data seen as intimate "(number of sexual partners, use of illicit drugs, among others)". (10)

In view of the chances of elimination, through the donors, of some situation of danger, the vote of self-elimination was adopted in which the person can eliminate his donation from the transfusion purpose. In the same way, the donor must be guided by the dimension of the confidence of his answers and his obligation on them. The donor's unexplained desire to seek the hemotherapy service in order to donate may signal personal causes, endangering the entire safety process. In the 80s and 90s, with the emergence of AIDS, people sought blood donation for the execution of serological tests anonymously. With the creation of the Screening and Counseling Centers (CTA), the need to seek donation as a means of obtaining test results tends to disappear. (10)

As for the purpose for blood donation, the donor can be identified as: spontaneous, replacement, summoned and autologous. No form of coercion should be used to induce donation. The spontaneous and habitual donor is the most desired and, consequently, the one most likely to promote better transfusion safety. (11) The serological tests to be used for the screening of the collected units should have high sensitivity and, when possible, high specificity. When identifying the need for the introduction of a new test in serological screening, it should be ensured the availability of acquisition in the market, registration with the Ministry of Health, equipment and necessary training. There is still

no available serological test with 100% sensitivity and specificity in the world market. The high sensitivity of the tests, required for use in hemotherapy services in laboratory selection, aims to increase safety for the recipient. However, the high sensitivity with low specificity leads to false-positive results, which can bring serious consequences to blood donors who will have to deal with the stigma of a supposedly reactive test, until the diagnosis is clarified. (12)

For hemotherapy services this results in the elimination of bags and blood waste. The so-called first generation tests, in which the antigen is obtained through the lysate of the pathogen, Used mainly in the last decades of 80/90, caused great emotional damage in false positive donors and a high cost for hemotherapy services, with the disposal of bags with suspected infection. In the last 30 years, new serological screening tests have been introduced, as pathogens were identified and reagents made available. Currently, the Enzyme Linked Immunosorbent Assay (Elisa) method is the most used in hemotherapy services, as it allows good reproducibility, easy execution and possibility of automation. (12)

The second- and third-generation Elisa tests use recombinant antigens and synthetic peptides, respectively. "Other types of tests are also done in screening blood donors, such as hemagglutination (HA), particle agglutination (PA) and chemiluminescence." The use of nucleic acid amplification and detection tests (NAT) is valuable for the confirmation of indeterminate reactions in serological screening tests, due to the high sensitivity and specificity they show. (12)

In Brazil there is extensive education regarding donor uptake, processing, recruitment and use of blood, blood components and blood products. Especially, in need of the inspection of diseases with a chance of transmission through blood transfusion, however Brazil has several strict regulatory and inspection guidelines to ensure the quality of the sengue and minimize the risk of contamination. (13)

– The Federal Constitution / 1988, in articles 197 and 199, confers on the public power the regulation, supervision and control of actions corresponding to the use of blood products, and the prevention of blood trade, in any aspect, throughout the national territory, mutually. – Decree No. 95,721/1988, which determines Law No. 7,649/1988, stipulates the imposition of the registration of blood donors, as well as the performance of laboratory tests on the blood collected, intending to prevent the increase of diseases. – Law 10.205/2001 determines the National Blood Policy and its obligations, validates the sale and regulates paragraph 4 of article 199 of the Federal Constitution. (13)

– Ordinance No. 1,840 / September 1996, of the Ministry of Health, launches the National Program for External Quality Control in Serology (PNCQES) – Ordinance No. 1,376 / November 1993, of the Ministry of Health, recognizes the changes in Ordinance 721 / GM, of 09.08.1989, which determines technical standards for collection, processing and transfusion of blood, components and blood products, requiring the determination of ABO, Rh(D), weak D antigen (Du) and tests to identify

hepatitis B and C, Chagas disease, syphilis, AIDS, anti-HTLV I/II and anti-HBc antibodies. It also orders the performance of tests for elimnation of malaria, sickling and abnormal hemoglobins. (13)

– Resolution No. 343/2002, of the Ministry of Health, agrees with the requirement of high-sensitivity laboratory tests in all donations, to discover blood-borne diseases, in addition to requiring that: "These tests must be performed on a sample taken from the day to be tested with diagnostic set ("kits") indicated in the National Health Surveillance Agency (Anvisa), in specialized laboratories for such a purpose. It is forbidden to test in a "pool" of blood samples. If new technologies arise that have use attested by Anvisa for use in "pool", this impediment will be network form anonymous. (13)

3 CONCLUSION

To conclude that it is of utmost importance each process in which the donor goes through until he can donate, that the coloration of the candidate for blood pain is of extreme importance to obtain safe blood, besides that it was possible in this article shows how much each step is necessary in the process to reduce the risks for the donor and recipient, In addition to being a process that has been evolving more and more, contact with new technologies and inspections, control resolutions to give the greatest security. All this so that it comes to minimize the risk more and more, even so it is a process in which you do not have 100% security, every donation has a risk. That is why it is so important in addition to the examination the coloration of the candidate donor, so that it can guarantee the safety of the donor and the recipient does not come if it gets contaminated or anything else.

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The use of pesticides and its association with parkinson's disease

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ABSTRACT
Brazil is one of the countries that consumes the most pesticides, and as a consequence, both rural workers and society in general are exposed to the risks that this use poses to physical and mental health. In this sense, Parkinson's disease exemplifies such risks, as it is a neuronal disorder that presents motor and non-motor symptoms that affect quality of life. The main objective of the research was to observe the relationship between the development of Parkinson's disease and the use of pesticides, considering that it is a neurodegenerative disease that affects rural workers who handle products with such active ingredients, as well as the general population that consumes crops treated with them. Therefore, the characteristics that permeate the disease were described, and data from Brazilian regions and states were collected, with a focus on Paraná regarding the use of associated active ingredients (Paraquat, Mancozeb, and Glyphosate), the crops that use them, and also Parkinson's mortality rates by region and states from 2013 to 2020, in order to establish a parallel between use and mortality. It was observed that both mortality and pesticide use increased during the associated period. The Central-West, South, and Southeast regions were the ones that used the three analyzed active ingredients the most, while the Northeast, Southeast, and South had the highest mortality rates. Additionally, parallels between use and mortality were observed in certain states, such as Rio Grande do Sul, for example. In conclusion, Parkinson's disease is multifactorial and may be associated with pesticides containing the active ingredients Glyphosate, Mancozeb, and Paraquat. In Brazil, Parkinson's mortality is increasing, as well as the use of these products, which, with the exception of Paraquat, which has been legally banned, rank among the top 10 most widely used pesticides. This calls for continuous studies that analyze the propensity for disease development and the use of these active ingredients.

Keywords: Parkinson, Pesticides, Health.

1 INTRODUCTION

The use of pesticides is a common practice worldwide, with approximately 2.5 million tons of pesticides being used globally. In Brazil, pesticide usage is widespread, considering its economy focused on the production and export of commodities, with a usage exceeding 300,000 tons, making it one of the largest consumers. In the last forty years, the country's agricultural area has expanded by 78%, while pesticide consumption has increased by over 700% (SPADOTTO, 2021). Given that there are few Brazilian studies analyzing and discussing the chronic effects of these agricultural pesticides, it is essential to develop more research to understand the implications of pesticides on the physical and mental health of the population. In this regard, a significant portion of the population directly targeted

by pesticides is rural workers, who are exposed to these chemicals daily and often handle them without the recommended and necessary protective equipment, thereby increasing the risk of exposure and the development of chronic problems. Therefore, one of the diseases that will guide the research is Parkinson's disease, a neurodegenerative disorder that presents both motor and non-motor symptoms and affects the quality of life of the affected population both physically and mentally. The study focused on determining which pesticides may be associated with Parkinson's disease. By analyzing the relationship between the increased use of active ingredients and mortality from the disease, hypotheses regarding the association between pesticide use and the onset of Parkinson's disease could be generated. The objective, therefore, is to provide a theoretical explanation of the various aspects surrounding Parkinson's disease, analyze which pesticides are associated with the disease, identify the crops that utilize them, examine the use of active ingredients, and investigate Parkinson's mortality rates by region and states, with a focus on the state of Paraná. This will enable us to understand an example of a chronic condition that affects rural communities and is associated with the physical and mental harm caused by the use of agricultural pesticides.

2 MATERIALS AND METHODS

The studies allowed for the analysis of the active ingredients Paraquat, Mancozeb, and Glyphosate, which have been scientifically proven to be associated with Parkinson's disease. Therefore, information was collected from different platforms. Data from ADAPAR were collected to determine which crops use these active ingredients; data from IBAMA were collected to observe the regions and states that use these pesticides the most; data from DATASUS were collected to visualize Parkinson's mortality by region and state. The objective was to establish a correlation between Parkinson's mortality and the use of scientifically associated pesticides.

3 LITERATURE REVIEW

3.1 PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

Parkinson's disease is primarily characterized by the progressive loss of dopaminergic neurons in the midbrain, which innervate the motor portions of the basal ganglia, particularly the putamen, as well as the STN, GPi/SNr, thalamus, and cortex of the nervous system, in the substantia nigra pars compacta, along with the presence of α-synuclein-positive cytoplasmic inclusions known as Lewy bodies in the lower brainstem (CERRI et al., 2019). Genetic and environmental factors combined lead to early loss of dopaminergic neurons in the ventrolateral region of the nervous system through different cellular pathways, including protein misfolding and aggregation, endoplasmic reticulum stress, and mitochondrial dysfunction. Regarding Lewy bodies, their main composition is α-synuclein,

and they initially concentrate in the olfactory bulb and brainstem but can spread to the limbic system and neocortex over time (OBESO *et al*., 2017).

Studies analyzing post-mortem human tissues, in vitro human cell lines, human brain organoids, and animal models have observed the accumulation of α-synuclein, mitochondrial dysfunction, impairment in protein production (involved in the ubiquitin-proteasome and autophagy-lysosome systems), neuroinflammation, and oxidative stress. These events are associated with disrupted vesicular transport, loss of microtubule integrity, excitotoxicity of neurons, disruption of trophic factors, dysregulation of the iron metabolic pathway, endoplasmic reticulum impairment, and enzymatic activation of poly(ADP-ribose) polymerase. Axonal mitochondria are particularly vulnerable, and these alterations contribute to impaired axonal transport, leading to initial neurodegeneration in distal axons. These mechanisms would result in apoptosis and/or necrosis (JANKOVIC, 2020).

Mitochondrial damage affects mitochondrial complex I, reducing organelle potential and promoting caspase cascade activation, leading to cell death. Certain genes associated with the disease, such as Parkin, PINK1, and DJ1, have deleterious effects that result in mitochondrial dysfunction, including impairment in mitophagy. Furthermore, organelle damage leads to the accumulation of oxidized dopamine and reduced glucocerebrosidase, with dopamine being associated with α-synuclein excess and lysosomal impairment. There is also an increase in pro-inflammatory cytokines and altered immune defense cells (JANKOVIC, 2020).

3.2 PHYSIOLOGY OF THE BASAL GANGLIA AND PARKINSON'S DISEASE

There are connections among the nuclei of the basal ganglia, and the concept is that within these connections, the flow of information remains through input processing to broad regions of the cerebral cortex, including the motor, associative, and limbic areas. The different pathways deal with different regions and functions, although they perform similar input operations. Excitatory information from the cortex and thalamus arrives at the nuclei of the basal ganglia (the striatum, composed of the caudate and putamen in humans). There, it is transformed and transmitted to smaller output nuclei (the globus pallidus internal segment, GPi, and the substantia nigra pars reticulata, SNpr) by two distinct pathways: the direct and indirect pathways. These nuclei send the segregated information to the respective cortical areas in the frontal cortex through the thalamus and also to the brainstem. The motor circuit plays a fundamental role in understanding motor signals and the symptoms of Parkinson's disease and other movement disorders (OBESO *et al*., 2017).

The output from the GPi and SNr is characterized by high-frequency inhibitory GABAergic neurons, which provide a continuous level of inhibition to the thalamus and target brainstem areas. The direct pathway has a facilitatory influence on movement by disinhibiting the thalamus, while the

indirect pathway suppresses movement by increasing thalamic inhibition. In Parkinson's disease, there is a mismatch between excitation and inhibition, resulting in movement disorders. Although complex, the disease substantially interferes with the motor loop due to the deficiency of dopamine, which is characteristic of the pathology. The basal ganglia play an important role in reinforcement learning. Dopamine reinforces activity patterns by altering cortical inputs and the direct and indirect pathways (OBESO *et al.,* 2017).

Dopamine is released at a slow rate of 5 Hz, sustaining its tonic background level in the striatum. The loss of this tonic activity is the predominant factor in the manifestation of the classical symptoms of Parkinson's disease. Thus, dopamine plays a significant role in the proper functioning between the direct and indirect pathways for inhibition and also interferes with the cortex-basal ganglia-thalamus-cortex pathway. If deficient, the neurons involved in this process can oscillate together, reducing the basal ganglia's ability to change production patterns, resulting in bradykinesia (difficulty in voluntary movements and slowness of reflexes and movements), one of the symptoms of Parkinson's disease. Other disturbances in neurotransmitters, such as glutamatergic and cholinergic systems, are associated with the disease, particularly in the associative and limbic circuits, where non-motor disturbances may occur. It is worth noting that not all motor disturbances are necessarily related to the basal ganglia (OBESO *et al*., 2017).

3.3 CLINICAL PRESENTATION OF PARKINSON'S DISEASE

The primary motor symptoms of Parkinson's disease include bradykinesia, rigidity, resting tremor, and gait disturbances. Non-motor symptoms include autonomic and sleep disorders, such as a high incidence of insomnia and REM behavior, cognitive problems, and psychiatric symptoms such as depression and anxiety (CERRI *et al*., 2019). Posture becomes stooped, with axial and limb rigidity, a shuffling gait, and a lack of arm swing while walking. Hypomimia (reduced facial expression) and micrographia (reduced handwriting size) may occur as a consequence of bradykinesia. Resting tremor primarily affects the legs. Gait disturbances can lead to shorter and faster steps, which can trigger balance loss and subsequent falls. Freezing of limbs can occur after years of living with the disease, along with oral motor problems such as soft and rapid speech, swallowing difficulties, and drooling. Dystonia (constant muscle contraction accompanied by abnormal movements, such as unilateral equinovarus foot and oromandibular dystonia) and postural problems, including abnormal forward flexion (camptocormia), forward flexion of the head and neck (antecollis), and scoliosis of the spine, may also be present (SVEINBJORNSDOTTIR, 2016).

Before the onset of motor symptoms, non-motor symptoms are observed in 60-70% of patients prior to diagnosis. These symptoms involve disturbances in autonomic function, sleep, cognition, and sensations, such as apathy, excessive daytime sleepiness, sleep disturbances, constipation, anhedonia,

memory problems, olfactory and gustatory dysfunction, mood fluctuations, excessive sweating, fatigue, pain, anxiety, and depression. Non-motor symptoms typically persist as the disease progresses and can be more bothersome than motor symptoms (SVEINBJORNSDOTTIR, 2016).

Neuropsychiatric symptoms are also observed in one-third to 40% of patients, such as visual hallucinations and illusions. Additionally, cognitive impairment and dementia are common and can occur at different stages, with deficits in goal-directed behavior and dysfunction in vision, speech, and memory. Progression occurs as neuropathological changes spread to cortical brain regions, varying among patients, usually starting unilaterally, with mild symptoms and a good response to treatment. As the disease progresses, motor symptoms spread contralaterally, and responses to medication become more difficult with side effects, in addition to the development of non-motor symptoms (SVEINBJORNSDOTTIR, 2016).

Biological sex, combined with age, genetic and environmental factors, and the immune system, generates clinical, pharmacological, and epidemiological differences. In women, motor symptoms emerge later, with greater postural instability, less rigidity, and more severe symptoms of fatigue, depression, pain, olfactory or gustatory impairments, restless legs, weight changes, excessive sweating, and gastrointestinal dysfunctions. In men, there is a higher risk of freezing while walking and developing camptocormia, worse clinical profiles of cognitive abilities, faster progression to advanced stages of the disease, and greater deficits in attention and memory (CERRI *et al*., 2019)

3.4 EPIDEMIOLOGY OF PARKINSON'S DISEASE

Parkinson's disease accounts for only 10% of patients with genetic mutations that could cause the disease (CERRI *et al*., 2019). The incidence of the disease varies and ranges from 5 to 35 per 100,000 new cases annually (SIMON *et al*., 2020). Between 1990 and 2015, the number of patients increased by 118% (6.2 million people). Furthermore, age-standardized rates increased by almost 22% in all regions of the world between 1990 and 2016. Projections for 2040 estimate a total of 17.5 million individuals affected (DORSEY *et al*., 2018).

The disease has a higher incidence and prevalence in the older population (RADHAKRISHNAN, 2018) and is the second most common age-related neurodegenerative disorder, affecting approximately 3% of the population aged 65 and over, and over 5% of the population aged 85 and over (CERRI *et al*., 2019). When it occurs in individuals under the age of 40, it is defined as early-onset Parkinson's disease and accounts for 3-5% of all cases of the disease (RADHAKRISHNAN, 2018). The incidence is twice as high in men compared to women, although female mortality rates are higher, and the disease progresses more rapidly in women (CERRI *et al*., 2019).

In Brazil, there are no official statistics reporting the number of patients affected by the disease. According to Hospital Albert Einstein, unofficial estimates suggest there are at least 250,000 individuals with Parkinson's disease in the country. However, a study conducted in the interior of Minas Gerais with individuals aged 64 and older revealed an incidence rate of over 3%. Considering that the Brazilian population in this age group is around 21 million people, the actual number of individuals affected by the disease would be over 600,000, excluding younger patients with the disease (VILELLA, 2019). According to IBGE, life expectancy in Brazil is projected to reach 78.6 years in 2030 and 81.2 years in 2060, indicating a progressive increase in the number of elderly individuals and a consequent rise in the number of Parkinson's cases.

3.5 ETIOLOGY OF PARKINSON'S DISEASE

The etiology of Parkinson's disease is substantially multifactorial, resulting from the interaction between environmental and genetic factors (CERRI *et al*., 2019). Several factors have been studied in association with Parkinson's disease, such as exposure to pesticides, living in rural environments, traumatic brain injury, and a history of melanoma. Limitations in research have generated conflicting etiological results (JANKOVIC, 2020).

Regarding genetic factors, the metabolite urate, an antioxidant and neuroprotective agent, can be used as a biomarker for Parkinson's disease. Elevated levels of urate have been associated with a lower risk and slower progression of the disease. Furthermore, a relationship has been observed between mutations in the GBA1 gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase), and the development of the disease. Another lysosomal enzyme involved is alpha-galactosidase (GLA), encoded by a gene on the X chromosome. Reduced activity of GLA has been associated with the disease, but this correlation is significant only in women. Additionally, the rs1136666 polymorphism in the GAPDH gene is also associated with sporadic Parkinson's disease and increases the risk in older men (CERRI *et al*., 2019).

Regarding environmental risk factors, chronic stress is the most prominent. Higher levels of chronic stress are associated with an increased risk of developing Parkinson's disease, with a higher incidence observed in certain sectors such as agriculture and metallurgy. Physical activity is also an important factor, as higher levels of activity during middle age are associated with a lower risk of developing the disease, better prognosis, and lower chances of severe complications (CERRI *et al*., 2019)

3.6 PESTICIDES ASSOCIATED WITH PARKINSON'S DISEASE

Byproducts of the Industrial Revolution, such as pesticides, solvents, and heavy metals, may be associated with higher rates of Parkinson's disease. This can be observed in countries that underwent

rapid industrialization, which was accompanied by increased cases of the disease, such as in China from 1990 to 2016, where the rates were high and more than doubled (DORSEY *et al*., 2018).

In the United States, a study conducted in an agricultural region found that long-term exposure to pesticides increases the risk of developing Parkinson's disease four to six times. Another study conducted in France found that the intensity of pesticide exposure is related to the development of the disease. However, in Brazil, pesticide use is widespread, as the country has a significant portion of its economy based on the production and export of commodities. Few Brazilian studies have analyzed the chronic effects of agricultural pesticides and discussed alternative models to counteract excessive pesticide use (VASCONCELLOS *et al*., 2019).

A study conducted in an agricultural region in California observed a relationship between exposure to certain pesticides and the risk of developing Parkinson's disease. The effects of ziram, paraquat, and maneb were analyzed, and when combined, they strongly increased the risk, which was higher than when administered individually or in pairs. The combinations of ziram and paraquat, and maneb and paraquat, in the work environment doubled the risk of the disease, especially for younger patients. The results suggested that these pesticides contribute to mechanisms that lead to the death of dopaminergic neurons, a characteristic of Parkinson's disease (WANG, 2011).

In Brazil, the National Health Surveillance Agency (Anvisa) banned the commercialization and use of paraquat in plantations starting from 2020, as it is not possible to determine acceptable levels for its administration considering the severity of the disease (VASCONCELLOS, 2018).

Paraquat causes generalized intracellular oxidative/nitrosative stress through a redox cycle or activation on the cell surface by NADPH oxidase. Mitochondria are directly or indirectly affected, and in neurons, the action of paraquat is believed to be mainly cytosolic. The mechanisms of paraquat toxicity have been compared to those of MPTP, which, when converted to MPP+, is sequestered via the dopamine transporter in dopaminergic neurons, substantially affecting complex I and causing oxidative stress and mitochondrial damage. However, while MPTP is an inhibitor of complex I, paraquat is inefficient in this action, although it modulates the redox cycle. Thus, it is inferred that the toxicity of MPP+ and rotenone is related to the inactivation or oxidation of mitochondrial proteins, while for paraquat, it involves oxidative modification of cytosolic proteins. Therefore, the initial targets and means of toxicity differ, although they share oxidative characteristics (BERRY *et al*., 2010).

In Brazil, the active ingredients Maneb and Ziram have already been legally banned (ANVISA, 2017). Maneb and Ziram belong to a family of fungicides called Dithiocarbamates, which are compounds derived from dithiocarbamic acid (NH_2CS_2H). Representatives of this family include sodium metam, ziram, ferbam, tiram, propineb, maneb, zineb, nabam, metiram, and mancozeb. In Brazil, five dithiocarbamates are allowed by Anvisa: mancozeb, metiram, propineb, tiram, and sodium metam (BALARDIN *et al*., 2017).

Mancozeb is associated with a higher risk of developing Parkinson's disease, as it has been found to cause neurodegeneration not only in dopaminergic neurons, which are commonly affected in the disease, but also in GABAergic neurons in *C. elegans* (NEGGA *et al*., 2012), a worm genetically similar to humans (KAMMENGA, 2019). Additionally, Mancozeb may be associated with behavioral changes, which have also been observed in the worm, indicating a potential biomarker of toxicity (PARKINSONISME VERENIGING, 2019). The effect on dopaminergic neurons may be due to the preferential transport of the fungicide into these cells through their presynaptic neurotransmitter transporters (MONTGOMERY *et al*., 2018). Montgomery et al. conducted a study using a dopamine transporter antagonist (GBR12909) in *C. elegans*, which appeared to protect dopaminergic neurons from chronic (24-hour) Mancozeb treatment.

A study using data from the AGRICAN cohort study sought to identify relationships between the incidence of Parkinson's disease and exposure to mixtures of pesticides or individual pesticides, including dithiocarbamate fungicides, rotenone, and the herbicides diquat and paraquat. While previous studies already indicated the association of maneb/mancozeb, ziram, rotenone, and paraquat with Parkinson's disease, this was the first analysis to implicate other dithiocarbamates, such as cupreb, ferbam, mancopper, metiram, thiram, and propineb, in the etiology (POUCHIEU *et al*., 2018).

Glyphosate-based herbicides are the most widely used in the world and their use is increasing. Human exposures to glyphosate are also increasing, with daily intake levels not being respected (MYERS *et al*., 2016).

Studies conducted in rats indicated that high levels of exposure would suggest neurotoxicity induced by glyphosate-based herbicides through multiple mechanisms (MYERS *et al*., 2016). Glyphosate is believed to be associated with neuroinflammation and the induction of oxidative stress in specific regions of the brain, such as the substantia nigra, cerebral cortex, and hippocampus. However, these studies used commercial formulations rather than pure glyphosate, and further research is needed to confirm the neurotoxicity (CATTANI *et al*., 2014).

Exposure to glyphosate has been suggested as a risk factor for neurodegenerative diseases such as Parkinson's and Alzheimer's, as it accelerates age-related neurodegeneration in conjunction with iron and paraquat, which can act via common mechanisms mediated by oxidative stress (PENG *et al*., 2007).

Thus, chronic and acute exposures to glyphosate can cause parkinsonism, which is a condition similar to Parkinson's disease (CATTANI *et al*., 2014). Some cases have been described in which contact with glyphosate resulted in a parkinsonism syndrome, such as the case of a 54-year-old man who accidentally sprayed the herbicide and developed clinical symptoms within a month, including slow resting tremor in the left hand and arm, as well as impaired short-term memory one year after the incident (BARBOSA *et al*., 2001).

It has been observed that glyphosate can be linked to the development of Parkinson's disease, as it induces autophagic and apoptotic cell death in differentiated PC12 neuronal cells, cytotoxicity in SH-SY5Y neuronal cells, degeneration of dopaminergic and γ-aminobutyric acid neurons in *C. elegans*. All of these indicate that glyphosate can act in different ways, but its effect on neuralcells is evident, leading to oxidative damage and subsequent cell death and neurodegeneration (CATTANI *et al*., 2014).

Therefore, exposures to glyphosate cause biological effects that are not immediately observable but are caused by early-life exposure and manifest in later stages of adulthood as chronic degenerative diseases or other health problems (CABALLERO *et al*., 2018).

4 RESULTS AND DISCUSSION

The results of the Review were subdivided into two parts. The first part will present the results related to pesticides in Paraná and Parkinson's disease, while the second part will present the results related to the sale of active ingredients and Parkinson's mortality in Brazil.

4.1 PESTICIDES IN PARANÁ AND PARKINSON'S DISEASE

The state of Paraná has a significant presence in agriculture and, as such, uses a wide variety of pesticides. The crops that have used the most pesticides from 2013 to 2021 are soybeans, corn, and wheat (SIAGRO, 2021), with herbicides, fungicides, and insecticides being the most commonly used compounds (SIAGRO, 2021).

Table 1: Volume of Pesticides Sold (in tons) in Paraná

2013	2014	2015	2016	2017	2018	2019	2020	2021
93.137,2	97.615,6	100.572,8	92.160,5	92.398,0	92.904,3	95.286,8	106.685,9	115.620,8

Source: Produced by the author based on ADAPAR data, 2022.

Paraquat, a compound associated with Parkinson's disease, had the importation, production, and commercialization of its technical and formulated products based on its active ingredient banned starting in 2017 through Resolution of the Collegiate Board of Directors - RDC nº 428, dated October 7, 2020 (OFFICIAL GAZETTE OF THE UNION, 2020). Therefore, the Paraná State Agricultural Defense Agency (Adapar) provided guidance to farmers and traders regarding the prohibition. However, the resolution allowed for the use of products in stock and acquired until the deadline for crop management in the 2020/2021 agricultural season (ADAPAR, 2020).

Table 2: Use of Paraquat in Paraná

2013	2014	2015	2016	2017	2018	2019	2020*	2021*
3,07%	1,97%	2,15%	5,08%	7,43%	5,77%	6,89%	5,85%	0,01%

*RDC 428/2020. Source: Produced by the author based on data from ADAPAR, 2022.

The active ingredient Paraquat, before its prohibition, was used in various crops such as avocado, cotton, rice, asparagus, banana, beetroot, cocoa, coffee, sugarcane, tea, citrus, coconut, kale, beans, apple, corn, olive, pastures, pear, peach, rubber tree, soybean, sorghum, wheat, and grape (ADAPAR, 2022).

In addition to Paraquat, dithiocarbamates are also associated with Parkinson's disease, and in Brazil, five of them are allowed by ANVISA: mancozeb, metiram, propineb, thiram, and metam-sodium (BALARDIN *et al*, 2017). In Paraná, the most widely used dithiocarbamate is Mancozeb, with several products containing this active ingredient, with or without usage restrictions. Metam-sodium is permitted with usage restrictions. Metiram is permitted with usage restrictions. Propineb is permitted with usage restrictions. Thiram has some products that have had their use canceled or permitted with usage restrictions (ADAPAR, 2021).

Table 3: Use of Dithiocarbamates in Paraná

Pesticide	2013	2014	2015	2016	2017	2018	2019	2020	2021
Mancozeb	0,51%	0,40%	0,67%	3,12%	2,68%	3,62%	3,54%	2,85%	2,50%
Metiram	0,18%	0,02%	0,03%	0,10%	0,08%	0,06%	0,05%	0,04%	0,03%
Propineb	0,01%	0,02%	0,03%	0,12%	0,09%	0,07%	0,06%	0,04%	0,02%
Metam-sodium	0,00%	0,00%	0,00%	0,01%	0,01%	0,01%	0,00%	0,01%	0,01%
Thiram	0,49%	0,41%	0,33%	0,19%	0,17%	0,16%	0,16%	0,15%	0,12%

Source: Produced by the author based on data from ADAPAR, 2022.

The active ingredient Mancozeb is used in crops such as avocado, chard, watercress, lettuce, cotton, garlic, endive, peanut, rice, irrigated rice, oats, banana, potato, beetroot, eggplant, broccoli, coffee, cashew, sugarcane, persimmon, starfruit, onion, carrot, barley, shallot, chicory, citrus, kale, cauliflower, carnation, chrysanthemum, pea, spinach, stevia, eucalyptus, beans, cowpea, pigeon pea, mung bean, broad bean, snap bean, fig, tobacco, gladiolus, guava, apple, papaya, mango, mangaba, passion fruit, watermelon, melon, corn, mustard, ornamentals, cucumber, pear, peach, bell pepper, cabbage, rose, arugula, soybean, sorghum, tomato, wheat, and grape (ADAPAR, 2022).

Other pesticides that may be associated with Parkinson's disease are hexachlorobenzene and glyphosate. Hexachlorobenzene has been prohibited in Brazil since 1985, but clandestine use was observed in Paraná in a study conducted in 2013, where 92.6% of the respondents claimed to be aware of the prohibition but continued to use it (VASCONCELLOS, 2018). Glyphosate, a probable carcinogen for humans (VASCONCELLOS, 2018), can act in different ways to induce neurotoxicity and oxidative stress (CATTANI *et al*, 2014). In Paraná, there is a wide variety of pesticides with

glyphosate as the active ingredient, with some being approved and without usage restrictions, while others have been canceled or have usage restrictions (ADAPAR, 2022).

Table 4: Use of Glyphosate and Glyphosate-based Herbicides in Paraná

Pesticide	2013	2014	2015	2016	2017	2018	2019	2020	2021
Glyphosate	16,27 %	10,20 %	8,8%	8,07%	6,92%	6,68%	6,16%	6,40%	7,29%
Glyphosate Acid Equivalent	7,50 %	3,35 %	4,17%	13,58%	13,96%	14,71%	12,84%	11,49%	9,64%
Glyphosate Potassium	-	-	-	6,65%	6,93%	6,22%	7,65%	7,96%	8,07%
Glyphosate Potassium Salt	2,30 %	0,77 %	0,93%	2,17%	2,05%	2,61%	2,34%	2,33%	2,17%

Source: Produced by the author based on data from ADAPAR, 2022.

The active ingredient glyphosate is used in the cultivation of avocado, pineapple, açai, cotton, genetically modified cotton, plum, peanuts, anonaceous fruits, fallow areas, rice, irrigated rice, oats, black oats, ryegrass, banana, sweet potato, yacon, beetroot, cocoa, coffee, cashew, sugarcane, persimmon, taro, star fruit, Brazil nut, carrot, rye, barley, citrus fruits, coconut, cupuaçu, oil palm, duboisia, pea, eucalyptus, beans, cowpea, fig, tobacco, ginger, guava, chickpea, guarana, yam, kiwi, lentil, apple, macadamia, papaya, cassava, mango, mangaba, passion fruit, quince, millet, corn, genetically modified corn, turnip, nectarine, medlar, pecan nut, pastures, pear, peach, pine nut, pinus sp, peach palm, radish, pomegranate, rubber tree, soybean, genetically modified soybean, sorghum, wheat, triticale, and grape (ADAPAR, 2022).

4.2 SALES OF ACTIVE INGREDIENTS AND PARKINSON'S MORTALITY IN BRAZIL

Between 2016 and 2022, the best-selling active ingredients were Glyphosate and its salts, 2,4-D, and Mancozeb, ranking 1st, 2nd, and 3rd, respectively. In 2015, 2014, and 2013, Glyphosate and 2,4-D remained in the top two positions, with Mancozeb appearing in the 4th, 8th, and 9th position, respectively. Thus, Glyphosate and Mancozeb, pesticides associated with Parkinson's, are among the most sold and used active ingredients (IBAMA, 2021).

From 2013 to 2020, the states with the highest sales of the active ingredient Mancozeb were Mato Grosso, Rio Grande do Sul, Paraná, Minas Gerais, Goiás, and São Paulo. In the analysis by region, the Midwest, South, and Southeast regions had the highest sales of the active ingredient. In the North region, the highest sales were concentrated in the states of Tocantins, Rondônia, and Pará; in the Northeast, in the states of Bahia, Maranhão, and Piauí; in the Southeast, in the states of Minas Gerais and São Paulo; in the South, in the states of Rio Grande do Sul and Paraná; and in the Midwest, in the states of Goiás, Mato Grosso, and Mato Grosso do Sul (IBAMA, 2022).

Table 5: Sales of Mancozeb by Federation Unit: 2013 to 2020, in tons. Highlighting the five states with the highest values for each year.

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**155,76**	**141,29**	**331,09**	**665,15**	**469,8**	**1040,41**	**958,27**	**1816,09**
RO	5,65	4,59	43,60	179,76	98,93	213,04	331,38	608,56
AC	0,00	0,00	0,00	0,00	0,00	0,00	1,31	3,47
AM	2,50	2,00	2,00	1,46	4,06	1,74	7,19	1,65
RR	0,02	10,29	0,54	0,17	3,78	1,69	8,30	71,90
PA	10,33	26,12	101,52	199,47	63,14	246,54	212,21	366,18
AP	0,00	0,00	0,00	0,00	3,79	2,49	0,02	0,00
TO	137,26	98,29	183,43	284,29	296,10	545,21	397,86	764,33
NORTHEAST	**370,49**	**1007,2**	**1185,93**	**1932,84**	**1948,74**	**3257,84**	**3434,49**	**5009,22**
MA	14,54	134,59	179,75	389,81	429,75	447,87	835,24	1317,78
PI	12,06	107,49	109,54	349,31	481,35	476,69	718,99	890,54
CE	23,48	14,13	9,08	21,15	39,00	10,44	30,54	68,74
RN	5,26	6,37	4,38	6,26	8,89	26,94	17,91	33,91
PE	100,76	142,53	8,88	12,99	45,97	13,99	10,99	33,31
PB	12,85	7,15	224,22	207,30	6,01	156,68	207,76	509,89
AL	3,57	6,11	2,52	5,80	2,73	9,93	8,68	16,55
SE	26,16	7,33	4,28	20,48	16,81	32,80	51,56	62,31
BA	171,81	651,50	643,28	919,74	918,23	2082,55	1552,82	2076,19
SOUTHEAST	**3300,02**	**3028,5**	**4722,98**	**6367,52**	**5111,17**	**8240,56**	**9630,08**	**8547**
MG	1463,80	1347,07	2265,79	3192,35	2314,07	3063,19	3474,37	4422,91
ES	202,76	163,91	158,03	171,56	213,24	225,89	207,88	250,52
RJ	131,75	69,93	76,39	61,62	68,76	75,97	70,52	103,50
SP	1501,71	1447,59	2222,77	2941,99	2515,10	4875,51	5877,31	3770,07
SOUTH	**2580,26**	**3432,92**	**7968,45**	**12928,24**	**13340,12**	**15858,87**	**17658,54**	**13466,62**
PR	503,48	652,35	2861,36	4485,74	2709,51	4774,18	3819,55	3932,48
SC	796,73	725,19	1226,48	1385,89	976,31	1185,55	1385,32	1393,34
RS	1280,05	2055,38	3880,61	7056,61	9654,30	9899,14	12453,67	8140,80
CENTRAL-WEST	**1758,34**	**4256,76**	**6231,93**	**8550,42**	**8274,49**	**12206,36**	**16669,47**	**21033,68**
MS	117,23	356,80	681,01	880,43	1261,80	1599,56	1687,20	2383,50
MT	480,40	1907,35	3342,58	4472,31	5155,39	7267,89	11917,30	14780,81
GO	1139,65	1937,84	2173,27	3091,16	1797,19	3239,08	3017,19	3804,80
DF	21,06	54,77	35,07	75,83	60,11	44,39	47,78	64,57
SALES WITHOUT SPECIFICATION OF FU	254,13	337,20	1134,05	2819,46	1671,09	30,99	771,74	654,26
TOTAL SALES	8.419,01	12.273,86	21.574,4	33.232,94	30.815,09	40549,92	49162,59	50526,87

Source: Produced by the author based on data from IBAMA, 2022.

From 2013 to 2020, the states with the highest sales of the active ingredient Glyphosate were Mato Grosso, Rio Grande do Sul, Paraná, Goiás, and São Paulo. When analyzed by region, the Central-West, South, and Southeast regions had the highest sales of the active ingredient. In the North region, the highest sales were concentrated in the states of Tocantins, Pará, and Rondônia; in the Northeast, in the states of Bahia, Maranhão, and Piauí; in the Southeast, in the states of São Paulo and Minas Gerais; in the South, in the states of Rio Grande do Sul and Paraná; and in the Central-West, in the states of Mato Grosso, Goiás, and Mato Grosso do Sul (IBAMA, 2022).

Table 6: Glyphosate Sales by State: 2013 to 2020, in metric tons. Highlighting the top five states with the highest values for each year.

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**5387,66**	**6588,48**	**7245,08**	**6914,11**	**7655,51**	**8529,74**	**10977,18**	**12225,46**
RO	1209,10	1761,05	1666,63	1426,89	1583,98	1853,71	2574,81	2501,86
AC	23,01	70,84	64,27	104,79	102,06	109,51	126,61	184,91
AM	67,13	20,53	29,96	22,58	55,72	54,78	48,80	80,15
RR	233,56	77,21	194,63	86,99	158,11	176,75	269,51	291,58
PA	1752,00	2090,22	2035,55	2502,50	2796,32	3177,47	3853,08	4517,56
AP	50,88	89,18	48,59	78,95	84,01	85,90	85,10	95,97
TO	2051,98	2479,45	3205,45	2691,41	2869,37	3071,25	4019,27	4553,43
NORTHEAST	**16891,08**	**19136,26**	**15355,59**	**15805,61**	**17984,52**	**16438,98**	**19603,59**	**22029,34**
MA	3721,84	5252,50	3876,38	4012,97	4808,45	4292,60	5084,15	4989,37
PI	2179,91	2326,31	2539,33	2538,83	3046,86	2514,62	3005,43	2878,06
CE	75,79	87,81	60,34	95,63	102,60	180,39	209,55	236,84
RN	47,90	50,34	61,05	74,90	59,48	65,46	70,17	143,64
PE	440,83	490,10	193,75	121,64	474,17	156,16	217,44	272,85
PB	269,06	103,61	495,96	461,95	132,65	547,78	607,51	972,16
AL	317,85	410,98	292,12	358,44	224,15	476,18	433,49	477,90
SE	144,60	166,10	243,47	266,27	176,91	205,19	327,52	476,52
BA	9692,50	10248,51	7593,19	7844,98	8894,90	8100,60	9648,33	11553,29
SOUTHEATS	**34270,23**	**32339,55**	**33849,37**	**31208,87**	**29973,28**	**34374,75**	**37482,87**	**39594,6**
MG	13235,50	12991,49	13176,70	13008,51	11856,35	13951,05	15669,97	17530,22
ES	1696,31	1773,32	1328,76	1271,69	1587,66	2096,62	1610,78	2089,42
RJ	247,59	245,97	201,50	244,04	234,44	246,57	245,63	181,96
SP	19090,83	17328,79	19142,41	16,684,63	16294,83	18080,51	19956,49	19724,69
SOUTH	**54453,2**	**58527,54**	**58841,58**	**50821,26**	**56105,38**	**56211,56**	**61697,73**	**66739,24**
PR	25495,20	25837,56	27712,84	22209,81	24121,69	25059,21	24632,85	28784,61
SC	4682,94	4658,50	5191,89	4711,28	5939,06	4922,88	5664,27	6420,35
RS	24275,06	28031,48	25936,85	23900,17	26044,63	26229,47	31400,61	31534,28
CENTRAL-WEST	**67435,6**	**69994,72**	**73332,58**	**73226,87**	**60332,01**	**65201,35**	**74494,63**	**79646,53**
MS	10732,13	12400,58	15144,09	13033,06	13085,41	13813,89	15477,38	18807,73
MT	36955,87	38189,67	38836,79	41846,22	31484,08	33638,86	38685,27	37888,87
GO	19447,37	19143,68	19095,57	18041,58	15486,98	17428,17	19978,27	22521,99
DF	300,23	260,79	256,13	306,01	275,54	320,43	353,71	427,94
SALES WITHOUT SPECIFICATION OF FU	6530,72	7361,29	5324,69	7655,49	1170,30	14200,01	13336,24	25879,31
TOTAL SALES	184.967,70	193.947,87	193.945,89	185.602,22	172.150,75	195.056,02	217.592,24	246.017,44

Source: Produced by the author based on IBAMA data, 2022..

From 2013 to 2020, the states with the highest sales of the active ingredient Paraquat Dichloride were Paraná, Rio Grande do Sul, Mato Grosso, Mato Grosso do Sul, and Goiás. When analyzing the regions, the Central-West and South regions had the highest sales of the active ingredient. In the North region, the highest sales were concentrated in the states of Tocantins, Rondônia, and Pará; in the Northeast region, in the state of Bahia; in the Southeast region, in the states of São Paulo and Minas Gerais; in the South region, in the states of Rio Grande do Sul and Paraná; and in the Central-West region, in the states of Mato Grosso do Sul, Mato Grosso, and Goiás (IBAMA, 2022).

Table 7: Sales of Paraquat Dichloride by Federative Unit: 2013 to 2020, in tons. Highlighting the five states with the highest values for each year.

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**96,14**	**129,23**	**128,47**	**271,53**	**263,35**	**265,72**	**410,79**	**153,80**
RO	47,09	70,01	69,38	57,62	58,64	51,41	134,19	61,68
AC	0,67	0,00	0,38	0,59	2,89	0,00	1,69	-5,96
AM	0,39	0,31	0,00	0,00	0,00	0,13	0,84	0,00
RR	0,00	0,00	0,00	0,00	3,36	4,73	8,10	0,81
PA	4,71	5,34	19,55	83,61	74,76	69,57	11,22	30,70
AP	0,00	0,00	0,00	0,00	0,69	0,00	1,22	0,23
TO	43,28	53,57	39,54	129,71	123,01	140,01	253,53	60,38
NORTHEAST	**588,73**	**521,3**	**579,97**	**718,13**	**754,1**	**609,41**	**1215,08**	**574,24**
MA	61,72	40,53	69,72	89,12	117,78	74,47	211,07	44,74
PI	28,98	27,81	36,90	68,02	68,96	67,60	131,55	32,96
CE	12,84	17,30	15,75	17,41	14,90	16,65	45,36	27,19
RN	10,63	5,90	3,76	7,43	13,90	15,80	25,16	22,93
PE	32,06	32,92	15,49	11,41	30,30	4,79	22,18	8,16
PB	32,99	15,70	51,08	49,70	10,28	28,18	41,06	37,20
AL	37,49	42,18	17,70	27,15	21,47	11,51	10,55	8,17
SE	3,37	8,94	79,91	13,96	5,70	3,80	4,29	6,65
BA	368,65	330,02	289,66	433,93	470,81	386,61	723,86	386,24
SOUTHEATS	**595,61**	**705,97**	**975,26**	**1007,31**	**1263,82**	**1065,29**	**1811,92**	**821,71**
MG	193,89	219,37	334,72	347,43	363,12	472,96	700,13	231,47
ES	45,75	82,87	86,71	93,25	174,07	58,04	55,87	108,24
RJ	13,29	10,77	12,33	12,86	6,64	0,80	0,00	0,00
SP	342,68	392,96	541,50	553,77	719,99	533,49	1055,92	482,00
SOUTH	**2073,17**	**3111,18**	**3610,76**	**4601,88**	**4522,52**	**3930,51**	**5932,63**	**3780,28**
PR	1200,09	1297,23	1426,33	2041,39	1828,12	1247,56	2125,92	1201,88
SC	214,16	202,76	239,61	270,54	261,81	306,59	340,15	218,10
RS	658,92	1611,42	1944,82	2289,95	2432,59	2376,36	3466,56	2360,30
CENTRAL-WEST	**1598,99**	**1830,09**	**2474,15**	**3131,03**	**3237,88**	**3289,79**	**5147,11**	**2292,02**
MS	672,43	908,30	939,59	1197,89	1485,95	1240,16	1777,66	891,73
MT	455,94	448,00	858,70	1023,86	1014,36	1320,88	1901,38	774,37
GO	460,37	461,16	665,82	900,16	718,83	717,84	1447,76	617,93
DF	10,25	12,63	10,04	9,12	18,74	10,91	20,31	7,99
SALES WITHOUT SPECIFICATION OF FU	1840,08	2106,78	2767,61	1908,28	1714,72	4039,13	1780,86	504,11
TOTAL SALES	6.792,69	8.704,76	10.536,60	11.638,19	11.756,39	13.199,97	16.398,14	8.120,21

Source: Produced by the author based on IBAMA data, 2022.

Parkinson's disease mortality in Brazil from 1996 to 2020 has been increasing in all regions of the country. The lowest values are found in the North region, while the highest values are in the Southeast region. Among the regions, the three with the highest data are in descending order: Southeast, Northeast, and South. When analyzing each region, for the period from 2013 to 2022, it can be observed that the highest mortality rates in the North region are in the state of Pará; in the Northeast region, in the states of Bahia, Pernambuco, and Ceará; in the Southeast region, in the states of São Paulo and Minas Gerais; in the South region, in the states of Paraná and

Table 8: Parkinson's Disease Mortality: Deaths by Residence according to Region/State (ICD-10 Category: G20 Parkinson's Disease)

	2013	2014	2015	2016	2017	2018	2019	2020
NORTH	**88**	**97**	**125**	**116**	**135**	**154**	**143**	**207**
RO	7	14	17	14	20	14	19	26
AC	5	2	7	3	6	11	5	2
AM	9	21	14	24	26	31	32	35
RR	2	44	4	2	2	6	1	8
PA	54	-	58	57	59	71	56	98
AP	2	2	4	1	4	4	8	14
TO	9	14	21	15	18	17	22	24
NORTHEAST	**558**	**628**	**661**	**720**	**729**	**739**	**863**	**957**
MA	42	46	50	55	45	60	57	74
PI	35	39	49	35	48	53	67	40
CE	109	122	134	154	163	155	172	184
RN	58	57	48	46	50	55	62	60
PB	48	56	50	56	65	54	65	66
PE	99	115	119	153	146	131	153	205
AL	23	19	23	45	30	31	31	34
SE	22	47	26	34	35	31	33	51
BA	122	127	162	142	147	169	223	243
SOUTHEAST	**1573**	**1786**	**1723**	**1831**	**1865**	**2091**	**2336**	**2231**
MG	352	386	397	429	428	473	582	525
ES	81	83	78	80	105	130	122	135
RJ	363	397	377	420	408	467	527	473
SP	777	920	871	902	924	1021	1105	1098
SOUTH	**618**	**645**	**609**	**723**	**771**	**925**	**892**	**959**
PR	195	218	193	242	259	298	266	286
SC	129	140	127	145	160	173	149	207
RS	294	287	289	336	352	454	477	466
CENTRAL-WEST	**197**	**198**	**231**	**216**	**259**	**289**	**341**	**336**
MS	41	49	45	39	41	61	61	48
MT	32	29	25	32	45	39	34	55
GO	84	87	104	93	104	119	169	157
DF	40	33	57	52	69	70	77	76
TOTAL	**3034**	**3354**	**3349**	**3606**	**3759**	**4198**	**4575**	**4690**

Source: Produced by the author based on DATASUS data, 2022.

It can be observed from the IBAMA and DATASUS data that the states with the highest mortality rates are among those that have used the associated pesticides the most.

Table 9: States with the highest use of active ingredients and mortality from Parkinson's disease.

REGION	FU: HIGHEST USE	FU: HIGHEST MORTALITY
North	Tocantins, Rondônia and Pará	Pará
Northeast	Bahia, Maranhão and Piauí	Bahia
Southeast	São Paulo and Minas Gerais	São Paulo and Minas Gerais
South	Paraná and Rio Grande do Sul	Paraná and Rio Grande do Sul
Central-West	Goiás, Mato Grosso and Mato Grosso do Sul	Goiás

Source: Produced by the author based on DATASUS and IBAMA data, 2022.

The collected data allowed for the development of parallels between the use of the active ingredients Paraquat, Mancozeb, and Glyphosate and mortality. When analyzing the crops, it is noted

that wheat, lettuce, and corn, which are the crops that use the most pesticides in general, also use the associated agricultural chemicals. It was observed that the Southeast and South regions are among the regions that use the active ingredients the most and also have the highest Parkinson's disease mortality. When looking at the states within each region, in terms of the highest levels of use of the three active ingredients and Parkinson's disease mortality, it is found that in the North, the states of Tocantins, Rondônia, and Pará had the highest usage, with Pará having the highest mortality. In the Northeast, Bahia, Maranhão, and Piauí had the highest usage, with Bahia having higher mortality. In the Southeast, both the highest usage and mortality were concentrated in the states of São Paulo and Minas Gerais. In the South, both the highest usage and mortality were concentrated in the states of Paraná and Rio Grande do Sul. In the Central-West, there was higher usage in the states of Goiás, Mato Grosso, and Mato Grosso do Sul, and higher mortality in Goiás. Thus, in certain states such as Pará, Bahia, São Paulo, Minas Gerais, Paraná, Rio Grande do Sul, and Goiás, it was observed that there was higher usage of the active ingredients Glyphosate, Mancozeb, and Paraquat during the same period when the highest mortality from Parkinson's disease was concentrated, allowing for inferences that these compounds may be associated with the pathology and be one of its causes.

5 FINAL CONCLUSIONS

Brazil is one of the largest consumers of pesticides, which implies the need for further studies on the exposure to agricultural chemicals and the risk of developing diseases that affect both the physical and mental health of the population, especially that of rural workers, who have greater contact and risk of exposure. In this context, one of the pathologies associated with pesticide use is Parkinson's disease, whose epidemiology corresponds to the second most prevalent neurodegenerative disease in the world, being more prevalent in the elderly population. It is characterized by degeneration of dopaminergic neurons in the substantia nigra's pars compacta in the midbrain, as well as the presence of Lewy bodies, which are rich in α-synuclein. It is a disease with multifactorial causes, resulting from the combination of genetic and environmental factors, leading to dopamine deficiency, which plays a role in various processes involved in movement production. As a result, it presents typical motor symptoms such as resting tremor, bradykinesia, forward flexion, gait problems, and rigidity, but also non-motor symptoms such as sleep disturbances and cognitive and psychiatric problems. Studies have analyzed the correlation between the use of pesticides such as paraquat, ziram, maneb, glyphosate, and mancozeb, and the risk of developing the disease, with the general mechanism of action being direct or indirect involvement in the death of dopaminergic neurons or neurotoxicity. In Brazil, paraquat, ziram, and maneb are prohibited, but mancozeb and glyphosate are allowed and among the three most commonly used active ingredients. There is a growing use of agricultural pesticides and Parkinson's disease mortality in all regions of Brazil, with the Southeast, South, and Central-West regions having

the highest usage, and the Northeast, Southeast, and South having the highest mortality. It was possible to establish some parallels of higher usage and mortality among states, such as Rio Grande do Sul, Paraná, São Paulo, Minas Gerais, Goiás, and Pará. Therefore, continuous study is needed to analyze the propensity for disease development and the use of these active ingredients in order to better understand the chronic effects of agricultural pesticides on the population.

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Drug regulatory decision-making: Evidence and real-world data as allies of randomized controlled trials

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ABSTRACT
With the Covid-19 pandemic, the world has been faced with the pragmatic search for effective treatment and highlighted the importance of real-world evidence and data as valuable for decision-making by different stakeholders. This evidence has brought new insights into efficacy, safety, and quality of drugs with patient-centered clinical outcomes. This paper describes some important elements of real-world evidence and data: 1) they are related to the patient's health status and/or the provision of health care routinely collected from various sources; 2) although, controlled clinical trial results are the basis for clinical decision-making, they can currently incorporate real-world evidence and data; 3) there is increasing use to support regulatory decision-making; 4) are underutilized sources to assess the impact on public health in risk minimization, health technology assessment, costs, and clinical decisions.

Keywords: Evidence, real-world data, controlled clinical trial, system of records.

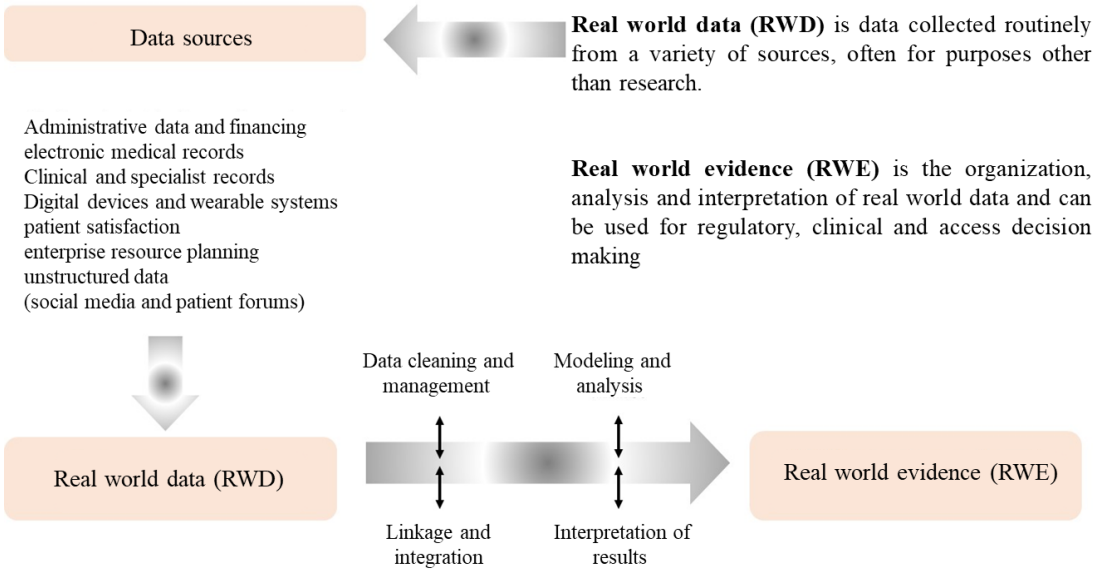
1 INTRODUCTION

1.1 THE POTENTIAL OF REAL-WORLD EVIDENCE AND DATA

With the Covid-19 pandemic, Real World Evidence (RWE) and Real-World Data (RWD) have contributed to broadening the view of patients and drugs excluded or not implemented in randomized controlled trials (RCTs) (KACIROTI *et al.*, 2021). It showed the world the need to maximize responses from stakeholders (researchers, funders, health systems, regulators, health professionals and patients) and the importance of scientific cooperation initiatives, data sharing and transparency.

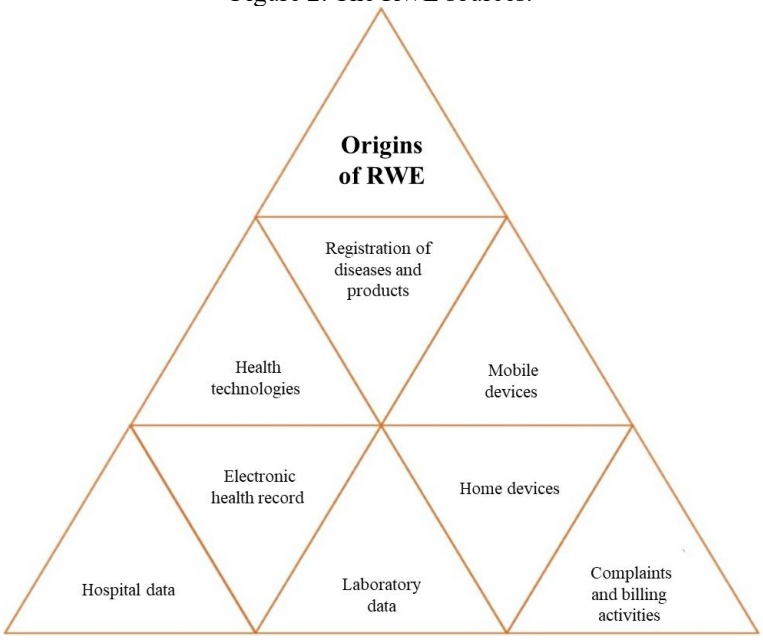
RWE studies rely on RWD (health records, data captured by mobile phones, other devices, data mining by Data Mining, Big Data, social media monitoring) Figure 1. They detect cost, benefits and risks, side effects and other long-term outcomes (DREYER, 2022; LIU; PANAGIOTAKOS, 2022).

Figure 1. Data fundamentals and real-world evidence.



In December 2016 the Food and Drug Administration (FDA) released the 21st Century Cures Act (Cures Act), accelerating the development and innovation of medical products. And in 2018, the FDA released guidance for evaluating RWE Figure 2 sources. RWE and RWD have become part of life sciences industry decisions by adopting methodology that meets the agency's regulatory standards in terms of efficacy and safety (FDA, 2020).

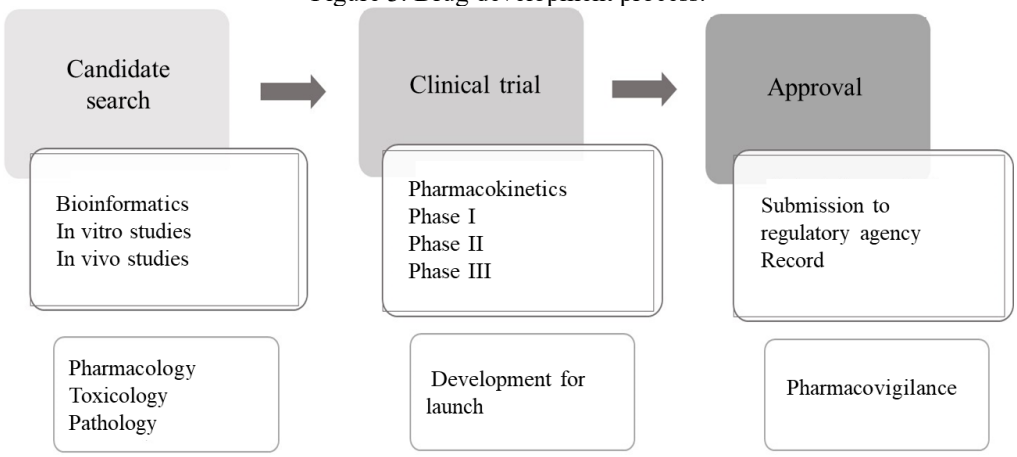
Figure 2. The RWE sources.



Much of the RWE and RWD literature expressed regulatory aspects (approval of new products for rare diseases). Currently, they are in the Research and Development (R&D) of biopharmaceutical companies applying RWD in: 1) pipeline strategy; 2) new sources of RWD to develop products; 3)

clinical development; (4) "big" RWD analysis; and (5) support for internal decisions (SCHUHMACHER; GASSMANN; HINDER, 2016) Figure 3.

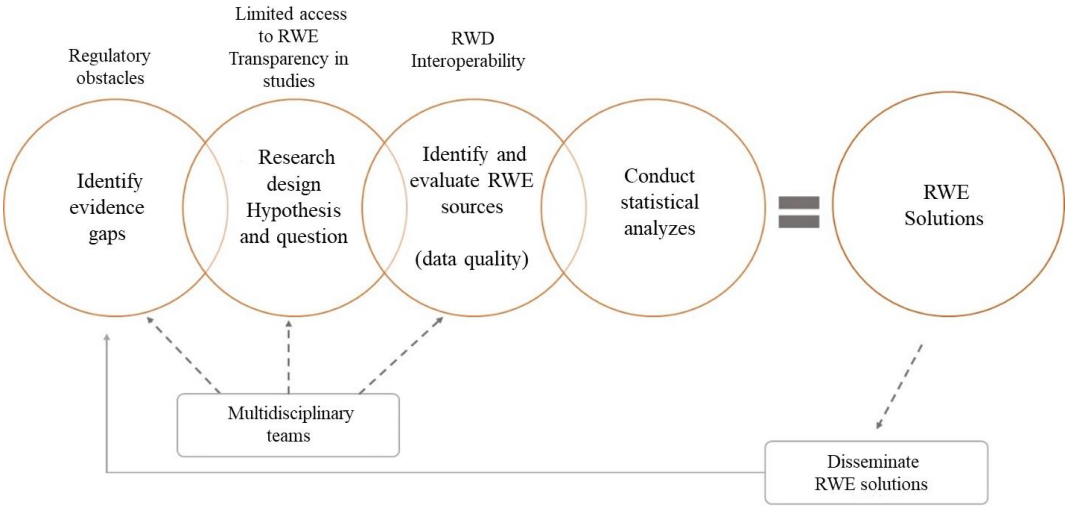
Figure 3. Drug development process.



A close look at the risks and benefits of an RWE drug is clinical evidence derived from the analysis of real-life data. And RWD are routinely collected data relating to the patient's health or clinical condition, captured from a wide variety of sources from part of routine care (SINDUSFARMA, 2022)

Understanding the scientific structure of RWE is a key factor and may start with drug treatment evidence gaps. This identification needs to include various perspectives of patients, stakeholders, healthcare professionals, and managers and policymakers. Failure in this step may result in the formulation of an incorrect research question, which may affect the rest of the RWE steps, generating evidence of little utility in decision making (Figure 4).

Figure 4. The challenges of structuring the RWE steps.

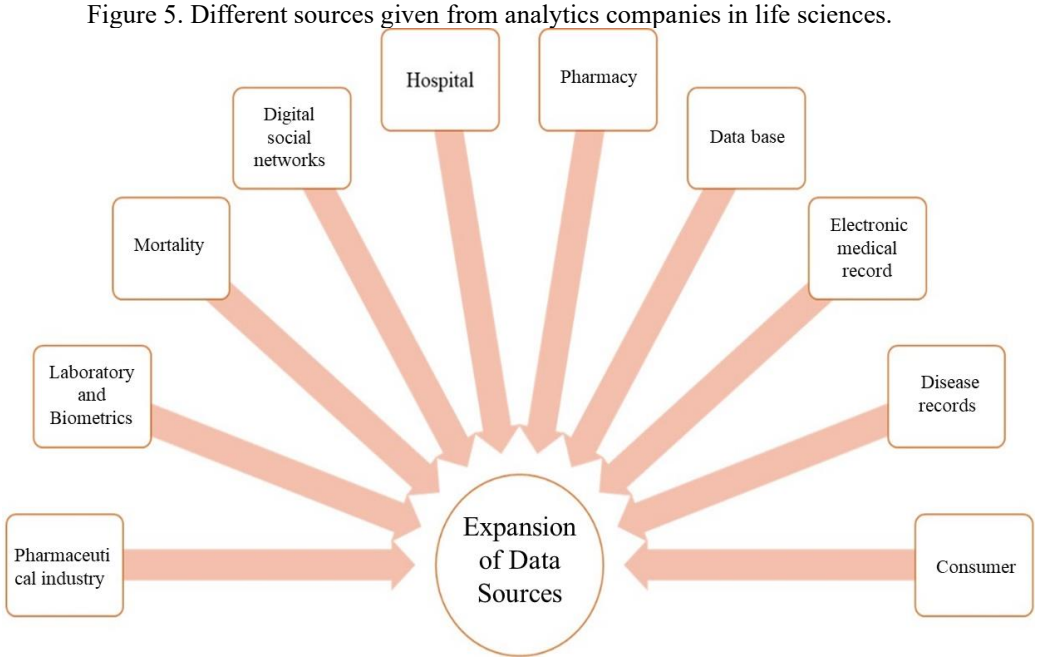


Another crucial step is the identification and evaluation of RWD. The quality of RWD sources varies significantly and there is limited research to understand this aspect. It is essential to structure a quality assessment model of the available RWD sources. Periodic evaluations are necessary to ensure the accuracy of the data (SINDUSFARMA, 2022).

Currently faced with regulatory pressures of care costs, stakeholders (researchers, funders, health systems, regulators, healthcare professionals and patients) are being guided by the right treatment to the right patient as measured by real-world outcomes. Some questions are among these actors: a) how to identify patients with lower risk and greater benefit of treatment "X"? b) how to manage the patient population, with a view to a policy, to promote the balance between clinical and financial outcomes? c) how to predict, identify, minimize, monitor and measure drug safety problems? d) how to ensure high standards of treatment adherence, patient education, support and follow-up to maximize the best outcome?

The life sciences industry (pharmaceutical, medical devices, biotechnology, digital therapy companies, and other innovators) works on investing in quality RWD and RWE to meet the demands of health management and health care outcomes. Today's analytics companies are growing to meet the demands of integrated data that have the breadth of patient health Figure 5.

Figure 5. Different sources given from analytics companies in life sciences.



Observing the exposed scenario goes through the pragmatism of Covid-19 in using research designs, in addition to RCT, in producing patient-centered evidence. It showed research advances (e.g. genomics, proteomics, gut microbiome, epigenomics, big data science, computational biology and artificial intelligence). It revealed flaws in the production and synthesis of evidence in medicine, public health and factors that influence clinical research (LONDON; KIMMELMAN, 2020). And it

reinforced the paradigm shift in how RCTs are designed, conducted, monitored, adapted, reported and regulated (SUBBIAH, 2023).

1.2 THE RELEVANCE AND CONSIDERATIONS OF RANDOMIZED CONTROLLED TRIALS IN DRUG R&D

The drug R&D and RCT scenario has a high cost to stakeholders (researchers, funders, health systems, regulatory bodies, health professionals and patients) around 1.5 to 2.5 billion dollars and inefficiencies and deficiencies of the health system (DIMASI; GRABOWSKI; Hansen, 2016; WOUTERS; MCKEE; LUYTEN, 2020). During the Covid-19 pandemic a number of scientific questions to be answered exceeded the responsiveness of RCTs. So, RWE studies were the main sources of evidence of symptoms, influence of patient characteristics, and the risk of morbidity and mortality (KACIROTI *et al.*, 2021; PETRILLI *et al.*, 2020; SULEYMAN *et al.*, 2020).

Since the 1960s, RCT has been the foundation for demonstrating the efficacy and safety of drugs for regulatory approval. However, after approval, patient outcomes may differ in clinical practice with no guarantee of safety to adverse effects. Given safety limitations, after the 90s, the FDA and EMA (European Medicines Agency) began using clinical practice evidence in terms of RWE and RWD and continue to establish legal aspects of nonrandomized trials in supporting evidence of RCT or assisting in clinical decision-making (EMA, 2023; FDA, 2023).

RCT researchers express concern that RWE may not be reliable in establishing causal relationships because it is neither randomized nor blinded, and RWD is outside strict quality control (EICHLER *et al.*, 2021). However, factors intrinsic to this design may limit the generation of evidence: a) rigid selection criteria that reduce external validity; b) certain conditions the design is not feasible; c) the duration is not always sufficient to evaluate long-term treatment or identify rare side effects; d) it is not always possible to perform in populations with specific diseases due to the difficulty of recruiting patients and e) they tend to take longer than real-life studies (SINDUSFARMA, 2022). And this may fail to generate evidence for practical decisions by stakeholders (researchers, funders, health systems, regulators, health professionals and patients) (CORRIGAN-CURAY; SACKS; Woodcock, 2018; SHERMAN *et al.*, 2016).

The RCT information vacuum is of interest to regulatory agencies, especially for certain patient groups. Although RCT plays a central role in determining treatment efficacy, there is little evidence on vulnerable subgroups. RWE and RWD are often the only source of information about treatment outcomes for patients with complications and vulnerabilities (high-risk family history, lifestyle factors, limited access to health care, and economic hardship) (DREYER, 2022).

RWD as a patient-centered research modality will become a routine source of data for RCT (ABERNETHY, 2023). This shows that it is necessary to advance in studies with non-interventional

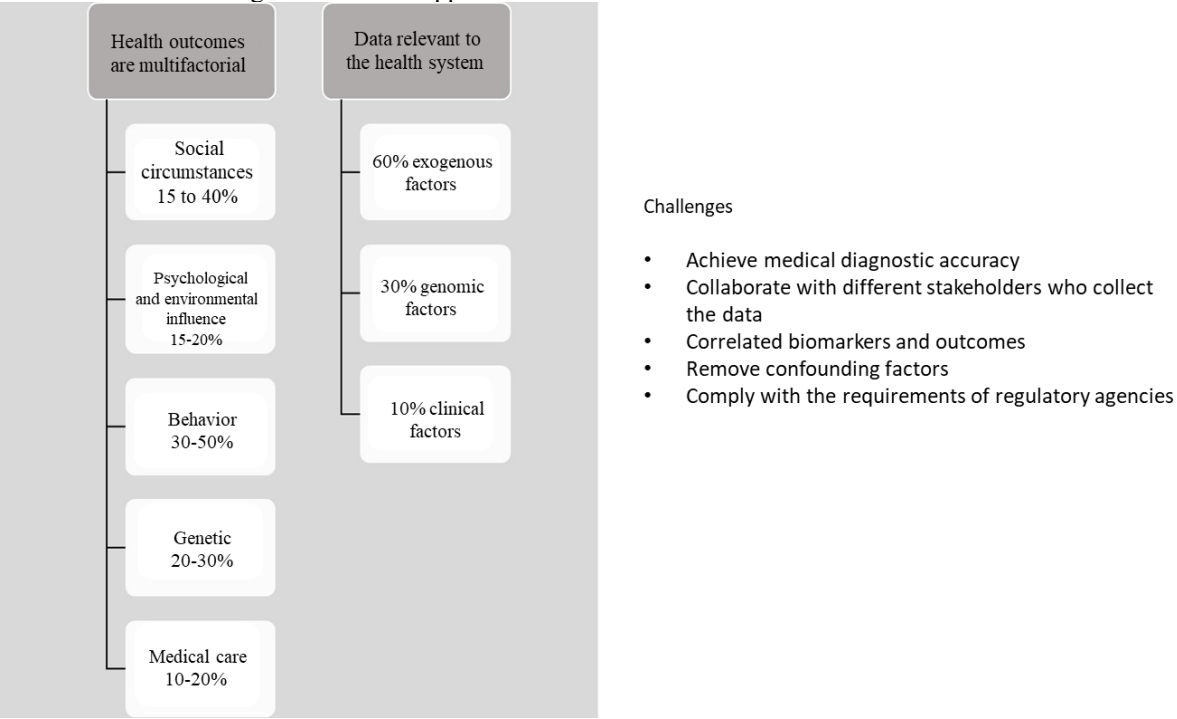
methodology of comparative efficacy, as they provide indispensable information on the risks and benefits of treatment in patients with complications. To do so, stakeholders (researchers, funders, health systems, regulatory bodies, health professionals and patients) interested in evidence should identify the specific health status or clinical phenomenon of interest and consider each step between clinical phenomena within the research database. Propose specific questions about possible errors or biases that affect each of the steps (SIMON *et al.*, 2022; VELENTGAS *et al.*, 2013).

The RWE and RWD are aggregated values to the RCTs. Tan et al (2022) showed proportions of those excluded from these studies and the importance of data collected during routine care. They studied electronic records of prescriptions and medical visits to quantify the proportion of people with a certain condition who were excluded from RCTs due to vulnerabilities such as multimorbidity, polypharmacy and age (adolescents or elderly). The exclusion rate was higher than 50% in adolescents who use several medications and similar values in the elderly over 80 years. Multimorbidity was excluded by 91.1% and concomitant medications by 52.5%. They identified gaps for cardiovascular disease and psychiatric conditions with implications for RCT outcomes. (TAN *et al.*, 2022).

The duty to care with concrete benefits to patients depends on the ability of different stakeholders the duty to learn. The requirement in the clinical process ensures that the research progresses without compromising the interests of patients (LONDON; SEYMOUR, 2023). This question is written in the work of Naggie *et al (2023) report the results of the RCT of the Accelerating Covid-19 Therapeutic Interventions and Vaccines 6 (ACTIV-6), in which 1,206 participants with mild and moderate cases of Covid-19 were not benefited with Ivermectin* (NAGGIE et al., 2023). Not all medical decisions are difficult, some care situations medical knowledge is sufficient and are straightforward. They become complex as the number of diagnoses, treatment options, risk of complications, and amount of patient data increases.

Healthcare is transitioning with a focus on value and outcomes when delivering patient care. Several factors play a role in this process and technology allows incorporating studies of RWE and RWD as a demand of the health ecosystem by recognizing that clinical decisions reflect the diversity of the population, contexts that people live and receive this care (CAVLAN, OLÍVIA *et al.*, 2018) Figure 6.

Figure 6. Holistic approach to healthcare with vision to RWE and RWD.



The scope of these studies has changed in the health value chain (pharmaceutical companies, biotechnology and health system). They have moved from monitoring the safety of post-marketing drugs, to supporting RCT outcomes and improving the treatment approach through observational studies. And the health system has recognized management and outcomes as principles in coverage decisions (EMA, 2023).

Investment is needed in the interface infrastructure between research and care, because the success of RWE and RWD will depend on robust, scalable data from different sources. Prospective RCTs may benefit from data collection in routine clinical settings. For example, by collecting accurate movement information from Parkinson's patients, temporal assessment will be longitudinal with support from electronic records, sensors, and environmental information. These sources can inform the history of patients before the start of RCT, allow monitoring of safety and efficacy after the end of the trial (ABERNETHY, 2023).

The real impact of this trend line involves: 1) strong engagement between science and policy; 2) more open, reliable and responsible scholarly communication practices among policymakers and 3) increasing digitization and visualization of scholarly communication. That will result in the availability and sharing of basic research data in scholarly communication as part of the Open Data movement (SHAHIN *et al.*, 2020).

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Partial Intravenous Anesthesia and epidural block for correction of Portosystemic Shunt in canine: Case report

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ABSTRACT
The Portosystemic Shunt is a vascular alteration that causes the diversion of blood flow from the liver to the systemic circulation, preventing the hepatic filtration of substances. The treatment of this deviation is surgical, therefore, in the anesthetic procedure, it is important to choose the drugs, avoiding those that go through the liver biotransformation process. The purpose of this report is to describe the use of partial intravenous anesthesia (PIVA) and epidural block in a case of repair of Portosystemic Shunt in a canine. Yorkshire, 1 year old, not spayed, weighing 2 kg, with congenital and extra-hepatic deviation. After MPA and with the animal induced, an epidural block was performed using lidocaine without vasoconstrictor and morphine. For maintenance, PIVA was performed with continuous infusion of remifentanil and lidocaine, offering good intraoperative analgesia, associated with local anesthesia, and reducing the need for the use of inhalational agents. During surgery, the patient had hypotension as the only complication, being related to the use of drugs that potentiated hypotension, such as acepromazine and morphine, but the patient was responsive to the load test with ringer lactate associated with ephedrine, to stabilize the condition and had a fast return anesthetic without painful stimulus, demonstrating that the association of the PIVA technique and the block was effective in the analgesia of the patient in question.

Keywords: Analgesia, PIVA, Biotransformation, Liver, Infusion, Sevoflurane.

1 INTRODUCTION

Portosystemic Shunt (SPS) or Portosystemic Shunt (DPS) is an atypical connection between portal and systemic circulation. This alteration produces deviation of the blood flow of the liver in different degrees (TALARICO, 2017) and toxic substances such as ammonia and others are sent directly to the systemic circulation without passing through the liver (SANTOS *et al.*, 2014).

SPS can be acquired or congenital and anatomically can be distinguished as intrahepatic, located inside the liver, or extrahepatic, located outside the parenchyma liver (REGINATTO *et al.*, 2011).

When the Portosystemic Shunt or Portosystemic Deviation is congenital, the treatment is surgical. Ideally, the referral should be early, so veterinarians who specialize in the field should make a quick and efficient decision regarding the choice of surgery (ADIN *et al.*, 2006). As cited by Havig & Tobias (2000), there is a low mortality in dogs and cats submitted to surgical correction of SPS. However, postoperative results are variable in both species.

The veterinarian and his team have the responsibility to recognize, evaluate, prevent and treat pain, acting to, in addition to protecting their patients, meet their demands (HELLYER *et al*., 2007). The responses to visceral pain stimulus are activated in the autonomous system producing changes in heart rate and blood pressure (MEINTJES, 2012), therefore, because it is a complex surgery, it is extremely important the presence of an experienced anesthesiologist to evaluate the physiological parameters and conduct as best as possible.

In this context, it is essential to use drugs that do not present hepatotoxicity. Avoiding drugs that go through the process of liver biotransformation, being the first choice the use of inhalational anesthetics as the most recommended in these patients. Moreover, when compared to injectable anesthetics, the recovery time of patients is significantly reduced when inhalational anesthesia is used (BELLARD *et al.*, 2016).

The present report aims to describe the anesthetic management with partial intravenous anesthesia (PIVA) and epidural block in correction of Portosystemic Deviation of a one-year-old canine.

2 CASE REPORT

A female female Yorkshire canine was attended, 1 year old, uncastrated and weighing 2kg with a diagnosis of Portosystemic Deviation. In the consultation the animal presented sialorrhea, walking in circles and incoordination.

Ultrasound examination showed a liver with decreased volume, regular contours, normoechogenic parenchyma, homogeneous, hepatic veins and portals not very evident, portal vein with a diameter of 0.26 cm in the portal hilum, presenting hepatopetal flow with a velocity of 9.19 cm/s (normal: 10 – 25 cm/s). AO: 0.46 cm; VDC: 0.52 cm; PV: 0.26 cm. VP/AP: 0.60. Value indicating the possibility of presence of extrahepatic deviation. In addition, dilated and tortuous vessel, coming from the portal vein, with craniodorsal path, towards the diaphragm, between the abdominal aorta artery and caudal vena cava, an image compatible with porto-azygos deviation, measuring approximately 0.45 cm in diameter in the region near the portal vein, 0.34 cm in most of the path and 0.51 cm in the diaphragmatic region.

In the blood count the parameters were within the normal range for the species, however in the biochemicals albumin, creatinine and urea were below the reference values and the (alamine

aminotransferase) ALT above the reference values. The coagulation times, protombin time (PT) and activated partial thromboplastin time (APPT) within the reference values. C-reactive protein CRP above the reference values. The preoperative electrocardiogram (figure 1) showed physiological sinus arrhythmia with a mean heart rate (HR) of 158 beats per minute (bpm).

Figure 1 – Pre-surgical Yorkshire electrocardiogram, 1 year, which underwent SPS correction under PIVA anesthesia and epidural block



3D computed ultrasonography was performed to confirm the diagnosis of Portosystemic Shunt. Regarding the pre-surgical-anesthetic exams, the patient was submitted to food fasting of 8 hours and water fasting of 4 hours aiming at the surgical-anesthetic procedure. In the pre-anesthetic evaluation, the patient presented alert behavior, with HR of 100 bpm, respiratory rate (RR) 10 movements per minute (rpm), and systolic blood pressure (SBP) 100mmHg, synchronous and strong pulse, normostained mucous membranes (NC), normohydrate (NH), capillary filling time (CPT) less than two seconds, rectal temperature (RT) 38.2 and glycemia 65mg/dL. According to the American Society of Anesthesiologists (ASA), the animal was classified as ASA III.

In MPA, the association of acepromazine (0.02mg/kg) and methadone (0.2mg/kg), both MI, was used, and after about 15 minutes trichotomy and venoclysis were performed. Pre-oxygenation was performed via mask for five minutes, followed by anesthetic induction consisting of the administration of propofol (slow *bolus* 4mg/kg, IV). Continuously, the animal was intubated with endotracheal probe number 3.0 and coupled to the anesthetic circuit without double reinhalation T of Baraka on spontaneous ventilation.

Anesthetic maintenance was performed with PIVA, using sevoflurane in a calibrated vaporizer, associated with continuous infusion of remifentanil (1mcg/kg/h) and lidocaine (2mg/kg/h). In addition, he received intraoperative fluid therapy with lactated Ringer's solution (RL) at the rate of 2ml/kg/h. Cephalothin was administered as a prophylactic antibiotic (20mg/kg) IV. Anesthetic monitoring was constant and performed with the aid of Doppler to measure noninvasive blood pressure, multiparametric monitor to visualize temperature, electrocardiogram, pulse oximeter

and capnograph, in addition to the constant verification of ocular reflexes and rotation of the eyeball, suggested by Guedel's plans. The patient presented a moment of hypotension in the intraoperative period, where a load test of 10ml/kg/h was used for 20 minutes and ephedrine 0.1mg/kg, IV.

Prior to the beginning of the surgical procedure, antisepsis and epidural block located between the seventh lumbar vertebra (L7) and the first sacral vertebra (S1) were performed, which was accessed with a Tuohy needle confirming the location by the pending drop test or by the loss of resistance to air application. Subsequently, morphine (0.1mg/kg) and lidocaine without vasoconstriction (3mg/kg) were administered.

The surgical procedure lasted a total of 180 minutes (3 hours) and anesthesia lasted 190 minutes (3 hours and 10 minutes). At the end of the procedure, the patient presented parameters of SBP 120mmHg, HR 100bpm, RR 20mpm, RT: 35.1 and glycemia 75mg/dL. Therefore, she presented hypothermia, even though she had been previously heated with a thermal mattress. Was used hot water bags to warm the patient and after 15 minutes was extubated. In the immediate post-anesthetic period, he received dexamethasone (0.25mg/kg), dipyrone (25mg/kg), maropitant (1mg/kg), ondansetron (0.5mg/kg) and metoclopramide (0.3mg/kg), all IV.

After the procedure, she remained hospitalized for two days receiving ondansetron (0.5mg/kg) IV, TID, metoclopramide (0.3mg/kg) IV, TID, benzoylmetronidazole (10mg/kg) IV, TID, maropitant (1mg/kg) IV, SID, dipyrone 25mg/kg IV, TID, methadone the day after the procedure (0.15mg/kg) SC, TID, dexamethasone (0.25mg/kg) IV, SID, domperidone (0.1mg/kg) VO, BID, lactulose syrup (0.5ml/kg) VO, IDB.

At hospital discharge, she was referred with benzoylmetronidazole (10mg/kg) VO, TID, for 7 days. Tramadol hydrochloride (4mg/kg) VO, QID, for 5 days. Dipyrone (25mg/kg) TID, for 2 days. Lactulose syrup (0.5ml/kg) BID, VO, continuous use. Continued use of feeding with hepatic ration, Elizabethan collar or use of surgical clothing until removal of the stitches, cleaning of the stitches with saline solution once a day until removal of the stitches, removal of the stitches in 15 days. After 15 days, the animal was stable, with no changes related to pain and discomfort.

3 DISCUSSION

The Portosystemic Shunt in the canine species is usually diagnosed in small dogs (TOBIAS, 2003) and is considered surgical, so it is important to determine the preoperative procedures. It can be extrahepatic or intrahepatic, congenital or acquired based on anamnesis, clinical signs, physical examination and complementary tests. The canine in the present report had a great similarity with that described in the literature, mainly because it is a Yorkshire (MEHL *et al.*, 2005).

In the patient in the present report, the deviation was congenital and extrahepatic (azygos), since liver function was impaired due to abnormal blood flow. In addition, the absorption, metabolism and exclusion rate of undesirable substances were also reduced (FUTEMA, 2010).

There are several parameters that should be evaluated, together, with the surgeon and anesthesiologist for the correction of SPS. The approach used in the preoperative evaluation is of great relevance for the identification of anesthetic risks and visualization of patient management characteristics (BRODBELT; FLAHERTY; PETTIFER, 2017)

Patients with DPS have laboratory test results, such as complete blood count and biochemical profile not specific for the disease (RULAND *et al.*, 2007). Meanwhile in the case described, the blood count was within the normal range for the species, but regarding the biochemicals, hypoalbuminemia, creatinine and urea were below the reference values and the ALT above the reference values. Patients with Portosystemic Shunt may present with changes in coagulation time and altered response to substances metabolized and excreted by the liver (KUMMELING *et al.*, 2006) but in the patient the coagulation times TP and TPPA were within the reference values. C-reactive protein was above the reference values, with what (GOW *et al.*, 2012) reports on the elevation of protein C in patients with SPS.

The patient was submitted to electrocardiogram to evaluate arrhythmias, enlargement of cardiac cavity, coronary pathologies and anesthetic risk, the referred presented physiological respiratory sinus arrhythmia, being considered a normal rhythm. The exam showed QRS complexes of low amplitude negative T wave, asymmetric and less than 25% of the R wave may be associated with increased parasympathetic activity in the sinoatrial node, however, it is an indicator of reduced sympathetic tone (NOGUEIRA et al., 2010). Liver disease commonly has cardiovascular disease. It is related to hyperdynamic disease, with cardiac index twice normal and low peripheral vascular resistance (WIKLUND, 2004).

This patient was classified as ASA III, was taken into account physical status, age and because it is a liver disease, that is, a systemic disease. Patients classified as ASA III are generally more likely to have lower blood pressure under anesthesia than those with less severe diseases because it is a systemic disease (REDONDO et al., 2007).

One of the drugs used in MPA was acepromazine IM, an agent of the phenothiazine class, at a dose of 0.02mg/kg, as cited by Saponaro *et al.* (2013), sedation scores in dogs receiving this dose of intravenous acepromazine are elevated up to 80 min compared to baseline values. The drugs of this class produce effect through antagonism of dopaminergic receptors, that is, depression of the central nervous system (BALDESSARINI &TARAZI, 2001).

Methadone, a potent opioid (dose 0.02mg/kg) was associated with acepromazine in order to produce neuroleptanalgesia. In addition, its action acts as an antagonist of NMDA-type receptors, being useful in cases of hyperalgesia and tolerance to opioids (WAGNER, 2009).

Before induction, the patient was pre-oxygenated for five minutes. Induction was with slow *bolus* of propofol (4mg/kg), IV. This drug exerts activity on GABA receptors and the synergistic effects observed may result in significant depression of the nervous system central (WIEDERSTEIN; AUER; MOENS, 2006). The main adverse effect of this general anesthetic is respiratory depression and apnea if administered quickly, however these clinical signs were not observed in the patient (WHITTEM et al., 2015). For this reason, she was immediately intubated for administration of the anesthetic.

For anesthetic maintenance, sevoflurane was used in a calibrated vaporizer associated with continuous infusion of remifentanil and lidocaine, being classified as a PIVA. Partial intravenous anesthesia has as its main advantage over inhalation alone, the decrease in the need for inhalational agents (ILKIW & PASCOE, 2003). In what Patel & Goa (1996) says, the use of Sevoflurane was described, which has some characteristics of pharmacokinetics, such as the speed of uptake by the blood from the lungs, distribution by the body and final elimination by the lungs, distributing by the body and final elimination by the lungs and other pathways therefore, allows rapid and precise adjustment to the desired effects and rapid recovery of physiological parameters, as observed in the patient.

The remifentanil used in continuous infusion at a dose of 1mcg/kg/h is a synthetic opioid, has high analgesic potency, with ultra-short action and duration and, therefore, should be administered in continuous infusion in the intraoperative period to promote good analgesia (SOUZA *et al.*, 2018), as observed in the present report.

Lidocaine was associated with remifentanil by continuous infusion and according to Robertson *et al.* (2005), the administration of lidocaine intravenously *(bolus* of 2 mg/kg, followed by 0.05 mg/kg/min) is intended to perform antinociception. The mechanism by which systemic administration of lidocaine produces analgesia is uncertain, but is believed to include an action on the Na+, Ca2+, and K+ channels and the NMDA receptor.

Regarding the epidural block, it was performed with the association of lidocaine (3mg/kg) and morphine (0.1mg/kg) in order to potentiate analgesia on pain physiology. The use of opioid analgesic agents serves as an important alternative in the control of nociception in animals and, mainly, by the epidural route, for the control of postoperative pain (POPILSKIS *et al.*, 2000). Morphine administered by this route stands out for its long-lasting systemic analgesic action and minimal side effects (PASCOE & DYSON, 1993). Lidocaine is the most versatile local anesthetic used in Veterinary Medicine, due to the short latency, moderate duration of effect and safe toxic

dose in dogs (DUKE *et al., 1994), it has analgesic and antihyperalgesic properties (SHAH et al., 2018).*

During the procedure, the referred patient presented hypotension, which may have been caused by the use of acepromazine, sevoflurane, propofol and even PIVA. PAS is responsible by tissue perfusion, with evidence for cerebral and coronary perfusion, and is calculated by the product between peripheral vascular resistance and cardiac output (HUBBELL & BEDNARSKI; MUIR, 1989).

A load test was performed in order to stabilize the patient's BP, which consists of increasing the intravenous fluids provided in a short period of time. Rabelo & Arnold (2007) cite that aggressive administration is necessary to obtain an adequate increase in volume to reestablish tissue perfusion and, consequently, increase blood pressure and stabilize tissue perfusion.

Hoffman + Lefkowitz (1996) determine the use of ephedrine as an agent of agonist actions directly and indirectly on alpha and beta receptors: the release of presynaptic noradrenaline from peripheral nerve endings to extracellular fluid increases cardiac output and blood pressure, but with variable effects on systemic vascular resistance.

The recovery of the canine was quiet and without serious intercurrences, only hypothermia, which is something expected in anesthesia, as well as indicated was controlled with the use of thermal mat and hot water bags after the procedure (GORCZAK *et al.*, 2021). And evidencing what was found by Duval *et al.* (2018), who state that the patient's recovery with the use of PIVA can be smoother. It should be noted that inhalational anesthetics are almost totally excreted immutably by the lung, with negligible accumulation in the body, allowing to complement anesthesia with other drugs that promote a quality analgesia, more complete and safer, in terms of metabolism (DORSCH & DORSCH, 2008).

The rate of postoperative intercurrence is commonly caused by hypoglycemia, while surgical mortality is low in most cases of extrahepatic deviations. The clinical improvement, in general, occurs on the first postoperative day (TOBIAS, 2007). In what Neto (2013) cites, from two to four months after surgery, the animal's liver regenerates, and may have a significant increase.

4 CONCLUSION

It is understood that anesthetic care in patients with SPS is related to preoperative management, monitoring care and the pharmacological protocol, i.e., MPA, induction and maintenance. The anesthetic procedure was effective, with an alteration occurring with the use of medications that potentiated hypotension, but having been responsive to the maneuvers performed to reestablish the hypotension. The patient had a return fast and without painful stimulus, having

been effective the epidural block associated with the PIVA technique to control pain in the animal, therefore the success of the procedure.

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Mediating effects of religious/spiritual coping on mental health

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ABSTRACT
The beneficial assets of religious/spiritual coping in mental health have been considered beneficial as coping strategies for physical and mental illnesses for many individuals, playing a significant role in their lives and can help them cope with their problems. In this sense, the aim of this study is to highlight the mediating effects of religious/spiritual coping on mental health. The study was developed through a bibliographic research, with a qualitative approach, with a search in the Scielo and PubMED databases, available in Portuguese and English, without date delimitation. The descriptors used in the search were coping, mental health, spirituality, religiosity. In this review, it was found that R/E is positively related to coping, resilience, well-being, happiness, hope, self-control and self-esteem, suggesting that the higher the R/E, the better mental health. It was concluded that the effects of religious/spiritual coping on mental health are determined, at least partially, by the structures of orientation and meaning that are strongly embedded in individual internal schemes, serving to cushion the consequences and impact of negative events and increase subjective well-being.

Keywords: Coping, Religiousness, Spirituality, Mental health.

1 INTRODUCTION

It is known that health is determined not only by physical, mental and social factors, but also by spiritual ones, which play an important role in the lives of human beings and influence many aspects of existence. They are also closely linked to mental health, including a wide variety of beliefs, emotions and behaviours, some of which are constructive to human functioning (KOENING, 2012).

According to Moreira-Almeida et al. (2014), religiosity/spirituality (R/E) is related to better overall health and longevity and lower frequency of use of health services. In mental health, it is related to a lower chance of faster development and recovery from cases involving depression, suicide attempt, and drug and alcohol abuse. There is also evidence that people with a well-developed spirituality tend to get sick less, have healthier lifestyle habits, and when they do get sick, develop less depression and recover faster.

R/E has a therapeutic effect on mental health, endowing individuals with valuable coping skills that are accessible regardless of financial, social, physical or mental circumstances. In addition, religion tends to prescribe healthy lifestyle practices, give social support to individuals (resulting in a sense of belonging and being cared for by their group) and help their adherents to develop cognitive structures that help them in the difficulties of life (PARGAMENT, 2001).

In addition, R/E reinforces individuals' internal locus of control, which allows them to respond to the same problem in a way that is beneficial to their well-being. Consequently, through the use of religious or spiritual strategies or practices such as prayer or meditation, they can counteract the harmful tendencies caused by their illness and can reduce stress and anxiety, decrease self-blame, stabilize emotional highs and lows, and improve self-esteem, self-awareness, as well as improve the management of obstacles such as panic attacks, generalized anxiety disorder, depression, insomnia, drug use, stress, chronic pain, and other health problems (ECCO; Lemos, 2016).

The beneficial assets of religious/spiritual coping (CRE) in mental health are considered beneficial regardless of age, race, gender, nationality, and socioeconomic status and appear to be higher for those in stressful circumstances, serving as a resource for individuals affected by mental illness, especially disadvantaged groups who experience substantial stress in daily life, higher rates of mental disorders, and who lack the social support and financial means to treat their disease (KOENING, 2007).

Religiosity and spirituality are prevalent coping strategies for both physical and mental illnesses for many individuals, playing a significant role in their lives and can help them cope with their problems. Thus, the religious/spiritual coping involves behaviors that help the human being to deal or adapt to difficult life situations, being fundamental to their sense of well-being and can help to deal with the negative aspects of existence (PARGAMENT, 2001).

In this sense, the aim of this study is to highlight the mediating effects of religious/spiritual coping on mental health.

2 MATERIAL AND METHOD

The study was developed through a bibliographic research, with a qualitative approach, with a search in the Scielo and PubMED databases, available in Portuguese and English, without date delimitation. The descriptors used in the search were coping, mental health, spirituality, religiosity.

3 DEVELOPMENT

3.1 RELIGION AND SPIRITUALITY

It is considered necessary to make a distinction between religion and spirituality in order to contextualize the theoretical framework on which this study is based. Religion is considered by the American Psychological Association (APA, 2010) as a belief system with spiritual practices organized

around the worship of an all-powerful deity or deities and includes behaviors such as prayers, prayers, meditation, and participation in rituals. Thus, it has generally been defined in terms of behavior, which includes frequency and/or participation in activities and practices that find their basis in culture and social participation. On the other hand, spirituality is understood as an individual experience, which includes feelings or experiences of admiration, harmony, peace and connection with the universe or higher power, which may or may not be related to religion (KOENING, 2012).

Religion has become a system of belief practices observed by a community, sustained by rituals that recognize, worship, and communicate or address the sacred, the transcendental. This rests on a set of writings or teachings that reveal the meaning and purpose or place that individuals occupy in the world, the responsibilities of each other and the naturalness of the afterlife, usually around the worship of an all-powerful deity or deities (APA, 2010).

This can be professed publicly through participation in a particular organization. This organizational affiliation entails attending religious services, gathering in a group to pray, or studying the scriptures, among other things. Religion is a form of spirituality, but not all spirituality is necessarily religious, although all religions claim to promote the spirituality of their followers through their beliefs (KOENING, 2012).

The term spirituality has been widely used in health care, the purpose of which has been applied to both people of various religious and non-religious confessions. This opens up a new category of spiritual but not religious people. According to Koening (2007), religion and spirituality are traditional means of coping, because they promote a locus of internal control in stressful situations and help to re-signify stressful events, in order to intrinsically motivate the individual to deal with the stressors of life.

According to Ecco and Lemos (2016, p. 41):

> The spiritual dimension depends on three components: the need to find meaning and fulfillment in life; the need to have hope and the will to live; need to have faith in yourself, others, or God. This holistic model of care, which validates the spiritual dimension and values biopsychosocio-spiritual integration, contributes to enhance the strengths of individuals and increase empowerment during the care process

Thus, in general, religion and spirituality do not necessarily correspond to the same phenomenon, however, religious and spiritual beliefs have the potential to influence the cognitive assessment of negative life events in a way that makes them less distressing (KONEING, 2012).

3.2 SPIRITUAL RELIGIOUS COPING

Lazarus and Folkman (1987, p. 141) defined coping as cognitive and behavioral efforts "to manage specific external and/or internal demands that are assessed as overloading or exceeding the

person's resources." This definition addresses the cognitive, affective and behavioral aspects of the coping process and also focuses on the effort associated with an individual's response.

Lazarus and Folkman (1987) developed the Transactional Model of Stress and Coping, which provides a framework for dealing with stressful events, where stress is considered as the effect that a challenging environment or situation has on an individual and coping is how that person responds and acts to manage, alter, or tolerate such stressful situations or events. The authors proposed two types of coping strategies: those aimed at alleviating negative emotions and those that include efforts to deal directly with stressful situations.

According to Helena and Polakiewicz (2015, p. 41):

> There is an interconnection between religion and health, religion and disease and religion and healing; This relationship may be linked to a physical illness, but linked to an existence of numerous possibilities connected to mental health. Coping or coping refers to the union of cognitive and behavioral strategies, used by people as a way to face stressful situations. Its definition is described as the creation of a set of defense of people to circumvent adversity and stress in their work and personal environment; may be focused on both problems and emotions, that is, individuals can guide these thoughts and actions to the cause of the problem situation (focus on the problem) or to regulate distressing emotions (focus on emotions).

Subsequently, Pargament (2001) developed the concept of religious/spiritual coping, which proposes that R/E is one of the ways through which individuals can deal with life situations through the internal force that emerges from their religious and/or spiritual beliefs and practices, that is, they are the different forms, related to the sacred, to understand and deal with the negative events of life. Thus, R/E provides meaning and purpose to life in times of crisis.

According to Pargament (2001), religious/spiritual coping alludes to a search for meaning as a force that guides life and directs people to face difficult situations that may arise throughout life. Such a search does not have a universal goal, as it can be oriented towards the material, physical, psychological, social, as well as spiritual, which can be good or bad.

Faced with critical situations, people often deny and avoid confrontation with their own mortality and vulnerability, seeking to protect their values; so the conservation of meaning is an initial trend that manifests itself in the most threatening situations (PARGAMENT, 2001).

Pargament (2011) classified religious/spiritual coping into two constructs: positive and negative. Positive coping translates into a secure relationship with the sacred and involves assessing obstacles in the light of divine providence, while negative coping is maladaptive and interprets challenges as the result of divine punishment and dissent. Both positive and negative constructs of religious/spiritual coping are considered relevant to mental health outcomes.

Puchalski et al. (2009) highlight the following aspects of religious/spiritual coping: cognitive, which refer to the way the individual understands the world around him, including questions such as "Why do bad things happen to good people?" "What happens after death?"; experiential, which have

to do with connection and inner resilience, encompassing questions such as "Am I alone or am I connected to something bigger?" "Can I find hope in this difficult situation?"; and behavioral aspects, which concern the ways in which a person's spiritual beliefs and inner spiritual state affect their behavior and life choices.

Corrêa, Batista and Holanda (2016) report that positive coping patterns are associated with benevolent outcomes, including fewer symptoms of suffering, psychological and spiritual growth as a result of the stressor.

Ingersoll (1998) proposed that the spiritual dimension of meaning is expressed in the form of a sense of having a life worth living, with purpose and of being at peace. Meaninglessness in life can result in various psychopathologies and R/E restores its purpose and meaning, which in turn reduces mental distress and cases of anxiety and depression.

Resilience involves the ability to recover after a disruption in life; In other words, it's the ability to get back to normal or even thrive in the face of hardship. Therefore, it is fundamentally linked to coping, which involves the various ways in which people respond to adversity in their efforts to recover. Thus, having a diversity of coping options is particularly useful to be resilient and religious/spiritual coping methods can expand this repertoire (PANZINI; FLAG, 2007).

According to Pargament (2011) the crises that individuals face often raise deep existential questions about their place and purpose in the world, the limits of their control and their finitude. In this sense, religious/spiritual forms of coping may be able to address the deeper dimensions of a crisis, responsible for a unique variation in relation to secular ways of coping, when it comes to adjusting to stressors.

Thus, religious/spiritual coping is a form of emotional coping and, to achieve this balance, it is possible to turn to this source of coping, developing a sense of positivity and resilience (NASR et al., 2012).

3.3 RELIGIOUS/SPIRITUAL COPING IN MENTAL HEALTH

According to the World Health Organization (WHO, 2001), mental health is defined as a state of well-being in which the individual is aware of his own resources, can cope with the normal stress of life, work productively and fruitfully and is able to make contributions to his community. From this approach, mental health encompasses not only as the absence of psychopathological symptoms (e.g., depression, anxiety, psychotic symptoms), but also by the presence of feelings of well-being.

R/E and mental health have generally been seen as allies, with positive religious/spiritual coping providing the necessary solace in times of distress. Religious/spiritual coping, as described by Pargament (2001), consists of the use of religious beliefs, attitudes or practices to reduce the emotional

suffering caused by stressful life events, such as losses or changes, giving meaning to suffering and making it more bearable.

Religious/spiritual beliefs and practices are used to regulate emotion during circumstances that are outside of individuals' personal control and provide a source of comfort and wisdom to help understand what otherwise seems meaningless and prescribes a ritual path to address basic spiritual questions of meaning, value and relationship (MOREIRA-ALMEIDA et al., 2014).

Religious/spiritual coping is considered a factor related to mental health during disasters, due to the ability of religious and spiritual beliefs to provide a powerful lens through which individuals and families can make sense of the events that occur in their lives (CORRÊA; BAPTIST; HOLLAND, 2016).

For Puchalski et al. (2009), adverse events take away the sense of normality and disrupt the daily routine and, in these moments, coping, through the beliefs and practices associated with R/E can provide an internal structure and help frame negative events in a positive light, helping to overcome these types of stressors that directly interfere with mental health.

Pargament (2011) points out that coping strategies determine the state of the individual in mental health and the proper application of this strategy results in a true assessment of the situation, sense of security, gain of support, flexibility, growth and achievement of an identity (PARGAMENT, 2011).

Religious/spiritual coping has been recognized as an important adaptive resource when people go through intense critical situations in their lives, as the individual tends to turn more often to God or to certain spiritual behaviors such as meditation and prayer, and apparently these resources are effective. In this conception Dalgalarrondo (2007, p. 32) states that this relationship has been observed in different studies, emphasizing that:

> The presence of the religious in the way of constructing and experiencing mental suffering has been observed by many of the researchers. This is the case both in studies with more qualitative and ethnographic contours, as well as in the most quantitative and epidemiological ones. This is also noticeable both for milder mental disorders, such as anxiety and depression, and for severe conditions, such as psychoses. The search for some relief from suffering, for some meaning to the despair that is established in the life of those who fall ill, seems to be something markedly recurrent in the experience, especially for the popular classes.

According to Koenig (2012), R/E has shown a low association with depression, but its resilient value among these individuals is important to get out of depressive conditions more quickly. Thus, there is a direct relationship between R/E and the improvement of mental disorders, acting as a mediating variable in the path between depressive states and quality of life.

According to Lucchetti et al. (2021), people suffering from depressive symptoms tend to seek refuge in religion, religious faith, and spirituality, which can positively influence mental health, producing positive effects through emotions and affective states that promote attitudes of hope,

forgiveness, increased self-esteem, peace, well-being, love, and companionship. In addition, R/E offers a powerful way to address existential questions that arise before extreme situations and they allow us to create new meanings in the face of an experience of loss.

According to Lucchetti et al. (2021), there is consistent evidence on R/E as a protective factor against depression, suicide, problematic substance use, and other diagnoses such as post-traumatic stress. Thus, it is associated with lower mortality, initiative to smoke, use of illicit drugs, satisfaction with life, meaning and purpose of life, and social commitment.

For Koening (2012), there is a strong association between R/E and mental health, suggesting a protective effect on health. However, Monteiro et al. (2020) note that when people believe in a punitive god, anxiety and depression can increase, pointing out that negative religious coping is associated with depressive symptoms, anxiety, and increased pain sensation in patients with chronic diseases and even suicidal behaviors.

However, religious/spiritual coping, when compared to other forms of coping, seems to be especially useful in situations such as bereavement or severe illness, where little direct control is possible. During extreme and uncontrollable stressors, such as disasters, an individual's perceived support by their deities or members of their religious congregation can reduce the deleterious outcomes of these events, and may provide the psychological underpinnings that promote mental health in the midst of an event that is largely out of their control (KOENING, 2012).

4 FINAL CONSIDERATIONS

R/E does not prevent stressful or distressing situations, as these are inscribed in the equation of life, however, it can help the individual to cushion stress and increase their level of well-being, leading to better mental health.

Thus, religious/spiritual coping allows individuals to find meaning in stressful and traumatic life events that would otherwise be difficult, if not impossible, to explain, such as death, terminal illness, accidents, situations that put mental health at risk.

Therefore, religious/spiritual coping is based on a system of meanings that empower the individual to make sense of stressful life events, and can function as a mediator between the dimensions of mental health.

In this context, it is understood that the effects of religious/spiritual coping on mental health are determined, at least partially, by the structures of orientation and meaning that are strongly embedded in individual internal schemes, serving to cushion the consequences and impact of negative events and increase subjective well-being.

In this review, it was found that R/E is positively related to coping, resilience, well-being, happiness, hope, self-control and self-esteem, suggesting that the higher the R/E, the better mental health.

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Analysis of chemical dependence among adolescents: A review

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ABSTRACT
The World Health Organization defines adolescence as the period of life that comprises the interval between 10 and 19 years. This is considered a critical phase, of intense changes that go through the physical, emotional and social development. External influences can lead to worrying risk behaviors that often contribute to increased alcohol and drug consumption in this age group. Curiosity and the search for ways to deal with problems are other reasons that lead some adolescents to try these substances. In this context, chemical dependence among adolescents is a public health issue that is perpetuated over different generations, unfolding with different temporal characteristics, causing significant damage, including family disagreements, accidents, involvement with criminal actions, and medical emergencies such as overdose. To face the problem, it is necessary to unravel its roots, understand and look for the warning signs and work on prevention. The treatment requires an efficient multidisciplinary approach and as early as possible, being necessary the understanding and humanitarian reception of the adolescent, encouraging him to regain control over his life and his future, guaranteeing for these individual promising possibilities.

Keywords: Adolescence, dependence, risk behavior, public health.

1 INTRODUCTION

Adolescence is widely recognized as being a period of great changes in the life of the individual. It is a milestone not only biological and hormonal, but also social. Evidently, so many changes, in a

relatively short space of time, provoke uncertainties, insecurities, fears, in short, a whole series of sensations for which, often, the adolescent, at the beginning of his journey towards maturity, is not yet prepared.

Unfortunately, a portion of these individuals seek the way out to overcome this troubled moment in their lives through the use of illicit drugs, which eventually leads to chemical dependence.

In fact, the present work aims to address, in a concise and updated way, the relationship of the current generation of adolescents with narcotic substances without losing sight of the sociocultural dilemmas, indicating possible solutions to such a broad and complex problem.

The following themes will be addressed here: i) drugs most used by adolescents and users' profile; (ii) genetic predispositions to substance abuse; iii) motivations and apologies; iv) social, educational, health and personal development consequences; v) new frontier: drug dependence; vi) dialogue and breaking taboos as a means of prevention.

At the end of this work, what is intended is to shed light on sociological and biological aspects of this arid theme, at the same time dynamic and challenging for educators, health professionals and civil society in general.

2 MATERIAL AND METHOD

The objective of this work is to present a revisional analysis on the profile of adolescent users, motivations, social consequences and personal-social development, as well as more recurrent substances of abuse, in order to understand the core of this condition. For this, a bibliographic review was carried out on the platforms of journals such as PUBMED, Scielo and Google Scholar, using the descriptors "chemical dependence", "adolescents", "young people", "school age". As inclusion criteria, we considered published articles that analyzed the adolescent population, chemical dependency and the factors involved in a qualitative-quantitative context.

3 DEVELOPMENTS

3.1 DRUGS MOST USED BY ADOLESCENTS AND USERS' PROFILE

Adolescence is the intermediate phase between childhood and youth, marked by major biopsychosocial changes, responsible for addressing aspects of emotional fragility and greater sensitivity that are institutional, attributing to the individual a certain discomfort. Current doubts generated in this phase exposes the adolescent to incalculable risks, such as the abusive use of tobacco, alcohol and other drugs (ZEITOUNE et al., 2012).

In this period, the subject recognizes himself with the group to which he belongs, settling on the behaviors of its members. And, if these are users of drugs, such as illicit drugs, the chances of an experimentation of these substances by the individual increase (ZEITOUNE et al., 2012).

Epidemiological data demonstrate that it is in this transition from childhood to adolescence that the experimentation and abusive use of licit and illicit drugs is established (MOMBELLI et al., 2010). According to Ribeiro et al. (2018), data from the latest Brazilian Report on Drugs demonstrate that the average age of the first interaction with tobacco and alcohol is 12 years and of marijuana and cocaine around 13 and 14 years. Information from the National Council of Justice shows that around 75% of adolescents who comply with socio-educational measures are drug users.

The VI National Survey on Psychotropic Drug Consumption among Elementary and High School Students of the Public and Private Education Networks in the 27 Brazilian Capitals of 2010 showed that the most prevalent drugs by users were alcohol (60.5%), tobacco (16.9%), solvents (8.7%), marijuana (5.7%), cocaine (2.5%) and crack (0.6%). It was also observed that the incidence of illicit substance use is higher among males, while in females, there is a predominance of the use of controlled medications, such as anxiolytics and amphetamines (GALDURÓZ et al., 2021).

According to this same study, a dominance of drug use was observed among older students, but 1/3 of students aged between 10 and 12 years reported having consumed alcohol at least once in their lives. The drugs most used by students of the public network were tobacco, cocaine and crack, while those of the private network were alcohol, solvents and medicines (GALDURÓZ et al., 2021)

A retrospective cross-sectional analysis performed by Mombelli et al. (2010) at the Psychiatry Unit of the University Hospital of Western Paraná, located in the city of Cascavel, determined that the profile of the eighty-one adolescent drug addicts hospitalized, where there was a predominance of males (79%), these, with a mean age of 15.46 years, and among the patients 92.5% were between 13 and 18 years old. Most did not attend school and lived with their families, being referred for treatment by CAPS-ad. All patients were initially diagnosed with abusive and chronic use of numerous psychoactive drugs; Most claimed to consume more than one type of illicit substance, including marijuana and/or crack cocaine.

In this study, there are reports from family members attesting that, before crack, adolescents already used other drugs, and could observe a pattern that went from substances considered lighter, such as cigarettes and alcohol, to heavier ones, such as crack itself, with marijuana being the first illicit narcotic to be consumed. The family history of abusive use of these substances was reported by 53.1% of adolescents at the time of hospitalization (MOMBELLI et al., 2010).

3.1.1 Genetic predisposition to substance abuse: alcoholism

Youth is an important phase for brain development, because ontogenetic maturation is completed in the third decade of life with the myelination of the cerebral lobes (PAUS, 2005). In this context, it is in this phase that the consequences of this development occur, which can be observed in

behavioral changes in mood, emotional instability and desire to perform new habits along with the famous identity crisis (FLIGLIE et al., 2004).

Thus, the use of certain substances, such as alcohol, can become something attractive and innovative, especially if they are used by family members in social life, which determines a greater vulnerability of the adolescent to want to investigate the curious stimulus. Therefore, the genetic factor is considered a means likely for the individual to enter this path, since the environment where he inhabits is also responsible for forming his identity and ideologies. According to KOHNKE (2008), there is a heredity in 50% in alcoholism in the CHRM2 gene, encoding the protein that forms the muscarinic receptor M2. In addition, the interaction of genes for genetic vulnerability to alcoholism was investigated and it was observed that the LL allele of the serotonin transporter gene (5-HTT) and for the Pro/Ser of the alpha6 gene (GABRA6) is more prevalent in people with alcohol dependence (SCHUCKITM et al., 1999).

According to Comings et al., several studies are being involved in the path to determine the genetics of alcohol, as in the case of the dopaminergic system (DRD1, DRD2, DRD3, DRD4 and DRD5), where associations were found mainly for the DRD2 gene for impulsive behaviors, drug abuse and alcohol dependence with the B1 allele variant.

In this sense, the family network that already has this genetic predisposition should be guided by multidisciplinary teams and psychological support not to allow the introduction of future generations in the insertion of the alcoholic environment. In this clash, parents and professionals should be aware of the multifactorialities of chemical alcohol dependence among young people linked to the genetic and behavioral factors correlated.

3.1.2 Motivation and apology

Adolescence is marked by intense maturation processes, be they physical, neuropsychological and social, which culminate in new skills, curiosities and discoveries related to the demands of the environment in which they live. The great vulnerability is also highlighted, since they seek autonomy, through activities that sometimes bring both physical and mental risks.

The study done by Komatz, Bono and Bazon (2021) with 120 adolescent offenders aged 13 to 18 years, all male, from the Initial Care Unit of the Foundation Center for Socio-Educational Assistance to Adolescents (CASA Foundation) located in Ribeirão Preto, identified the motivation for the use of drugs, especially marijuana, as an adjunct to reduce the symptoms of depression, anxiety, tension or suffering in the context of life, but also as a means of socialization in social groups.

In highlight there is the desire to want to be accepted and integrate into groups, with great influence on the part of friends, to aggregate and be accepted. The curiosity to experiment is something that, despite environmental influences, is intrinsic to each individual, since in this age group they are

more submissive to the physical and social environment. Experimentation sometimes occurs due to lack of information about the subject and also as a way to take refuge to forget the problems. (CORREA; SILVA; BOUSFIELD, 2020).

Silva and Pereira (2020) in their exploratory, descriptive and qualitative research made with 06 female adolescents, highlight that initially the use of drugs occurs by experimentation and pervades several types of substances, until the one for frequent use is elected. Added to this are feelings of curiosity, as well as the desire to meet the expectations of groups of friends. A welcoming and safe family environment presents itself as a protective factor for drug use, however, it was noted that the discovery by parents occurs with explosive attitudes, with both physical and verbal aggressions.

Tick et al. (2020) points out that the use of drugs is seen as a way of enabling pleasure or to escape from problems and that promotes "happiness", producing changes in the emotional state, sensations and degree of consciousness of individuals. The causality of drug use, both licit and illicit, is based on social norms such as the search for one's own well-being, the feeling of exclusion, lack of opportunities, anxiety. It is important to highlight that the family history of use of psychoactive substances leads to a greater probability of the adolescent reproducing such an attitude, by influence or even in the fact of having a certain person as a reference. There is also a lack of belonging, especially in relation to the family and social groups; traumas experienced; repression generated by social standards. It is also necessary to emphasize the conception of neutrality and naturalness, often praised by the media, that certain social patterns have added to certain psychoactive substances with the idea of fun, beauty, joy and adventure.

3.1.3 New frontier: drug dependence

Drug addiction is a condition that can affect people of all ages, including teenagers. According to data from the World Health Organization (WHO), the problem affects about 10% of the world's population.A priori, it is considered drug dependence the continuous use of a substance that generates impulse in the individual, causing episodes of withdrawal in his absence.

In today's society, psychotropic drugs are the main drugs related to drug dependence, being drugs that act on the central nervous system. Thus, changes in the individual occur by biochemical modifications of behavior, affecting mental state, mood and cognition. Specifically in adolescents, the indiscriminate use of medications is due to various factors. In addition, during this period, significant changes may occur in the individual's life, such as the transition from school to college or insertion in the labor market. Thus, the significant increase in stress can result in more serious pathologies, such as anxiety and depression, leading to a greater demand for substances that provide relief, pleasure and physical and mental well-being (KATZUNG, 2014).

Thus, this population becomes susceptible to the use of medications that are mostly associated with abuse. On the other hand, the family environment is an important modulator in the life of the adolescent, where factors such as solid family ties, quality of relationships, clear and coherent establishment of rules and limits, monitoring and supervision are aspects that protect the adolescent against substance abuse (SCHENKER, 2003).

Thus, recent research on the use of drugs by adolescents indicates that there is a consensus that dysfunctional families, characterized by a pathological pattern of communication, absent the establishment of limits and lack of affection are the most common among adolescent's dependent on these drugs (ACSELRAD, 2015). In summary, drug dependence can generate negative effects for the health of adolescents, including unwanted side effects, damage to the nervous system in formation and dependence. Thus, the prevention of drug dependence in adolescents is fundamental. Doctors and health care professionals should monitor teens' use of medications and advise against prescribing to patients who do not fall under the use of potentially harmful substances.

3.1.4 Social, educational, health and personal development consequences

The growth of abusive use and chemical dependence increase the risk of problems in the spheres of the individual's life. One of the main consequences reported by the users was the family breakdown that, due to the use of drugs, triggered fights and estrangement from the family, corroborating the feeling of marginality contained in chemical dependence. (ALVAREZ et al., 2014)

According to Capistrano et al. (2013), drug users report that chemical dependence entails physical, material and, mainly, moral losses, highlighting the learning difficulty, which leads to school dropout, job loss and even prison. In this context, it is known that excessive drug consumption can generate work problems, since the low level of lucidity resulting from the drug in the central nervous system generates disorganization and implies the performance of activities at work.

Added to this, another obstacle pointed out by drug addicts was the impairment of their health, since the drug makes users vulnerable to acquiring sexually transmitted diseases and serious liver problems. (CAPISTRANO et al., 2013)

Dalpiaz et al. (2014) analyzes the use of drugs as a risk factor for the development of several diseases, such as: cancers, psychiatric disorders, heart problems, lung, in addition to suffering from a series of symptoms caused by the use of drugs, such as: weight loss, loss of appetite, tremors, convulsions, anxiety, and can reach the extreme of a cardiac arrest. Each drug has numerous physical and psychic impacts on the human body, the severity of which may vary according to its consumption. We can mention some symptoms related to each type of drugs, such as: alcohol can cause tremors, anxiety, tachycardia, vomiting, mood swings, mental confusion; nicotine manifests itself with restlessness, irritability, anxiety; marijuana also generates anxiety and restlessness, in addition to

depression; Cocaine and crack can cause depression, anxiety, lethargy, physical exhaustion, weight loss.

Still in the field of health, Marques et al. (2016) state that the use of psychoactive substances cause various damages to oral health such as halitosis, gingivitis, even causing mouth cancer. The use of these drugs will often increase the pain threshold of the user, camouflaging the symptoms and this causes him to delay the search for the health service, increasing the criticality of the case.

In addition, drug users, in most cases, feel inferior and have a block in interaction and communication, thus becoming more impulsive, uncontrolled and with aggressive attitudes. (ALVAREZ et al., 2014)

According to the World Health Organization, in Brazil, the consumption of alcohol and other drugs, except tobacco, represent 12% of all severe mental disorders in the population over 12 years of age. Given this, chemical dependence reveals itself as a significant obstacle to global public health, since it increases the risk of social, family, educational and labor problems, thus being a threat to well-being.

3.1.5 Dialogue and breaking taboos as a means of prevention

Drug abuse in contemporary societies has generated constant concern in the public debate. The pleasure or escape mechanism associated with its use puts on the agenda the "normalization" of society and its methods of control. What was culture, commemorative object or antidote against existential suffering has become a disease and, therefore, needs treatment. In addition to the issue of personal and collective health, there are the implications with criminality and violence. (MONTEIRO, 2013)

Prevention focused on drug use/abuse can be defined as a method of planning, implementing and implementing numerous techniques aimed at reducing specific vulnerability and risk factors. For an effective prevention, it is necessary a community insertion of the proposed practices, in addition to the collaboration of all the available social segments, aiming at the reduction of the initiation in consumption, the frequency and intensity, and the consequences of the use. (ZEFERINO; FERMO, 2012).

Zeferino and Fermo (2012) highlight, as well as, the vulnerability to drug abuse being greater in individuals dissatisfied with their quality of life, in those who have poor health, do not have appropriate information on the subject of drugs, have easy access to substances and are not integrated into the community.

Prevention has as its main axis to collaborate for the construction of citizenship, through the dissemination of knowledge among individuals and communities, through lectures with the intention that, with knowledge, individuals can fight for better living conditions. Such actions can be done on three fronts: first with informational programs in individuals who have not had contact with the drug,

but are at initiation age in order to offer knowledge about its consequences and avoid contact with the drug; in a second moment, the proposal is to reach individuals who have already had contact, but do not use it often, aiming to distance them from abusive use; on the third front, emphasizing programs that include people who already make habitual use, aiming to minimize the consequences.

Given this, it is observed the need to always raise awareness of the population, using debates and lectures as preventive work, offer quality information, aiming at reducing the consequences of drug abuse. Added to this, the presence of the family is also an essential tool in offering adequate support, in order to promote spaces for dialogue on this theme that today is still treated as taboo before society

4 FINAL CONSIDERATIONS

Given all that has been addressed and scrutinized in the course of the present work, the difficulty, whether of the previous or new generations, in facing the addition of narcotic substances is incontrovertible.

Not by chance, the topic is worthy of heated debates and is at the center of several public policy programs, sociological discussions and scientific research.

There is no single or definitive solution to this interdisciplinary and multifaceted problem, which has challenged society for many decades.

Interestingly, at the same time that the evolution of scientific research unveils several previously obscure aspects on the subject, the complexity of modern life seems to deepen the sociocultural problematic that underlies the question.

In short, the conclusion is that only an interdisciplinary, technical and sensitive approach to the treatment of the individual as a whole can prove fruitful.

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Care trajectories of users with severe psychological distress in the Psychosocial Care Network: Existentialist perspectives

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ABSTRACT

This study aims to present partial results of broader research that resulted in the master's thesis entitled "Life Stories and Severe Psychic Suffering from the Perspective of Existentialist Psychology: Existential Narratives." The study aimed to investigate the processes of constitution of severe psychic suffering from the autobiographical narratives of users of the Psychosocial Care Network (RAPS) in a municipality in the north of Santa Catarina, Brazil. The narratives were elucidated based on the perspective of Existentialist Psychology, outlined by the French philosopher Jean-Paul Sartre (1905-1980) in his intellectual trajectory, in which his ontology and method replace the subject in his dialectical and temporal constitution. The elicitation of the narratives followed a script adapted from the "Life Story Interview" developed by the American researcher McAdams (2012). The division and conduction of the narratives proposed by the script served as a basis analyzing and gatheringng the singular elements present in the axes of meaning. This text aims to discuss the notion of care from an existentialist perspective based on the narratives of these subjects, specifically, at the time of the interview in which they were invited to tell their care trajectories, which refers to the movement they made in the search for help for their suffering condition. The discussion on the notion of care from Sartre sought to bring this theory closer to the logic of an expanded clinic as the foundation of care in Psychosocial Care. Finally, it is considered that the logic of the expanded clinic, associated with an existentialist understanding of human suffering, can enable the construction of emancipatory practices in the territory, effectively breaking with the biomedical logic of a purely curative nature.

Keywords: Psychosocial Care, care practices, expanded clinic, existentialist psychology, Severe Psychic Suffering.

1 INTRODUCTION

In this chapter we intend to present part of the results of broader research that had as its final product the master's thesis entitled "Life stories and severe psychic suffering: existential narratives". The cited research was developed in the period from 2021 to 2023 and aimed to investigate the life histories of users in severe psychological distress of the [1] Psychosocial Care Network of a city in the

[1] The construct of severe psychic suffering outlined by Costa (2003) in his thesis refers to the so-called "psychotic" experiences, considering that the classical concepts are imprecise in the delimitation of the phenomenon and its complexity. It starts from the phenomenological and existential understanding that the psychopathological experience is, first of all, a possibility of being in the world, which unfolds to any person, materializing as human suffering (Costa, 2003). This experience can become unbearable in the face of the impasses that reality imposes on the singular subject, and the understanding becomes that psychophysical symptoms are, in fact, "a way out forged by the subject to face an unbearable

north of the State of Santa Catarina, to later elucidate them from the perspective of Existentialist Psychology, developed by the French philosopher Jean-Paul Sartre (1905-1980) as a philosopher and writer. The narrative venture followed a script adapted from the "Life Story interview" outlined by the American researcher McAdams (2012).

The results presented here refer to the moment in which users were invited to narrate about their "care trajectory", which refers to the path taken by these subjects to the various treatments, including the insertion in the Psychosocial Care Center (CAPS) until the present moment. Although the objective of this study was not to understand the therapeutic itineraries[2] of each participant in the search for help for their condition of suffering, the intention was to know how they launched themselves in this trajectory, that is, what made each subject seek help for the first time and the sequence of the care process. To understand whether or not it was a spontaneous search, who he turned to, what door he knocked on, etc. The objective was to visualize the period in which the emotional accesses resulting from suffering became unbearable for himself, or for his network of coexistence.

Psychosocial Care reflects a paradigm shift to think about mental health care practices, as a result of numerous struggles and political movements that advocated the overthrow of the asylum logic and therapeutic interventions based on social isolation and behavior control aimed at subjects in severe psychological distress. With the Brazilian Psychiatric Reform, sanctioned in 2001, the provision of care to people in this condition began to be assumed by a network of public policies, devices and equipment articulated among themselves, territorially based, focusing on social inclusion, aiming at interventions at different levels of complexity, characterizing the Psychosocial Care Network (RAPS) (Chaves & Nascimento, 2020).

The Ministry of Health (2009), proposes an analogy to think about this logic, in which a network is woven by interconnected wires and tied by nodes. The nodes spread over several points of the network, which allows their consistency and does not break easily. This analogy aims to reflect on the need for services to be articulated in different points of attention by a line of care. This line, in turn, refers to the paths that the user travels through the network, and accesses the different equipment according to their demand (Municipal Secretary of Health, 2020).

The path taken is defined from the construction of a Singular Therapeutic Project (PTS), which is characterized as a fundamental instrument in the care process. This instrument is developed by the health teams together with the user and his family, being considered central actors in the construction

situation" (Havrelhuk & Langaro, 2020, p. 40). The concept of psychic suffering and severe psychic suffering tries to delimit the magnitude of the suffering as it occurs in the lived experience of the subject. Thus, we have a reference to the existential dimension of anguish as an inseparable part of human reality.

[2] According to Cabral *et al.* (2011.p.4434), "therapeutic itinerary" is a term introduced by the socio-anthropological literature, to designate: "the paths traveled by people in search of therapeutic care, which do not necessarily coincide with predetermined schemes or flows. Their choices express individual and also collective subjective constructions about the illness process and forms of treatment, forged under the influences of various factors and contexts. These choices will define actions that, step by step, will constitute a certain path."

of care, conferring autonomy to those who provide care (Brasil, Ministério da Saúde, 2009). The PTS considers the unique demands of these subjects, their historicity and the context in which they are inserted (Schneider et al., 2020).

The notion of expanded clinic refers to the need for an interdisciplinary and horizontal care, which considers all the dimensions that constitute the subject, placing the focus in this look at the integrality of his life, being the process of suffering an expression of this set. Thus, the disease and its symptoms cannot be the only parameter for the interpretation of the occurrences and even the only target of the intervention. In this sense, knowledge intersects in the construction of care, taking into account the specific needs of the subject at each moment of his trajectory. It is on this logic that health actions and practices should be based (Schneider et. al, 2020).

Sartre was an important critic of his time in relation to the hegemonic model of classical psychiatry and the model of asylum as an offer of care. The ontology and epistemology proposed by the philosopher is one of the first that breaks with dualisms and ahistorical views in understanding the phenomenon of the subject and his suffering. For him, human reality is par excellence dialectical, when dealing with the human movement in the world, in which it is made and is made by this real context. It is through the human acts of totalization-detotalization-retotalization that human reality is constructed (Bocca, 2021; Sartre, 2002; Schneider, 2010). In other words, there is no possibility of separating the experience from the human that is implied in it, it is only by the inclusion of the subject in this equation that the experience can be understood (Bocca, 2021; Haverlluck & Langaro, 2020; Schneider, 2009).

Freedom is constitutive of the human condition, it is at the basis of its indeterminacy: "man is not first to be free later: there is no difference between man's being and his free being" (Sartre, 2015, p. 68). When Sartre asserts that there is no difference between "man's being and his free being," he is saying that there is nothing that determines existence, there is nothing that precedes it (Bocca, 2021; Ehrlich, 2002). To escape from its indeterminacy of being is that the subject is elected perpetually, continually puts himself in question, this is what differentiates humanity from other beings (Schneider, 2011). The recognition of the other as freedom, allows him to undertake himself in this way, to recognize himself as autonomous and possible to pursue his own project (Dhein, 2013; Schneider, 2011). It is understood that this perspective accompanies and deepens the principles of Psychosocial Care and the need for comprehensive and longitudinal care, which constitutes the logic of an expanded clinic (Schneider et al., 2020).

In view of the above, this work aims to discuss the notion of care by existentialist logic, based on narratives of the subjects of this research, users of the Psychosocial Care Center (CAPS) of that city. Subsequently, it is intended to carry out interlocutions between the notion of integral care in the

Psychosocial Care Network and Existentialist Psychology, in order to present it as a possible foundation for the provision of care in an expanded clinical logic (Schneider et al, 2020).

2 METHOD AND METHODOLOGICAL PROCEDURES

The research had a qualitative design, with exploratory-descriptive cross-sectional characteristic,[3] aimed to investigate the processes of constitution of severe psychic suffering starting from the autobiographical narratives of users with severe psychic suffering of this city.

Three users were included in follow-up at CAPS II, two women and one man aged 30 to 50 years, who met the following criteria: a) history of follow-up at CAPS II equal to or greater than 6 months b) who had in their clinical history report of psychotic crises; c) who did not have cognitive impairments that prevented him from answering the interview questions; d) who was not, at the time of the research, in a period of severe psychic crisis; e) who was at a moment in his treatment in which talking about his life history would be considered an important clinical strategy in his care process, according to his Singular Therapeutic Project (PTS) and the evaluation of the CAPS technical team; f) who was over 18 years of age and was not tutored; g) who agreed to participate in the research.

The narrative interview was chosen as a technique for data collection in this study, since the narratives allow access to the experienced, from the experiences shared by the research participants (Flick, 2009). Narrative methodologies have been used in the fields of social research for the study of biographical experiences for a long time (Flick, 2009). It is noteworthy that the life history and experiences of severe psychological suffering are configured as the object of study of this research.

The instrument selected for data collection was the *Life Story Interview* (McAdams, 2012), based on an adaptation of its script. The instrument was designed to allow the subject to construct the narrative in an integrative way, considering the positive and negative experiences in their trajectory, their desires and impasses and their future project.

For McAdams (2012), the biographical narrative allows life memories to be approached in their entirety, in the sense that the episodes narrated follow the perspective of psychic temporality, where the past is experienced when narrated in the present and the future begins to be imagined in the very act of narrating.

In order to stimulate the autobiographical narrative, it is suggested to the participant that he imagines his life as a story or film, to later perform a general summary presenting the chapters and significant periods that make up the plot of his story, highlighting events and characters that, in each

[3] This study was evaluated by the Ethics Committee on Research with Human Beings of the Federal University of Santa Catarina (UFSC), and was approved by the respective Committee, according to the opinion consubstantiated No. 5,694,923.All these procedures had as a principle to guarantee the ethical aspects that govern Resolution No. 510 of April 7, 2016, of the National Health Council, regarding research in the Humanities and Social Sciences, considering its specificities and research practices.

scene rescued through memory, are central in the episodes narrated. The highs, low points and turning points that he considers to have happened in his life story are highlighted (McAdams, 2012).

This enterprise adopted as perspective the Sartrian phenomenological-existential methodology, with the objective of conducting the analysis of the content of the narratives, using the progressive-regressive method. In this understanding, every biography is a singular-universal, because each individual is singularized by permanently synthesizing the objective reality that is shared (Maheirie, 2002; Maheirie & Pretto, 2007; Schneider, 2011).

Here in this work, part of the results found will be presented, which refer to the moment of the narrative interview in which the users were invited to tell their trajectories in the search for help to their condition of suffering. With this, the objective is to debate the notion of care from the existentialist perspective, as a foundation for thinking strategies and practices of care with these subjects, in a logic of expanded clinic.

3 THE SEARCH FOR CARE AND THE ENCOUNTER WITH PSYCHOSOCIAL CARE

We will begin by presenting brief elements of Anah's story[4] and her search for help for her suffering. The participant reported that she sought psychiatric follow-up spontaneously at the time she was in college, as she reports:

> (...) when I started college, I felt very difficult to get in the classroom (...) there was a person who told me that I had no difficulties relating, I was just quieter, only in my head I had (...) this was very evident to me and I asked for help from a psychiatrist (...). She prescribed me paroxetine, nortriptyline and some other antidepressants... diagnosed me as social phobic... The medication made me more talkative and I started to interact a little more.

The situations that Ana presented about her trajectory help in understanding the difficulty of this moment for her. He spent much of his childhood and adolescence, as he put it, "inside the bedroom." But at the same time, wanting and not being able to socialize, both in childhood and adulthood, was what was most "dubious" to him, according to his own perspective. Ana ends up blaming herself for her socialization difficulties, but when narrating her story brings situations of loss of her very young mother, of having been raised by great-uncles, having received a very rigid education, without freedom to find friends and, even more serious, having suffered sexual violence within her own home:

> I was molested right; it wasn't a pleasant experience at all. I feel like a pretty low point in my life. I feel kind of guilty, I could have said no, avoided it and didn't. I was less than 10 years old and I was becoming a young girl, I was getting my period out. And it was just like that, whenever I remember, guilt comes over me. The one who molested me was my grandfather, actually my great-uncle, who was in my grandfather's place. When my great-aunt would go out

[4] All names are fictitious and were removed from the IBGE list of the most common names in Brazil in the 2000s, which is available on the https://censo2010.ibge.gov.br/nomes/#/ranking website (IBGE, 2016). None of them resemble or match the actual names of the participants

> to pray a rosary at other people's homes, he would stay with me and it would happen. So, it was a person who was supposed to protect me, had to be on my side. He was in the shoes of a father actually, it was a very remarkable experience, a remarkable thing.

This experience produced deep marks in Ana, who lived these experiences in the deepest solitude and had to elaborate reflexively only with the few affective and rational elements that she had at her disposal, of someone who lived as if in favor in the house of uncles who cared for her. In this direction came his blame for the situation, even though, in fact, he was a victim. This psychic dynamic will mark his trajectory, reaching the moment when in early adulthood, already in college, he is able to seek help for his entire trajectory of suffering.

In Ana's narrative can be identified paradoxical elements to her experimentation reported on this period of graduation, when she mentioned that "a person" (did not specify who) told her that she did not have difficulties of interaction, only was quiet. The paradox in his speech is that there was someone there, and that what was said by the other reveals a certain closeness and some weaving, otherwise he would be unlikely to speak of his suffering to that other. Either way, what is illustrated here is that the experience of being someone with difficulty getting along belongs to Ana's world. For her this is an irrevocable fact, it circumvents her entire being, just as it is an irrevocable fact that she committed "holes", in her form of expression, in several different professional environments, even though she did not know how to tell the interviewer what these "holes" were: "Good question... For those who saw from the outside it was fine, I was doing well, but for me no, I knew I was punching holes." (Ana). We see here, again, the expression of Anah's ontological insecurity and her guilt as a mark of her way of being.

This certainty makes it impossible for them to weave themselves, to be seen as someone who is intellectually and professionally successful, being against the desire to be happy and achieve things in their lives, and perhaps this point is one of the factors that aggravates their suffering. Hence, he sought the psychiatrist in an attempt to seek relief from the suffering that had been with him for some time. In fact, medication provided him with some relief from symptoms by reducing the tension experienced by the self-other conflict (Sartre, 1943/2019, Schneider, 2011). However, having their suffering classified as a mental illness categorized as a "social-phobic disorder" contributed to the experimentation of being crystallized and condemned to be the one that is not woven (Cooper, 1967; Laing, 1975). The influence of psychiatric rationality on his being is visible when he says: "I have diagnosed ADHD and he spoke louder" (Ana).

Ana incorporated the psychiatric diagnosis as a way to understand herself and, in some way, justify her inadequacy to the demands of the social world. The problem is not the diagnosis, it is not the objective to debate the viability or infeasibility of the psychiatric diagnosis itself, because knowing how to identify common signs can be of some value for the construction of interventions that help in suffering (Dalgalarrondo, 2018), to the extent that every subject is a singular-universal (Schneider,

2009). The issue is the organic and psychologizing reductionism to this category, which ends up confirming the know-how of being of these subjects, who end up defining themselves from the perspective of a knowledge of professionals who have recognized technical power, making suffering an insurmountable condition. In addition, the nosological classification removes the understanding of the construction of this suffering in the biography of the existent, that is, it disregards the various experiences lived in a situation (in the sociological, anthropological and psychological dimensions), not accessed by the medical gaze that stops only at the symptoms (Schneider, 2009, 2011, 2017).

When Ana already married ends up getting pregnant, she interrupted the treatment for three years, after a certain time she seeks psychiatric follow-up again in the scope of supplementary health, due to depressive symptoms related to the work environment, being treated by a professional who accompanies her for a period of seven years. Thus, about two years after the interview, she began to have more intense emotional access in one of the schools in which she worked, at which time she was referred to the CAPS and away from work. This brief report by Ana about the paths taken to reach the CAPS demonstrates how much her suffering has evolved over the years, being a process in her history and not isolated occurrences. She also describes how until she arrived at the CAPS, her suffering was reduced to signs and symptoms and the search for control through medications, without seeing Ana's person as a whole, reduced to her disease. It will be in the CAPS that she will receive a more integral care, seeking to insert in therapeutic processes that expand her field of possibilities of insertion in reality.

The second interviewee, Maria, said that the first time she thought about asking for help was due to a suicide attempt, which occurred during the period of her second marriage. The first "door that knocked" was that of a religious institution linked to the egregore of Kardecist spiritism, "*only then I went and I was not well, I was practically surrendered*."

Mary was in a very intense state of psychic suffering, she needed support, not only spiritually, but mainly in the field of mental health. She continued: "So my daughter went with me to the hospital and there they decided to admit herself. I was in a suicidal crisis and I was all scratched" (Maria). Although she stated during the interview that since she was a child she experienced as if she had, in her words, "a voice inside the mind", there was a long journey to get to the care for her serious situation, and only after the suicide attempts in adulthood, that she began to receive help, with the support of her daughter. She went through four psychiatric hospitalizations, until she was referred to the CAPS. In her case, she described arriving at this care center as one of the great "watersheds" in her life, a "turning point." He highlights the psychosocial accompaniment in the referred service as something that provided him with support in changing course for the plot of his "film".

When she resumes her story Maria discusses that if her life were a movie, it would be the horror type. Like Anne, Mary lost her mother at an early age and was raised by a relative. And in the same

way, she ended up being abused by her adoptive parent, from 2 to 5 years of age, and ended up contracting syphilis, a fact that was only discovered at the age of 40 when diagnosed with Neurosyphilis, a condition that had serious complications due to the absence of early treatment. His existential trajectory was marked by much suffering, lived in the most absolute solitude, without having with whom to share his emotions and thoughts, from the earliest childhood. This situation may be the basis of the voices he had been hearing for a long time and the worsening of his psychosocial condition.

It is striking how Mary recognizes in the CAPS the service that will treat her not only as a patient, but as a person, who has desires, projects and who would like to rebuild her life. Therefore, he sees in CAPS and his team of professionals one of the main mediators to be able to rebuild his life and authorize himself to dream of new possibilities.

Likewise, Joseph said that at the age of 17 he began to see "figures", however, for him, it was a spiritual experience, so much so that these occurrences were not the reason why he sought help. She mentioned that, approximately, in 2016, she began to experience depressive symptoms (she did not eat or get out of bed), which were intensifying more and more, to the point of not being able to work. He says that he had been working at a car dealership for about three years, and that he was expecting career promotion, a fact that did not occur.

The first request for help was to his mother, who welcomed him promptly and assisted him in the search for a psychiatrist. He did not make clear the occurrences that led him to the CAPS. He mentioned, however, that in the same period in which he sought help, he was unable to leave the house because he believed that someone was chasing him in the street.

As was done in the case of Maria and Ana, it is also worth resuming some points of the history of this interviewee. He played football from the age of seven to 17, even participating as a reserve player for a professional team, and was almost hired as a starter, however, he said he did not achieve this title because at the time he did not make himself viable in the desired career. At the age of 17 he narrated having lived hallucinatory experiences (via figures), understanding such experiences as phenomena of a spiritual order. Moreover, the concomitance between the career break and the narrated experience is perceived, which raises suspicions about being correlated, suspicions that could only be verified by a longitudinal follow-up.

Joseph may not have brought a whole experience of suffering before the age of 17. Joseph's narrative of his story focuses less on experiences of suffering arising from his social relationships and he perceives himself as having been a cheerful boy who liked to have fun. He speaks of the death of a friend, as a teenager, as a point that affected him greatly. However, in his narrative, there are not many occurrences that make very clear the social determinants in the construction of his suffering. Thus, his entry into the psychotic condition still appears to him as magic, as if "suddenly" that he began to hallucinate. The narrative of her story is of a common story, of any child who had his development

without more destructuring sociological or anthropological conditions, unlike Ana and Maria. But is that really how your existential trajectory happened? What family or socio-cultural facts did he not perceive as significant and fail to tell us?

Perhaps José's situation is even more vulnerable, because as he does not locate concrete social conditionings, his emotional lack of control is attributed to himself, to his neurochemical decompensation, to his psychopathology, as if he were a morbid entity, corroborating with a medical and pathologizing logic to which he is subjected. In this way, José, even more intensely than his two colleagues, who were able to locate effective occurrences in their stories that provoked psychic suffering, attributes his suffering to a mystique and, subsequently, the condition of illness, without being able to establish, in a very clear way, situations of his life history and the development of his schizophrenia process. In any case, the need to ask for help in the face of the intensification of suffering occurred in the professional profile, which points to the possibility of this profile being a major issue for this interviewee.

Like Ana, some of José's statements in the interview also make a clear influence of psychiatric rationality on how one experiences oneself in the world. The first answer he gave about what he believed to be these "figures" was: "*I think it was a lack of medicine.*" (Joseph). When the interviewer asked him if he made any correlation between his symptoms and the events of his life, he replied: "I'*ve always been nervous, I think I was born like this, my whole family is like this, it's a family thing*" (José). This is the only cue about his family, who are all nervous, but do not cite concrete facts and real events.

There are other statements of José in the interview that illustrate this same point, however, the above expressions are already sufficient to correlate the influence of psychiatric rationality on elements of his know-how, as was observed and discussed in the case of Ana. Thus, if on the one hand he knows himself to be like someone "nervous", on the other, he says he experiences himself "much better" and that he is already almost gaining "high" and, paradoxically, says he thinks: "that *what I have is not even a disease, it is a phase of life*."

The divergence in the discourse of this interviewee points to the crossings of two distinct rationalities that conflict in today's anthropological context (Schneider, 2010), namely: the thesis of mental illness and the antithesis of this same thesis, responsible for the overthrow of the asylums, and which consequently influenced the Psychiatric Reform in Brazil, constituting what is meant by Psychosocial Care (Amarante, 1995). These statements of José point out that, even in a slow process, there are possibilities of deconstruction of the reductionisms implied in suffering.

Given this, it is worth highlighting some passages that illustrate the importance of accompaniment in this service of Psychosocial Care, for the process of deconstruction of suffering: *"I like to come here, I know several people, we create a bond"* (José); "*I like to come here, here I get along*

with everyone, here no one will judge me, because everyone has their issues, here I can be myself." (Mary)

The two interviewees are talking about the relationship with the other users and professionals of the service, clearly expressing the logic of welcoming the singularity that the psychosocial mode brings, unfolding in the affective weaving to this place. Mary also brings the experimentation of being able to be herself, that is, of being able to be recognized in her subjectivity and also recognize other singularities. The continuous exercise of being-with-others, of being recognized and cared for in its idiosyncrasy, little by little, enables the reconstruction of the desire to be and, consequently, openness to the future (Sartre, 1943/2019).

4 THE LOGIC OF CARE IN AN EXISTENTIALIST PERSPECTIVE

The word care has its origin linked to the Latin word *cogitatus* (Contatore, et al., 2017), whose meaning refers to: "meditated, thought and reflected". The meaning of this word for the Portuguese language takes several forms: "special attention, restlessness, concern, zeal, care that is dedicated to someone or something, object or person of this care

As seen, the term assumes a range of different meanings, but that, in general, refer to the forms of relation/mediation of a person or group of people towards others (Contatore *et al.*, 2017). Relationship of being *implicated-with-the-other; together-with-the-other; interested-by-the-other* (Contatore *et al.,* 2017).

The care taken in an existentialist sense, must start from this same principle: "being-with-the-other". What is only possible when the subject is recognized as existence, that is, as freedom (Freitas, 2018). To clarify this point of this debate, we will briefly discuss this "being-with-the-other", or else, "we" within this perspective For Sartre, there are concrete experiences in which the "I" and the "other" are not in conflict, but in community, as the philosopher says:

> (...) There are certain concrete experiences in which we find ourselves, not in conflict with the other, but in community with him. And it is true that we often say WE (...) the subject we do not seem conceivable except **by referring, at least, to the thought of a plurality of subjects that apprehend themselves simultaneously and mutually as subjectivity, that is, as transcendences – transcendent, and not as transcendences-transcended. (Sartre, 1943/2019, p.512)**

Sartre refers to a distinct way of relating subjects, and that takes place in contradiction: "with the experience of my being-object For-another or with the experience of being-object of the Other for me. In the "we" subject, no one is an object, it is "a plurality of subjectivities that mutually recognize each other as such" (idem, p.512). The recognition of others as subjectivity therefore involves overcoming the conflict of the I-object-for-other and the other-object-for-me. The crossing of these two possibilities of relation, results in being-with-the-other constituting the "we" (Freitas, 2018;

Schneider, 2011). These premises are at the basis of the Sartrian theory about groups, a conception that the philosopher evolves and deepens *in the work Crítica da razão dialética* (1960), in which he outlines the progressive-regressive method (Freitas, 2018).

There are also different ways of experiencing this "we", as a collective experience of object for a "third party", or as "we-subject" that goes through the sharing of a common project. The philosopher warns that this last experience is not a constituent condition of human reality, it is a psychological experience (Schneider, 2011). This third possibility is produced by the quality of the collective experience, it must be built hard by the subjects engaged with each other, on a daily basis, it is about this "we" in community (Freitas, 2018; Schneider, 2011)

This brief sketch of the notion of "we" in Sartre was to illustrate what is recognized, here in this work, by relationships and feasible care practices. It is understood that care in health care networks should start from this need pointed out by the philosopher to be-with-the-other, to understand him as a subject in his integrality, recognizing that he must actively participate in the construction of his care, giving coordinates about his own singular therapeutic project, as the protagonist of this project, and the health professional as the mediator in **therelationship between the subject his suffering and his actions in the world, or rather, between the person and himself, in the sense that mediation, when viable, can help in the deconstruction of the knowledge in which the subject is alienated, that is, the objective of care as mediation is to mark/flexibilize** *the crystallized cogito*, facilitating the resumption of autonomy over his project of being, as long as being responsible for your choices and actions in the world. (Schneider *et. al.*, 2020).

To keep in mind that this weaving process is not something "given" or "natural", is to consider that the abandonment of the classical biomedical conception about the disease, as an object detached from the subject who falls ill, is a continuous and daily process in which each action matters, both of the team that cares and of the subject that is cared for, (Contacte) *et al.*, 2017; Schneider *et. al.*, 2020;).

An expanded clinic is a powerful tool for the construction of care practices for the promotion and prevention of diseases in the psychosocial sphere, allowing the overcoming of biomedical rationality of only a curative nature, breaking with the institutionalizing logic still very present in substitutive services, which maintains the traditional practices of "intramural" care, as Rotelli (1991) warned.

To the extent that one understands the dialectical process between the objective and subjective conditions in the constitution of severe psychic suffering, the presuppositions of another clinic (psychosocial, extended) that goes beyond the simple control of symptoms is placed, since it does not focus on the subject himself, but on his context of relations, promoting a reconstruction of historical sociological bond or the construction of new enabling bonds, in the direction of a critical social integration of the subject in the world.

For this reason, existentialism is invested as an important foundation in the understanding of human psychic suffering and in the constitution of strategies that are in fact linked to an expanded clinic, providing subsidies for a psychosocial care clinic that emancipates the subject.

5 FINAL CONSIDERATIONS

It is necessary to reflect on the invisibility of psychic suffering in childhood, which has its roots in concrete events that occurred in the lives of these patients and bring deep marks to their life stories, making care only arrive when the situation is already very serious and has already become a crisis, with all the severity and impacts that this situation brings. It is interesting to note how the process of loneliness and the need for these children to solve their dilemmas and impasses in the face of their social experiences and the resulting sufferings, without having many cognitive and emotional parameters and without sociological mediations, which leads them to a guilt and an understanding that "it is something in my head", losing the nexus with the fabric of the social determinants in which they were involved. In this direction, the psychiatric diagnoses "fit like a glove", for the person to understand that the problem of suffering is his, of a "disease" that takes him, leading to a pathologization of what should be seen as a victimization and an unfolding of the social game and the troubles of family life. (Szasz, 1979).

Although it was verified in the narratives of the interviewees a great importance of the CAPS in the process of overcoming suffering, which demonstrates a certain advance in care practices, it is still known that the logic of the expanded clinic referred to just above is far from reaching its full potency (Schneider et. al., 2020). The intervention should not only take place with the user, but also in their sociological and anthropological context, considering that social relations and sociological mediations are what in fact promote the constitution of this process of suffering (Schneider, 2010, 2011). Therefore, the intervention must also take place at the root of the problem, that is, in the territory of belonging of these subjects, which is recommended by an expanded clinic. This is a great challenge for the psychosocial mode, to get out of the walls of the services and the clinic developed there and win the streets and cities. Or also, on the other hand, to make the families and the city itself understand that that space of care is also theirs and that the quality of life of the users who transit there need this sociocultural mediation.

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SEVEN publicações acadêmicas

Considerations about the facets of prejudice aimed at people with disabilities: Deaflympics and Paralympics

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ABSTRACT
The object of research deals with issues related to forms of prejudice to be faced if effective social inclusion is to be achieved, as well as comprehensive accessibility for people with disabilities, including discussion about the Deaflympics and Paralympics. The methodology used is based on doctrinal and legal analysis, collated with information provided by civil society organizations dedicated to the segment. The objectives present the search for an adequate denomination, including discussion about the conceptual binomials ableism versus overcoming and poorness versus heroism, as present in the social imaginary directed to people with disabilities. As a partial result, it defends a general coordination of public policies, which assume the character of State policies, which have the character of operating a paradigmatic change, in society itself, to face the problem.

Keywords: Capability x overcoming, poorness x heroism, Deaflympics, Paralympics, public policy.

1 INTRODUCTION

To account for the object of study, the theoretical assumption that the article follows concerns the conceptions formulated by Gadamer, when it deals with the problems of prejudices, or the previous concepts that all of us, as human beings, are carriers, because we were educated with such concepts, inserted in the social environment that surrounds us. Thus, by affirming that, if such concepts are not brought to the light of reflection, behold, these conceptual and, here, legal-legal constructions, direct our gaze, focusing on certain situations and, in the same way, covering up others, whose perspectives end up escaping us, in a given historical moment considered. In the same way, the legislator, within his social function, as an interpreter of this same reality, places in the legal text the type of understanding that he managed to substantiate as a norm to regulate the facts to which it is addressed. (GADAMER, 2004, pp. 426 et seq. and 447 ff.).

Therefore, when approaching as a theme the distancing and approximations of an effective social inclusion of people with disabilities, it is necessary to highlight that, both the constitutional and legal framework that is available, today, along with the struggle of the entities of organized civil society that, in the most varied spheres in which this same society is structured, they seek the enforcement of such rights and their expansion. However, to the extent that the complexity of the problem presents itself, leaving the levels of invisibility to which it was posed, behold, practically without exception, they are faced with the challenges caused by the numerous prejudices that surround this condition. Because of this, considerations are presented about the basic binomials with which the problem of inclusion was presented, with its confrontations, characterized by ableism versus overcoming, as well as coitadism versus heroism. Thus, the principles erected from such concepts, previously mentioned, were substantiated to direct the gaze, either of the legislator and even, before the legislator, of society, in relation to the conditions of people with disabilities, in such a way that one must also deal with such conceptions present at the levels of the social imaginary, that is, of the gaze that society directs to such a condition. In the same way, we are faced with the previous concepts that we are carriers, existentially considered, as well as the prejudices that end up directing the gaze that turns to people with disabilities.

Therefore, it is necessary to highlight, with real insistence, the search for an adequate terminology, which seeks to express meanings and meanings capable of operating an approximation with the challenges faced by these people, from the prejudices instituted by a corponormativity inherent in the social structures, to the questions of formation of these subjectivities and, therefore, of the social context in which such circumstances are inserted, by the treatment that is intended for the occurrence of the obstacles to this effective inclusion. It should also be highlighted, once again, the intrinsic interrelationship between the rights established in our legal system, with the actions of the entities of organized civil society that try to seek the conquest, maintenance and expansion of the rights of equivalence to be exercised by people with disabilities and that precede, in turn, the very legal formulations that follow them, as a result. That is why the methodological decision to bring here, the speeches of such entities, especially when they are articulated around events of international level and of historical relevance to this cause. Hence the issues related to the Deaf and Paralympics.

2 WHO ARE PEOPLE WITH DISABILITIES? FROM THE CONCEPT TO THE NATURALIZATION OF PREJUDICE

It is necessary, then, immediately, to present the definition of person with disabilities provided for in the Brazilian Law of Inclusion, Law No. 13,145/15, to avoid possible errors arising from the most diverse conceptualizations that have come to be established over time. In this sense, according to the aforementioned law, known by the denomination of Statute of the Person with Disabilities, it is defined that:

> A person with a disability is considered one who has a long-term impairment of a physical, mental, intellectual or sensory nature, which in interaction with one or more barriers, can obstruct their full and effective participation in society on equal terms with other people. § 1 - The evaluation, when necessary, will be biopsychosocial, carried out by a multidisciplinary and interdisciplinary team and will consider:
> I – the impediments in the functions and structures of the body;
> II – socio-environmental, psychological and personal factors;
> III – the limitation in the performance of activities; and
> IV – the restriction of participation. (Brazilian Law of Inclusion, 2015 p.8-9).

Moreover, to contextualize the social impact of such a legal definition, it should be considered that according to the Brazilian Institute of Geography and Statistics (IBGE), in the census conducted in 2010, Brazil has 45 million people with some disability, which corresponds to 23.9% of the population. These data also show which deficiencies are the most prevalent in the Brazilian territory. In first place appears the visual impairment with 18.8%, just after the motor disabilities with 7%. With 5.1% there is hearing impairment and with 1.4% appear mental and intellectual disabilities. (IBGE – Senso/2010). Data from the last Census/2022 are not yet available. However, it is possible to estimate that, if the same criteria are maintained regarding the definition of people with disabilities, confronted with the Brazilian population progression, such data tend to increase.

In the wake of such conceptualizations, it is also worth highlighting the correct term to define someone with a disability, which was established by the Secretariat of Human Rights of the Presidency of the Republic, through Ordinance No. 2,344/2010, which establishes: "where it reads People with Disabilities, read 'People with Disabilities'"; which came to substantiate the definition in the sense that people with disabilities are those who "present significant physical, sensory or intellectual differences, resulting from innate or acquired factors, of a temporary or permanent nature", so that:

> People with disabilities are those who have long-term impairments of a physical, mental, intellectual or sensory nature, which, in interaction with various barriers, can obstruct their full and effective participation in society on equal terms with other people. (Article 1 of Legislative Decree No. 186/2008).

Such definitions should be highlighted, since it is in search of dealing with the importance of social inclusion of people with disabilities, emphasizing that such inclusion is based, fundamentally, by the way of political participation, in a broad sense, given the very definition of the expression "politics", when seeking, equally, the origin of the term, derived from the Greek word politeia, which means to expose, discuss and implement solutions to all matters related to the polis (city or state), as well as matters that are related to the community. This approach, in turn, refers to the activity of citizens, that is, those who love the city and/or State and, as such, deal with public affairs with their vote or with their militancy, as in the case in question, through entities from organized civil society, in order to generate a political agenda that, acting on the Powers of the State itself, will establish an establishment and expansion of rights focused on this segment, both in terms of implementing the

respective legislations that substantiate such rights, and to act so that they leave the merely formal sphere of legal statements and become concreteness in social relations.

Because of this, with regard to political representation, the relationship between representatives and the represented becomes fundamental for common objectives to be achieved. However, the action is not so simple, because several factors interfere in these processes, from the political campaign itself considered, to the effectiveness of the mandate of the elected. Thus, regarding this theme of the search for political representation by voting, in a representative democracy, such as the one in which we are inserted, in general, It can be considered that there are six essential factors to be considered and that decide the vote:

> 1 - Government evaluation; 2 – The identity of the candidates; 3 – the level of recall of the candidates; 4 – the curriculum of the candidates and whether they use it to show the voter that they can solve the main problem that afflicts the electorate; 5 – the growth potential of the candidates, which combines with the rejection of each of them with their respective level of knowledge; 6 – and the fact that it is not possible to count on political support, that is, popularity and sympathy do not transfer. (ALMEIDA, 2018 p.19)

Thus, considering these points raised, some of them can significantly demonstrate the difficulties that people with disabilities face when running for elective office. Among the main obstacles to this political representation, one can highlight the identity, that is, of the candidate presenting himself as such and, thus, falling into the social common sense, considering him capable, or not, to solve the problem that afflicts the electorate, combined with the possible rejection he faces due to his own condition. In addition to the curriculum itself, in which weigh the general difficulties of access, from training, to the professional placement itself.

It must be considered here that the ableist view of the disabled person can also start from them to themselves, because it is common not to find ourselves[1] capable, or doubt the capacity of our peers, since there is a "naturalization" of the disability of the disabled person. In this sense, we highlight the statements of Vitória Bernardes (2019), as a psychologist and member of the Hellen Keller Feminist Collective, who is a National Health Counselor and quadriplegic, according to which:

> Ableism is to the disabled as racism is to black people and sexism is to women; and it is based on the premise of the disability and unproductivity of the disabled person. Ableism is the structure that prevents us from being at the center of decisions, occupying spaces of power or at least feeling represented in these spaces, in addition to preventing social access, because it disconfigures the capacity of the person with disabilities, disregarding the plurality and differences in disability and overvalues capacities that are often not even necessary for certain activities. (BERNARDES, 2019, p. 01).

[1] The use of verb tenses in the first-person plural has, therefore, as motivation, the fact that one of the authors is a person with a disability, which also implies the use of an inclusive language, since it refers to someone who experiences the problems that are dealt with in these writings.

According to Mello (2016), ableism acts in different ways, but always with the aim of oppressing people with disabilities, because:

> By the body, we have analytical and discursive characteristics: sexism, in the case of discrimination by sex; homophobia, in the case of discrimination based on sexual orientation; racism, in the case of discrimination based on skin color or ethnicity. In the case of disability, there is an absence in the active lexicon of the Portuguese language. (MELLO, online. 2016).

In this sense, it can be added that the generic use of the expression disability: "It has an admittedly aggressive, pejorative and subversive connotation, in order to mark the commitment to develop an analytical normalization of the body against all those who flee from the body/functional and cognitive standards"; socially accepted and imposed as aesthetic standards and measuring capacities for any acts of life. (MELLO, online. 2016).

In this way, the challenge goes far beyond the campaign and the construction of coherent proposals, through the search for political representation. Thus, it is part of the challenge of the disabled person to deconstruct the imaginary of disability that is attributed to the group; which is impactful, in its consequences, for the theme in question, since, according to Silva (2006), the social imaginary in which we are inserted is determinant for our actions:

> The social bond serves as a cement to life in society. However, it is only updated by the forces of shared values, of images revered together and of feelings and affections intensified in communion. There is no social bond without imaginary. The knot between social and imaginary ties, in societies marked by contradiction and conflict, depends on the paradigm of complexity: the irreconcilable is reconciled in the experiences of each day. In rational abstraction, the contradictory must be purged. In the concrete of everyday practices, the paradox feeds the imaginaries. In each character, yes and no, good and evil, truth and illusion, ideology and culture, understanding and explanation, affection and unreason coexist. (SILVA, Juremir Machado, 2003, p.21).

Thus, here we highlight the two levels of the social imaginary that are intertwined regarding the theme of effective social inclusion of people with disabilities, either through political representation or through the militancy of active citizenship groups, given that the double scope of naturalization of the problem is being faced, regarding the issue of capacity applied to people with disabilities, socially questioned, as well as the internalization of these issues by the part of of the disabled person himself, who, in this way, taking into account the process of formation of his subjectivity, begins to admit himself as what the social environment begins to affirm. It becomes, therefore, impossible to disregard the entire cultural construction established around people with disabilities, with regard to the systematic social questioning of their capacities, which certainly influences any political proposals that may be presented, especially in the case of candidacies for elective offices.

Therefore, it is necessary, once again, to discuss the theme about ableism, since it is a characteristic of fundamental importance for the essence of understanding and the complexity of its meanings when the subject is prejudice related to people with disabilities. The term in question

becomes complex because it affects the person with disabilities in all social segments; and can be exemplified in a simple way with the translation of the significant term of people with disabilities, globalized in the English language as "Disability", which, in free translation, means disabled, but in our social construction was translated as crippled, giving the idea of useless, incapable, among other things. In addition, it should be noted that the use of this expression would mean, in principle, disabled only for certain functions, not for all, although this is the socially stratified and employed generalization.

However, by not identifying a Portuguese-language word for the prejudice derived from the disabled person, Mello suggests that we adopt the term in English *ableism*, translating the same to ableism in the Portuguese language. And it does so for two reasons: the first is the urgent demand to be able to highlight a peculiar form of oppression against people with disabilities and, consequently, to give greater social and political visibility to this segment; the second derives from the need to deconstruct the barrier between people with and without disabilities, and it is then necessary to explore the intricacies of the corponormativity of our social structure, by naming a type of discrimination that materializes in the form of a mechanism of interdiction and biopolitical control of bodies based on the premise of (in)capacity, that is, in what people with disabilities can or are able to do (MELLO, Online. 2016). From then on, the term ableism came to be identified as the name used to define the forms of prejudice against people with disabilities. In this way, ableism is understood as "a neologism that suggests a departure from capacity, from aptitude by disability." (MELLO, online, 2016). Given this, the author closes his reasoning with the following statement:

> Ableism may even be an insufficient category in the Portuguese language, but it is the capacity to be and that is repeatedly denied to people with disabilities in various spheres of social life. Therefore, for practical purposes, I propose its adoption in movements, in academic productions and in official public policy documents. (MELLO, Online, 2016).

From the above, it can be inferred, then, that a paradigm shift is necessary regarding the social meanings of the expression disability, or disabled, which can operate, before any other considerations, by an adequate communicational process, which clarifies such meanings and proposes the terms in a more inclusive and, therefore, less exclusionary way. In this sense, Débora Diniz, as an anthropologist and professor at the University of Brasília and researcher at ANIS – Institute of Bioethics, Human Rights and Gender; as well as Lívia Barbosa, social worker, professor at the University of Brasília and also a researcher at ANIS, affirm that, first of all, it is necessary to understand the principle of communication and the social impact of this. Therefore, "communication is the key concept to allow people to learn from the already-said or already-written – it is not always by standard listening or by eye reading" (DINIZ; BARBOSA, 2010).

From this, then, it is necessary to think the context, to recognize the different realities and the discourse present in that reality, so that, in this way, we can understand the signs and the way in which communication was built in that place. In view of these statements, then, the aforementioned authors draw a parallel with Mello's concepts in order to seek a consensus in relation to the theme addressed regarding the discrimination suffered by people with disabilities. Thus:

> We don't know how to describe the discrimination suffered by people with disabilities, so we resort to a compound term – "discrimination on the grounds of disability". Imagine we use something similar for racism: "discrimination suffered because of skin color." It would be an anachronism similar to the linguistic weaknesses of the past in which we spoke of "people of color," among so many other disqualifiers of existence marginal to the ideal human type. (DINIZ; BARBOSA, 2010)

For Dias (2001), ableism is a conception present in the social that reads people with disabilities as not equal, but less able or not able to manage their lives. And complete:

> Ableism is defined as a network of beliefs, processes and practices that produces a particular type of understanding of self and body (body pattern), projecting a pattern typical of the species and therefore essential and fully human. Disability for the ableist is a diminished state of the human being. (DIAS, apud Campbell, 2001, p. 44).

However, it is possible to understand ableism as a discourse disseminated within the social context by which people with disabilities are excluded, diminished and placed in a place separate from others, creating the need for inclusion or even integration, in which both the disability and the disabled person are spectacularized. In this context, the role of the media comes in, because when constructing notes, news, reports with wrong terms, based on coitadismo (people with disabilities are worthy of pity, because of their disability), heroism (overeffort that makes overcome the disability), or even in the judgment of those who claim that a person with a disability "suffers" or wins despite the disability, if it is before the consolidation of the referred prejudice already normalized.

But, in addition to the technical error of writing or textual construction and, in general, of communication as a whole, this practice masks the need to discuss the ableist ills present in society, because, while, the discourses of overcoming, heroism, ableism and others are worshipped, appealing to the character of emotional subjectivity, this causes that, socially, if Assume a position of passivity, in which one does not need to question the fact that, if there were accessibility, policies of inclusion and compliance with the laws, this heroic discourse would fall to the ground and the practices would be daily, making inclusion something natural. This, then, is one of the worst contours of the problem to be discussed.

3 ANOTHER FOCUS ON THE ISSUES RAISED

In an article dedicated to the edicts of the newspaper Zero Hora, of 07.12.21, Rafael Hirt Moreira, as Commercial Coordinator of the 24th edition of the deaf olympics, not only informs about the realization of this sporting event of international dimensions, to be held in the City of Caxias do Sul/RS, as he makes a call for the effective participation of all, since it is the most important event of the world deaf community, Since it will bring together about 6,000 athletes, from something around a hundred nationalities, it will compete in 21 sports. It also highlights that two approaches should be highlighted for the event: "The inclusion of the deaf community, which accounts for 5% of the world's population (around 10 million people, in Brazil alone)"; as well as alert to the market potential, by asking: "how many business opportunities can arise in the most diverse niches in which we operate"? Moreover, it states something that impacts the objectives pursued in this article, in the sense that: "The motto of the International Committee on Sports for the Deaf is: *Per ludos aequalitas,* or equality through sport. And this is what the deaf community seeks and needs: equality and inclusion! " (MOREIRA, 2021, p. 21).

When dealing with the subject, the International Committee itself points out that from the occurrence of the first games, in Paris, 1924, to the last edition, in Turkey, in 2017, since it is an event to occur Every four years, the goal to be pursued has always been and still is to advocate for a paradigmatic change in society in relation to the deaf, so that:

> At a time when societies everywhere saw the deaf as intellectually inferior, linguistically impoverished and often treated as outcasts, Monsieur Rubens-Alcais (creator of the event) envisioned the international sporting event as the best answer to prove that the deaf were more than they were seen. (...) The Deaflympics are distinguished from all other IOC-sanctioned games by the fact that they are organized and administered exclusively by members of the community they serve; that is, only deaf people are eligible to serve on the board and executive bodies of the ICSD - International Committee for Sports for the Deaf. (INTERNATIONAL COMMITTEE, 2021, p. 01).

In addition, in what impacts the present article, it is worth mentioning statements contained in the News Portal of the Padre Anchieta Foundation, according to which: "At a time when there is more and more talk about the fight against ableism, sport becomes one of the important instruments to show the potential of these people and leave stereotypes behind." (PORTAL DE NOTÍCIAS PADRE ANCHIETA, 2021, p. 01). And in the same sense that, through events of this nature, this desired transformation can be carried out with regard to society's own perception of the deaf and, therefore, people with disabilities, Gustavo Perazzolo is positioned as Interim President of the ICSD - International Committee of Sports for the Deaf:

> Deaf people have subverted many barriers over time, whether ensuring education and accessibility or basic day-to-day rights. In sport it was no different, the deaf community has always been a pioneer, having created the second oldest multi-sport event in history and the first that involved people considered non-standard. Sport is something that unites everyone as

> a society, a bond that breaks down differences and leads everyone down a path of respect, and the deaf have proven this with a lot of grit and pride over time. The Deaf Olympic movement is the link between sport and the deaf community, a banner of diversity and a beacon of equity in every corner of the world. To be involved with this movement is not only to commit to the future of society, but to practice the act of empathy with those different with whom we are. (PERAZZOLO, 20121, p. 01).

When it is sought to draw some parameters about issues such as accessibility, inclusion and equality, in relation to the present theme under discussion, however, it is necessary to pay attention, clearly, to the respect for the differences inherent to the diversity of manifestations of this condition, given the reference made to another event, of an international character, involving people with disabilities, which refers to the Paralympics, whose last edition was held after the Olympic Games themselves, in Tokyo, from 24.08 to 05.09.21, which do not include deaf people. Thus, in the Mídia Ninja News Portal, in an article signed by Carol Bastos and Maria Paula, there is the questioning about the fact that the Deaf Olympiad, being the second multi-sport event in the world, because it is the second, instituted only after the Olympic Games of the Modern Age, has already brought medals to Brazil, but the lack of visibility makes few know the games. In this way, they pose the question: "Deaf Olympics – why weren't the deaf in the Paralympics?" In this sense, then, it is worth mentioning that there were some initiatives to unify both international events, but without success, given that, in the statements of Jorge Rodrigues, as President of the Association of the Deaf of São Paulo:

> It is a very delicate subject, because it opens a gap for unfavorable interpretations and we are not against the existence of the Paralympics, on the contrary, we appreciate and celebrate a lot. But it's not for us deaf people. (...). It involves a question of belonging: the deaf community doesn't feel comfortable competing with listeners and doesn't think it's fair. Also, there's the issue of accessibility, right? It would have to adapt all the games so that it is accessible to the deaf as well, which would require learning (again) on the part of Paralympic athletes. (RODRIGUES, 2021, p. 01).

Mister, then, to present a brief contextualization of this other event, of international level, held in function of people with disabilities. In this sense, the International Paralympic Committee presents a brief history about the occurrence of the Games, stating that the first competition of its kind was organized in 1948 by Ludwig Gutmann, in the treatment of their patients with spinal cord injuries. From 1948, then, with the stimuli and wide adoption, the 1st edition of Stoke Mandeville Games was established. The competition became annual and, from the 1950s, began to receive foreign athletes. The milestone, however; and which converges with the history of the Olympic Games, it takes place in 1960, when the Stoke Mandeville Games are held in Rome, host city of the Olympics, soon becoming the first Paralympics, proper, in 1960. Moreover, after some incidents in which certain venues of the Olympic Games have not expressed interest in holding the Games, since 1988, it is held in the same place that hosts the Olympic Games. Then, Brazil's first participation took place in 1972, and our first medal came in 1976. In Brazil, in turn, there is the Brazilian Paralympic Committee; and

the country is considered a Paralympic power, due to the medals obtained, notably in the last games, Tokyo, which showed the following result: 22 gold, 20 silver and thirty bronze medals, leaving the country in seventh place in the world ranking. (C0MITÊ PARALÍMPICO INTERNACIONAL, 2021).

In the channel Fora de Série, under the responsibility of Alison Paese, André Barros and Rafael Capelli (2021), there is an article that deals with the importance of inclusion and the Paralympics as a mirror, in which Claims:

> Inclusion is not about seeing from the showcase. It's about getting a seat equal to the table. Inclusion is about belonging. Launch of culture even, place where diversity meets inclusion. That thing that is not pamphleteering, is not lip service, is not only in words. It is something natural, something already understood and followed onward. (PORTAL DE NOTÍCIAS CANAL FORA DE SÉRIE, 2021, 2021, p. 01).

Next, they propose to answer the question: "Why is Brazil a power in the Paralympics?" They add:

> The sagacity to organize a unified representation of Brazilian Paralympic sport was fundamental for the sport to be widely disseminated in the country. More than that, so that there was always a feeling of inclusion and belonging, focusing on preparing athletes for performance at a high level. (...). Not only: the CPB (International Paralympic Committee) also has the incentive of private initiatives and strategic partnerships for the construction of projects for the inclusion, capture and development of athletes throughout Brazil. A mixture that results in investments by the federal government, support from companies in projects and fundamental initiatives to transform and expand the reality of the country's Paralympic athlete. (PORTAL DE NOTÍCIAS CANAL FORA DE SÉRIE, 2021, 2021, p. 01).

Still in what impacts the present article, in an article signed by Lucas Biccudo, (2021), in the same News Portal just mentioned above, when commenting on the Paralympic Games, focusing on the binomial ableism and its counterpart, which can be defined as overcoming, as an expression coined to define the success and results achieved by people with disabilities, in these sports competitions, the following is positioned:

> Without using that is overcoming just by seeing someone without leg, arm, wheelchair, blind or with paralysis. These people train too much. People with disabilities suffer from ableism, which is when someone says, explicitly or implicitly, that they are "an example of overcoming", "if he can do it, I can do it too", "I have nothing and I still complain". Reduce the condition of the other before your own. It's not overcoming, it's training. Go out there and train what they train. Disability is nothing more than a characteristic. We have to get everyone seated at the table. No one looking through the window. (BICCUDO, 2021, p. 01).

Now, it is possible to complete the approach that ableism finds, socially, the other side of the same coin, regarding the references to people with disabilities, given that these people, either have their capacity diminished, in general, starting to be considered as disabled, because they do not fit the definitions of corponormativity instituted, or, are presented as an example of overcoming, in which, by their own effort, they overcome their own disability. One can refer, therefore, also to the binomial

"coitadismo" versus "heroism". Thus, it is not intended, here, to disqualify the aforementioned international events, whether they refer to the Surdolympics, or to the Paralympics, but, rather, to show that it should be noted that, in both cases, the emphasis is precisely on these binomials of ableism versus overcoming, as well as coitadismo versus heroism, which, in the final analysis, comes to cover up the theme of operating a real and effective social inclusion, since a mistaken understanding is normalized that even with such obstacles, behold, they can be overcome, by dedication and excessive training.

There is one of the problems of such approaches, since this can lead to an even greater omission of society as a whole, to elaborate and institute effective forms of inclusion, from the simplest forms of physical accessibility, to the most complex, referring to education, health, safety and even professional issues. Moreover, such athletes, when presented as ideals of overcoming, end up producing, in addition to the visibility that they can ensure to their condition as people with disabilities, unfortunately, the exclusion of the much more significant contingent of those who, in no way, achieve the success of becoming participating athletes, or consecrated in such events.

In both cases, wrong postures are ratified in the face of the problem, that is, for society the paradigm is formed that individual effort and exhaustive training are enough to reach excellent performance, in such a way that the social conditions that hinder access, in a broad way, since they can be overcome, do not need to be eliminated, or even, diminished. Therefore, the exclusionary postures turn out to be naturalized, that is, treated as normal and without the need to be modified. In the same way, the heroism of the athlete who overcomes these obstacles ends up placing even more pressure on people with disabilities, who have not achieved such performance and who do not see themselves represented by this performance, so that they end up internalizing, in themselves, as already mentioned, a position of inferiority in the face of the results that this minority obtains.

The complexity of the problem is also evident and that is why reference was made to the two events, at an international level, involving people with disabilities, in the sense that this generic classification should be examined very carefully, since the claim for equal treatment and conditions does not in any way imply standardization of these conditions, because they must be faced in their own specificities, given that it has been shown not to be possible, for example, to bring together the categories of deaf athletes with the competitions of athletes that are constituted from other disabilities and that, thus, integrate the Paralympics. This, then, is the question that equality must, without a shadow of a doubt, take into account diversity, that is, the deep respect for differences, which do not refer only to bodies, but also to psychological conditions and, therefore, to the subjectivity of each one, always compared with the social or contextual conditions that involve people with disabilities.

4 FINAL CONSIDERATIONS

Even though a protective system has already been achieved in the legal system, which proposes to operate an equivalence of conditions of people with disabilities, to the others, without disabilities, of which it can be cited, without demerit of any other, the Statute of the Person with Disabilities, Law No. 13,146/2015, as well as the very institution of the model of biopsychosocial evaluation of disability, that emanate and embody the constitutional principles of the dignity of the human person and the express prohibition of any forms of discrimination, the problem is not solved only through formal statements of laws. Thus, the experience with such legal instruments has shown that, for the real realization of such rights to equal conditions, public policies are necessary that aggregate, not only the legislative, executive and judicial instances of the powers of the State, but, above all, the social organizations themselves that are concerned and are destined to the pain voice to people with disabilities, in order to expand their political participation in all decision-making spheres, going through this process of inclusion through the levels of political representation. In this way, this political representativeness would be in better conditions to be constituted, together with the entities of organized civil society, as instruments of active citizenship, to institute a political agenda strong enough for such public policies to become public policies of the State no longer linked to the ideological processes that assume the transitory power in our representative democracy.

Moreover, even if one invests in all the factors necessary for an effective participation in international events, such as those mentioned, which undoubtedly give visibility to some aspects of the problem of this effective inclusion, but which may take on the opposite character, in the sense of covering up actions necessary to make this inclusion truly effective, this context would be demanding a joint action of such public policies, leaving its character of one-off actions. What is required, therefore, concerns a general coordination of such public policies, of a permanent nature, aiming to carry out the constitutional and legal dictates, as well as the punctual guarantees already received by people with disabilities, so that they do not suffer setbacks, but can be expanded, to the extent that new perspectives that this effectiveness can unveil are perceived.

Fundamentally, however, all these instances must shelter those to whom such public policies and normative measures are addressed, making use of the epithet already consecrated in some of the civil entities dedicated to the theme and which is embodied by the expression: "nothing about us, without us". This means that without giving voice and guaranteeing the full manifestation of people with disabilities, about what, really and truly, they face, in terms of exclusion and the search for effective inclusion, one would be robbing these people of the fundamental right to decide about their own existential conditions. Because of this, it is possible to act in a virtuous circle, in which the conditions of possibility of effective accessibility are propitiated, starting from its simplest forms of physical instruments of access to facilities, to a real accessibility to the levels of education, health,

employment and careers, entertainment, as well as all the rights guaranteed to all citizenship, without any form of exclusion and/or discrimination. Moreover, these specific forms of inclusion must necessarily be debated, first of all, by those who face them, on a daily basis.

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The impact of sleep on the health of higher education students: Literature review

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ABSTRACT
Introduction: The study of sleep-in medicine is recent and assessing health impacts is a current necessity. Healthy sleep and sleep hygiene are fundamental for the proper functioning of the nervous system, with significant impacts on physical and mental health, including for higher education students, who have a change in their routine in the face of the new challenges experienced when entering this new stage of life. Objective: to analyze and synthesize the most recent research on the impact of sleep on the health of higher education students, in order to identify the consequences and the most effective approaches. Methodology: The searches were performed in the PUBMED and LILACS databases, using the search process through vocabulary controlled through descriptors and Boolean operators "and" and "or". Conclusion: Sleep plays a fundamental role in physical and mental health. Deprivation or an unregulated sleep routine can cause several consequences in relation to the health of the university student, the most common are: Hypertension, Metabolic Syndrome, stress, depression and other mental disorders. These are impacts that often become irreversible and decrease life expectancy. Sleep hygiene measures are simple and very effective forms of treatment, but the change in lifestyle habits is complex adaptations

Keywords: Impact of sleep on the health, higher education students.

1 INTRODUCTION

Sleep is a special physiological state that occurs in a cyclical manner in a wide variety of living beings of the animal kingdom, but defining sleep is not a simple task, either from the physiological

point of view or based on the behavioral description of the individual who sleeps. (FERNANDES, 2006)

We can say that, in sleep, individuals are immobile, or with a limited repertoire of movements, which are involuntary, automatic, without defined purposes. Reactivity to auditory, visual, tactile and painful stimuli is reduced or abolished in relation to wakefulness, particularly in deep sleep phases, requiring an increase in the intensity of the stimulus to bring the individual back to wakefulness. (FERNANDES, 2006)

However, the history of sleep medicine is relatively recent. Scientific experiments on sleep in humans only began a little over half a century ago. Until the 50s of the twentieth century, most people imagined that sleep was a passive or inactive part of our daily lives. Today, we know that our brain remains very active while we sleep. In addition, sleep affects our daily performance and our physical and mental health in many ways, but we are only beginning to understand how this actually occurs. (MAGALHÃES, 2007)

The evolution of knowledge about sleep, both in experimental and clinical practice, was possible from the domain on the recording of brain waves through the Electroencephalogram (EEG), which allowed the objective discrimination between relaxed wakefulness and sleep, as well as between their different stages. (FERNANDES, 2006)

Thus, sleep comprises a sequence of phases that can be identified through its EEG pattern, and these phases arise naturally under the influence of a regulatory mechanism of the central nervous system. Researchers Harvy and Loomis pioneered the first system of categorizing sleep phases, describing several essential EEG features that are used in the current classification system. Nowadays, these phases of sleep are called stages 1, 2, 3 and 4.

Subsequently, Aserinsky and Kleitman identified a distinct pattern of EEG sleep, characterized by low voltage and rapid activity, which was correlated with rapid eye movements. These researchers also recognized that this phenomenon was associated with dreams. This stage was called REM (rapid eye movement) sleep, which occurs alternately with the stages described by Loomis, which, by exclusion, were grouped as non-REM sleep (NREM).

After understanding the essence of sleep, the importance of it becomes the primary factor for the continuity of reasoning. The proper functioning of our nervous system depends on the need for sleep. Research involving animals has demonstrated the essential importance of sleep for survival.

Too short sleep causes drowsiness and inability to concentrate. It also leads to memory and physical performance failures and reduces the ability to perform mathematical calculations. If sleep deprivation continues, hallucinations and mood swings may develop. Without sleep, neurons can suffer energy depletion or be polluted by byproducts of normal cellular activity that cause them to function

imperfectly. Sleep also gives the brain a chance to exercise important neuronal connections that might otherwise deteriorate from lack of activity. (MAGALHÃES, 2007)

Sleep and related disorders play an important role in a large number of diseases and can affect almost all fields of medicine. As examples we have asthma attacks and strokes, which tend to occur more often during the night and early morning, perhaps because of hormonal changes, heart rate variations and other factors associated with sleep. Sleep also affects some types of epilepsy in complex ways; REM sleep seems to help prevent seizures, while deep sleep can make them easier. Sleep deprivation can also trigger seizures in people with some types of epilepsy. (SOARES, 2006)

The concern with the care of the physical and mental health of the human being has been gaining more and more attention in recent years, which is evidenced by growing publications on the subject. The need for this care extends to the various layers of the population, among them the one that includes students of Higher Education. It is brought up in the literature, for example, that the academic environment can become a source of stress for a considerable portion of the population of this level of education. (PADOVANI, 2014)

In addition, changes in life habits, after entering these spaces, can bring impacts that directly affect the quality of life of this group. This is because, Higher Education has a dynamic that will require a series of responsibilities not experienced until then in the previous school trajectory. Therefore, changes in lifestyle habits are expected to cope with the new demands. (MUNIZ, 2021)

Given this, healthy sleep is a tool capable of assisting in the issue of regularity and quality so that it is an effective instrument. Thus, the denomination of a healthy sleep can be characterized as sleep hygiene.

Sleep hygiene therefore has as its general objective to facilitate a restful and sufficient (but not exaggerated) sleep. In addition to recommendations on diet, physical exercise and the consumption of alcohol, tobacco, coffee, other measures have been added to sleep hygiene. These, more recent, arose from the premises of stress reduction methods (cognitive behavioral strategies) and, above all, from stimulus control procedures. (GOMES, 2005)

2 OBJECTIVES

The objective of this literature review is to analyze and synthesize the most recent research on the impact of sleep on the health of higher education students, in order to identify the consequences and the most effective approaches, as well as to provide a solid theoretical basis for future interventions and development of sleep hygiene measures.

3 MATERIALS AND METHODS

3.1 DATABASES

The searches were performed in two bibliographic databases — PubMed and LILACS. At the end of the searches in each database, the duplicate references were excluded.

3.2 TIME LIMIT

We selected articles published between 2015 and 2023 (including those available online in 2023 that could be published in 2024)

3.3 LANGUAGES

Articles written in English and Portuguese were selected.

3.4 DESCRIPTORS

The search process was used through vocabulary controlled through descriptors and Boolean operators "and" and "or". With this strategy, there was a recovery of specific references, ensuring the detection of most of the published works within the pre-established criteria.

The descriptors used were "*Health Impact*", "*Sleep*" and "college student*" were* combined with the associations and operator "and". As it was not the objective of this review to evaluate the impacts on students of other levels, the term was specific to "college student" in the search.

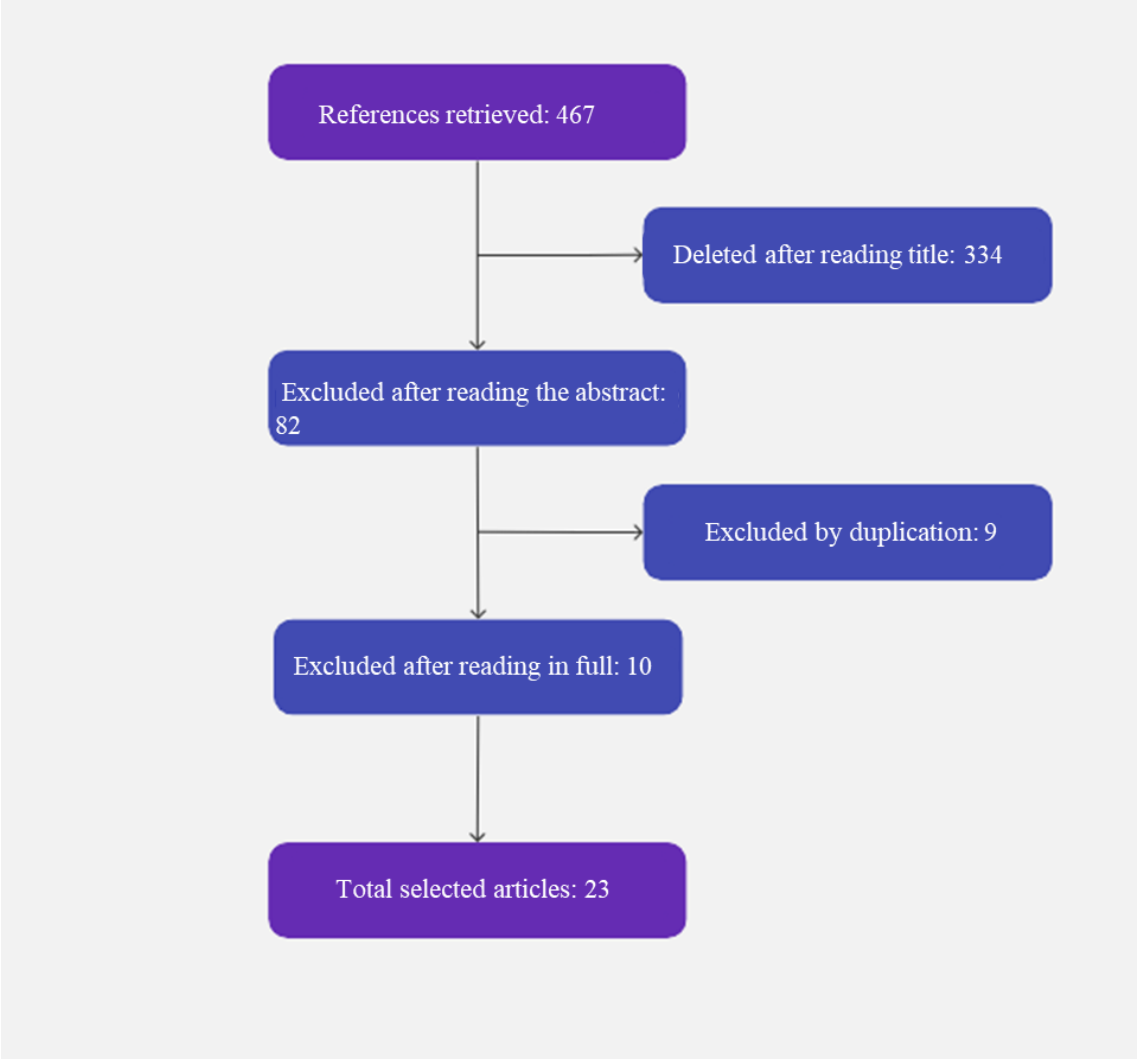
3.5 INCLUSION AND EXCLUSION CRITERIA

We included all original articles indexed in the period between the first of January 2015 and August 16, 2023, with experimental design (clinical trials, randomized or not) or observational (case-control studies, cohort studies and before and after studies). Articles that analyzed observational studies with cross-sectional analysis, phase I or II studies and studies conducted in pregnant patients were excluded.

3.6 PROCESS OF SELECTION AND ANALYSIS OF ARTICLES

Figure 1 shows the process of selecting the articles in their different stages and the respective number of articles retrieved in each one. The captured references were included in a unique library in the Zotero program. Two medical students were responsible for the selection and reading in full of the selected articles; After the selection, a library was created in which all the selected references and the respective complete articles in PDF format were contained. A total of 20 original articles were included in the present review (Figure 1).

Figure 1- Flowchart of the selection process of the researched articles. The number of articles in each step is indicated.



Source: Own Authorship

4 DISCUSSION AND RESULTS

4.1 EPIDEMIOLOGY

Sleep disorders are among the clinical disorders with the greatest health and socioeconomic impact. They are as common as asthma and diabetes; however, few are properly diagnosed and treated. As an example, it can be mentioned that only 5% of patients with insomnia consult primary health care and 69% never mentioned to doctors their sleeping difficulties. Vgontzas and Kales reported that sleep disorders are very prevalent in the general population and that insomnia is the most common, and, when chronic, usually reflects psychological and behavioral disorders (SOUZA, 2004)

The prevalence of sleep disorders in a hospital population in Milan, Italy, for one year, with a sample of 1,347 women and 1,171 men, between 6 and 92 years of age, and found 12.8% of insomnia complaints, more prevalent in the orthopedics sector (17.5%). Insomnia

initial (39.1%) and maintenance (32.1%) were the most prevalent. There was a higher prevalence among women and an increase with age in both sexes. (SOUZA, 2004)

4.2 SLEEP STAGES

The characterization of the sleep phases can be made based on 3 physiological variables that comprise the electroencephalogram (EEG), the electrooculogram (EOG) and the submental electromyogram (EMG). Through them are characterized 2 fundamental sleep patterns: without rapid eye movements (NREM) and with rapid eye movements (REM). NREM sleep is composed of 4 stages in an increasing degree of depth, stages I, II, III and IV. In NREM sleep, there is muscle relaxation compared to wakefulness, however, some basal tonicity is always maintained. EEG exhibits progressive slow-wave increases as one progresses from stage I to stage IV of NREM sleep. (FERNANDES, 2006)

During stage 1, which is shallow and fleeting, we drift off to sleep, return to wakefulness, and can be awakened with ease. In the EEG, this stage is characterized by the presence of waves of low amplitude and frequency from 3 to 7Hz (theta waves). Our eyes move very slowly and muscle activity gradually slows down. When we awaken from this stage, it is often possible to have fragmented memories of environmental events that occurred in the period. When we enter stage 2, our eye movements stop, and our brain waves become slower. The so-called K complexes arise, which are accompanied by occasional bursts of 5 to 7 waves of 12 to 15Hz, in the form of crescendo-decrescendo, the so-called 'sleep spindles'. In stage 3, extremely slow waves (0.3 to 2Hz), the so-called delta waves, begin to appear, interspersed with smaller, faster waves. In stage 4, the waves are almost exclusively delta frequency. It is very difficult to wake someone up during stages 3 and 4, which together are called the delta stage or deep sleep. At this stage, there is no eye movement or muscle activity. People awake during deep sleep do not orient themselves immediately and often feel 'groggy' and disoriented for a few seconds after they awaken. Stages 1, 2, 3, and 4 are collectively called non-REM sleep (NREM). (MAGALHÃES, 2007)

4.3 CHANGE OF ROUTINE IN UNIVERSITY STUDENTS

Admission to the University is characterized by significant and complex changes in the way students think in different areas of their lives, being able to develop intellectually and personally (PAPALIA, 2006). First, admission often represents the first important attempt to implement a sense of autonomous identity, an attempt that is translated through professional choice (or attempted choice), which is a typical developmental task in the passage from adolescence to adulthood (ERIKSON, 1976). Adjusting to the university thus implies socially integrating with the people of this new context, participating in social activities and developing satisfactory interpersonal relationships. (Diniz & Almeida, 2006)

Students often have irregularity in sleep, as well as high levels of stress, as a result, they are fit into a risk group with a high probability of presenting sleep disorders (RIOS, 2019). Due to numerous tasks performed, it is worth noting that its alteration can cause physical, occupational, social, emotional and cognitive disturbances, compromising the quality of life (CALDAS, 2009; CARLETO, 2018).

Since their academic training, the student is in circumstances that already put them in contact with the area of activity, which is characterized by changes in routine. (Smith, 2012; BRANDT, 2019). The quality of sleep is an essential element to human health and the quality of life of university students, which represent the future of the country, so it is essential that they are healthy people (SCHNEIDER, 2010; SANTANA, 2018).

4.4 IMPACTS OF SLEEP ON THE ROUTINE OF UNIVERSITY STUDENTS

Today, there are several ways of presenting both numerical and linguistic data. Given this, the use of tables refers to several benefits such as conserving and restricting data loss, greater specificity and, in addition, provides a better analysis of the data that are grouped in order allowing comparisons and conclusions.

This article presents Table 1 to demonstrate the impacts of sleep on the routine of higher education students. Thus, Table 1, below, summarizes the results and discussions that the authors of their respective articles carried out during their research.

Table 1: Analysis of the results of the articles

Quality of Sleep and Depression in College Students: A Systematic Review	Education and the application of sleep hygiene policies can prevent, in some cases, the development of depression and improve sleep quality in other cases.
Sleep and Health Among Collegiate Student Athletes	Poor sleep health and sleep disorders are a growing concern among the college athlete population and have recently been recognized by national and international sports regulatory bodies. These habits reflect on the health of the athlete and on their school and sports performance.
Poor sleep quality and insufficient sleep of a collegiate student-athlete population	College athletes often experience poor sleep quality, regularly get insufficient sleep, and commonly exhibit daytime sleepiness reflecting on the performance of their activities and causing health impacts.
The Impact of a Randomized Sleep Education Intervention for College Students	A brief, personalized online sleep education intervention improved sleep behaviors, sleep quality, and depression scores. This new approach to dealing with sleep deprivation, poor sleep habits, and mood among college students may offer an effective and inexpensive remedy while still preventing disease.
The Impact of Ashwagandha on Stress, Sleep Quality, and Food Cravings in College Students: Quantitative Analysis of a Double-Blind Randomized Control Trial	The method used can be a safe and effective intervention in young adult populations to help regulate sleep, manage stress and its detrimental impacts on health, sleep and satiety in less than 30 days.

Sleep difficulties in college students: The role of stress, affect and cognitive processes	These findings suggest that the effect of poor sleep quality is reflected in stress and further intensifies quality sleep difficulties.
Poor sleep quality and its related risk factors among university students	Through physical activity and good sleep quality can be important factors in improving quality of life and preventing disorders in university students.
Insomnia among medical and Paramedical Students in Jordan: Impact on Academic Performance	A high prevalence of insomnia was found in this group of students. There is an impact on the health of students and academic performance was significantly associated with ISI scores and self-reported sleep quality.
Internet Addiction, Sleep Quality and Depressive Symptoms Amongst Medical Students in Delhi, India	Significant correlations were found between potential internet dependence (ID), sleep quality and depression ($p < 0.001$). The study concluded a strong correlation between ID, disturbed sleep quality and depression.
Mental health and sleep habits during preclinical years of medical school	Depression, anxiety and sleep habits showed a cyclical change associated with the academic/seasonal cycle. Medical students who contemplated fewer hours of sleep presented greater severity.
Stress and sleep in college students prior to and during the COVID-19 pandemic	The results suggest that within the U.S. college student population, the impact of stress and sleep may not be entirely negative during the pandemic.
Sleep disorders as primary and secondary factors in relation with daily functioning in medical students	Insufficient sleep is a common problem in medical students and several sleep disorders have been found. The results suggest that sleep disturbances may have negative impacts on students' daily functioning.
Academic adaptation in university students: associations with stress and sleep quality	Better rates of adaptation to university were correlated with better sleep quality and lower stress levels. The importance of working on the development of positive emotional aspects in university students is evidenced to favor the processes of academic adaptation.
Factors associated with sleep quality of university students	The results highlight socioeconomic and mental health factors that interfere in sleep quality and demonstrate the need for reflection and proposal of interventions capable of minimizing this problem.
Changes in sleep quality during an academic semester in health careers students	There was a significant increase in poor sleep quality at the end of the academic semester, with the change being greater in the students of the professional cycle, causing loss in the quality of life and health of those involved.
Factors associated with poor sleep quality in nursing students from a private university in the state of Ceará	Sleep is essential for the physical, psychic and social well-being of individuals. Its poor quality/quantity may lead to functional impairment in the performance of social roles and interpersonal relationships.
Prevalence of behavioral health risk factors and their simultaneous occurrence in students of a public university in Pelotas, Rio Grande do Sul, 2017	Inadequate sleep time, lack of physical activity and smoking negatively impact routine, health and quality of life in the medium and long term.
Sleep quality and associated factors in undergraduate nursing students	Low income, high stress level, and smoking were associated with poor sleep quality. The results challenge the proposition of interventions capable of minimizing poor sleep quality in nursing students.
	There was a high prevalence of the outcome in the sample. In addition, poor sleep quality occurs differently between men and women. The

Sleep quality and associated factors in university students in the Midwest of Brazil	importance of monitoring poor sleep quality in university students and the health impacts that these habits have on the health of these habits is highlighted
Sleep quality and risk factors for hypertension among university students	Students are at high risk of developing overweight, due to physical inactivity, alcohol consumption and sleep quality, and consequently susceptible to the development of hypertension in the future.
Screen time and Sleep Quality among College and University Students of Karachi	Because negative impacts have been determined on sleep quality and increased screen viewing of various versions of the devices (screen time), influencing the recommended level of screen viewing among college students and college students (age 17-24) is a public health issue.
Sleep quality of university students and its interface with metabolic syndrome and health indicators	College students with poor sleep habits are more likely to have metabolic syndrome compared to good sleepers.
Sleep quality and daytime sleepiness in university students: prevalence and association with social determinants	The high prevalences of poor sleep quality and EDS observed in university students were due to biological factors and, for the most part, behavioral factors.

Source: Own Authorship

5 CONCLUSIONS

Several studies have proven that sleep has a fundamental role in physical and mental health, and that sleep hygiene measures are simple and very effective forms of treatment, but the change in lifestyle habits is of complex adaptations. The benefits of sleep quality is multifactorial and this explains the success of sleep clinics in Brazil and worldwide.

Sleep deprivation or an unregulated routine can cause several consequences in relation to the health of the university student, the most common are: Hypertension, Metabolic Syndrome, stress, depression and other mental disorders. These are harmful both in the short, medium and long term. These are impacts that often become irreversible and decrease life expectancy.

The most efficient way to prevent health damage is a regular sleep routine aimed at maintaining a balance between physical well-being and the fast-paced routine of medical students. Drug treatment has been part of the current therapeutic regimen. What is observed is that people are aware of the importance of sleep, however the permanence of the regularity of healthy sleep habits does not progress.

Fortunately, we have seen in recent years, healthy lifestyle habits being incorporated into society as a desired but difficult standard. The digital world and its characters are concretizing routines indicated for maintenance and prolongation of life. However, this wave of healthy living has an effect on higher social classes and their predominantly young audience. This can bring a healthier future, but it is necessary to expand the age group and income.

The income of patients is also a decisive factor at the time of sleep and routine, and this greatly restricts with the population of lower purchasing power due to the need to contemplate work, study and family with quality times.

Despite difficulties, it is possible to establish a better quality of life for higher education students, reducing medication burden with the simple act of sleep hygiene. It is known that adherence to new life habits comes in a particular way from each individual, but with the presentation of evidence and awareness of this public the engagement becomes very expressive.

Therefore, it is seen that the articles related to the methodology applied corroborate and ratify the importance of awareness and measures of focus on routine for sleep hygiene to better provide quality of life and prevention of damage to the health of university students. These facts place us before a fundamental responsibility in the correct orientation of the routine and responsibilities of academics.

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Alzheimer's Disease in Dentistry: Repercussions and management in oral health

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ABSTRACT
Alzheimer's disease is one of the most prevalent forms of neurodegenerative dementia that mainly affects elderly individuals, manifesting itself through cognitive disorders that include gradual memory loss, communication difficulties and temporal and spatial disorientation. So far, the etiology of this disease remains uncertain, and its most challenging feature is the lack of a definitive cure, which makes treatment focused on delaying its progression and controlling symptoms. To achieve these goals, it is essential to adopt a multidisciplinary approach involving physicians, nurses, physiotherapists and dentists. The purpose of this work is to present the fundamental principles related to Alzheimer's disease, as well as its implications for oral health, offering guidance to dental professionals on how to conduct care for these patients. The dental surgeon assumes a crucial role in guiding and instructing the patient's caregivers and family members, in order to guarantee the maintenance of the oral health of these individuals. In addition, the professional must plan a treatment that prioritizes adequacy, prevention and promotion of oral health, seeking to provide greater comfort and well-being and, therefore, improving the quality of life of patients with Alzheimer's.

Keywords: Alzheimer's disease, Dental management, neurodegenerative diseases, dentistry.

1 INTRODUCTION

Alzheimer's disease is currently recognized as the most prevalent cause of dementia in humanity, configuring itself as a global health concern with significant impacts for individuals and society. This scenario becomes more complex in the face of the increasing aging of the world population in recent decades (Lane CA et al., 2017; Weller J et al., 2018). Alzheimer's disease is characterized as a neurocognitive disorder with neurodegeneration, characterized by the progressive loss of neurons (KUMAR et al., 2016). Its signs and symptoms can start with short-term memory loss,

deficits in visual and spatial orientation, language dysfunction, irritability, and cognitive deficits (Alzheimer's Association, 2022).

The discovery of this disease was carried out by Alois Alzheimer, a physician who worked in a psychiatric clinic of the University of Munich during the late nineteenth and early twentieth centuries. on November 3, 1906, he described the first documented case of a degenerative disease, later named "Alzheimer's disease" in his honor (Hippius H et al., 2003; Zhagn et al., 2014). The case of a woman named Auguste D., who at the age of 51 showed signs of progressive memory loss, hallucinations and difficulty concentrating, was crucial for the initial understanding of this disease. Subsequently, language alterations and temporal and spatial disorientation were observed, which progressed rapidly. The patient died four and a half years after the onset of symptoms, presenting an advanced stage of dementia. After the autopsy performed for Alzheimer's, protein deposits were found in the patient's brain, senile plaques in the extracellular space, and neurofilamentary lesions inside neurons distributed throughout the cerebral cortex (Grøntvedt GR et al., 2018; Hippius H et al., 2003).

Initially, Alzheimer's disease was associated with cases of pre-senile neurodegenerative diseases, differentiating itself from the known cases of senile dementia in the early twentieth century. Since then, the term "Alzheimer's disease" has come to encompass cases of neurodegenerative dementia with features of brain lesions, such as senile plaques and neurofibrillary tangles, regardless of the age of symptom onset. Currently, there are no treatments capable of halting the progression of the disease, but there are medications available to treat the symptoms of dementia (Hippius H et al., 2003; Small DH et al., 2006).

The diagnosis of Alzheimer's disease is made through a detailed anamnesis and the clinical history of the patient, starting with the diagnosis of neurocognitive disorder (NCD), which can manifest itself in different degrees, from mild with memory deficits and visual and language disorders, to moderate and severe, characterized by more severe disorders of motor coordination, inability to basic daily activities and aggressiveness (KUMAR et al., 2016).

In addition, Alzheimer's disease can lead to several problems for the oral health of the patient, often leading to deterioration of oral health. It is common to observe active caries disease, periodontal disease and hyposalivation, caused by the medications used for the treatment of Alzheimer's disease (Mancini M et al., 2010). There is a scarcity of preventive measures directed to the oral health of these patients (Boccia A, 1992). Therefore, it is essential that the dentist is properly qualified for the proper and accurate management of patients with this condition, including the instruction and training of caregivers and family members for the correct maintenance of the patient's oral health (Gurgel ALA et al., 2012). In addition, treatment and follow-up should be conducted by a multidisciplinary team aimed at improving the patient's quality of life, focusing on the preservation of comfort and well-being (Frenkel H, 2004).

1.1 CONCEPTS AND EPIDEMIOLOGY

1.1.2 Concepts

Alzheimer's disease is a fatal and progressive neurodegenerative disorder that is predominantly associated with advanced age, constituting the most common form of neurodegenerative dementia among elderly individuals, accounting for about 70% of all cases recorded globally (APOSTOLOVA et al., 2012). This pathology is typically manifested by the gradual decline of cognitive and neuropsychiatric capacities, leading to progressive difficulty in daily activities. In the early stages of the disease, recent memory loss is noted, while older memories tend to be preserved until a certain stage of the process (Sereniki et al., 2008).

In addition to memory deficits, Alzheimer's disease is accompanied by a number of behavioral disorders, such as depressive symptoms, aggressiveness, hallucinations, hyperactivity, temporal and spatial disorientation, difficulties in communication, reduced discernment and judgment, impaired reasoning, and mood swings (Raskind MA., 1995). This complex interplay of symptoms makes proper diagnosis and treatment a challenge for healthcare professionals and requires a multidisciplinary approach to provide the best care to patients affected by this debilitating disease. Therefore, it is crucial that the scientific community continues to deepen its research on Alzheimer's disease, seeking to better understand its pathophysiology, develop prevention strategies and find more effective therapeutic interventions to improve the quality of life of patients and their families.

1.1.3 Epidemiology

Currently, in the Brazilian territory, there is a significant portion of the population, approximately 1.2 million individuals, who live with different manifestations of neurodegenerative dementia, and annually about 100 thousand new cases are officially diagnosed. The magnitude of this problem is not limited only to Brazil, since, according to information released by the World Health Organization (WHO), Alzheimer's disease, one of the most prevalent forms of dementia, affects around 35.6 million people around the globe.

This health condition is revealed, therefore, as a crisis of global scope that demands urgent confrontation. Projections by Alzheimer's Disease International indicate that, by the year 2030, the number of affected individuals could reach the alarming figure of 74.7 million, in view of the aging of the population. Even more impactful is the estimate for the year 2050, when it is projected that approximately 131.5 million people will be facing the disease in question.

These data corroborate the need to address the problem in a comprehensive and systematic way, directing efforts to research, prevention, early diagnosis and adequate treatment of this degenerative disease, in order to mitigate its devastating effects both for patients and for their families and caregivers. In addition, policies of care and support for this vulnerable population should be

implemented and improved, aiming to ensure a better quality of life and well-being for individuals affected by the spectrum of neurodegenerative dementias. Only with effective and committed actions will it be possible to face this growing public health crisis on a global scale.

2 CLASSIFICATION AND STAGES OF THE DISEASE

The clinical picture of the disease in question is classified into four stages, and the evolution is generally slow, although there is considerable variation in the duration of these stages. In some cases, the progression of symptoms occurs more slowly, allowing functional levels to be kept reasonable for a longer period. In contrast, in other situations, the deterioration is faster, but occurs constantly. In addition, there are also cases where the disease progresses in bouts of worsening followed by phases of stability, which can last for up to a year or more (Oboudiyat C et al., 2013).

The four stages of the clinical picture are described as follows:

1. Stage 1: Represents the initial form of the disease, characterized by changes in recent memory, changes in personality, visual abilities and notion of time and space.
2. Stage 2: Refers to the moderate form of the disease, manifested by difficulties in speech, communication, performing simple day-to-day tasks and motor coordination. In addition, the presence of agitation and insomnia is common.
3. Stage 3: Configures the severe form of the disease, where individuals face resistance in the execution of daily activities, as well as present aggressiveness, urinary and fecal incontinence, difficulty feeding and progressive motor impairment.
4. Stage 4: Represents the most advanced and terminal form of the disease, with bed limitation, mutism, pain when swallowing, and propensity to intercurrent infections (Alzheimer's Association., 2022).

In addition to these four stages, there are seven other subdivisions with specific characteristics:

1) Preclinical stage: Characterized by being silent, without observable cognitive loss.
2) Stage of Mild Cognitive Impairment: Presents the first signs of cognitive loss.
3) Mild Stage: Symptoms include forgetfulness and loss of recent memory, noticed by family and friends.
4) Moderate Stage: Mental confusion, agitation, anxiety, apathy, and aggressiveness are typical of this stage.
5) Moderately Severe Stage: Characterized by the inability to deal with personal tasks, loss of the notion of time and space and dependence.
6) Severe Form Stage: At this stage, the patient requires full-time care, manifesting urinary and fecal incontinence, delusions and hallucinations, which often requires hospitalization.

7) Very Severe Stage: Speech is lost, the inability to move occurs and consciousness is affected (Albert MS., 2011).

This detailed classification of the stages of the disease allows for a better understanding and identification of the different levels of cognitive and functional impairment that patients may experience throughout the course of the disease.

3 PATHOPHYSIOLOGY - WHY DOES ALZHEIMER'S DISEASE OCCUR?

The main changes found in the brain in cases of Alzheimer's disease involve histological and macroscopic modifications. At the histological level, the presence of plaques resulting from the deposition of amyloid protein in the extracellular space is observed, especially in the vicinity of the neuronal connections and in the walls of the blood vessels. These senile plaques are associated with inflammatory processes and abnormal neuronal dysfunction, resulting in synaptic loss and cell death in the brain regions responsible for cognitive functions (Sereniki et al., 2008). In addition, neurofibrillary tangles occur due to hyperphosphorylation of the tau protein, which can affect axons and dendrites. The disease also leads to progressive reduction of brain volume, as well as a decrease in the number of neurons and synapses (KUMAR et al., 2016; CENINI et al., 2012).

Macroscopic changes are evident in the form of cerebral atrophy, characterized by narrower gyri, enlarged grooves, reduced brain weight and increased ventricles (LOTT et al., 2006). The exact mechanism by which amyloid plaques and neurofibrillary tangles cause damage is not yet completely understood, and there are two main hypotheses to explain the pathophysiology of the disease. The first is the amyloid cascade hypothesis, which suggests that the neurodegenerative process begins with proteolytic cleavage of the amyloid precursor protein (APP), leading to the aggregation, deposition, and production of β-amyloid (Aβ) and senile plaques. These events eventually result in neuronal death, loss of synapses, and progressive neurotransmitter deficiency (Hardy J et al., 2002).

The second hypothesis is the cholinergic cascade, were cholinergic system disorder results in memory impairment, similar to the symptoms of Alzheimer's disease (Bartus RT et al., 1999). The degeneration of cholinergic neurons and the reduction of cholinergic markers in the cerebral cortex are present in patients with the disease (Auld DS., 2002), which leads to cognitive impairments. In addition, a sustained immune response and inflammation was observed in the brains of patients with Alzheimer's disease, suggesting that inflammation may be a third central pathological feature (Alzheimer's Association., 2022). Experts have proposed that astrocytes and microglia cells are associated with inflammatory responses by releasing pro-inflammatory molecules such as interleukins (IL), prostaglandins (PG), leukotrienes, thromboxanes, clotting factors, complement factors, and proteases (Parihar MS et al., 2002).

Genetic aspects also play a significant role in the etiopathogenesis of the disease. About one-third of Alzheimer's disease cases are familiar with an autosomal dominant monogenic inheritance pattern (Smith MAC., 1999). The allele of the apolipoprotein E type 4 gene (apoE4) has been shown to be associated with increased numbers of senile and vascular plaques, as well as deficiencies in cholinergic function in the brains of patients with the disease (Malamud N., 1972).

Other risk factors for developing Alzheimer's disease include toxicity to infectious agents, aluminum, reactive oxygen substances (ROS), and neurotoxic amino acids. In addition, the presence of hypertension, diabetes, dyslipidemia, smoking, cardiovascular disease, obesity, sedentary lifestyle, inadequate eating habits and traumatic brain injuries also increase the risk of the disease (Alzheimer's Association., 2022). In conclusion, Alzheimer's disease is a complex condition that involves a number of changes in the brain, including amyloid plaques, neurofibrillary tangles, brain atrophy, and inflammatory responses. Genetic and environmental factors also play a significant role in the development of this neurodegenerative pathology. A deeper understanding of these mechanisms is essential for the development of effective therapeutic approaches for Alzheimer's disease.

4 DIAGNOSIS

The diagnosis of Alzheimer's disease (AD) resembles that of other dementias and is carried out through a comprehensive assessment that includes formal mental status examination, clinical history, physical examination, laboratory tests, and neuroimaging (Jack C.R. et al., 2011). However, there is no definitive laboratory test for the diagnosis of AD, and it is necessary to exclude other dementia conditions. The definitive diagnosis of AD can only be confirmed by histological evaluation of brain tissue, through necropsy or biopsy of brain tissue (Caramelli, P et al., 2002).

The initial evaluation begins with the complete anamnesis and the conventional neurological examination, in which the first signs of abnormalities and their evolution, history of previous diseases, medications and habits of the patient are observed. Cognitive, behavioral, and functional changes are also assessed in this context (Alzheimer's Association., 2022). The differential diagnosis of AD is complex, especially to distinguish it from other dementias. The modified Hachinski ischemic score can be used to help distinguish vascular dementia from AD when neuroimaging is not available, but its usefulness is limited (Hachinski VC et al., 1975).

Routine laboratory tests, such as complete blood count, erythrocyte sedimentation rate, glycemia, alkaline phosphatase, transaminases, urea, creatinine, electrolytes, among others, are recommended, as well as neuroimaging tests, such as magnetic resonance imaging and computed tomography, to check for other treatable causes of dementia that may aggravate symptoms (Sayeg, 2012). Biomarkers, such as beta-amyloid levels in cerebrospinal fluid and beta-amyloid deposits in the brain detected by positron emission tomography (PET), are being studied to aid in the accurate

diagnosis of AD, but are not yet widely used in clinical practice (Jack C.R. et al., 2011; McKhann GM et al., 2011).

AD is characterized by the abnormal accumulation of toxic beta-amyloid plaques in the brain, which can arise about 20 years before the onset of symptoms (STAHL, 2014; KUMAR et al., 2016; Panza F et al., 2019). The diagnosis of AD can be established based on the following criteria: onset after the age of 40, most often after the age of 65; presence of dementia confirmed by physical examination and examination of the patient's mental status; absence of systemic or brain disorders that may be responsible for progressive deficits in memory and cognition, although deviations from these criteria do not exclude the diagnosis of AD, as patients may present with mixed dementias; and deficits in more than two areas of cognition (Caramelli, P et al., 2002; Chételat G et al., 2020).

For cognitive assessment, the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale (ADAS) and the Clock Test can be used (Pinto TCC et al., 2019; Sunderland et al., 1989). The Clinical Dementia Rating (CDR) is an instrument used for disease staging and global assessment of dementias (Galvin JE et al., 2009). The Lawton Scale can be useful for assessing functionality in basic and instrumental activities of daily living (Koskas P et al., 2014). The paintings of Carolus Horn, a painter who developed AD, demonstrate changes in color patterns and figures throughout the progression of the disease, with a tendency toward simpler, more childlike depictions (Maurer K et al., 2004).

The prognosis for AD is usually marked by an inevitable cognitive decline, with an average survival of approximately 7 years from diagnosis. In advanced dementia, palliative measures may be more appropriate than aggressive interventions or hospitalizations (Alzheimer's Association., 2022).

5 TREATMENT (MEDICATIONS AND INTERACTIONS)

Alzheimer's disease is a condition still without known cure, requiring an often-multidisciplinary treatment that involves the collaboration of physiotherapists, speech therapists, occupational therapists and psychological support (CARVALHO et al., 2016). Research is ongoing to understand the mechanisms underlying the disease and the development of drugs for its treatment. The main goal is to relieve existing symptoms, slow the progression of the disease and preserve intellectual functions for as long as possible, allowing many patients to maintain their independence in daily activities for longer (STAHL, 2014).

The recommended treatments can be pharmacological or not, and the best results are obtained when treatment is started in the early stages of the disease (CARVALHO et al., 2016). Currently, two groups of drugs are used: cholinesterase inhibitors and glutamate receptor antagonists (STAHL, 2014; Stahl, 2018). Acetylcholine, an important neurotransmitter in memory and learning processes, undergoes reduced activity in Alzheimer's disease due to neuronal degeneration and the action of

enzymes that degrade it (Rees TM et al., 2003). Although several drugs are being tested, acetylcholinesterase inhibitors have been shown to be the most effective treatments, being indicated for mild or moderate forms of the disease (Lane RM et al., 2004). These medications have demonstrated documented efficacy, helping patients maintain their everyday skills and ability to socialize. Among cholinesterase inhibitors, the main ones are donepezil, rivastigmine, and galantamine, which have similar results (Alexander GC et al., 2021). Donepezil is considered first-line due to the single daily dosage and good tolerability. Rivastigmine, in addition to inhibiting acetylcholinesterase, also inhibits butyrylcholinesterase, but may cause adverse cholinergic effects at high doses (Grossberg GT, 2003; Sereniki et al., 2008). Galantamine, in addition to inhibiting acetylcholinesterase, modulates nicotinic receptors, but the clinical impacts of this modulation are not yet fully understood (Maelicke A et al., 2000).

Another class of drugs used are glutamate receptor antagonists, especially Memantine Hydrochloride, which improves the transmission of nerve signals and functional and cognitive capacity in cases of moderate to severe Alzheimer's (Alexander GC et al., 2021; Jarvis et al., 2003; ORESTES V, 2005). This drug can be used in conjunction with cholinesterase inhibitors, but requires special attention in patients with renal failure (Alexander GC et al., 2021).

In addition to the medication approach, non-pharmacological interventions, such as cognitive rehabilitation, occupational therapy, physiotherapy, psychotherapy and music therapy, have been shown to be effective in managing the behavioral and psychological symptoms of the disease (CARVALHO et al., 2016). It is recommended that family members follow the evolution of symptoms in a diary to evaluate the effectiveness of treatment. The continuity of treatment should be reassessed by the physician after one month of initiation, being mandatorily maintained for a minimum period of 3 to 6 months to observe the favorable results. Regular, as-prescribed administration is crucial to achieving the desired outcome (Alzheimer's Association., 2022).

6 IMPLICATIONS FOR ORAL HEALTH AND DENTAL CARE

Patients diagnosed with Alzheimer's disease (AD) often have deficits in oral health due to difficulty in performing basic self-care activities (BADL) (Rabelo, R. et al., 2020). These problems are usually associated with increased caries index, worsening of periodontal problems (such as gingivitis and periodontitis) due to deficiency in plaque control, accumulation of lingual saburra and hyposalivation caused by the medications administered (Boccia, A., 1992). In addition, it is common the occurrence of lesions in the mucosa due to the use of poorly adapted and worn prostheses, as well as the presence of fungal infections in the mucosa, which can lead the patient to face chewing difficulties and dysphagia. Note the lack of preventive actions aimed at health promotion and adequacy of the oral environment of these patients (Adam, H. et al., 2006).

Aiming at the well-being, quality of life and general health of these individuals, it is crucial that the patient is evaluated in a multidisciplinary approach, so that the dentist can plan and execute a personalized treatment with greater safety (Ettinger, R. L., 2000). As well as other areas of health involved in the care and treatment of people with AD, dentistry should act according to the particularities of each patient, considering the phase of the disease: initial, intermediate and final (Miranda, 2010).

In the initial phase of the disease, which can last on average 4 years, although the patient has recent memory loss, frequent forgetfulness and communication problems, it is still possible to perform the treatment in the office (Frenkel, H., 2004; Little, J. W., 2005). At this stage, it is crucial to carry out planning and preventive treatment, since with the progression of the disease, in-office treatment becomes more difficult (Varjão, F. M., 2006). During the initial phase, it is the ideal time to perform dental procedures, with attendances in the morning, with calm, punctuality and short duration, focusing on the adequacy of the oral environment and the instruction of the patient, family members and caregivers on the correct oral hygiene (Ghezzi, E. M. et al., 2000). During the service, it is important to keep the dental chair in a sitting or semi-inclined position for greater comfort of the patient, to be careful to avoid accidents with sharp instruments and always have the presence of a caregiver or family member during the care. When talking to the patient, one should lower the mask, show a smile and maintain direct and gentle eye contact, conveying tranquility and security. It is essential to provide guidance on oral hygiene, plaque control, periodontal treatment, occlusal adjustments and adequate adaptation of prostheses.

Treatment planning should aim to minimize future problems and anticipate oral health issues, treating as soon as possible and using restorative materials that contribute to the maintenance of oral health (Henry, R. G., 1999). It is also important to apply fluoride and instruct a less cariogenic diet. For patients with hyposalivation, the prescription of artificial saliva may be indicated for greater comfort (Turner, L. N. et al., 2008; Mancini, M. et al., 2010). At this stage, it is easier to train caregivers and family members, and maintenance and investment in dental treatment are extremely important. With the advancement of the disease, the difficulties of hygiene and acceptance of the patient to perform dental procedures increase (Gurgel, A. L. A. et al., 2012).

In the intermediate phase of the disease, which can last on average from 2 to 8 years, memory, language and cognitive loss disorders worsen, leading to a lack of understanding of the patient and more aggressive behaviors. In this phase, it is common the lack and difficulties of expressions and languages to report pain, making the attention of the dentist important (Souza, A. C. A. R. et al., 2006). In-office care becomes more difficult in the intermediate phase, and home care can be initiated for greater comfort of the patient and family. Dental planning and treatment should be directed to the most urgent needs, with the aim of eliminating possible foci of infections and acute inflammatory/infectious

processes, relieving and avoiding episodes of pain and stress of the patient (Henry, R. G., 1999; Fiske, J. et al., 2006). For more invasive procedures, sedation can be used for greater patient comfort, avoiding stress and discomfort. The use of benzodiazepines and anxiolytics should be considered carefully, together with the patient's physician (Friedlander, A. H. et al., 2006). In this phase, caregivers and family members should be trained and obtain the knowledge and skills to perform the correct hygiene of the patient's oral cavity. Special attention should be given to poorly adapted prostheses, the removal of which can provide comfort and a more favorable condition for the patient, avoiding ulcers and traumatic lesions on the mucosa, in addition to preventing possible accidents such as swallowing or aspiration of the prostheses (Turner, L. N., 2006; Chalmers, J. M. et al., 2003).

In the terminal or final phase of the disease, which can last up to 10 years, the patient presents total disorientation, accentuation of cognitive dysfunctions, fecal and urinary incontinence, and total dependence (Little, J. W., 2005; Friedlander, A. H. et al., 2006). In this phase, palliative care is paramount to provide better quality of life to the patient. Complex and invasive treatments should be avoided as much as possible, prioritizing minimum oral health conditions, in order to eliminate and prevent acute foci of infection that can cause aspiration pneumonia and affect the general health status of the patient (Frenkel, H., 2004; Mancini, M. et al., 2010).

The dentist must participate in the home treatment plan or in the intensive care unit (hospital bed care). It is noteworthy the difficulty of caregivers in promoting an adequate maintenance of oral health in this final phase of the disease, making it extremely important the periodic presence of a dentist to perform regular dental care, aiming at the prevention of possible diseases and infectious foci, contributing to improve the quality of life and well-being of the patient (Miranda, A. F. et al., 2010; Frenkel, H., 2004). Recently, studies have indicated that periodontal disease is a risk factor for the progression of Alzheimer's disease. The connection between periodontal disease and AD can be explained by the spread of infectious or inflammatory agents that migrate from the oral cavity to the brain (Ranjan, R. et al., 2018). Research has shown that there is a seven times higher density of oral cavity bacteria found in the brain tissue of patients who have died of AD compared to healthy individuals (Olsen, I. et al., 2015). The oral bacteria most often found in the brain are: Pg, Fn, Pi, H. pylori, B. burgdorferi and spirochetes (treponema). PG, the main pathogen of periodontal disease, is found significantly in the brain tissue of patients who have died of AD (Borsa, L. et al., 2021).

Thus, the presence of a dentist in the general and multidisciplinary treatment plan of the patient with AD becomes extremely important, aiming at the prevention, promotion and maintenance of oral health, avoiding the emergence of foci of infection that may aggravate the systemic condition of the patient (Mansur, F. V., 2006; Miranda, A. F. et al., 2010).

7 FINAL CONSIDERATIONS

Based on the above, it is evident that the progressive impairment of cognitive functions in patients diagnosed with Alzheimer's causes significant problems in the maintenance of oral health, resulting in severe complications in the oral cavity, with the manifestation of pain and stress for the affected individual. In this sense, it is extremely important that the dentist acquires in-depth knowledge about the disease and its different stages, as well as being able to deal with this public, thus ensuring due and adequate care. The improvement of the oral health conditions of this group of patients will enable an increase in their general well-being and quality of life.

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Radiographic examination and dental treatment of patients with florid cemento-bone dysplasia: Narrative review

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ABSTRACT
Flowering cemento-osseous dysplasia is a benign condition characterized by changes in the process of bone formation and the deposit of mineralized tissue in the soft tissues of the oral cavity. The diagnosis of flowering cemento-osseous dysplasia is accompanied by radiographic examinations, and treatment depends on the severity of the condition and the patient's symptoms. Thus, it is important for patients to undergo periodic dental examinations to monitor the progression of the condition. A literature review on the radiographic examination and dental treatment of patients with this condition was conducted with searches in February 2023, in the PubMed, Scielo, Lilacs and BBO databases, following certain criteria for selection. Seven articles were identified and in them, there is evidence that some patients may not have clinical symptoms, but it is possible that patients develop periodontal disease. Having, as a potential complication of the condition, the possibility of losing teeth due to the rapid progression of periodontal disease. In addition, in rare cases, flowering cemento-osseous dysplasia can progress to a more serious condition such as a cemento-ossifying fibro-osseous lesion or an adenomatous odontogenic tumor.

Keywords: Cementum bone dysplasia, radiology, dentistry.

1 INTRODUCTION

Flowering cemento-osseous dysplasia is a benign condition and, in most cases, causes no symptoms. However, in some rare cases, there may be complications associated with the condition,

especially if it is not diagnosed early and treated appropriately (NAM et al 2022; BASTOS et al., 2022).

Dental treatment for flowering cemento-osseous dysplasia depends on the severity of the condition and the symptoms presented by the patient. In most cases, treatment is conservative and involves only regular monitoring of the condition. However, in more severe cases, more aggressive treatment may be needed. In more severe cases, treatment may include surgery to remove abnormal bone tissue, periodontal therapy to prevent gum inflammation, and even extraction of affected teeth (NAM et al. 2022).

Tooth loss due to periodontal disease progression is one of the potential complications of flowery cemento-osseous dysplasia. Gingival inflammation can develop around the affected teeth, which can lead to loss of bone tissue and loss of teeth (NAM et al 2022; KATO et al. (2020).

In addition, in rare cases, flowering cemento-osseous dysplasia can turn into a more serious condition, such as a cemento-ossifying fibro-osseous lesion or an adenomatous odontogenic tumor. These conditions may require more aggressive treatment, such as surgical removal of the affected tissue (BASTOS et al. 2022).

Thus, it is essential that patients undergo regular dental checkups to detect the condition early and monitor the progression of the disease. Early treatment can help prevent complications and preserve the patient's oral health (SOLUK-TEKKESIN et al 2022). Given this, it is possible to note the relevance of conducting a study that seeks to analyze the influence of radiographic examination and dental treatment of this condition.

Thus, this study aims to make a literature review on radiographic examination and dental treatments of patients with flowery cemento-osseous dysplasia.

2 METHODOLOGY

A systematic narrative review on flowering cemento-osseous dysplasia was performed. The searches were made in February 2023, in the database PubMed, Scielo, Lilacs and BBO and with the terms "*cemento-osseous", "dysplasia"* combined with the Boolean operator AND.

The inclusion criteria were: free complete studies, published from 2012 to 2022, in English and whose main focus was to analyze the importance of the radiographic diagnosis of flowery cemento-osseous dysplasia for dental treatments, preferably case series studies, cohort studies, retrospective and comparative. The exclusion criteria were: incomplete articles, duplicates, literature reviews, case reports (only one case), articles outside the chosen time range and studies that were not relevant to the theme.

The search strategy used "*cemento-osseous AND dysplasia"* found 147 articles in total. By filtering the free full texts 77. In the screening stage, after reading the titles, 37 remained and 14 of the

abstracts. Then, the complete reading of the works was made, and seven articles were selected at the end to compose the sample of this study.

3 RESULTS AND DISCUSSION

Seven articles were identified that address the radiographic examination and/or dental treatment of flowery cemento-osseous dysplasia. It was noted that the highest prevalence of this condition is in women, black women and over 30 years of age (chart 1).

Table 1. Articles that address the radiographic examination and/or dental treatment of flowery cemento-osseous dysplasia. 2023

Author(s)/year	Type of study	Goal	Findings	Conclusion
ARSAN (2022)	Comparative study	To compare mandibular cortical thickness (CTh) and fractal dimension (FD) in patients with cemento-osseous dysplasia (COD) and controls, measured with cone-beam computed tomography	The lower TC values were lower overall in COD patients than in controls (P = 0.01), specifically in sCTh, mCTh, and pCTh (P ≤ 0.042). Alternate CTh was also significantly lower in the COD group (P = 0.005). There was a significant correlation between lower and alternating CTh measurements (r = 0.636, P < 0.001). No significant differences were observed in cortical or trabecular FD between the groups (P ≥ 0.072)	Female patients with COD had significantly lower and alternate hCT than healthy controls. Both groups had similar cortical and trabecular bone textures
BASTOS et al. (2022)	Case series	To evaluate the clinical-pathological characteristics of osteonecrosis related to flowery cemento-bone dysplasia (FCOD), highlighting its histopathological aspects and bone structure	The mandible was most affected by osteonecrosis related to FCOD. There was a predominance of black Brazilian women in the fifth and seventh decades of life. Osteomyelitis was present in 82% of the cases, while bone resorption and bacterial colonization were present in 100% of the cases of osteonecrosis related to FCOD. Thick basophilic lines were observed in all cases (100%). Actinomycosis and osteoclasts were not frequent	This study showed that the preference for female adults, mandibular location and some findings such as osteomyelitis, bone resorption and bacterial colonization were the most frequent histopathological features in FCOD-related osteonecrosis. In the absence of a close clinical and radiographic correlation, the morphology of the necrotized bone similar to cementum could help to recognize FCOD
SOLUK-TEKKESIN et al (2022)	Case series	To highlight the importance of clinical and radiological findings for the definitive histopathological	A total of 276 cases of BFOL were identified and reassessed for the study. The most common type of BFOL was cemento-osseous dysplasia (n =	Our results document several clinical, radiological and histopathological findings of BFOLs. Even if some

		diagnosis of benign fibro-osseous lesions of the jaws	135), followed by cemento-ossifying fibroma (n = 77), fibrous dysplasia (n = 53) and juvenile ossifying fibroma (n = 11). The female/male ratio was 3.4:1 with a strong predilection for the 4th decade (n = 102). The mandible (n = 209) was the predominantly affected mandible. Prominent osteoblastic border around the bone lesion was commonly observed for cemento-ossifying fibroma (n = 60/77), followed by cemento-osseous dysplasia (n = 23/135). The predominant ossification patterns showed some differences between the groups. The most common radiological feature was the mixed radiolucent/radiopaque internal structure	histopathological differences are observed, clinical and radiographic correlation is mandatory before definitive histopathological diagnosis of BFOLs for the prevention of possible diagnostic errors or inadequate treatments
KATO et al. (2020)	Retrospective cross-sectional paired study	To compare the radiomorphometric parameters of the trabecular and cortical bone mandibular of women with and without cemento-osseous dysplasia (OCD)	The mean age of both groups was 46.84 ± 11.38 years. The average index of MCW was 3.12 mm (2.15–4.55) for the COD group and 3.52 mm (1.90–4.70) for the without COD (p = 0.034). The mean FD value of the COD group (1.2039 ± 0.0926) was lower than the of the non-COD group (1.2472 ± 0.0894) in the anatomical region of interest of the mandibular cortical (p=0.031), while no difference was detected in the alveolar trabecular bone. Grade C3 of MCI was more frequent in the COD group (p=0.009)	Women with COD had lower values of radiomorphometric parameters in the mandibular cortical bone than women of the same age without COD. These results suggest that, In addition to the dental care recommended in the literature, women with OCD also require more attention and screening for low bone mineral density
KATO et al. (2020)	Retrospective case series study	To describe a series of 66 cases of infected cemento-osseous dysplasia (OCD) and to discuss the demographic distribution, the clinical-radiographic characteristics and the	The case series study showed a female/male ratio of 21:1. The mean age of those affected was 57.4 years. The mandible was the most affected site (95.5%) and the flowering subtype was the most infected OCD	Clinicians, maxillofacial surgeons, and oral rehabilitation professionals should be attentive to the diagnosis of COD, since infection is a frequent complication,

		Treatment of this condition	frequent (62.1%). Tooth extraction was the main factor associated with the development of infection associated with a COD lesion. The literature review recovered 30 studies reporting 46 cases of this condition. Asian women in their 40s and 50s were more affected. Surgery for removal/curettage of necrotic bone has been recognized as an approach suitable for the treatment of this infection. The clinical-demographic data of the study were similar to the data collected in the literature	whose management is challenging
NAM et al. (2022)	Retrospective study	To evaluate risk factors and symptoms in patients with cemento-osseous dysplasia (OCD)	OCD was more prevalent in female patients. All but three cases were focal COD. Most patients presented symptoms when the lesion was smaller than 1.5 cm. Symptoms were observed when the apex of the tooth was included in the lesion or there was a local infection around the lesion. History of tooth extraction and previous endodontic treatment was assessed, and history was not a significant predictor for the onset of symptoms	OCD is a benign fibrous bone lesion and most cases are asymptomatic. However, if symptoms occur, surgical treatment is necessary. In this study, the risk factors associated with symptomatic patients were lesion size, apical involvement and local infection
PICK et al (2022)	Retrospective study	To evaluate the incidence of fibroosseous lesions and to reassess the efficacy of case-specific treatment management from a clinical, radiological and histopathological perspective based on 14 years of data	Forty-four patients with radiological and/or histopathological diagnosis of benign FOLs were identified and reassessed. Cemento-osseous dysplasia was the most common group of FOLs present in our cohort of patients (45%), followed by ossifying fibroma (39%) and fibrous dysplasia (16%). The diagnostic imaging technique of choice was CBCT (68%), followed by PAN (18%), with most patients (95%) being submitted in addition to biopsy. The mean age of the patients at the time of diagnosis was 40.54 ± 13.7 years, and most of the lesions were located in	An interdisciplinary approach that analyzes all case-specific factors, including demographics, medical history, intraoperative findings, and, most importantly, histopathological and radiological features, is essential for an accurate and key diagnosis to avoid inadequate treatment

			the mandible (86%), and the female sex was predominantly affected (73%)	

Source: The Authors, 2023

Cemento-osseous dysplasia is a benign condition that affects bone tissue and the tissue that lines the roots of teeth (cementum). In cemento-osseous dysplasia, bone and/or cementum tissue is replaced with new abnormal bone and/or cementum tissue, resulting in dense, sclerotic areas in the bones of the jaw or maxilla. (BASTOS et al. 2022; SOLUK-TEKKESIN et al 2022)

The condition can be classified into three different types: periapical cemento-osseous dysplasia (PFCD), focal cemento-osseous dysplasia (DCOF), and flowery cemento-osseous dysplasia (DCOF). Flowering cemento-bone dysplasia is the most common form and can affect multiple areas of the jaw and maxilla. (BASTOS et al. 2022)

Cemento-osseous dysplasia can affect the planning and execution of orthodontic treatments and dental implants. In the case of orthodontic treatments, the presence of dense, sclerotic areas on the bones can make it more difficult to move the teeth and adjust the braces. The orthodontist should carefully evaluate the condition before starting any treatment and consider adjusting the treatment plan according to the location and severity of the cemento-osseous dysplasia. (PICK et al 2022; KATO et al. 2020; CONSOLARO et al., 2018)

In the case of dental implants, the presence of dense and sclerotic areas can hinder the placement of the implant and proper bone integration. The dentist should carefully evaluate the condition before starting the procedure and consider modifying the surgical technique to accommodate the affected area. (KATO et al. 2020; CONSOLARO et al., 2018)

In both cases, it is important to perform additional radiographic examinations to assess the extent and location of cemento-osseous dysplasia before initiating any treatment. Regular monitoring is also important to detect and treat any complications that may occur during or after treatment. (PICK et al 2022)

This pathology can affect the planning and execution of surgical dental treatments, especially in cases of more extensive injuries.

According to the study by Chrcanovic et al. (2015) cemento-osseous dysplasia can interfere with the planning and execution of bone grafts for the placement of dental implants. The authors reported a case in which the presence of cemento-osseous dysplasia in the maxillary region affected the local bone density and made it difficult to perform a bone graft for the placement of an implant. The surgical planning had to be modified to accommodate the condition and ensure a satisfactory result.

Another study, published by Liu et al. (2017), addressed the relationship between cemento-osseous dysplasia and mandibular fractures. The authors reported a case of a patient with cemento-osseous dysplasia who presented with a mandibular fracture after a mild trauma. The condition affected the bone density of the jaw and made the fracture more difficult to treat. The authors highlighted the importance of careful evaluation of cemento-osseous dysplasia before any surgical procedure on the jaw.

In addition, a study published by Hodzovic et al. (2019), discussed the surgical treatment of cemento-osseous dysplasia in patients with severe symptoms. The authors reported that cemento-osseous dysplasia may present symptoms such as pain, swelling and loss of sensation, and that in severe cases, it may be necessary to perform surgical removal of the affected area. The study highlighted the importance of careful assessment of the condition to determine the best course of surgical treatment.

4 FINAL CONSIDERATIONS

Dental treatment for flowering cemento-osseous dysplasia depends on the severity of the condition and the symptoms presented by the patient. One of the potential complications of flowering cemento-osseous dysplasia is tooth loss due to periodontal disease progression.

The dentist should carefully evaluate the initial examinations of each patient before starting any treatment and consider the possibility of adjusting the treatment plan according to the diagnosis, location and severity of cemento-osseous dysplasia. In cases of dental implants, the presence of dense, sclerotic areas can hinder implant placement and proper bone integration.

It is recommended to perform periodic radiographic examinations to evaluate the extent and location of cemento-osseous dysplasia in the course of dental treatments.

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Metallic species in yerba-mate and their infusions: Interrelationship of its distribution with phenolic compounds and melanoidins

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ABSTRACT

Yerba mate (Ilex paraguariensisis), also known as mate, is a plant traditionally cultivated and consumed in different South America countries, where its green or roasted, dry leaves are usually employed to prepare chimarrão or mate tea, respectively. Mate presents a very complex chemical composition, rich in bioactive compounds, including polyphenols and melanoidins, wich in turn can have several several health effects, mainly due to their antioxidant capacity and their role in the prevention of multiple diseases, such as cancer, diabetes, and cardiovascular diseases. In addition, mate also tends to accumulate essential and potentially toxic trace metals, and their presence in beverages prepared as infusion from the dried leaves of the plant may be influenced by factors associated with the preparation of those infusions. The extraction of metallic ionic species to the infusions it dependent of the nature of phenolic compounds and melanoidins present in mate, since this group of bioactive compounds are capable of associate with metal ions through complexation. This type of association can lead to the formation of compounds with different solubilities in aqueous media, consequently impacting the solubility of metal ions in the infusions. Moreover, the presence of different chemical forms of metal ions in infusions may influence their absorption by the human body. Thus, it is essential to carry out studies to evaluate and understand how the essential and potentially toxic trace elements present in yerba mate may be related to potential impacts caused by these minerals on the general health of consumers of its hot infusions. The present review aims to establish a connection between the chemical composition of yerba mate and the presence of metallic species in its infusions.

Keywords: *Ilex paraguariensis*, infusions, trace metals, bioactive compounds.

1 INTRODUCTION

The yerba mate *(Ilex paraguariensis*) is a plant native to subtropical regions, produced mainly in southern Brazil, northern Argentina, Paraguay and Uruguay (BASTOS et al., 2007). Traditionally, the green or toasted yerba mate is used as an input for the preparation of tonic and stimulant drinks, such as tereré, mate and mate tea (DANIEL, 2009).

The yerba mate has several biological activities beneficial to health, resulting from the action of bioactive compounds, such as polyphenols, xanthines, caffeine derivatives, saponins and minerals (BASTOS et al., 2007; HECK and MEJIA, 2007; JUNIOR and MORAND, 2016; CAHUÊ et al., 2019).

Polyphenols – including chlorogenic acids, flavonoids, stilbenes and lignins – are responsible for part of the bioactive properties of yerba mate, which have relatively strong antioxidant activity and even act in the prevention of cancer, diabetes and cardiovascular diseases (ROBBINS, 2003; SOTO et al., 2011; ZHANG et al., 2019). Another pertinent characteristic of this class of compounds is the ability to complexe to ionic metallic species and change their chemical form and, consequently, their availability or distribution, in the leaves of mate and its infusions (STELMACH et al., 2013; MUSCCHINO and MUSCI, 2014).

In addition, it becomes increasingly important to conduct studies with yerba mate in order to better understand its therapeutic benefits and possible side effects associated with its content of metal ions, since this plant is a very rich source of minerals considered essential to the body. Such metallic species are naturally absorbed and accumulated in the leaves of mate, but can also be a result of soil and water contamination due to anthropogenic activities (SAIDELLES et al., 2010).

Currently, studies involving the determination of metal ions in mate and its infusions essentially address the determination of the total concentrations of elements considered essential or potentially toxic, such as Al, As, Ba, Ca, Cd, Cr, Cu, Fe, K, Mg Mn, Ni, Pb and Zn (ALBERTI et al., 2005; BRAGANÇA, MELNIKOV and ZANONI, 2011; Giulian et al., 2009; MARCELO et al, 2014; Pozebon et al, 2015; SAIDELLES et al., 2010).

In infusions of mate or mate tea, the metallic species present in yerba mate may be distributed in the form of free ions or complexed to bioligands, such as polyphenols, melanoids, among others (MUCCHINO and MUSCI, 2014). It is important to emphasize that there are several factors that influence the distribution of these elements both in the dried leaves of green or toasted yerba mate, as well as in their infusions. Thus, the present work seeks to review how the chemical composition of mate can be affected by conditions dependent on agronomic variables associated with its cultivation, as well as dependent on the storage process and its industrial processing. In addition, we also review

how the availability of essential and potentially toxic trace metals present in the dried green and toasted leaves of mate, and in their respective infusions, may be affected by such conditions.

1.1 LITERATURE REVIEW

1.1.1 Yerba Mate (Ilex paraguariensis)

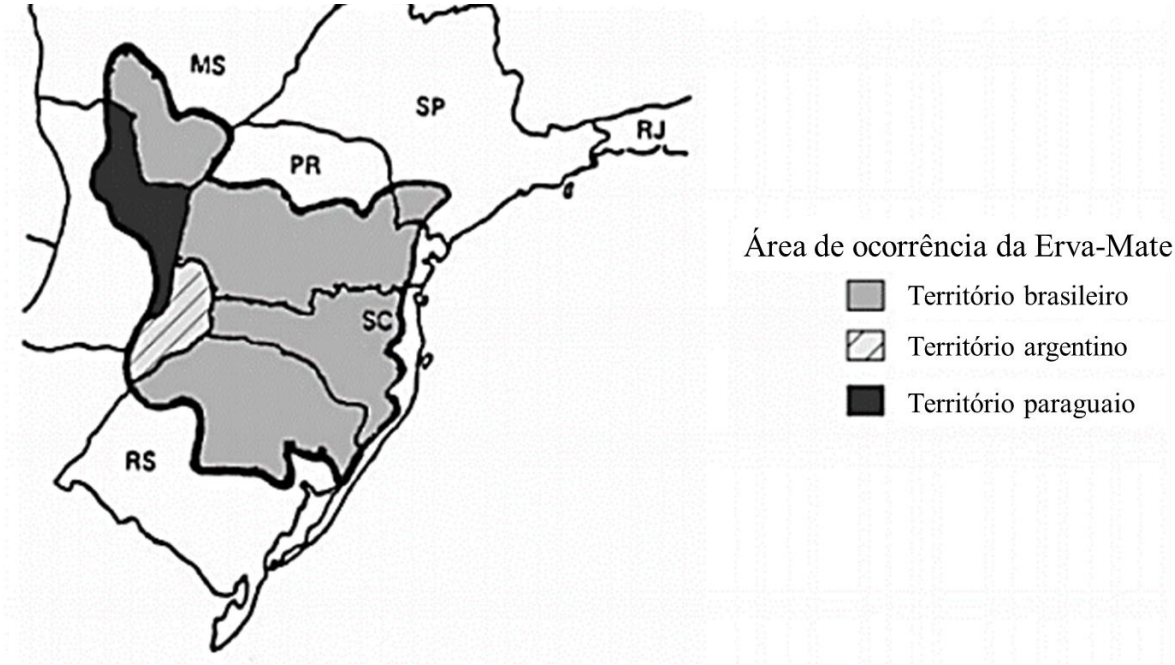
Mate tea, mate and tereré are stimulant drinks derived from yerba mate and are very popular in South American countries such as Brazil, Argentina, Paraguay and Uruguay. These drinks are usually prepared from the infusions (hot or cold) of the dried leaves of *Ilex paraguariensis* (Figure 1**), a plant native to South America** (**Figure 2**) and belonging to the Aquifoliaceae family (GAWRON-GZELLA, CHANAJ-KACZMAREK and CIELECKA-PIONTEK, 2021; HECK and DE MEJIA, 2007).

According to data provided by Embrapa (Brazilian Agricultural Research Corporation), the area of natural occurrence of yerba mate in Brazil corresponds to approximately 540,000 km2 (EMBRAPA, 2022). Historically, mate has been of great importance for the economy of several municipalities in southern Brazil, figuring as the main non-timber product of the region. The largest producers in the country are the states of Rio Grande do Sul, Santa Catarina, Paraná and Mato Grosso do Sul, the latter representing less than 1% of national production (IBGE, 2019).

Figure 1: Leaves of yerba mate (*Ilex paraguariensis*) (HECK and MEJIA, 2007).



Figure 2: Map of the area of natural occurrence of *Ilex paraguariensis* in some South American countries (adapted from OLIVEIRA and ROTTA, 1993).



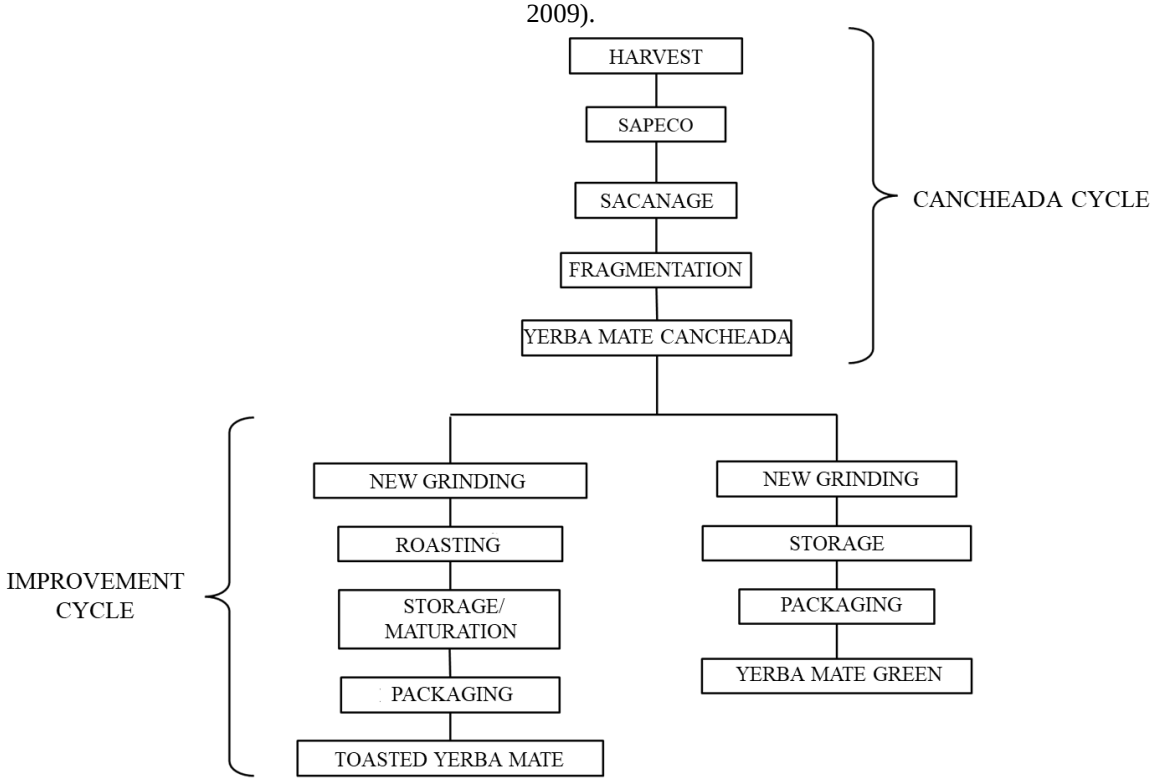
Between 2010 and 2017, there was a growing export of mate to the USA and African, Asian and European countries, signaling the expansion in the yerba mate market beyond the MERCOSUR countries (FAO, 2020). The commercial interest in yerba mate and its derivatives is mainly due to its numerous health benefits, which are linked to the presence of about 200 compounds with bioactive properties, such as saponins, alkaloids, polyphenols, essential oils, vitamins and minerals, among others (HECK and DE MEJIA, 2007).

There are several studies that attest to the positive effects that the regular consumption of mate has on the body (BASTOS et al., 2007; MIRANDA et al., 2008; Boaventura et al, 2012; KIM et al., 2015; JUNIOR and MORAND, 2016; RIACHI and DE MARIA, 2018; CAHUÊ et al., 2019), such as antioxidant activity, anti-inflammatory, stimulant to the central nervous system, diuretic action, hypocholesterolemic and hepatoprotective effects, in addition to providing good digestion, reducing the risk of cardiovascular diseases and acting in the control of diabetes and obesity (BASTOS et al., 2007; BRACESCO et al., 2011; RIACHI et al., 2017; GAWRON-GZELLA, CHANAJ-KACZMAREK and CIELECKA-PIONTEK, 2021).

Thus, in addition to the typical drinks prepared from yerba mate, its concentrated extracts can be used in the formulation of creams and face masks, which help in the reduction of free radicals of the skin, in the composition of anti-obesity drugs or thermogenic supplements. In the food industry, this herb is used for the preparation of functional foods, non-alcoholic energizing drinks, and its essential oil and chlorophyll can become an input in the composition of candies and gums or even as natural dyes and preservatives (MAZUCHOWSKI and RUCKER, 1997;

GAWRON-GZELLA, CHANAJ-KACZMAREK and CIELECKA-PIONTEK, 2021; Villanova, 2021). It is important to note that, despite the increasingly expressive export rates of yerba mate, the vast majority of this national product is still destined for domestic consumption, mainly in the forms of tereré, mate tea and mate (JUNIOR and MORAND, 2016).

Figure 3: Stages of the industrial processing of yerba mate (adapted from HECK and MEJIA, 2007; DANIEL, 2009).



As for the production of green and toasted yerba mate **(Figure 3)**, the processing of the leaves and branches of the plant can be divided between the cycles of cancheamento (or primary transformation) and processing.

In this way, the canching process includes the following steps:

a) Harvesting: the leaves and branches are harvested by pruning leafy branches for the preparation of the cancheada or fragmented grass;

b) Sapeco: consists of the rapid heating (10 s to 3 min) of the leaves at high temperatures (± 500 °C) to deactivate enzymes that promote oxidation (peroxidase and polyphenoloxidase), thus avoiding the blackening of the leaves of the herb after drying. In this process, the leaves lose approximately 20% of their moisture, acquiring the golden-green color, characteristic of a product with good quality;

c) Drying: the sapecadas leaves are introduced into heating chambers (±100 °C) for a period of 8 to 24 h. At this stage the process of dehydration of yerba mate is completed (the

remaining moisture is of the order of 3 to 6 %), which is fundamental for the quality of the final product;

d) Fragmentation: the dried product passes through mechanical chippers and then is subjected to sieving to obtain the yerba mate cancheada.

As for the processing cycle, the industrial processing of mate can be carried out for the production of two different products: green yerba mate and toast:

a) green yerba mate: the grinding of yerba mate for the preparation of mate is carried out by a set of pestles until obtaining a very fine product, unlike the herb for the production of tereré, which is marketed in a fragmented form, but not ground. As for the storage time, the green yerba mate should be kept in stock for the shortest possible time, to ensure the maintenance of its green color;

b) Toasted yerba mate: used for the preparation of mate tea, the roasting of the product is carried out at relatively high temperatures (180 to 215 °C) for a period between 15 and 17 min. The maturation (aging) of mate, on the other hand, consists of increasing the concentration of compounds such as methylxanthines and polyphenols, and aims to develop and assign specific flavors to the drink, being preserved for up to 12 months.

The cultivation and harvesting of yerba mate can be conducted in different ways, depending on the producer and the region where they are carried out, as well as its industrial processing that may differ depending on the desired flavor for the mate, through the use of different times and temperatures in its different stages and also depending on the type of wood used for toasting and drying the product. It is worth mentioning that the way industrial processing is conducted can affect not only the quality of the product, but also the organoleptic characteristics and chemical composition of mate (ESMELINDRO et al., 2002; BASTOS et al., 2007; DANIEL, 2009; GAWRON-GZELLA, CHANAJ-KACZMAREK and CIELECKA-PIONTEK, 2021).

1.1.2 Chemical composition of yerba mate

The chemical composition of mate is quite complex and its varied amount of numerous organic compounds is directly associated with the bioactive properties that the regular consumption of yerba mate has on the human body. Are part of the composition of mate: essential oils, nutrients (carbohydrates, proteins and lipids), phenolic compounds, saponins, methylxanthines (caffeine, theophylline and theobromine), minerals and vitamins – mainly water-soluble, such as vitamins A, B1, B2, C and E (ESMELINDRO et al., 2002; HECK and DE MEJIA, 2007; BERTÉ et al., 2011).

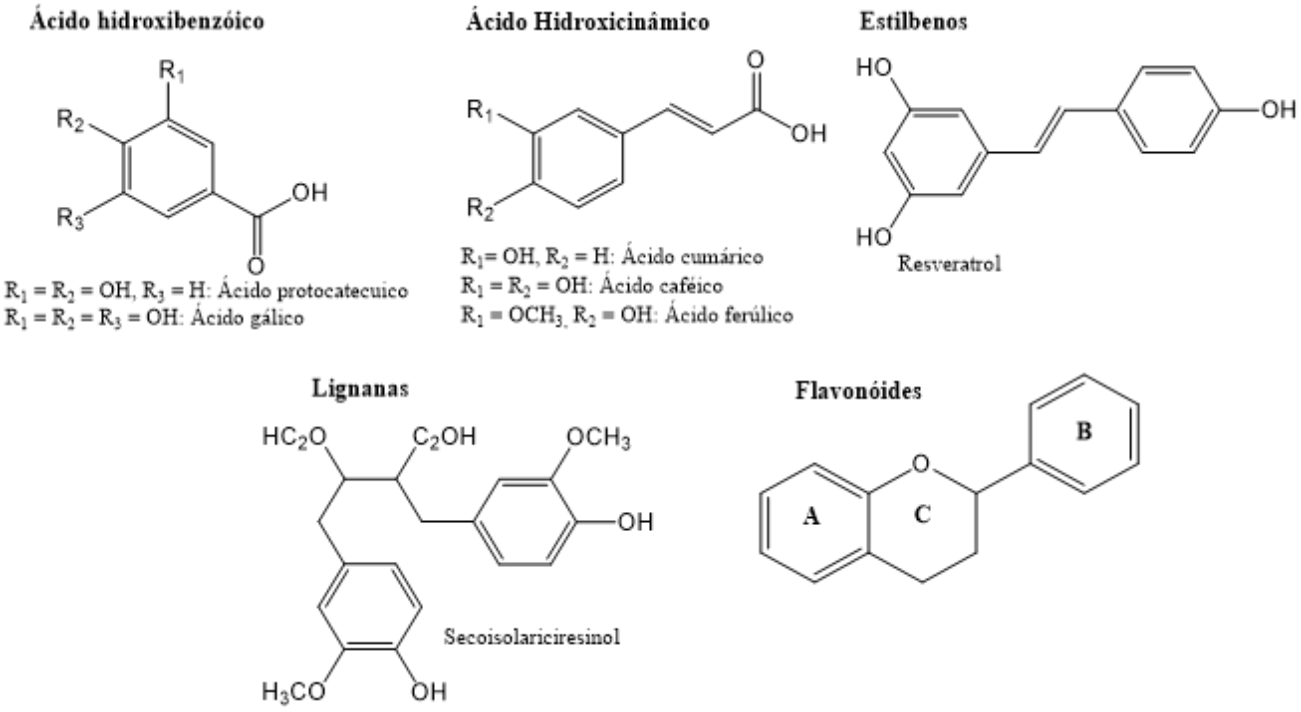
1.1.3 Phenolic compounds

During the development of a plant, its secondary metabolism produces compounds that aid in protecting against environmental stressors such as pests, solar radiation, and extreme temperatures. Among the secondary metabolites of yerba mate are phenolic compounds (or polyphenols), responsible for several bioactive properties, which also confer flavor, astringency and bitterness to fruits, vegetables, coffees, wines and teas (MANCH et al., 2004; VAUZOUR et al., 2010; ARCHELA and DALL'ANTONIA, 2013; ABBAS et al., 2017; RIACHI and DE MARIA, 2017).

Other external factors that accompany the development of yerba mate should impact on the presence of phenolics, such as conedaphoclimatic ditions (climate, air humidity, soil type, atmospheric composition, wind and river precipitation), fertilizer use, genetic variability and different culture media (MANACH et al., 2004; HECK, SCHMALKO and DE MEJIA, 2008; RIACHI and DE MARIA, 2017; RIACHI et al., 2018). Industrial processing, storage or maturation must also change the chemical composition of mate, since these compounds are easily oxidized (ESMELINDRO et al., 2002; ISOLABELLA et al., 2010; RIACHI et al., 2018).

Yerba mate is an important natural source of phenolic compounds (**Figure 4**), mainly chlorogenic acids (GCA) (caffeolquinic, dicaffeolquinic and ferulic acids), which are powerful antioxidants capable of chelating to metallic ionic species (BASTOS et al., 2007). In smaller quantities, flavonoids, stilbenes and lignans are also present, which should contribute to the bioactive properties of the plant (BASTOS et al., 2007; ARCHELA and DALL'ANTONIA, 2013; ABBAS et al., 2017; RIACHI and DE MARIA, 2017).

Figure 4: Chemical structure of phenolic compounds present in yerba mate.



Among the benefits to human health that a diet rich in polyphenols can provide, are listed the ability to combat reactive species involved in aging and / or chronic, autoimmune, inflammatory, osteoporosis, diabetes mellitus and the prevention of diseases associated with oxidative stress, such as cancer, neurodegenerative and cardiovascular diseases (MANACH et al., 2004; SOTO et al., 2011; Hardman, 2014; ABBAS et l., 2017).

As mentioned earlier, an important property of polyphenols is their ability to form complexes with metallic species. By acting as ligands of metal cations, polyphenols interfere directly in the chemical form with which these elements are distributed in yerba mate, and influence their absorption by the human body and establish, consequently, their degree of toxicity or essentiality (POHL, STELMACH and SZYMCZYCHA-MEDEJA, 2014; MUCCHINO and MUSCI, 2014).

1.1.4 Melanoidins

Melanoidins are nitrogenous polymeric compounds (macromolecules) of brown color, formed in the final stages of the Maillard reaction (RM), and consisting of reducing sugars and proteins (or amino acids) (BEKDAM, 2008), are associated with color, flavor and aroma of foods that undergo any type of heat treatment, such as baked goods, teas, coffees, wines or beers. In addition, they also have bioactivity, acting as antioxidants and antimicrobial, antihypertensive and anti-inflammatory agents (BEKEDAM, 2008; SHAHEEN et al., 2021; SINGH, TRIPATHI, CHANDRA, 2021; FENG et al., 2022).

Although their structures are not completely elucidated, it is well established that melanoidins are compounds of relatively high molar mass, with hydrophilic and anionic properties, capable of forming stable complexes with positive species and relatively low molar mass, such as metal cations (MORALES, FERNÁNDEZ-FRAGUAS, JIMÉNEZ-PÉREZ, 2005; COELHO et al., 2014; FENG et al., 2022).

1.1.5 Trace metals in yerba mate

Elements considered essential are essential to maintain the regular functioning of the human body, and are divided between micronutrients and macronutrients. In plants such as yerba mate, macronutrients are typically found in concentrations greater than 1000 mg kg^{-1} and these include Ca, K, Mg and Na; the micronutrients (or trace elements), such as Cu, Ni, Fe, V, Zn and Mn, represent a concentration lower than 100 mg kg^{-1} (GOLDHABER, 2003).

In contrast, potentially toxic metals such as inorganic As, Cd, Hg and Pb are of great concern from a toxicological point of view, since the chronic exposure of the body to these elements must cause serious damage to health, including cancer, damage to the neurological and cardiovascular systems, memory loss, damage to the kidney, among others. It is important to consider that even the elements considered as essential are likely to cause toxic effects to the body, when ingested in excess or when present in relatively high concentrations in food and beverage samples (CAO, et al., 2010; Saidelles, 2010; WHO, 1996).

The U.S. Food and Nutrition Board of the Institute of Medicine establishes Reference Daily Intake (DRI) levels for trace and potentially toxic metals, providing useful parameters to prevent nutritional deficiency or poisoning caused by some metal species. The DRIs (**Table 1**) include Allowable Daily Recommendation (RDA), Adequate Intake (AI) and Maximum Tolerable Intake Level (UL) and each of these values correspond to the average daily intake of a nutrient, and that may vary according to the age group of an individual (GOLDHABER, 2003).

Table 1: Recommended values of daily intake for essential and potentially toxic elements (GOLDHABER, 2003; NIH, 2022).

Element	RDA (mg/day)	AI (mg/day)	UL (mg/day)
Zn	11 (men) 8 (women)	ND	40
Cr	9	0.035 (men) 0.025 (women)	ND
Mn	ND	2.3 (men) 1.8 (women)	11
Fe	8 (men and women > age 51); 18 (women aged 19−50 years)	ND	45
Se	0,055	ND	0,4
Ca	1000 (men 19 – 70 years old and women 19 – 50 years old) 1200 (men aged > 70 years and women aged > 51 years)	ND	2500
Mg	400 (men aged 19 – 30 years) and 420 (men aged > 31 years) 310 (women aged 19 – 30 years) and 320 (women aged > 31 years)	ND	350
Mo	0,045	ND	2

ND: not available; the values presented are established by the U.S. Food and Nutrition Board of the Institute of Medicine and are representative for men and women between 19−70 years and > 70 years, unless otherwise indicated; RDA (allowable daily recommendation): average daily intake sufficient to meet the daily nutritional needs of almost all (97-98%) healthy individuals; AI (adequate intake): concentration of adequate daily intake, is used when scientific results are not sufficient to establish the RDA; UL: Maximum tolerable level of intake that would likely not expose an individual to side effects.

Yerba mate has a huge tendency to accumulate metals in its tissues, such as Al, As, Cd, Co, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, Pb, V and Zn (HECK and MEJIA, 2007; KARAK and BHAGAT, 2010; SAIDELLES et al., 2010). The absorption of these elements by the human organism depends not only on their concentrations, but also on the physico-chemical forms with which they are found in the plant. Thus, it is of paramount importance to seek a more in-depth knowledge about the distribution and behavior of such elements in mate, aiming to establish the real therapeutic or toxicological effects that a regular consumption promotes.

It is important to emphasize that the concentration of trace and potentially toxic metals in yerba mate can vary due to external or internal factors, such as age of the leaves, presence of natural or synthetic fertilizers, soil type and pH, air pollution, and above all, as to the ways of processing and storage of mate (GIULIAN et al., 2009; KARAK and BHAGAT, 2010; SAIDELLES, 2010).

Jacques et al. (2007) studied how agronomic variables influence the concentration of metals in yerba mate leaves. In general, the mineral content was higher in plants grown in shaded areas, as well as in young leaves, where the concentration of some nutrients (K, Ca and Mn) progressively decreased with the age of the leaves. The use of nitrogen fertilizers increased the content of Ca and Mg, while fertilizers based on K and N, or only based on K, increased the levels of Mn and K, respectively. Thus, the study concluded that the metabolism of yerba mate and the absorption of certain metallic species are strongly influenced by their growing conditions, as well as the absorption of certain metallic species.

Another factor that should change the mineral content of the leaves of yerba mate are the different regions where the plant is grown. Marcelo et al. (2014) classified yerba mate samples according to their countries of origin, based on the determination of the total concentration of some metals in samples produced in Argentina, Brazil, Paraguay and Uruguay. From the data obtained, they concluded that the Brazilian samples were characterized by low concentrations of Ba, Ca, Mg and Al, while the Argentine samples had high levels of these same metals. In addition, Argentinean, Paraguayan and Uruguayan samples showed similar concentrations of Cu and P. Thus, the researchers were able to develop a new way to classify and characterize yerba mate according to the presence and content of metallic species.

However, the mineral content present in the leaves of yerba mate differs as to the mineral content of its infusions. Pozebon et al. (2015) studied this relationship and found that for most of the elements analyzed, the extraction rate for hot infusions ranged from 20 to 60%, for which Al, Ba, Ca and Sr were less leached when compared to Li, Rb and Pb, suggesting that some elements are more extracted than others. In addition, the authors emphasize that the extraction efficiencies are directly associated with the conditions used in the preparation of the infusions and should vary

according to the water temperature, the extraction time, the degree of grinding of yerba mate (particle size), among other factors.

2 CONCLUSION

In the present review, we address how the influence of industrial processing, cultivation conditions of yerba mate, its genetic variability and the way its infusions are prepared can influence the chemical composition of its beverages and, in turn, also impact on its bioactive properties. It is important to emphasize the relationship between the presence of polyphenols and melanoidins and the distribution of metallic species, especially in infusions derived from green and toasted yerba mate, but also in their dry masses. Nevertheless, to better observe this relationship, it is extremely important to carry out more in-depth studies, which are also concerned with the bioavailability or bioaccessibility of these species in the infusions mentioned here, in order to deepen the knowledge about the true nutritional value of yerba mate in the different forms of consumption.

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Experience report of a speech-language pathology and audiology student in the extension project "Sapeca: Mental health and technology"

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ABSTRACT
Mental health is determined by multiple factors and directly interferes with quality of life. Adolescence is a period marked by several transformations and discoveries, among which the new capacities to feel, think and act stand out. In addition, this phase brings the need to redefine the being about its identity and its environment.

Keywords: Mental Health, Adolescent, Education, Technology.

1 INTRODUCTION

Mental health is determined by multiple factors and directly interferes with quality of life. Adolescence is a period marked by several transformations and discoveries, among which the new capacities to feel, think and act stand out. In addition, this phase brings the need to redefine the being about its identity and its environment. This is a critical moment in the prevention of mental disorders since changes that appear at this age can lead to difficulties in adult life. Much of the adolescent's day happens at school, and it is in this environment that social-emotional skills are developed and, simultaneously, learning occurs.

2 OBJECTIVE

To report the experience of a speech therapy undergraduate student in the project "Sapeca: Mental Health and Technology."

3 METHODOLOGY

This is a descriptive, qualitative, experience report study about the first two meetings held in an extension project. Activities at the school took place monthly, on Saturdays. There was the participation of 7 adolescents in the first meeting and 10 in the second, both sexes, aged between 13 and 14 years. The strategy used by the project to establish a dialogue capable of sensitizing them about mental health was the learning of basic computer notions.

4 EXPERIENCE REPORT

In the first meeting, it was noticed the lack of knowledge of most adolescents concerning the notebook and, consequently, its functions and possibilities. Thus, the first step was to present some features and programs present in the device. The second was to address the theme, "Who am I?" through questions that provoked the observation of singularities. Participants used the Writer® text editor software to scan their answers. For the second meeting, the theme addressed was "What is happiness for you?" and for this activity, the proposal was to elaborate a "mural of happiness" containing images. The participants used Google® to search for images and later developed the wall in the text editor. At the end of each meeting, a conversation circle was formed to sensitize adolescents about mental health, starting from the key issues they presented about the theme addressed.

5 CONCLUSION

From the careful observation of the evolution of the participatory posture of the adolescents during the meetings and the feedback offered by the school coordination, it is concluded that the objective of the meetings was achieved because there was the adherence of the students to the project and aroused of reflection about mental health.

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Incident with multiple victims: Report of realistic simulation in a public university

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ABSTRACT
Teaching through simulation allows training in real conditions, with actors and partners, in an interactive way in a controlled environment. The realistic simulation provides the student with contact with the practice for the development of capacities and skills, bringing him closer to reality.

Keywords: Simulation Exercise, Interdisciplinary Health Team, Active Learning, Accident with Multiple Victims.

1 INTRODUCTION

Teaching through simulation allows training in real conditions, with actors and partners, in an interactive way in a controlled environment. The realistic simulation provides the student with contact with the practice for the development of capacities and skills, bringing him closer to reality. Training was conducted during an incident involving multiple victims in a university environment, without compromising the safety of those involved.

2 OBJECTIVE

To report the experience of professors and students of speech therapy, nursing, medicine and dentistry courses during the organization of realistic simulation of VMI in a public university in the state of Sergipe.

3 METHODOLOGY

Descriptive study type experience report on the organization of realistic simulation involving incidents with multiple victims, during a head-on collision between a passenger car and a bus, on the lawn of a public university in the state of Sergipe.

4 EXPERIENCE REPORT

Academics from health courses simulated victims, first responders, curious people and family members at the scene. The simulation had partnerships such as fire department, federal highway police (PRF) and military (PM), SAMU, University Hospital of Lagarto and Air Tactical Group, which dynamically demonstrated the interdisciplinary action to ensure the safety of the scene, remove the victims from the wreckage and enable the action of rescuers. In addition to the student-actors, ambulances, motorcycles, PM/PRF vehicles, fire department vehicles and a rescue helicopter were present. The preparation of the scene, makeup of the victims and the performance of the student-actors highlighted the desperation of the "relatives" and victims during the incident. This activity provided the participants with maturity in how to behave and part of the psychological pressure involved in this type of situation. In addition, having the presence of public security professionals at the event reinforced the importance of interdisciplinarity. This activity has a high impact on the education of health professionals.

5 CONCLUSION

The organization of the event allowed to expand the knowledge about the performance of health professionals in VMI. The visualization, in practice, under realistic conditions, of the performance of professionals and academics allowed us to reach a new perspective beyond that which the theoretical approach would be able to provide us. The engagement of those involved, the resources employed and the desperation of the "family members" made it possible to understand the skills required to manage such a complex scene.

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SEVEN publicações acadêmicas

Hypertension in the elderly: Determining factors for non-adherence to drug therapy, potentiated by the Covid-19 pandemic

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ABSTRACT
Objective: To discuss and highlight in the literature the determining factors of non-adherence of elderly patients with RAS to drug therapy, potentiated by the COVID pandemic 19. Material and method: This is a literature review that aims at the analysis and synthesis of the determining factors for the non-adhering of the elderly with hypertension to drug treatment. We analyzed the publications produced between 2017 and 2022, with full texts and available in the Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS) and Google Scholar, in addition to the manual of the 7th Brazilian Guidelines on Arterial Hypertension and the World Health Organization (WHO). Results: The search in the databases resulted in the identification of 1,203 articles. After the final reading, 32 articles were selected that contemplated the objectives discussed in the development of this work. Final considerations: It was found that many factors interfere with the non-adherence of the elderly to drug therapy, factors that are linked to the elderly and the health system, as the patient presents difficulties in following the proposed therapeutic scheme, either due to its complexity, forgetfulness, adverse effect of the drug and its belief in alternative empirical drugs.

Keywords: Hypertension, Pharmacological treatment, Elderly, Therapeutic adherence.

1 INTRODUCTION

Systemic arterial hypertension (SAH) can be defined as a chronic multifactorial disease, evidenced by the increase in diastolic and\or systolic pressure ≥ 140 mmHg and/or ≥ 90 mmHg Queiroz et al. (2020). Despite its easy diagnosis and effectiveness of treatment using a diversified therapeutic arsenal, quite efficient and with few adverse effects, its control worldwide is difficult because it is often

an asymptomatic disease, which hinders adherence to care Jardim et al. (2019).

This comorbidity has a frightening prevalence globally, especially in the elderly population. The involvement in this population can be explained by physiological mechanisms inherent to the aging process itself, considering that with advancing age the stiffening of the arteries is part of the senescence process. According to Barroso et al. (2020), "with aging, Systolic Blood Pressure (SBP) becomes a more significant problem, resulting from progressive stiffening and loss of compliance of the great arteries" (p. 72). This makes age one of the main risk factors for SAH.

The factors that determine the non-adherence of the elderly with arterial hypertension to the medication treatment of SAH are not easy to understand, but scientific evidence shows that many factors can contribute to non-adherence to drug treatment, among them the difficulty of access to health services and medications; sociodemographic factors; problems in following complex therapeutic regimens; adverse effects; insufficient guidelines to understand and follow the prescriptions; ineffective relationship between patient and professional; among others. The same evidences also point out that cognitive deficit, low education and degree of dependence are relevant risk factors and that are strongly associated with non-adherence to antihypertensive treatment, especially medication in the elderly Luz et al. (2021).

It is also important to emphasize that for Vasconcelo et al. (2017), although the drugs for the control of arterial hypertension are freely available in the SUS, the frequent lack of these, results in the discontinuity of treatment and in the difficult control of blood pressure of the lower extracts, which favors abandonment and non-adherence to therapy.

The importance of the Unified Health System in the control of arterial hypertension and other health problems is unquestionable, however the difficulties presented by it, contribute significantly to the non-adherence to drug therapy, among many difficulties stand out the lack of knowledge and training of health professionals with regard to NCDs, the short time spent in the consultations and unavailability for follow-up, the lack of incentives and the inability to assess the degree of adherence. Especially the failure in surveillance, which is mainly configured in not emphasizing that the clientele that do not have regular consultations and that do not make regular surveillance of arterial hypertension are the least adherent to the therapy (Pinto et al., 2021).

One should also take into account the pandemic period that had its fuse in Brazil at the beginning of 2020 and intensified throughout the year, leaving many elderly unassisted, given that the population in question in addition to being the main risk group of contamination by the pathogen, social isolation and distancing policies, measures adopted to control the disease have made access to the BHU increasingly difficult (Cesário et al., 2021).

The follow-up of hypertensive elderly in Brazil takes place mainly at the level of primary health care, whose main care models are the Basic Health Unit (UBS) and the Family Health Strategy (FHS).

Although both strategies provide a significant contribution not only to the control of hypertension but also to other comorbidities, a study conducted in a large city in São Paulo aimed to verify adherence to the treatment of hypertension and other Chronic Non-Communicable Diseases (NCDs) in both models of care. It showed that in both models of care, adherence, especially adherence to drug therapy, was of concern (Almeida et al., 2019).

Nursing as a professional category plays a crucial role in the control and follow-up of patients with arterial hypertension. Since the professional nurse is the main actor in health education strategies and is closer to the community and patients, he is an important member of the multidisciplinary team in terms of raising the awareness of hypertensive elderly people about the severity of their disease and the importance of following drug treatment. Considering that the lack of awareness on the part of the elderly of the importance of following the therapy may reflect worsening of their chronic condition (Ramos et al., 2021).

Given the above, it is evident that adherence to drug treatment of hypertension is a common problem especially in the age group of the elderly and is the greatest challenge faced by health professionals in the adequate control of hypertension (Costa, 2020). Based on this assumption, this study aims mainly to discuss and evidence in the literature the determining factors of the non-adherence of elderly patients with SAH to drug therapy, in order to create scientific theoretical support that help health professionals to deal with the problem in question, acting on specific points in order to improve the quality of life of the elderly population with hypertension.

2 MATERIALS AND METHODS

This is a literature review that aims to analyze and synthesize the determining factors for the non-adherence of elderly patients with hypertension to drug treatment. The integrative review aims mainly to integrate findings of empirical and theoretical works, allowing the synthesis of results and the deepening of the understanding of a specific phenomenon. This facilitates the understanding of the theme in a broad, objective way and with vast information, allowing the scientific and theoretical knowledge of the reader (Casarin et al., 2020).

This study is based on the observation and inquiry that many social, demographic, and cultural factors, among others, compromise the follow-up of drug therapy among elderly patients with systemic arterial hypertension (SAH). And that have a negative impact on the control of the disease and on the quality of life of this population. Based on this assumption, the contents of articles published in full were analyzed, following the methodological rigor explained by authors with knowledge about the research in question (Mendes, Silveira & Galvão).

In the first stage, the theme or questioning of the integrative review was identified, consisting in the elaboration of the research question and the theme to be delimited for its construction. As well

as for the definition of the keywords to be used in the search strategy of the studies. As explained, the following question arose: What factors contribute to the non-adherence of the elderly with Systemic Arterial Hypertension (SAH) to drug therapy?

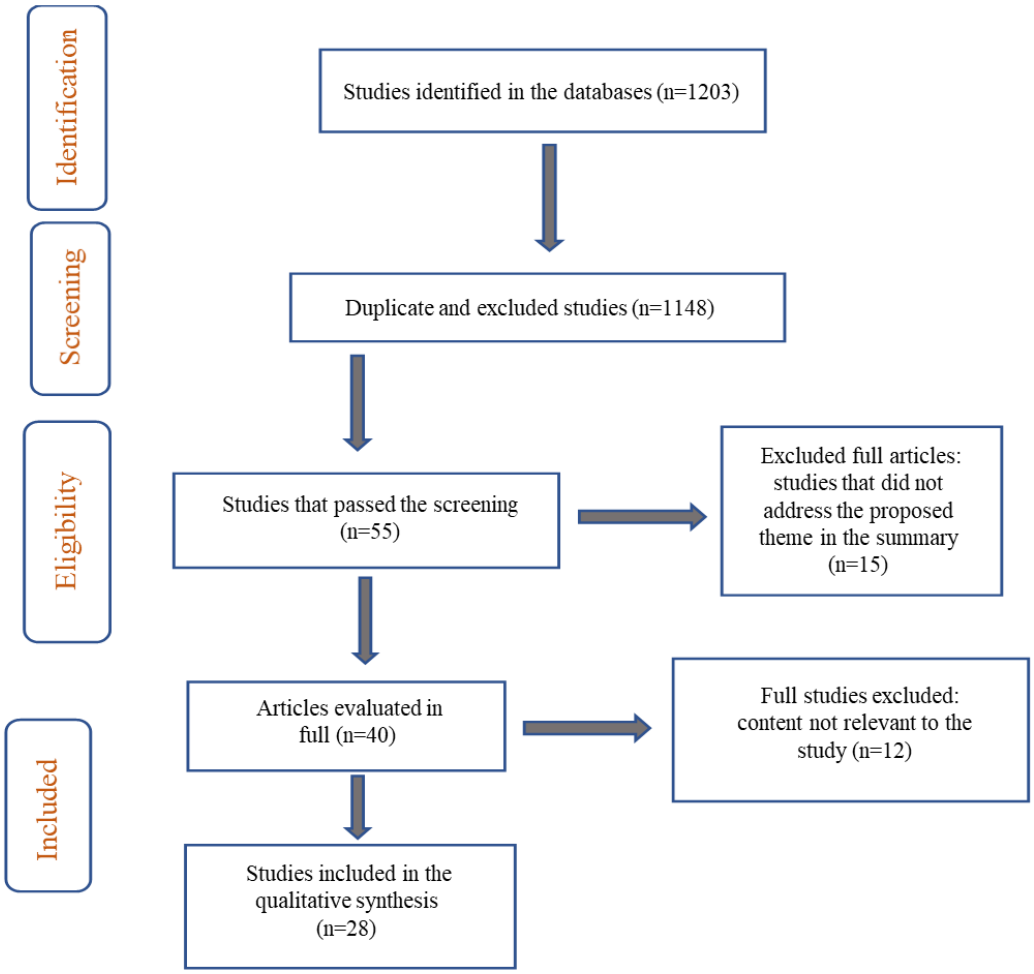
In the second stage, inclusion and exclusion criteria for studies were established from the literature search. For this purpose, studies were collected in databases to identify the studies to be excluded or included in the research. The following inclusion criteria were adopted: to be an eligible article published in full, to be available online, to be written in Portuguese, English or Spanish and to contemplate the achievement of the objectives of the proposal. Manuscripts that did not meet these criteria, or that were not related to the proposed theme, were discarded after careful and thorough reading of the title, abstract and introduction.

Subsequently, study descriptors were defined according to the Health Sciences Descriptors (DeCS). The descriptors were searched in combination using the Boolean operator "AND" in order to facilitate the search in the databases, namely: "arterial hypertension", "pharmacological treatment", "elderly" and "therapeutic adherence".

The stage corresponding to data collection was carried out from March to April 2022 and the publications produced between 2018 and 2022, with full texts and available in the databases Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS) and Google Scholar, as well as the manual of the 7th Brazilian Guidelines on Arterial Hypertension and the World Health Organization (WHO) in Portuguese or English, were analyzed.

The search in the databases resulted in the identification of 1,203 articles. Articles were excluded because they did not contemplate the proposed objective, for repetition or for not obeying the inclusion criteria, for duplicity and for not answering the guiding question. After the final reading, 32 articles were selected to be discussed in the development of this work. The methodological steps of selection of articles for the construction of this work are presented in the flowchart of Figure 1, as follows:

Figure 1. Prism flowchart: characterization of the number of articles searched in the databases: LILACS, SCIELO, GOOGLE SCHOLAR. Pinheiro-MA, November, 2022.



Source: Authors

3 RESULTS AND DISCUSSION

The table below presents the description of the bibliometric profiles of the selected articles. Included are: title of publication, author, type of study, objective, journal, year of publication and database in which the article was published.

Table 1. Description of the bibliometric profile of the selected articles

Title	Author(s)	Type of study	Goal	Magazine	Year of publication	Database
Adherence to therapy in people with hypertension	Pinto; Saraiva; Marques	Integrative review study	To know the facilitating and hindering factors of adherence to therapy in people with HTN	Egitania science	2021	Google Scholar

Adherence to antihypertensive treatment in the elderly with cognitive impairment	Luz; Griep; landim; Alencar; Macedo; Leal	Systematic review study	To analyze the influence of cognitive impairment on adherence to antihypertensive treatment in the elderly	Cogitare Nursing	2021	Scielo
Adherence to treatment and lifestyle habits of hypertensive patients	Dallacosta; Restellato; Turra	Cross-sectional study	To analyze adherence to antihypertensive treatment and lifestyle habits of hypertensive patients	Care is key	2019	Lilacs
Adherence to pharmacological treatment of hypertension in primary health care	Gewehr; Bandeira; Gellati; Colet; Oliveira	Cross-sectional study	To verify adherence to the pharmacological treatment of arterial hypertension and factors associated with low adherence in hypertensive patients enrolled in primary health care	Health debate	2018	Scielo
Adherence of the elderly to drug treatment at different levels of health care in the city of São Paulo, Brazil	Manso; Prado; Andrade; Mascarenhas	Experimental, cross-sectional study	To present how two groups of elderly people attended in two different public health services, in the city of São Paulo, the capital, experience their drug treatment	Magazine Kairos-gerontology	2018	Google Scholar
Therapeutic adherence in hypertensive elderly: an integrative review	Pinheiro; Santo; Sousa; Silva; Santana	Integrative review study	To identify evidence on therapeutic adherence in hypertensive elderly	Revista de enfermagem do Centro-Oeste mineiro (RECOM)	2018	Google Scholar
Functional illiteracy in health in hypertensive elderly people in primary care	Costa; Coata; Nakano; Apolinário; Santana	Cross-sectional study	To investigate whether inadequate functional illiteracy in health would be independently associated with inadequate blood pressure control in hypertensive elderly people	Brazilian Journal of Nursing (REBEn)	2019	Google Scholar

			treated in PHC			
Analysis of the prevalence of cardiovascular diseases and associated factors in the elderly, 2000-2010	Massa; Duarte; Filho	Serial longitudinal study	To analyze the change in the prevalence of cardiovascular disease (CVD) between 2000 and 2010 and its association with socioeconomic factors and risk factors in the elderly	Revista Ciência e saúde coletiva	2017	Scielo
Nurses' role in the identification of factors associated with non-adherence of the elderly to the treatment of systemic arterial hypertension	Ramos; Adeodato; costa; Lima; Pereira; Silva	Integrative review study	To describe the nurse's role in identifying the factors for non-adherence to the elderly in the treatment of systemic arterial hypertension	Research, Socyety And Developmen t	2021	Google Scholar
Knowing and combating poor adherence to therapy in hypertensive elderly patients	Costa	Field study	To know the profile of the public that is most affected by the disease, and to know the reasons that lead them to adhere to the therapy proposed by the multidisciplinary team	UNIFESP Electronic magazine	2020	Google Scholar
Blood pressure control and associated factors in a multidisciplinar y hypertension treatment service	Jardim; Souza; Barroso; Jardim	Descriptive study with a quantitative approach	To present the results of a long-term team-based therapeutic strategy of hypertensive patients in a health service	SBC	2019	Lilacs
Lifestyle and adherence to therapy in a group of people with hypertension	Pinto; Gonçalves; Marquês	Quantitative, descriptive and cross-sectional	To evaluate life and adherence to therapy in a group of people with HTN, in a personalized care unit	Global Academic Nursing Journal	2021	Google Scholar

Lifestyle and adherence to treatment of systemic arterial hypertension in elderly men	Falcão, Silva; Junior; Moura; Silva; *et al.*	Cross-sectional study with a quantitative approach	To evaluate the lifestyle and adherence to treatment of systemic arterial hypertension in elderly men	Brazilian journal on health promotion	2018	Lilacs
Qualitative study of the perception of hypertensive and diabetic users about health in primary care	Camargo; Tenani; Bulgareli; Guerra, *et al.*.	Qualitative study	To describe the perception of hypertensive and diabetic users about health care provided in Basic Health Units	Journal of Medical Science	2021	Lilacs
Failure in the diagnosis and drug treatment of hypertension in Brazilian elderly - FIBRA Study	Santamaria; Borin; Leme; Neri; fattori	Descriptive, cross-sectional	To investigate the prevalence of diagnostic failure in the use of antihypertensive drugs and in the efficacy of drug treatment of hypertension, and the association of these parameters with sociodemographic and health variables and access to health services in non-institutionalized elderly	Journal of science and health	2018	Scielo
Factors associated with adherence to pharmacological treatment in the elderly using antihypertensive medication	Aquino; Cruz; Silvério; Vieira; Bastos; Leite	Cross-sectional population-based study	To analyze adherence to pharmacological treatment and associated factors in the elderly who use at least one antihypertensive medication	Brazilian Journal of Geriatrics and Gerontology	2017	Lilacs
Factors associated with the adherence of adults/elderly to the treatment of arterial hypertension in primary care	Barbosa; Bertelli; aggio; Scolari; Marcon; Carreira	Quantitative, cross-sectional study	To evaluate the factors that influence the adherence of adults/elderly to the treatment of arterial hypertension	Journal of Nursing UERJ	2019	Scielo

Behavioral factors associated with medication adherence in the elderly and outpatient care	Abreu; Santos; Ilha; Silva; Martins; Varela	Cross-sectional study	To evaluate the relationship between behavioral factors and adherence to drug therapy in the elderly in outpatient care	Revista de enfermagem do Centro-Oeste mineiro (RECOM)	2019	Lilacs
Factors associated with non-adherence to treatment of patients with systemic arterial hypertension	Vascocelos; Silva; Miranda	Integrative review study	To analyze in the scientific production what are the associated factors, the non-adherence to the treatment of arterial hypertension	Unit Graduation Notebooks	2017	Google Scholar
Arterial hypertension in the elderly - a prevalent disease in this population	Queiroz; Aquino; Brito; Medeiros; Simões; Teixeira	Integrative review study	To analyze and synthesize the scientific facts about arterial hypertension in the elderly population	Brazilian journal of developmen t	2020	Google Scholar
Hypertensive patients assisted in a secondary care service: cardiovascular risk and social determinants of health	Nobre; Lima; Oliveira; Vieira; Júnior; Costa	Analytical Sectional Study	To investigate the relationship between social determinants of health and global cardiovascular risk in hypertensive patients assisted in secondary care services of the Unified Health System	Collective health notebooks	2020	Scielo
Interaction between drug treatment, meta pressure and depression in hypertensive patients assisted by the family health strategy	Soares; Guedes; Rodrigues; Dias	Cross-sectional study	To analyze how the interaction between adherence to drug treatment, meta pressure and depression occurs in a probabilistic sample of hypertensive patients assisted by the Family Health Strategy, from Governador Valadares, Minas Gerais, Brazil	Public health notebooks	2021	Lilacs

Functional health literacy of hypertensive and diabetic elderly patients assisted in the family health strategy	Scortegagna ; Santos; Santos; Portela	Cross-sectional study	To evaluate the functional health literacy of hypertensive and diabetic elderly enrolled in the Family Health Strategy	EAN Magazine	2021	Scielo
The nurse and the issue of patient adherence to the treatment of systemic arterial hypertension	Salles; Sampaio; Pereira; Malheiros; Gonçalves	Qualitative study	To identify the resources used by the family health strategy (FHS) nurse to stimulate patient adherence to the treatment of systemic arterial hypertension	Journal of Nursing UERJ	2019	Lilacs
Blood pressure among hypertensive elderly people assisted by the family health strategy	Luz; Costa; Griep	Cross-sectional study	To investigate the prevalence of uncontrolled blood pressure (BP) and associated factors in hypertensive elderly people assisted by the Family Health Strategy in a municipality of Piauí, Brazil	Brazilian Journal of Geriatrics and Gerontology	2020	Scielo
Hypertensive crisis: clinical characteristics of patients with hypertensive urgency, emergency and pseudocrisis in a public emergency service	Pierin; Flórido; Santos	Cross-sectional study	To evaluate patients with hypertensive crisis, classified as urgency, emergency or hypertensive pseudocrisis; and identify the associated variables.	Eistein Magazine	2019	Scielo
Trends in access to and use of health services in PHC among the elderly in Brazil in the years 2008, 2013 and 2019	Cesário; Santos; Mendes; Júnior; Lima	Transverse; descriptive	Contribute to the identification of the conditions and trends of access to and use of primary health care (PHC) services by the Brazilian elderly in the years 2008, 2013 and 2019	Science and Health Journal	2021	Lilacs

Use of health services and adherence to social distancing by adults with chronic diseases in the COVID-19 pandemic, Brazil, 2020	Malta; Gomes; Silva; Cardoso; Ramos; *et al*	Cross-sectional study	To investigate the association between self-reported diagnosis of Chronic Noncommunicable Disease (NCD) and adherence to social distancing and use of health services during the COVID-19 pandemic	Free Theme Magazine	2021	Scielo

Source: Prepared by the authors with research data (2022).

3.1 ADHERENCE TO THERAPY

The concept of adherence to drug therapy is addressed by the World Health Organization (WHO) and can be understood as the extent to which the individual's behavior - use of medications, following a diet, and/or making changes in lifestyle do not coincide with the recommendations of health professionals.

The process of adherence to drug therapy can be influenced by a variety of variables ranging from individual to sociodemographic. Such as gender, age, marital status, years of schooling, among others. Based on this assumption, it is understood that the degree of adherence to medications is related to diversified factors, with emphasis on the satisfactory level of information and interest of the patient in committing to a therapeutic plan that requires behavioral changes and effort, considering that it involves the rupture with unhealthy habits acquired in the course of life (Almeida et al., 2019).

In contrast to what has already been exposed, non-adherence to the treatment of a certain pathology basically consists of not following the therapeutic regimen proposed by a health professional. With regard to pharmacological treatment, non-adherence means abandonment of the use of prescribed medications, without adequate guidance, or their inadequate execution. Either in not taking at the recommended time or in the realization of small interruptions of the prescribed therapy. Such practices configure low adherence to treatment, which has repercussions mainly on the persistence of high BP values (Gewehr et al., 2018).

3.2 DETERMINING FACTORS FOR NON-ADHERENCE TO THERAPY

A study conducted by Pinto et al. (2021), identified strong evidence that the existing difficulties in the health system contribute to the decrease in adherence to therapy. Among these factors, one of the most significant is the difficulty in following the treatment in the health centers, the main contributor in the adequate control of arterial hypertension. Either by the lack of free medication in the popular pharmacies that make up the unit, or even by the insufficiency of professionals to conduct the treatment efficiently.

As expounded by Camargo:

> Among the principles that stand out in guiding the reorganization of the work process in Primary Health Care, we can mention the expansion of the population's access to the resources and services of the Basic Health Units. In this context, access is directly related to the availability of continuous care consultations and spontaneous demand, nursing procedures, tests, medications, collective activities, group care, among others (CAMARGO, 2021, p. 5).

Even with the remarkable advances of the Brazilian unified health system, it is observed that access to health services still presents deficiencies, being considered selective and exclusionary in most cases, presenting socioeconomic and geographical barriers in relation to the guarantee of universality (Santamaria et al., 2019). This situation worsens to disproportionate levels when evaluated from the regional point of view, considering that poorer regions of the country, such as the north and northeast, present marked discrepancies in terms of access to health in general.

According to Pinheiro et al. (2018), institutional factors may be related to adherence, as these are not limited only to the attendance of consultations or the appropriate use of the prescribed medication. It complements by affirming that the institutional bond should be understood more than the adstriction to a health service or enrollment to a program, since it means the establishment of a continuous, personal and non-transferable temporal relationship. demonstrating that failures in this process can lead the elderly with arterial hypertension not to adhere to drug treatment.

According to Jardim et al. (2019) the bond established between patient and health professionals is of fundamental importance for the patient to follow up the drug treatment of SAH, which makes it a relevant factor for adherence, because it is during routine consultations that the information about the treatment, as well as the doubts raised about the effects of these evenings remedied. In his study, carried out in a multidisciplinary treatment center focused exclusively on the treatment of SAH, he found that, of the 1548 patients included in the study, 68% had BP control.

Corroborating with Jardim, for Costa (2020) "it becomes essential that the health team be able to detect problems in the care axis that justify the failure in the therapeutic adherence of these patients and propose intervention measures" (p. 7). Corroborating with these findings are also the surveys made by Santamaria et al (2019) which "it is estimated that one third of the hypertensive population is unaware of the clinical diagnosis of the disease and among those diagnosed, only thirty percent have controlled pressure" (p. 8).

According to Aquino et al (2017) "access to medicines may represent the first barrier to adherence" (p. 9). Regarding the availability of medication in Basic Health Units, they are not always available. This makes it difficult to follow the drug treatment of arterial hypertension, especially in the elderly population of the lower strata of society. For the author, the amount of medications and the consequent number of medications taken throughout the day can also negatively influence adherence to drug therapy in hypertensive elderly.

A study showed that low follow-up to drug therapy is interconnected with the complexity of the drug regimen (Barbosa et al., 2018). This constitutes polypharmacy as a significant factor for the non-adherence of hypertensive elderly to the prescribed drug treatment. The use of multiple medications can compromise adherence to drug treatment, making follow-up more difficult especially for elderly people (Abreu et al., 2019).

Also according to Abreu et al. (2019) "the progressive use of many medications (five or more) which configures polypharmacy, may represent complications to the elderly, as it exposes them to a greater risk of drug interactions, adverse drug reactions and non-adherence to medication" (p.5). Another preponderant factor among hypertensive elderly and that is also addressed by the author is the fact that they take the medication only when they present symptoms of the chronic condition.

Another significant factor that interferes with the proper use of medications are the comorbidities associated with hypertension. According to the World Health Organization (2003) the existence of comorbidities contributes significantly to non-adherence to drug therapy. It can be understood that the number of morbidities that manifest themselves in the elderly population leads to the exacerbated consumption of drugs, contributing to the patient's non-adherence to treatment as it becomes more difficult to remember all the medications that should be used.

The time of study is also presented as an important factor for the follow-up of drug therapy. A study by Scortegagna et al. (2021) showed a strong association between functional health literacy and schooling.

The World Health Organization, in addition to what has already been explained, also points out that the belief is an important factor in non-adherence to drug therapy by hypertensive elderly. This may be associated with the perception of the elderly about the risks and benefits inherent to this pathology. It is noteworthy that in the elderly population the use of medicines based on herbs, roots, among other substances of natural origin is frequent and in part is related to cultural ties transmitted from generation to generation.

3.3 REPERCUSSIONS OF NON-ADHERENCE OF HYPERTENSIVE ELDERLY TO DRUG THERAPY

Aging and hypertension have a direct association as has already been perceived, usually acting as a predictor of other diseases. Most of the diseases prevalent in the elderly population are associated or originate with arterial hypertension and represent a considerable risk factor, which has repercussions on even more serious problems. When the control of high blood pressure is not achieved, the quality of life of this elderly person is directly affected, affecting the cognition, behavior and social of this individual (Queiros et al., 2020).

Hypertensive crises represent the first symptomatic manifestations resulting from the elevation

of blood pressure. They are also one of the main complications that lead to the search for emergency services. These are characterized by severe and gross elevation of blood pressure and are classified into three distinct categories: hypertensive urgency, hypertensive emergency and hypertensive pseudocrisis. Such events are strictly related to non-adherence to medications, taking into account that for the adequate control of BP, especially in the elderly, it is necessary to use hypotensive agents, these constitute the first approach. Because its administration aims to reduce blood pressure levels as an initial treatment (Pierin et al., 2019).

Elevated BP values are routinely associated with risk for ischemic heart disease, stroke, chronic kidney disease, and early mortality. Advanced age is considered an immutable risk factor for the development of hypertension in the elderly, and associated with ineffective follow-up of drug treatment can lead to complications such as Cardiovascular Diseases (CVD) (Barroso et al., 2020). This statement was consistent in a study conducted by Massa et al. (2019) that analyzed the change in the prevalence of cardiovascular diseases among the elderly in the period from 200 to 2010, and found that the association between increasing age and progressive increase in cardiovascular diseases was prevalent in all analyses.

In a study conducted with patients with cardiovascular disease treated at a referral hospital for the disease in question, it was found that 60% of the sample had already undergone previous hospitalization due to arterial disease, evidencing the lack of adherence to treatment, especially medication, and even in the use of instituted medication, patients had severe complications that culminated in hospitalization in a coronary center (Abreu et al., 2018)

An analysis provided in the 7th Brazilian Guidelines on Arterial Hypertension showed that in addition to the risks for coronary artery disease (CAD) and stroke, hypertension represents a similar risk for other outcomes, such as: Heart Failure (HF), atrial fibrillation, valvular heart diseases, peripheral arterial disease and Chronic Kidney Disease (CKD).

According to the Ministry of Health, hypertension is responsible for 40% less deaths from stroke, 25% of deaths from coronary artery disease and, in association with diabetes mellitus, 50% of cases of end-stage renal failure. Such complications still often lead the elderly to seek health services, which has repercussions in an increase in the number of hospitalizations and in additional costs to the health system (Pinheiro et al., 2018).

3.4 FACTORS RELATED TO THE ELDERLY WITH HYPERTENSION

According to data from the 2013 national health survey, the prevalence of self-reported hypertension in people aged between 60 and 64 years was 44.4%. And in the more advanced age groups, between 65 and 74 and 75 years or more, the hypertensive rate was even higher, corresponding to 52.7% and 55.0%, respectively. This demonstrates a predominance of the pathology in the elderly

population. It should be noted here that the RAS besides being frequent in this population, is an important risk factor for cardiovascular events and is associated with functional disability and death in the elderly (Santamaria et al., 2019).

Age is a significant factor inherent to the elderly with RAS for non-adherence to drug therapy, considering that visual and cognitive limitations are more prevalent in this population. A study conducted in Rio Grade do Sul with the objective of verifying adherence to the pharmacological treatment of arterial hypertension and its associated factors in the Family Health Strategy, observed low adherence to therapy among elderly people over 64 years of age (Gewehr et al., 2018).

For Abreu et al. (2018), forgetfulness is a relevant factor for non-compliance with drug therapy. Forgetfulness, especially in the elderly submitted to drug therapy of SAH, may occur as a result, among other factors, of polypharmacy, mental disorders and cognitive impairments, which may hinder the recognition and memorization of medication administration times.

With regard to polypharmacy, this is mainly due to the significant number of comorbidities present in the elderly population, which leads to the use of several drugs and consequent high number of daily doses, making it difficult for the elderly to remember the medication and the recommended times for taking. It is also noteworthy that adverse effects can discourage or lead the elderly to abandon certain medications for fear of major complications. It is understood from this that the concomitant use of multiple classes of drugs with several doses throughout the day, both of antihypertensive drugs and other drugs, can contribute to ineffective compliance with treatment due to its complexity (Leão, 2018). A study showed that the higher the number of associated antihypertensive drugs, the lower the adherence to SAH treatment (Gewehr et al; 2018).

Contributing to these statements, a study conducted in Piauí showed that hypertensive patients stop taking medication for SAH at least once a year, and that they forget to take it properly at established times at least once a month. This is partly associated with cognitive limitations such as memory lapses. The same study also highlights the low level of education as a contributing factor to non-adherence to measures to control hypertension among the elderly, especially medication. Considering that the association between RAS control and lower schooling may reflect the difficulty in knowing the disease and its risk factors, as well as adherence to control measures (Falcão et al., 2018).

Another factor inherent to the elderly that influences non-adherence to medication treatment of hypertension is the absence of symptoms of the chronic condition. Among the elderly investigated in a study to assess the degree of adherence to drug therapy in hypertensive patients, there were those who took the medications only when they had symptoms of the chronic health condition, and therefore had a lower level of adherence than those who followed the treatment continuously (Abreu et al., 2018).

Not least, the income factor presents itself as an obstacle in the adherence to drug treatment of this pathology. In a cross-sectional study conducted with a sample of 384 people, it was demonstrated that the majority of participants reported needing to buy antihypertensive medication (Luz et al., 2021).

With regard to beliefs as a determining factor for non-adherence to antihypertensive medication, it can be deduced that the elderly are more likely to adopt measures based on empiricism, because they bring with them years of experience and a baggage of knowledge passed from generation to generation. Contributing to this, the asymptomatic course of the disease itself can lead the elderly to believe that hypertension is an intermittent disease and that it can be treated only with non-pharmacological therapies, simply with stress relief or home remedies, such as teas or mixtures without any scientific proof (Costa, 2020).

3.5 FACTORS RELATED TO THE HEALTH SYSTEM

As already explained, the difficulty in accessing health services is one of the main obstacles to the adequate follow-up of the treatment of arterial hypertension among the elderly. And even if the difficulties of access to the health service are reduced, there are subjective components (perception about what the disease is, knowledge about the treatment) that need to be treated with caution. For this, it is necessary to invest in effective communication between the health professional and the patient (Soares et al., 2021).

According to Cesário et al. (2021) PHC is considered as one of the essential mechanisms for coping with NCDs, so that the finding of expansion in the USF registry, associated with greater demand and care at this level of care reinforces the relevance of the consolidation of PHC so that it is possible to qualify health care for the Brazilian elderly, for the sake of a healthy elderly population.

A factor of great relevance that interfered considerably making it even more difficult to access health services was the COVID-19 pandemic. A study conducted by Malta et al. (2020), exposes that in the COVID-19 pandemic, NCDs have become even more worrisome, with these diseases and their behavioral and metabolic risk factors aggravating cases, increasing hospitalization time and mortality rates from COVID-19. In addition, the social distancing measures adopted to control the spread of the virus have left many of the elderly unassisted, due to the compromise of access to the UBSs. The present study also showed that individuals with NCDs reported greater demand and difficulty in using health services during the pandemic.

Allied to this, the complications faced by Community Health Agents (CHA) in performing their activities stand out. These strategically inserted in the FHS teams play a fundamental role in the follow-up of patients with NCDs at the home level, carried out during home visits. A study carried out with the objective of verifying the difficulties faced by this technical category in the context of the covid-19 pandemic, demonstrated that a total of 46.9% of a sample of 1978 CHAs participating in the first

phase of the research did not obtain education or training on the disease. This has become an obstacle in the adequate approach of patients at home by these professionals. It is noteworthy that these play the role of counselor, especially to patients with arterial hypertension, removing doubts about the appropriate use of medications, and the simple fact of being able to enter the home, represents a considerable risk to the follow-up of the treatment of these elderly (Nogueira et al, 2021).

Another significant factor for non-adherence to hypertension medication treatment, which is strictly linked to the Brazilian health system, concerns the difficulty in obtaining medication at health centers. A study showed that although the SUS distributes essential medications free of charge, especially those of chronic use, the lack of these medications was reported in the analyzed service stations (Manso et al., 2018).

The ineffective relationship established between health professional and patient is by far shown to be an important factor related to the health system that can contribute negatively to the fulfillment of drug therapy. It is known that many professionals do not provide quality care, that they do not pass on the necessary information about the follow-up of the treatment and the risks of its abandonment. It is understood that the embezzlement in the reception of the elderly, and the lack of information, especially about the use of medication, by some professionals, interferes with treatment adherence in elderly patients (Ramos et al., 2021).

In view of the above, a comprehensive approach is necessary, aiming at adherence to treatment and blood pressure control, with more accurate blood pressure controls, careful monitoring and review of preventive and therapeutic measures adopted. In this context, the professional-user relationship stands out, which requires effective dialogue to favor the understanding of treatment and the appropriate use of medications (Nobre et al., 2020).

3.6 NURSING CARE IN THE CONTEXT OF ADHERENCE OF HYPERTENSIVE ELDERLY TO DRUG THERAPY

It is observed that the challenges of treatment adherence, in the control and prevention of SAH in Brazil, are strictly linked to the provision of services in primary health care, more precisely to the Family Health Strategy. And nursing as a professional category plays a role of fundamental importance within the FHS, acting to favor treatment adherence, prevention, monitoring and control of SAH. Focusing on the fundamental principle of person-centered practice, involving their family members, at the individual and collective level (Salles et al., 2018).

Within the FHS, the nurse works with the multidisciplinary team in the treatment and control of SAH. Among its attributions, the nursing consultation and the home visit are essential for care, as it allows the nurse to know the predominant characteristics of the SAH patients registered in the strategy, which facilitates their actions. Through scientific knowledge and the role of educator, nurses should

train patients with the disease to adhere to treatment, improving their quality of life (Salles et al., 2019).

According to Marta (2021) "the empowerment of the patient through the transmission of the therapeutic objectives, the means and competencies to achieve them, as well as the risks associated with the disease, motivate the patient to comply with the therapy" (p. 12). Thus, the nurse plays a fundamental role acting within the FHS, with regard to the orientation of the elderly about their treatment, specifically the medication. By resolving doubts, providing guidance on the effects of drugs, compliance with times of intake, the correct dosage and its benefits, the nurse becomes an indispensable tool for the follow-up of drug therapy. In addition to stimulating the client's autonomy, aiming at co-responsibility for their health.

Corroborating with Ferreira, Dallacosta et al., (2019) in their study states that the professional nurse plays a role of fundamental importance acting precisely in the awareness of this SAH carrier about the importance of the continuous use of medication.

Among the resources that should be used by the professional nurse to combat the non-adherence of elderly patients to drug therapy, health education stands out, which is fundamental, especially in this age group, where physical and cognitive capacities present considerable strain. To this end, a dialogued relationship should be established, and educational actions should be carried out with the elderly, in order to solve their doubts and anxieties regarding the use of medications, favoring a comprehensive and qualified care to the elderly with SAH (Falcão et al., 2018)

According to Costa et al. (2019) the importance of paying attention to the level of education when drawing up a care plan aimed at the hypertensive elderly, with the objective of ensuring that drug treatment is not withdrawn, is that in Brazil although many elderly have some level of education measured in years, many of these individuals cannot read, writing and doing mathematical math, which makes it impossible for them to solve their everyday demands.

It is understood from this that it is mainly up to the nurse, one of the main professionals responsible for the monitoring of the elderly with SAH, to use qualified listening and plan resolutive actions, focus on health education, guide on healthy life habits in an objective and clear way, fostering self-care. Provide care based on humanized practices that promote empathy, as they facilitate adherence, blood pressure control and the consequent success of drug treatment (Ramos et al., 2021).

4 FINAL CONSIDERATIONS

Understanding the barriers faced by elderly patients with Systemic Arterial Hypertension (SAH) in following the proposed treatment and unveiling the main factors that contribute to non-adherence to drug therapy by this public, becomes crucial for the professional categories dedicated to their direct care to take accurate initiatives in the elaboration and implementation of intervention strategies that favor greater adherence to treatment and consequent improvement of levels tension, thus

preventing serious repercussions on the health of these elderly. In view of the above, a scientific approach on hypertension in the elderly and the factors that determine non-adherence to drug therapy potentiated by the COVID-19 pandemic has become relevant.

Therefore, the general objective of the research was to discuss and evidence in the literature the determining factors of non-adherence of elderly patients with RAS to drug therapy. It was found that many factors interfere with the non-adherence of the elderly, factors that are linked to the elderly themselves and to the health system, as they present difficulties in following the proposed therapeutic scheme, either because of their complexity, forgetfulness, adverse effects of the medication and their belief in alternative medicines of an empirical nature. And the one for presenting flaws in its operationalization and professional training.

Starting from the objective of identifying the most relevant factors for the non-adherence of the elderly with arterial hypertension to drug treatment, it is evident that those related to the health system, the difficulties in accessing services stand out, due to the discontinuity of services in the pandemic peaks, especially at the level of primary health care PHC and the fragility in the patient/health professional interaction, which has been accentuated by the pandemic. And the hypertensive elderly are presented with a considerable degree of relevance to age, forgetfulness, polypharmacy, the adverse effects of the prescribed drugs, little knowledge about the disease, other comorbidities and belief. The discontinuity of access to health care and the serious consequences were pointed out that showed that patients who required care related to COVID-19, were prioritized, to the detriment of patients in routine care or follow-up procedures.

Regarding the repercussions resulting from the abandonment or inappropriate use of antihypertensive medications in the life of the elderly. It should be noted that these represent serious risks to their health, and the most pointed out according to studies, those referring to the cardiovascular system, hypertensive crisis, Stroke and Chronic Kidney Disease (CKD). The nurse, playing a fundamental role in the prevention and promotion of health, especially at the level of primary care, is shown to be a fundamental piece in the control of hypertension among the elderly, and it is mainly up to him to strengthen the patient's bond with the service. Thus, it can act on specific factors and prevent changes in blood pressure levels, thus avoiding more severe situations in the health of this elderly.

To obtain the results of this research, it was hypothesized that the follow-up of the drug treatment of SAH is influenced by factors inherent to the elderly and to the health system. It can be observed the predominance of many factors both linked to the patient and the system. It should be noted that this is a literature review study and covers a specific period of time, a population with pre-established age, and articles in Portuguese. This is the limitation of this study. The care services for the elderly with hypertension in the municipality were not totally interrupted with the Covid-19 pandemic, however, they suffered some kind of discontinuity. This points to the need to implement plans for the

resumption of services, with reinforcement of strategies that involve risk stratification, disease management and case management, in addition to the inclusion of innovative approaches to care for arterial hypertension in the elderly.

Given this, it is recommended the elaboration of studies that contemplate other audiences and that address the theme taking into account other time intervals, as well as other realities and different cultures. It is also suggested that the determining factors for non-adherence to drug treatment in patients with other chronic non-communicable diseases be investigated, since these are often associated, especially in the elderly population. The elucidation of the factors of non-adherence to drug treatment, not only of arterial hypertension, but also of diseases associated with it provides a contribution, especially for health professionals, for a better conduct of care measures.

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Antimicrobial nanocomposites: Cellulose fibers loaded with silver nanoparticles in health products

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ABSTRACT
Polymeric nanocomposites based on cellulose fibers, mainly cotton, and loaded with silver nanoparticles have been used mainly in health products (such as endotracheal tubes, bandages, medical dressings, mesh, catheters and filters) thanks to the fact that these nanoparticles have broad-spectrum antiseptic properties. Based on the analysis of scientific publications, this work aims to investigate how these nanocomposites have been prepared and characterized in general, with regard to the characteristics and properties of silver nanoparticles and their synthesis by chemical, photochemical, physical and biological methods and how they are impregnated in cellulosic fibers. Specific considerations will also be made regarding the antimicrobial mechanism of nanostructured silver and its toxicity to humans.

Keywords: Cotton, Silver nanoparticles, Polymeric nanocomposites, Antimicrobial activity.

1 INTRODUCTION

According to Silva, Viana and Mohallem (2009), nanosciences study nanomaterials, which are materials in which at least one of their dimensions has a size between 1 and 100 nm. Nanotechnology, on the other hand, deals with the processes of preparation and characterization of nanomaterials.

It is worth noting that materials prepared by nanotechnological processes do not necessarily have nanometric size, but may have nanometric structures in their composition, resulting in nanostructured materials. In fact, some research advocates that sizes up to 300 nm be considered as belonging to the nanoscale (CADIOLI; SALLA, 2006; GUAZZELLI; PEREZ, 2009).

Esteves, Barros-Timmons and Trindade (2004) define nanocomposites as hybrid materials in which at least one of their constituents has nanometric dimensions.

Analogous to traditional composites, we have in nanocomposites the combination of at least two distinct phases, called reinforcement and matrix, the latter being the phase in which the first is dispersed. The matrices can be polymeric, metallic, ceramic or carbonaceous. The reinforcements can be fibrous or particulate (LEVY NETO; Pardini, 2006). In the case of this work, the nanocomposites are said to be polymeric depending on the class of materials to which their matrices belong.

This work is a bibliographic review and aims to analyze scientific publications on the preparation, characterization and antimicrobial properties of polymeric cellulose nanocomposites (as matrix) and silver nanoparticles (Ag NPs) (as filler).

These nanoparticles have broad-spectrum antiseptic properties and, therefore, are promising in the constitution of health products, such as: endotracheal tubes, bandages, medical dressings, mesh, catheters and filters.

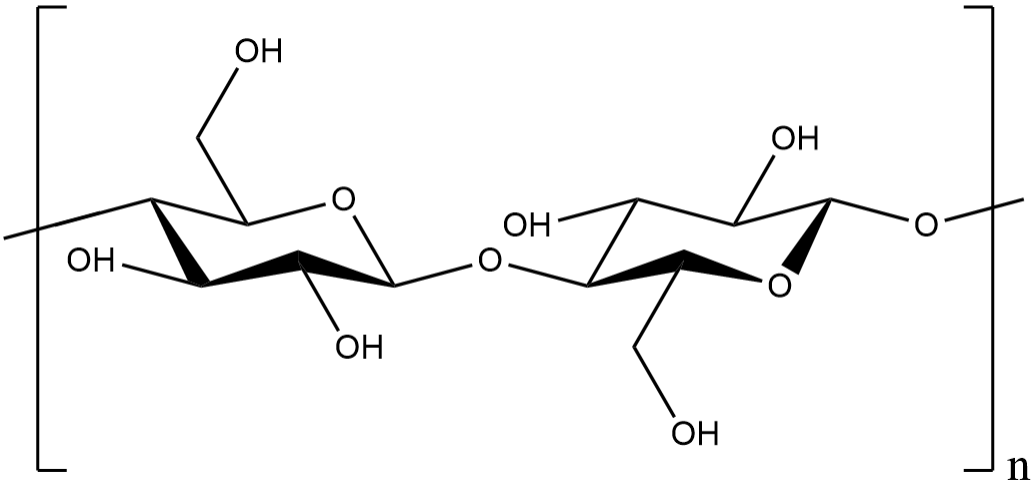
2 CELLULOSE

Cellulose, a constituent of the primary cell wall of green plants, many forms of algae and oomycetes, is the most abundant organic polymer in nature and also the most versatile organic raw material. It is a polysaccharide with molecular formula $(C6H10O5)_n$ that, when hydrolyzed in an acidic medium, produces a large number of monomeric units of β-D-glucose (also known as β-D-glucopyranose). Cellulose was isolated and characterized in 1838 by the French chemist Anselme Payen (SHREVE; BRINK JUNIOR, 1980).

The monomers are joined by glycosidic bonds β-(1,4) in an unbranched chain forming a linear structure (Figure 1). In addition, the hydrogen bonds between the hydroxyl groups of juxtaposed chains contribute to cellulose being fibrous, resistant and insoluble in water and in a large part of organic solvents. It is worth mentioning that the bonds between the monomers are resistant to the action of oxidizing agents, reducing agents and weak bases (FONSECA, 2003).

The pulp used in the production of paper is obtained from the pulp of the wood. The textile industry uses vegetable fibers, such as: hemp, jute, sisal, pita, rami, raffia, linen, paina and cotton (RIBEIRO, 1984).

Figure 1 – Cellulose repeating unit.



Source: Author (2023).

2.1 COTTON

Cotton, the most widely used natural fiber in the world, originates from India (where the oldest pieces were woven, dating back to 3000 BC) and Ethiopia. However, some historians say that cotton was already known and cultivated among the Aztecs (in Mexico) in 5000 BC (CHATAIGNIER, 2006).

Cotton is almost entirely composed of cellulose (with mass content ranging between 88 and 96 %) and contains small portions of protein, pectin, wax, ash, organic acids and pigments. Its fibers are able to absorb up to 32% of the moisture of completely saturated air. They can serve as food for insects and be completely decomposed in the environment, by certain fungi and bacteria, in about three months, and are therefore biodegradable. (RIBEIRO, 1984).

The cotton fiber grows in the seeds of several plants of the genus *Gossypium*, family *Malvaceae*. In each pit, 1200 to 1700 fibers are developed, which have the functions of protecting the grains of the seed and assisting their transport by the wind when ripened. The length of the fibers varies from 13 to 50 mm, while the thickness can measure from 20 to 40 µm from the point of adhesion, from where they thin to the tip (ERHARDT *et al*., 1976).

Cotton is used in the manufacture of a number of textile products and other products, such as: fishing nets, coffee filters, tents, explosives (nitrocellulose) and paper. It is also present in the daily life of hospital environments. The most common items where we find it are: the hydrophilic cotton itself, the gauze, the bedding that lines the beds and the clothes of the professionals who work there.

Since cotton is susceptible to microbial contamination under appropriate temperature conditions, the products based on it undergo physical and chemical treatments in order to remain aseptic (GAO; CRANSTON, 2008).

3 NANOPARTICLESS

The ISO/TS 27687:2008 standard defines a nano-object as a material in which one, two or three of its external dimensions belong to the nanoscale (CEN, 2008). Then this same standard defines nanoparticles as being nano-objects with all three external dimensions at the nanoscale. The other two types of nanoobjects are nanofibers (two nanoscale dimensions) and nanoplates (at least one nanoscale dimension).

According to Holister *et al*. (2003), the transition from microparticles to nanoparticles can lead to a series of changes in the physical properties of a material. One of the factors responsible for this is the increase in the ratio between surface area and volume. For example, gold is a material of yellow color, when it is in bulk (macroscopic) form, and red, when its nanoparticles are dispersed in aqueous medium.

Another issue is that within a matrix or in a liquid medium, nanoparticles aggregate easily. This can be explained by the fact that these nano-objects have a large surface energy. When they cluster, the system acquires lower energy values (LEVY NETO; Pardini, 2006).

Dispersing agents are also used or treatments of the surface of the material are made (polymer encapsulation or functionalization, for example) to ensure the dispersion of the nanoparticles, through mechanisms of electrostatic repulsion and / or steric impediment. Otherwise, agglomeration prevents the special properties of the nanomaterial, related to the nanometric dimension, from being evidenced (LEVY NETO; Pardini, 2006).

At the nanoscale, phenomena arise that do not appear at the macroscale. This is not only due to the reduction in size, but also to the changing importance of fundamental natural forces. Gravitational, frictional and combustion effects give rise to the effects of electrostatic forces and two aspects linked to them: van der Waals forces and Brownian motion (DURÁN; MATTOSO; MOORS, 2006).

4 SILVER NANOPARTICLES

In nature, silver is found in the native form or in the ores argentite (silver sulfide, Ag2S), chloroarginite (silver chloride, AgCl) and pyrargirite (silver sulfoantimony, Ag_{3SbS3}). However, this metal is obtained mainly by application of the Parke process in lead ores containing small amounts of silver or as a by-product in the anodic mud of the electrolytic refining of nickel, copper, gold and zinc (LEE, 2009).

The earliest reference to metal appears in the book of Genesis when it is mentioned that Abraham was very rich in cattle, gold, and silver. Although man is said to have known silver since prehistoric times, portions of the metal's slag have been found in Asia Minor and the Aegean islands, indicating that it was being isolated from lead through surface mining around 4000 BC (WEEKS, 1968).

Pure silver is a white, shiny, glossy metal (depending on the degree of polish). Its ductility and malleability are inferior only to those of gold and palladium. It has the highest electrical and thermal conductivities of all metals and is stable to pure air and water. However, it is attacked by ozone, hydrogen sulfide, and sulfur-containing air. When newly deposited, it is the best reflector of visible light, but it quickly stains and loses its reflection (EMSLEY, 2011; GREENWOOD; Earnshaw, 1997; LEE, 2009).

The main applications of silver are in: photographic emulsions, dental amalgams, jewelry and ornaments, electrical contacts, printed circuits, batteries, mirror manufacturing, welding, brazing, catalysis and control of fission reactions in pressurized water nuclear reactors (KLOPROGGE; PONCE; LOOMIS, 2021).

4.1 PROPERTIES OF SILVER NANOPARTICLES

Some of the properties of macroscopic silver are also presented by Ag NPs, such as: good conductivity (electrical and thermal), chemical stability and catalytic activity. However, these properties can be controlled depending on the size of the nanoparticle, its shape and polydispersity (SIGNORI *et al*., 2010).

According to Kiss, Miotti and Ferraz (2011), the properties of nanoparticles vary with increasing size. When we have larger and larger nanoparticles, the number of atoms on the surface is proportional to the square of the diameter of the nanoparticle, while the number of atoms in the inner region is proportional to the cube of the diameter. For this reason, they present increasingly expressive crystalline characteristics, which did not exist before.

According to Melo Júnior *et al*. (2012), the color of colloidal silver is a result of the absorption of electromagnetic radiation in resonance with surface plasmons. With the increase in the size of the particles, the system starts from yellow and passes through orange and violet until it acquires the characteristic coloration of macroscopic silver.

4.2 ANTIMICROBIAL ACTIVITY OF SILVER NANOPARTICLES

Various heavy metals in very small amounts (which can be expressed in parts per million) can be biocides or antiseptics, such as silver, copper, and zinc. This antimicrobial capacity is called oligodynamic action, resulting from the action of metal ions (PELCZAR JR.; CHAN; KRIEG, 1996).

Still according to the same authors, in antiquity, water was stored in silver or copper containers because people realized over time that the containers of these metals kept the water suitable for human consumption. During the Middle Ages, solutions of silver nitrate (AgNO3), known as "Lunar Caustic", were given to patients with nervous disorders, epilepsy and syphilis.

Moving forward in chronology, we have the use of 3 to 1 % AgNO solutions as antiseptic eye drops in the prevention of neonatal gonorrheal ophthalmia. This prophylaxis was established by Karl Credé in 1884 in the United States. However, antibiotics eventually replaced $AgNO_3$ for this purpose (TORTORA; FUNKE; CASE, 2005).

The authors point out that, recently, there has been renewed interest in the use of silver as an antimicrobial agent, especially in cases where there are antibiotic-resistant bacteria. The most common formula is a topical cream based on silver sulfadiazine for use in burns.

Currently, dressings to which Ag NPs are incorporated are employed in the treatment of open wounds, burn infections and chronic ulcers. Ag NPs are broad-spectrum antimicrobial agents that have action against bacteria (Gram-positive or Gram-negative), filamentous fungi, yeasts and viruses (EL-RAFIE *et al*., 2012).

The first scientific documents reporting the use of colloidal silver in the medical field date from the late eighteenth century. other related research was developed in the period between 1910 and 1920 (GIBBS, 1999).

Sadeghi *et al*. (2012) compared the bactericidal activity against *Escherichia coli* and *Staphylococcus aureus* of different silver nano-objects (nanoparticles, nanorods and nanoplates) stabilized by the polymer poly (N-vinyl-2-pyrrolidone) (PVP), by the methods of disc diffusion and Minimum Inhibitory Concentration (MIC).

Staphylococcus aureus is one of the main Gram-positive bacteria that cause disease and can be found on the skin in regions such as: armpits, inner part of the elbows, between the buttocks, in the groin and in the lower part of the heel. Some of its strains are resistant to methicillin. *Escherichia coli,* a Gram-negative bacterium and also pathogenic, resides in the thin portion of the intestine, and can be found in areas of the body contaminated by feces and urine (GRICE *et al*., 2009).

They found that the antimicrobial effect of the nano-objects is dependent on their shapes and sizes, due to their different surface areas, and that the nanoplates were the ones that showed the best bactericidal activity for the microorganisms tested.

Klemenčič *et al*. (2010) studied the efficiency of different forms of silver in the protection of cellulose fibers against biodegradation in test soil (simulating the biodegradation of the material in the environment), according to ISO 11721: 2003. The samples were buried in the soil for periods of 3 and 12 days.

The cotton fabrics were functionalized by the exhaustion method with: (a) Ag NPs with an average diameter of 30 nm, dispersed with the aid of a dispersing agent and ultrasound, generating the material M1; (b) commercial dispersion of AgCl in water, originating the material M2 and (c) colloidal silver, consisting of nanoparticles with an average diameter of less than 10 nm, resulting in the material M3. The tissue samples were immersed in the respective dispersions and left for 30 minutes and at

room temperature under agitation and rotation. Finally, they were squeezed and dried at room temperature as well.

The degree of biodegradation was monitored by: SEM, color measurement (parameter of the uniform color scale CIE L*a*b*, of the International Commission on Illumination), tensile strength, degree of polymerization and Fourier Transform Infrared Spectroscopy (FTIR). The authors concluded that large concentrations of Ag NPs in the M1 material led to insufficient antimicrobial activity, due to the mechanism of release of silver cations (Ag1+) from the agglomerates for the medium to be deficient. In the case of M2 material, the dissociation of AgCl in the presence of moisture was high, providing better protection against degradation than that observed for M1 material. Finally, the M3 material exhibited the best protection, probably due to the synergistic action of the nanoparticles and Ag^{1+} cations released.

The antimicrobial action of Ag1+ cations on microorganisms is already known. However, the action of Ag NPs is not yet well resolved (HEBEISH *et al*., 2011).

Morones *et al*. (2005) reported the presence of small Ag NPs adhered to the bacterial membrane and also inside the cell, which may contribute to a better understanding of the bactericidal action of this nanomaterial. There are two main mechanisms proposed.

4.2.1 First mechanism

The metallic silver (Ag0) in the nanoparticles can be oxidized to the Ag1+ cation, in aqueous medium, by the action of the dissolved oxygen present in it, according to Equation 1:

$$O2\ (aq) + 4\ H3O1+\ (aq) + 4\ Ag\ (s) \rightarrow 4\ Ag^{1+}\ (aq) + 6\ H2O\ (l) \quad (1)$$

According to Mijakovic *et al*. (2006), the Ag1+ cation has a great affinity for sulfur and phosphorus atoms, which causes two situations to happen. In the first, the Ag1+ cations react extra or intracellularly with the thiol (–SH) groups present in the proteins that make up the bacterial cell membrane, denatured them.

In the second, Ag1+ cations can interact with portions of phosphorus in the DNA, causing damage that prevents the performance of normal metabolic functions, and the cell can no longer divide (GUPTA; BAJPAI; BAJPAI, 2008; MORONES *et al*., 2005).

4.2.2 Second mechanism

Starting from water and dissolved oxygen in the medium, the Ag1+ cation can catalyze the formation of nascent oxygen, which oxidizes the molecules that make up the microorganism. The interesting thing is that, according to this mechanism, it is not necessary that there is a direct contact

between the Ag1+ cation and the microorganism, since the radical formed can diffuse through the medium (KIM *et al*., 2007).

4.3 TOXICITY OF SILVER NANOPARTICLES

Although silver is not considered toxic, most of its compounds are. This is because they can be absorbed by the circulatory system, leading to the deposition of Ag0 in various tissues of the body, which can cause argyria, a condition characterized by bluish or blue-gray pigmentation of the skin and mucous membranes. In addition, the ingestion of silver in high concentrations can cause side effects such as: neurological and kidney problems, indigestion and headache (KLOPROGGE; PONCE; LOOMIS, 2021).

Guazzelli and Perez (2009) warn that nanomaterials may be more toxic than the corresponding compounds at the macrometric scale. They have greater chemical reactivity, biological activity and catalytic action, due to the huge surface area they have. For the same reason, nanomaterials with different shapes and sizes can exhibit completely different toxicities.

Also according to the authors, due to their small size, nanomaterials are more easily absorbed by cells and tissues. They are so small that the immune system itself cannot detect them. Some studies have shown that in *vivo* tests with synthetic nanoparticles, there was the formation of free radicals, which caused: inflammation, disturbances in cellular functions and the subsequent development of tumors due to DNA damage.

Ahamed, Al-Salhi and Siddiqui (2010) critically discussed the recent findings related to the risk of human exposure to NP Ag, mainly in the areas of: cosmetics, sunscreens, textiles, food and medical products.

Based on the results of a large number of *in vitro* studies with mammalian cells, one of the authors' findings was that Ag NPs are toxic to cells derived from the skin, brain, vascular system, reproductive organs, and especially the liver and lung.

In addition, in vivo *toxicity studies* in rats and mice demonstrated that after being administered by inhalation, ingestion, or intraperitoneal injection, NP Ags were found in the bloodstream and caused toxic effects in several organs, including the brain.

Beer *et al*. (2012), using the MTT colorimetric assay, investigated the relationship between the viability of A549 cells of the lung and the fraction of Ag1+ cations present: (a) in suspensions of Ag NPs and (b) in their supernatant after ultracentrifugation. The concentration of Ag1+ cations was determined by Atomic Absorption Spectrometry (AAS) after acid digestion.

The results showed that cell viability decreases with the increase of the fraction of Ag1+ cations. Cells exposed to a suspension of Ag NPs containing a fraction of Ag1+ cations of 69 % had a viability of 54 %, while for the case of the fraction to be 39 %, the viability was 92 %.

The study also concluded that there are no statistically significant differences between the toxicities of the suspension of Ag NPs and their supernatant. Only suspensions in which the fraction of Ag1+ cations was less than or equal to 2.6 % were shown to be slightly more toxic than their respective supernatants.

5 CELLULOSIC NANOCOMPOSITES WITH SILVER NANOPARTICLES

The processing of nanocomposites is determined based on the nature and characteristics of the matrix and reinforcement. Therefore, in this work, we will first pay attention to the fact that the matrix (cellulose fibers) is polymeric and the charge (Ag NPs), metallic.

Cellulose fibers are made by living organisms and then extracted and processed. That is, there are no synthetic syntheses involved in obtaining them. They have low specific mass and are biodegradable, non-toxic and recyclable. Additionally, extraction and processing costs are low. These are some of the advantages of using these fibers (LEVY NETO; Pardini, 2006).

Since, in general, cellulose fibers do not tolerate temperatures higher than 200 ° C, care must be taken in choosing the technique of preparation of nanocomposites in which they will be one of the constituent elements.

Ag NPs are often immobilized on the fibers of a range of textile products, giving the fabrics an antimicrobial effect that allows them to be used in the making of bandages, gauze, bed sheets and surgical clothing. The most frequently used fabric is cotton (HANH *et al*., 2014; Kozicki *et al*., 2013).

5.1 PREPARATION OF NANOCOMPOSITES

According to Esteves, Barros-Timmons and Trindade (2004) and Maneerung, Tokura and Rujiavanit (2008), polymeric nanocomposites loaded with metallic nanoparticles can be prepared by three main strategies. They are:

a) The mixture of the components.
b) The polymerization of the monomer *in situ* to generate the matrix, in the presence of metallic nanoparticles.
c) The reduction of cations or metal complexes in a containing medium or in the polymer matrix itself, that is, the *in situ synthesis* of the nanoparticles.

In the case of nanocomposites consisting of cellulose fibers, among the three strategies listed, the second is not feasible. That's because the fibers are extracted and not synthesized.

In most cases, the manufacturing process involves the separate synthesis of the Ag NPs, which are then impregnated in the matrix (first strategy). Cotton fibers have large surface areas containing hydroxyl groups, which assist in the fixation of NPs Ag. However, crosslinking or adsorption agents may be used (BREITWIESER *et al*., 2013; RAVINDRA *et al*., 2010).

However, Dallas, Sharma and Zboril (2011) comment that *in situ* reduction prevents the formation of nanoparticle aggregates (which would drastically reduce the extent of the antimicrobial property) and leads to the obtaining of nanoparticles with a narrow size distribution. That would be the advantage of the third strategy over the first.

Another option is to perform some type of surface treatment to functionalize the surface of the fibers, nanoparticles or both, in order to improve the adhesion between the reinforcement and the matrix at the interface (LEVY NETO; Pardini, 2006).

The process of treating cellulose fibers tensioned with alkaline solution is called mercerization, after John Mercer, who, in 1844, performed the first experiments on the behavior of cellulose in soda bleach or caustic potash. He observed that the cotton fabric samples showed: shrinkage (from 20 to 30 %), increase in tensile strength (in the order of 25 %) and increase in affinity for dyes (from 30 to 40 %). When the operation is performed in the absence of tension, it receives is called leaching or caustification.

This treatment with alkaline solution is widely used to functionalize cotton fibers. In the same way that there is an increase in affinity for dyes, the modified surface can improve the adhesion of other types of compounds.

5.2 FOULARDAGEM

The foulard is a machine used in the process called foulardagem (or padding, in English), popularly known as impregnation, which has the function of impregnating a wide variety of compounds (dyes, pigments, microcapsules, protectors against ultraviolet rays, bactericides and bacteriostatics) in textile products. Prior to the foulardagem process, a depletion step is carried out, in which, inside a vat, the fabric is immersed in a bath that contains the compound to be impregnated.

In the foulardagem itself, the compound present in the bath absorbed by the fabric is forced to penetrate the interior of the material by the action of two rubber cylinders that keep the system pressed. There are configurations in which several pairs of cylinders can be placed in sequence.

After foulardagem, the tissue is processed, usually in a dryer, to consolidate the fixation of the compound in the tissue. There are some derivations of the foulardagem process. They are:

a) Pad-stream: sequence of: impregnation, vaporization, washing, drying and winding.
b) Pad-batch: sequence of: impregnation, cold rest, washing, drying and winding.
c) Pad-dry: sequence of: impregnation, drying, washing, drying and winding.
d) Pad-dry-stream: sequence of: impregnation, drying, vaporization, washing, drying and winding.

6 SYNTHESIS OF SILVER NANOPARTICLES

The development of new ways of preparing metallic nanoparticles has been extensively investigated. There are two general types of production of these nanoparticles. The first type is characterized by aggregation techniques, in which atoms are aggregated to form the nanostructure (bottom up) and the second is composed by removal techniques, in which there is removal of material to form the nanostructure (top down) (EUSTIS; EL-SAYED, 2006).

Ag NPs can be prepared by a variety of synthetic routes involving chemical, photochemical, physical and biological methods.

6.1 CHEMICAL METHODS

According to Durán, Mattoso and Morais (2006), chemical approaches are the most commonly employed because they provide the synthesis of nanoparticles in a liquid medium. Generally, in addition to the medium, three types of compounds are used: a precursor of the metal (the simplest are the salts that contain the cation of the metal, such as $AgNO_3$), a reducing agent (which will promote the reduction of the cation of the metal) and a stabilizing agent (which will prevent the aggregation of the nanoparticles formed, keeping the colloid stable).

Tran *et al*. (2013) explain that the formation of silver colloids involves two phases, one of nucleation and the other of growth. These phases can be controlled in order to obtain nanoparticles with the desired size and shape, by adjusting some parameters of the synthesis, such as, for example, the temperature (usually high temperatures), the pH and the speed of agitation of the system.

The most commonly used reducing agents are: sodium borohydride ($NaBH_4$), formaldehyde, sodium citrate, hydrazine (N2H4), ascorbic acid, glucose and also the liquid medium itself such as dimethylformamide (DMF) and ethylene glycol (DALLAS; SHARMA; ZBORIL, 2011).

According to Budama *et al*. (2013), the reduction with N2H4, provided that it is stoichiometrically controlled, does not form dangerous by-products, according to Equation 2:

$$4\ Ag^{1}+ (aq) + N2H4\ (aq) \rightarrow 4\ Ag\ (s) + 4\ H1+ (aq) + N2\ (g) \qquad (2)$$

As examples of stabilizing agents, Tran *et al*. (2013) cite poly (vinyl acetate) (PVA), PVP and sodium oleates. Some synthetic polymers can act simultaneously as reducers and stabilizers, such as polyacrylamide.

El-Nour *et al*. (2010) say that Ag NPs can also be reduced in microemulsion, which is a biphasic system consisting of an aqueous phase (where the precursor of the metal is usually located) and another organic phase (where the reducing agent is found), under vigorous agitation. The interaction between the reactant species depends on mass transport across the interfaces, mediated by a quaternary

alkylammonium salt. Although nanoparticles with uniform size are obtained by this method of preparation, it is a generally costly approach.

6.1.1 Preparations involving chemical methods

Ilić *et al*. (2009) evaluated the antimicrobial efficiency, before and after repeated washing, of cotton fabrics loaded with Ag NPs, with an average diameter of approximately 10 nm, against the bacteria *Escherichia coli* and *Staphylococcus aureus* and the fungus *Candida albicans*.

The nanoparticles were synthesized by reducing Ag1+ cations in an argon atmosphere with $NaBH_4$ and without the use of any stabilizer. For the impregnation stage, the tissue was immersed in the colloids, cured at 100° C for 5 minutes, washed and dried at room temperature. Some samples of the nanocomposite obtained were dyed with the dye C. I. Direct Red 81.

Although the tissues loaded with colloid at a concentration of 10 ppm exhibited good antimicrobial efficiency before washing, the study indicated that they did not have a good durability against them due to the detachment of the nanoparticles from the fibers. The content of silver detached from the nanocomposite was determined by AAS.

This detachment was slower for tissues loaded with colloid at a concentration of 50 ppm, which showed microbial reduction above 99%, even after washing. It is worth mentioning that, in the results of many publications, the presentation of percentage values of reduction of microorganisms is recurrent, which will be referred to in this text only as microbial reduction, calculated by Equation 3:

$$R\,(\%) = \frac{A_0 - A}{A_0} \cdot 100\,\% \qquad (3)$$

In Equation 3, we have that: **"R (%)"** is the microbial reduction; "**A0**" is the number of colony-forming units (CFU) in the control sample (in the absence of a silver compound) and "**A**" is the number of CFU in the sample loaded with a silver compound.

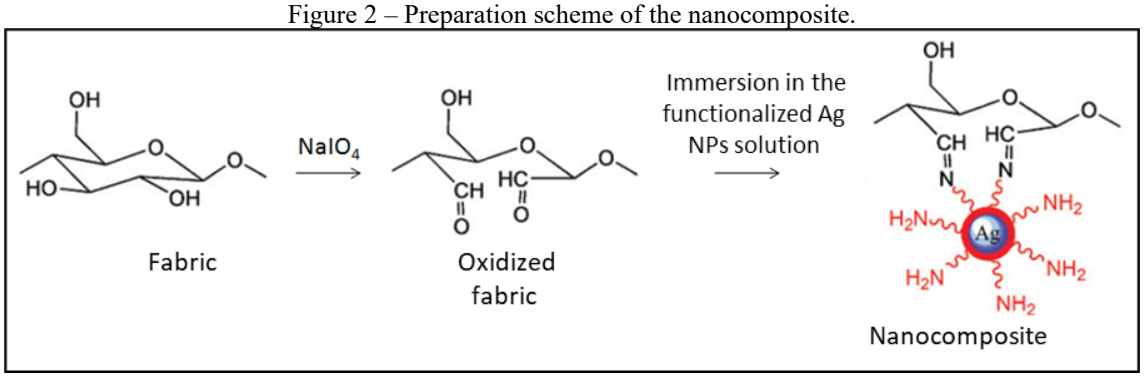
The antimicrobial activity was not affected by the dyeing of the tissue with the dye. Other results showed that, starting from the colloid with a concentration of 50 ppm, there are changes in the color of the dyed tissues that are noticeable to the naked eye, since $\Delta E^* > 1$, according to the CIE color scale L*a*b*.

Zhang *et al*. (2013) studied the durability, against washing, of an antibacterial cotton fabric loaded with Ag NPs. In the first step of the preparation of the material, they used a hyper-branched amino finished polymer (HBP-NH2) to obtain the nanoparticles, through the reduction of Ag1+ cations from an aqueous solution of $AgNO_3$, and also functionalize them, without any other reducing or stabilizing agent. Initially the system was stirred at room temperature and then heated.

Subsequently, the cotton fabric previously oxidized by an aqueous solution of sodium periodate ($NaIO_4$) was dipped in the solution containing the Ag NPs functionalized by the polymer, for a period of 30 minutes and at room temperature. The overall process of nanocomposite preparation can be seen in Figure 2.

Due to the presence of aldehyde groups, it was possible to adhere the functionalized nanoparticles to the oxidized tissue by means of chemical bonds. Thus, after exposure of the nanocomposite to 50 consecutive washes, the silver content (measured by Inductively Coupled Plasma Atomic Emission Spectrometry, ICP-AES) decreased from 149.88 to 116.08 mg/kg, demonstrating good durability against washing. The microbial reduction of *Escherichia coli* and *Staphylococcus aureus*, also after this number of washes, was 96% on average.

Figure 2 – Preparation scheme of the nanocomposite.



Source: Adapted from ZHANG *et al*. (2013, p. 2093).

In an initial step, Shateri-Khalilabad, Yazdanshenas and Etemadifar (2017) prepared Ag NPs by in *situ* reduction of Ag1+ cations (from $AgNO_3$), with the use of ascorbic acid, on the surface of a cotton fabric previously treated with potassium hydroxide (KOH).

Subsequently, the tissue impregnated with the nanoparticles was immersed for 60 minutes in an alcoholic solution of prehydrolyzed n-hexadecyltrimethoxysilane. Finally, it was cured at 110°C also for 60 minutes, forming a high-density, low-energy layer around the tissue. One of the purposes was to produce a super-hydrophobic fabric.

The resulting nanocomposite showed excellent antibacterial activity (against *Escherichia coli and* Staphylococcus aureus*) and protective action against UV-A and UV-B radiation (in the range of 280 to 400 nm, with a protection factor of 296).*

The material also demonstrated the maintenance of its properties after 5 washes, lasting 45 minutes each, with a solution of concentration equal to 5 g/L of a non-ionic detergent (Triton X-100) at 50° C, according to ISO 105-C10:2006. This is because the hydrophobic coating prevented the particles from being removed from the surface of the nanocomposite.

From the bacterial cellulose produced by *Acetobacter xylinum*, Maneerung, Tokura and Rujiravanit (2008) reduced *in situ*, Ag1+ cations (from an aqueous solution of $AgNO_3$ with a concentration of 0.001 mol/L), using as a reducer NaBH4 (at concentrations of 0.001, 0.01 and 0.1 mol/L). First, the cellulosic film was immersed in the nitrate solution for 60 minutes. Then, the reduction began, lasting 10 minutes. Finally, the nanocomposite was washed with ultrapure water to remove excess reducer and by-products, and freeze-dried (frozen at a temperature of – 40°C and vacuum-dried at – 52°C).

The size of the nanoparticles and their distribution were evaluated by Transmission Electron Microscopy (TEM). A higher concentration of the reducing agent provided the formation of nanoparticles with a smaller average diameter (5.47 nm) and a narrow size distribution ($\sigma = 2.20$ nm). The X-ray Diffraction (XRD) technique complemented the observation of the formation of the nanoparticles, through which the planes (111), (200) and (311) characteristic of the cubic structure of the centered face of Ag0 were observed in the diffractograms. It is worth mentioning that the Energy Dispersive X-ray Spectroscopy (EDS) did not identify boron in the elemental composition of the nanocomposite, which is something positive, considering the toxicity of this element.

The resulting nanocomposite exhibited strong antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*, evaluated by the methods of counting colonies formed and disc diffusion.

The authors emphasize that the prepared nanocomposite can be used as a skin substitute, in the treatment of extensive burns, and in the making of active dressings. It keeps local temperature and humidity at adequate levels, accelerating the processes of epithelialization and angiogenesis, as well as contributing to the relief of local pain and inhibiting microbial contamination.

Initially, Budama *et al*. (2013) synthesized the amphiphilic and block copolymer polystyrene-co-poly(acrylic acid) (PS-b-PAA) by radical polymerization by atomic transfer. Then, the copolymer was dissolved in toluene and heated to 135° C for 20 minutes to form reverse micelles. Subsequently, a solution of AgNO 3 was added to the system containing the micelles, under vigorous agitation, so that the Ag1+ cations would bind to the carboxyl groups in the micellar nuclei. This stage was carried out under the shelter of light for 2 days. Finally, the Ag 1+ cations in the nuclei were reduced to Ag NPs by the action of N2H4. The nanoparticles obtained were characterized by TEM and XRD, revealing that the average diameter of these chemical entities was 20 nm.

Clean and dry samples of cotton fabric were introduced into the system where the micelles containing the nanoparticles were found and left under agitation for 30 minutes. Then, the tissues were dried at room temperature and placed in an oven for 5 minutes and at 135° C, to bind the micelles to the tissue surface, covalently, through the carboxyl groups in the PAA chains and the hydroxyl groups of the cellulose.

At the end, the antimicrobial activity against the bacteria *Escherichia coli* and *Staphylococcus aureus was evaluated* by the disc diffusion method. It was observed that the bactericidal effect remained up to 5 washes for the first microorganism and up to 20 washes for the second.

Osorio *et al*. (2012) synthesized, in *situ*, Ag NPs using as reagents the precursor AgNO3 (in aqueous solution) and the reducing agent butylamine (in alcoholic solution). The concentration of $AgNO_3$ was fixed at 1 nM, while the concentrations of the agent were 1, 2, 4 and 5 nM. The substrates were woven of wool and cotton. The systems were shaken throughout the synthesis, which lasted 120 minutes. The temperature of 45° C and pH 7 were kept constant. A comparison was made using an aqueous and an ethanolic system. At the end, the nanocomposites were: washed twice with diluted detergent, rinsed three times with cold water and dried.

MET and EDS analyses confirmed the formation of Ag NPs on the surface of both textile products. The ICP-AES analyses (with the samples digested in 9 % nitric acid solution and for 60 minutes) indicated that the amount of silver deposited per gram of cotton for the aqueous system was up to sixteen times higher than that found for the ethanolic system. The amount deposited per gram of wool was up to three times higher for the aqueous system. These differences may be due to better solubilization of Ag^{1+} cations in aqueous medium, which leads to an increase in the deposition of Ag NPs.

The formation of Ag NPs on the fibers was also shown to be dependent on the sequence of addition of the reactants. The simultaneous addition of salt and reducing agent resulted in a mass (of Ag NPs) three times smaller than that formed when butylamine was added before $AgNO_3$.

Hebeish *et al*. (2011) synthesized Ag NPs with an average diameter between 6 and 8 nm using hydroxypropyl starch (a type of chemically modified starch that therefore will not be considered as a natural extract) as a reducing and stabilizing agent. They were then applied to cotton fabrics in the presence and absence of the liquid Printofix Binder MTB EG binding agent. The samples were dried at 70° C for 3 minutes and cured at 150° C for 2 minutes.

The nanocomposites obtained (with and without the binder) were evaluated for their antimicrobial activities against *Escherichia coli* and *Staphylococcus aureus*, before and after 5, 10 and 20 washing cycles with hot water, sodium carbonate at a concentration of 2 g/L and a non-wetting agent at a concentration of 5 g/L. Emphasizing that each wash lasted 45 minutes.

Prior to washing, the microbial reduction was greater than 95 %. After 5 washing cycles and in the absence of the binding agent, there was detachment of the nanoparticles, which caused the microbial reduction to be below 74%, an unsatisfactory result. However, the presence of the binding agent ensured microbial reductions above 92% even after 20 washing cycles, demonstrating the importance of this agent in the fixation of the nanoparticles to the tissue surface.

Breitwieser *et al*. (2013) prepared nanocomposites of viscose fibers (artificial cellulose fiber, manufactured from wood chips of low-resinous trees or the linter of the cotton seed) and Ag NPs, using

microwave and conventional heating (in reflux and sealed pot). Both forms of heating kept the system at a temperature of 80° C for comparison purposes (but other temperatures were also employed), and in the case of microwaves, the synthesis time was 4 minutes, while for conventional heating, this time was 120 minutes. This is one of the advantages of using microwaves to promote the heating of systems.

As a reducing and stabilizing agent, sulphated chitosan was used, a green, biodegradable and biocompatible polymer. According to Laranjeira and Fávere (2009), chitin is a natural polymer extracted from the exoskeleton of crustaceans and insects, while chitosan is obtained by deacetylation of chitin in alkaline medium. In turn, chitosan can be chemically modified through a sulfation reaction with chlorosulfonic acid to obtain sulfated chitosan

The preparation of the nanoparticles took place: *in situ, in* aqueous medium, with agitation and in the absence of light and air. The resulting materials were submitted to antimicrobial assays against *Escherichia coli* and showed high bactericidal action.

Characterizations by Dynamic Light Scattering (DLS), Ultraviolet and Visible Spectroscopy (UV-Vis) and TEM found that both heating techniques led to the preparation of very similar materials, which differed only in the shape of the nanoparticles on the fibers: elongated when using microwaves and spherical for conventional heating. No evidence of specific effects from the use of microwaves was obtained.

6.2 PHOTOCHEMICAL METHODS

According to Tran *et al*. (2013), photochemical methods are those in which nanoparticles are obtained through the reduction of metal ions, by the action of excited chemical entities formed in the irradiation process, such as radicals.

The main advantages of this type of synthesis are:

a) It is a clean process (as it does not use chemical reducing agents) and easy to perform.
b) It allows the reduction of metal ions *to occur in situ*, as it is a process of high spatial resolution.
c) It is quite versatile, since the synthesis can be done in various media, such as: polymeric films, emulsions, micelles, glasses.

6.2.1 Preparations involving photochemical methods

Hanh *et al*. (2014) were able to immobilize Ag NPs, with an average diameter of 12 nm, on the surface of cotton tissues by *in situ* synthesis using gamma irradiation. At 30° C, the Ag1+ cations were reduced using a dose of 13.8 kGy. An aqueous solution containing $AgNO_3$ at a concentration of 1,5 mmol/L and chitosan (stabilizer) at 1 % was started. The presence of nanoparticles formed in the tissue, at a concentration of 1696 ± 80 mg/kg, was confirmed by SEM and XRD.

The microbial reduction of the nanocomposites prepared against *Escherichia coli* and *Staphylococcus aureus* remained above 99.00 % even after 40 washing cycles. In addition, through tests on rabbits, it has been found that impregnated tissues are innocuous to the skin, proving that this approach holds promise for preparing stable and safe antibacterial tissues.

Kozicki *et al*. (2013) used the screen printing method and type C ultraviolet irradiation (UVC), with energy of up to 10000 mJ/cm2, to obtain silver-based antimicrobial finishes on cotton fabrics. The printing folder was composed of: water; AgNO3 at concentrations of 0,01 to 10 % (w/w); a thermally crosslinkable acrylate copolymer (binding agent) and a thickener. UVC irradiation was responsible for the reduction of part of the Ag1+ cations of the system.

Although there was no formation of Ag NPs, this study presented an easy and quite innovative preparation method. In fact, the material obtained was a composite, consisting of cotton fibers coated by a film containing silver products (Ag0, AgCl and silver oxide) with a size of up to 1000 nm, among which, aggregates and cubic particles.

Initially, it was observed that there was a change in the color of the fabric (Figure 3) and that it depended on the energy of UVC radiation and the content of AgNO 3 in the formulation of the printing paste. The techniques of SEM and EDS proved the formation of the films on the wires.

Figure 3 – Uniform before printing, after UVC irradiation and after a wash.

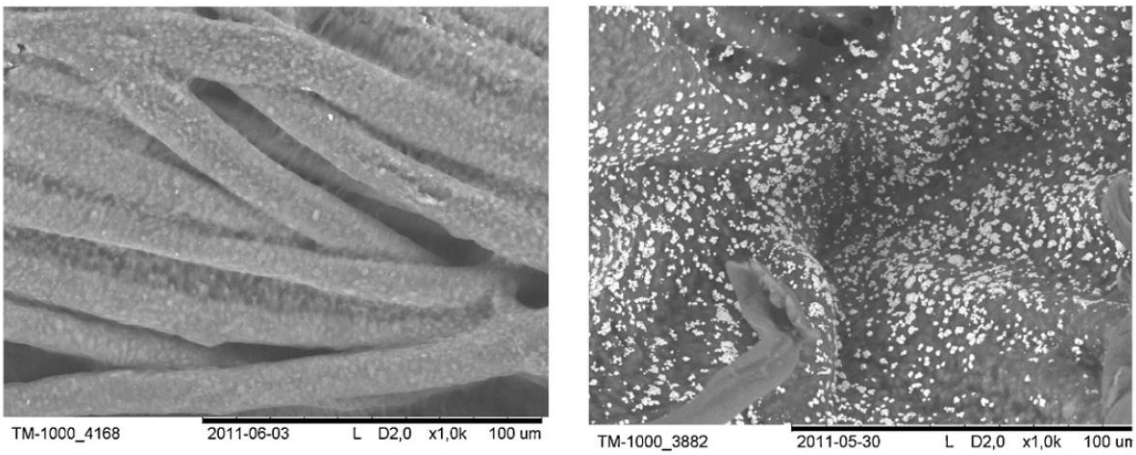


Source: Kozicki *et al*. (2013).

Microbiological assays revealed that the prepared nanocomposites inhibited the growth of the following microorganisms: *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus*. The curious thing is that the antimicrobial activity increased after the washing cycles (50 in total), responsible for exposing the silver products, previously covered by the polymeric film (Figure 4).

Perera *et al*. (2013) investigated two approaches to impregnate cotton fabrics with Ag NPs. In both cases, the precursor was $AgNO_3$. The first of these consisted of the previous synthesis of the nanoparticles using sodium citrate as a reducing agent (under agitation and at 70° C). Then, the tissue samples were immersed in the colloid obtained (for 30 minutes, under agitation and at 50° C), pressed, air-dried and cured in an oven (for 3 minutes and at 120° C).

Figure 4 – Photomicrograph obtained by SEM (magnification of 1000 x).



Source: Kozicki *et al*. (2013).
Note: On the right we have the composite before washing and, on the left, the same after 50 washing cycles. For this sample, the irradiation energy was 10 J/cm2 and the AgNO3 content in the printing paste was 1 % (w/w).

The second was an *in situ* photoreduction, employing ultraviolet radiation to reduce Ag1+ cations. After the tissue samples had been soaked by the nitrate solution, pressed and dried at 50°C for 10 minutes, they were irradiated for a period of 60 minutes, at a distance of 100 mm from the lamp.

The results of UV-Vis and SEM showed that there was agglomeration of the nanoparticles obtained by chemical reduction. On the other hand, the photoreduction provided a uniform distribution of the same on the surface of the tissues. The antimicrobial activity was qualitatively evaluated by the disc diffusion method against *Staphylococcus aureus* and *Escherichia coli strains*. The nanocomposites prepared by photoreduction showed better bactericidal effect, even after repeated washing cycles.

A differential of this study was the comparison between some physical properties of the tissue and the nanocomposites. Tensile strength and elongation at rupture were not affected by the impregnation of the nanoparticles. On the other hand, properties such as the crease recovery angle, the flexion length and the flexion stiffness were not significantly altered only in the nanocomposites prepared by photoreduction.

6.3 PHYSICAL METHODS

Evaporation-condensation and laser ablation techniques are the predominant physical approaches to synthesizing Ag NPs (PERERA *et al*., 2013).

There is also the technique of size reduction by grinding, in liquid medium and in the presence of a surfactant, which can be prolonged for periods of time longer than one month (DURÁN; MATTOSO; MOORS, 2006).

In evaporation-condensation preparations, nanoparticles are synthesized after the starting material is placed in the center of a tube furnace at atmospheric pressure and vaporized by a carrier gas. The drawback is the large amount of energy required for preheating and stabilization of the furnace operating temperature, which, in general, are very time-consuming steps (TRAN *et al*., 2013).

According to El-Nour *et al*. (2010), laser ablation is a process of removing material by irradiation with a laser beam, usually from a solid surface immersed in a liquid medium. It is a way to prepare metallic colloids directly almost always without the addition of chemicals, which implies a purer final material. The characteristics of the nanoparticles formed depend on some parameters, such as: laser wavelength, duration of laser pulses, laser creep, ablation time, liquid medium used and presence or absence of surfactants.

6.4 BIOLOGICAL METHODS

Biological synthesis is nothing more than the reduction of Ag1+ cations by the action of reducing agents, which can also function as stabilizing agents, present in fungi, yeasts, bacteria and plant extracts. These compounds contain functional groups, such as hydroxyl (–OH), carboxyl (–COOH), amine (–NH2), and thiol (–SH). The rate of reduction of metal cations, in general, is high and the process gives in ambient conditions of temperature and pressure (BAJPAI *et al*., 2007; TRAN *et al*., 2013).

The biosynthesis of metallic nanoparticles has been pointed out as a promising green preparation technique, because it employs renewable reagents (instead of chemicals) and non-toxic or very low toxicity solvents and is low polluting (BHATTACHARYA; GUPTA, 2005).

6.4.1 Preparations involving biological methods

Ravindra *et al*. (2010) prepared Ag NPs with an average diameter of approximately 20 nm, using as reducing agents the extracts of the leaves of *Eucalyptus citriodora* and *Ficus bengalensis*, separately.

These extracts, which also aid in the adhesion of nanoparticles to cotton fibers, contain polysaccharides composed of: p-mentane-3,8-diol; β-sitosterol; α-D-glucose and mesoinositol. The

functional groups present in the molecules of the enumerated compounds are able to reduce the Ag1+ cations to nanoparticles, which are additionally stabilized by the chains of these molecules.

In aqueous medium (and under normal conditions of temperature and pressure) were gathered: the extract of the leaves of one of the trees, the cotton fibers and $AgNO_3$. The reduction occurred for a maximum time of 5 minutes. For the complete impregnation of the fibers with the nanoparticles formed, the system was stirred for 24 hours. At the end, the resulting material was washed and dried.

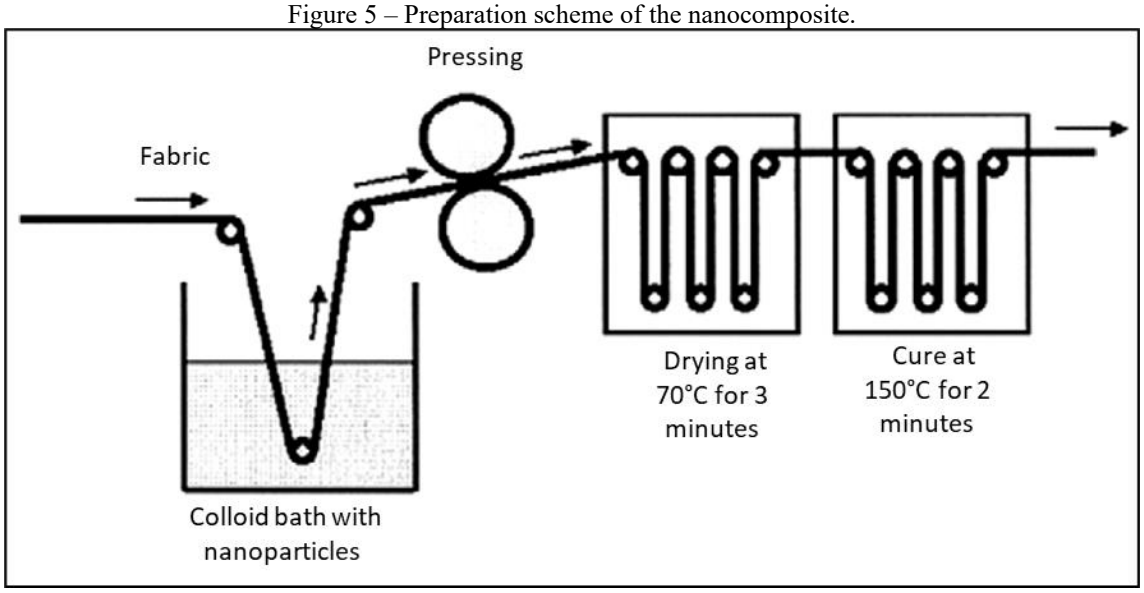
The authors proved that the loaded fibers exhibited excellent antimicrobial activity against *Escherichia coli*. It was also observed that, after an immersion time of around 100 hours, in saline solution, there is the detachment of approximately 25% of the nanoparticles of the nanocomposite.

El-Rafie *et al*. (2010) prepared Ag NPs (with average diameter around 5 nm) using AgNO3 and the biomass filtrate of the fungus *Fusarium solani* as a reducing agent, under ambient conditions and for 48 hours.

Then, the colloid obtained was applied to cotton fabrics, with and without the aid of a binding agent (in this case, the liquid Printofix Binder MTB EG). The preparation scheme of the nanocomposites is shown in Figure 5, where it is possible to observe a process of foulardagem (pressing) and a curing step at 150° C for 2 minutes.

The study determined the antimicrobial activity of the nanocomposites obtained, against the bacteria *Escherichia coli* and *Staphylococcus aureus*, before and after 20 washing cycles. It was found that the average initial microbial reduction was 94 % for the two microorganisms tested. After washing the nanocomposite without the binding agent, this average percentage decreased to 50,85 %. On the other hand, the addition of the binding agent caused the average percentage to decrease to 89.5%.

Figure 5 – Preparation scheme of the nanocomposite.



Source: Adapted from EL-RAFIE *et al*. (2010, p. 780).

El-Rafie *et al*. (2012) deepened the study done in 2010 and optimized the condition for the biosynthesis of Ag NPs with the following parameters: AgNO3 concentration (0.078 g/100 mL), biomass concentration (10 g/100 mL), pH of the reaction medium (12), temperature (25° C) and reaction time (24 hours).

Thus, well-stabilized nanoparticles were obtained at a concentration of 2000 ppm, with an average diameter between 8 and 15 nm. The authors also report that the reduction of $Ag^{1+\ cations}$ occurs by the action of enzymes and proteins excreted by the fungus and present in the biomass filtrate.

Yang *et al*. (2012) proposed, for the first time, a method of preparation of Ag NPs by hydrothermal synthesis, using bacterial cellulose (cellulose polymer synthesized by some bacteria and consists of nanofibers in network) as the only reducing and stabilizing agent, in the form of purified membranes and soaked with AgNO3 solution.

The synthesis was performed in a sealed container of polytetrafluoroethylene (PTFE), at 80° C, and lasted 4 hours. The hydroxyl groups present on the surface of the nanofibers were responsible for the reduction of the $Ag^{1+\ cation}$ and subsequent stabilization of the nanoparticles formed. They were able to obtain nanoparticles with an average diameter between 11.2 and 23 nm. The nanocomposite showed a good bactericidal action against *Staphylococcus aureus,* which was evaluated by the MIC assay, in triplicate and with the appropriate controls.

Although cotton was not used as a matrix, but bacterial cellulose, the proposal was interesting because it employed an environmentally correct preparation method. This process can be experimented with other cellulose compounds (perhaps oxidized cotton fibers) to obtain products with bactericidal action, such as self-sterilizing fabrics.

El-Rafie, El-Rafie and Zahran (2013) synthesized Ag NPs using as reducing agents, as well as stabilizers, water-soluble polysaccharides extracted from four marine macroalgae (*Pterocladia capillacae*, *Jania rubins*, *Ulva faciata* and *Colpmenia sinusa*). The synthesis was developed for 60 minutes, under agitation, at a temperature of 70° C and with the pH of the system adjusted to 10. The $AgNO_3$ concentration was 0.1 mmol/L.

The nanoparticles obtained were characterized by UV-Vis and SEM. The smallest mean diameter was observed for the nanoparticles synthesized using extracts of *Ulva faciata* and *Pterocladia capillacae* (7 nm). The largest mean diameter was observed for those prepared using the extract of *Colpmenia sinusa* (20 nm).

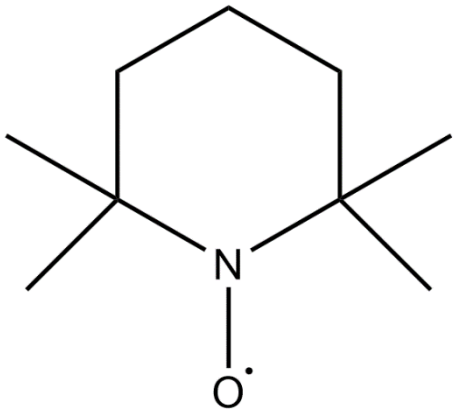
Then, silver colloids were applied to cotton fabrics in the absence and presence of citric acid (2%) or a binding agent (1%). The impregnation of the particles was followed by a drying process (at 70° C and for 3 minutes) and a curing process (at 150° C and for 2 minutes).

The antimicrobial activity of the resulting nanocomposites was evaluated against the bacteria *Escherichia coli* and *Staphylococcus aureus*, before and after a certain number of repeated washing

cycles. The study concluded that it is a function of the previous treatment received by the tissue, the size of the Ag NPs and the species of algae used to extract the polysaccharide. The best result obtained was the one in which the nanoparticles were prepared using the extract of *Ulva faciata* and the tissue was previously treated with the binding agent, even after 10 washing cycles.

Cao *et al*. (2013) deposited, *in situ*, Ag NPs on jute fibers previously submitted to the selective oxidation method by the compound known as TEMPO, which is the radical (2,2,6,6-tetramethylpiperidine-1-yl)oxy (Figure 6). The fibers were immersed in an aqueous solution of $AgNO_3$ at a concentration of 0.015 mol/L, sheltered from light, during the night. The system was then heated in a domestic microwave oven. As the heating time increased from 5 to 10 minutes, the average diameter of the nanoparticles obtained was from 50.0 to 90.0 nm.

Figure 6 – Structure of TIME.



Source: Author (2023).

Jute is a very hygroscopic vegetable textile fiber that contains in its composition, on average, 65 % cellulose. It is extracted from the plants of the genus *Corchorus*, widely cultivated in Asia. The oxidation of the fibers (initially treated separately with aqueous solution of sodium hydroxide (NaOH) and dimethylsulfoxide bath) by TEMPO causes the hydroxyl group of position 6 of the cellulose to be oxidized to an aldehyde or carboxyl group, which will act simultaneously in the reduction of the Ag^{1+} cations and in the stabilization of the nanoparticles formed. This process is carried out under normal conditions of temperature and pressure, with pH adjusted between 10 and 11 and in the presence of sodium bromide (NaBr) and sodium hypochlorite (NaClO).

The authors indicated that the prepared nanocomposite could be useful in applications such as: ultrafiltration, antibacterial dressings, food packaging, water treatment and in the biomedical area.

7 FINAL CONSIDERATIONS

The impregnation of cellulose fibers, especially cotton, with Ag NPs is already a reality to prepare nanocomposites with antimicrobial effect that can be used in health products. Both *in situ* and *ex situ* syntheses are used to obtain Ag NPs.

It is interesting to observe that less aggressive preparation methods are sought to the environment when biosyntheses with various natural reducing agents are proposed. In these, the energy consumption is minimal. Perhaps, for this reason, the physical methods of nanoparticle synthesis have not been prioritized.

Another point that deserves to be highlighted is the concern with the durability of the nanocomposite. Once the nanoparticles are impregnated on the surface of the fibers, they can detach from it, which would lead to a decrease in microbial reduction.

Given this possibility, most publications presented results of tests that verified what happens to the material after a series of washes, either by evaluating the antimicrobial activity or by the silver content in the washing water. Regarding antimicrobial assays, there was a predominance of tests against the bacteria *Escherichia coli* and *Staphylococcus aureus*.

Also to minimize the detachment of the nanoparticles, some binding agents or coating layers were used to better fix the nanoparticles in the fibers. These were also previously treated to improve the adhesion between matrix and load.

It is also possible to emphasize the evaluation of the color of the samples after the impregnation of the Ag NPs, based on the results of color measurements in the CIE scale L*a*b*, even if, compared with the antimicrobial effect, the appearance is not in the foreground.

The techniques that predominated in the characterization of nanoparticles or nanocomposites were: DRX, MET, UV-Vis and EDS. Mechanical assays were not much emphasized in the publications, since they are not determinant for the use of nanocomposites of which the antimicrobial effect is primarily desired.

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SEVEN
publicações acadêmicas

Stem cells of dental origin and their applications: A literature review

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ABSTRACT
Stem cells are undifferentiated cells with the capacity for self-regeneration and formation of functional cells of tissues and organs. Current studies in biotechnology aim to understand and control the differentiation of these cells for scientific applications. Several types of stem cells are derived from dental tissues, including dental pontal stem cells (DPSCs), stem cells isolated from the pulp of exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), apical papilla stem cells (SCAPs) and dental follicle cells (DFCs). These cells have potential for different applications in dentistry and tissue regeneration. Studies have investigated their properties and differentiation capacity for clinical and therapeutic use. The present review aims to evaluate what is known about these cells, as well as the possible clinical applications in regenerative therapies in current dentistry.

Keywords: Dental Stem Cells, Tissue regeneration, Regenerative Dentistry.

1 INTRODUCTION

Stem cells are populations of undifferentiated cells characterized by the great capacity for self-regeneration and duplication, in addition to the potential to originate different types of functional cells that constitute tissues and organs of the organism[1]. Several current studies in the areas of biotechnology seek to understand and control these differentiation processes for use by science[2].

These cells are categorized according to their differentiation potential, being classified into totipotent, pluripotent, multipotent, oligopotent and unipotent. In addition, these cells are also classified according to their origin, divided into embryological stem cells, adult tissue stem cells, resident tissue stem cells, and induced pluripotent stem cells [1].

Mesenchymal stem cells are human somatic stem cells, have attracted attention due to their potential for practical use. Mesenchymal stem cells have low immunogenicity, accumulate at the site of tissue injury, and secrete growth factors, cytokines, and bioactive substances. For these reasons, they have attracted attention due to their potential for therapeutic use[3]. Several types of stem cells have been found in dental and periodontal tissues, evidencing the possibility of extraction and use of these cells in dentistry.[4][5].

Therefore, the objective of this work is the evaluation of the main stem cells of dental origin, as well as the possible clinical applications focused on dentistry due to their high therapeutic potential of tissue regeneration and their other uses in bioengineering.

2 METHODOLOGY

For the development of this literature review, the database was used *PubMed* and *Scielo*, to find articles that addressed the topic related to stem cells of dental origin and their applications in dentistry, using the following descriptors: dental stem cells, tissue regeneration, in Portuguese and English languages. We selected papers with publication date from the year 2003 to the present date (2023) that presented information relevant to this review.

3 LITERATURE REVIEW

3.1 STEM CELLS OF DENTAL ORIGIN

There are numerous types of stem cells originating from dental tissues, such as dental tip stem cells (DPSCs), stem cells isolated from the pulp of exfoliated primary teeth (SHED), periodontal ligament stem cells (PDLSCs), apical papilla stem cells (SCAPs), and dental follicle cells (DFCs)[4][5].

3.1.1 Dental pulp stem cells

In some studies, mesenchymal stem cells were isolated and obtained from the dental pulp of deciduous teeth, first premolars and third molars extracted, these being called Dental Pulp Stem Cells. DPSCs have the ability to differentiate into odontoblast-like cells and produce mineralized tissue both in *vivo* and *in vitro*. In addition, these cells can differentiate into bone, muscle, endothelial, chondrocytes and adipocytes[3][7]. Also, the production of dentin-like structures with pulp tissue inside and one and a lining of odontoblastic cells after DPSCs transplantation in immunocompromised rats have been observed in studies[5].

3.1.2 Stem cells from the pulp of exfoliated primary teeth

Multipotent stem cells were found in exfoliated human deciduous teeth (SHED), which have characteristics such as high proliferation rate, clonogenic and differentiation capacities for different tissues, such as bone tissue, nerve cells, adipocytes and odontoblast([5][3]. In comparison, the SHEDs demonstrated a higher proliferation rate in relation to the DPSCs, but they have difficulties in forming a complex similar to the complete dentin-pulp in vivo[3][6].

3.1.3 Periodontal ligament stem cells

Mesenchymal stem cells were found in the periodontal ligament, with the capacity to differentiate into mesenchymal, ectodermal and endodermal strains *in vitro*, which suggest the multipotency of these cells[8].

The PDLSCs, under certain experimental culture conditions, differentiated into cementoblast-like cells, adipocytes, and collagen-forming cells. These cells demonstrated the ability to generate structures similar to cementum and periodontal ligament, and contributed to the repair of periodontal tissue[9].

3.1.4 Apical papilla stem cells

The apical papilla is described as a connective tissue positioned at the root apex of teeth that are still developing[10], which becomes present from at least two-thirds of the root has already been formed, being well visualized histologically above the epithelial diaphragm. Although the apical papilla is a continuation of the dental pulp, in cases of pulp necrosis, the papilla fights the process of necrosis of the pulp and tends to survive due to its access to the apical collateral circulation[11].

Another type of mesenchymal stem cells were isolated from the apical papilla of permanent teeth with incomplete development. SCAPs have the ability to differentiate into several different cell lines, being odontoblasts, osteoblasts, nerve cells, adipocytes, chondrocytes and hepatocytes, demonstrating a high therapeutic potential in the large area of health[12].

3.1.5 Dental follicle cells

The dental follicle is an embryonic connective tissue, derived from the neural crest cells, that surrounds the enamel organ along with the developing dental germ papilla. In addition to the function of forming the periodontium tissues (alveolar bone, periodontal ligament and cementum), the follicle plays an important role in coordinating tooth eruption by regulating the resorption and formation of the alveolar bone, thus evidencing its crucial role in dental development[13][14].

DFCs are characterized as pluripotent stem cells, precursors of periodontal tissue, and can differentiate into cells of the alveolar bone, periodontal ligament and cementum *in vivo*. In addition, they also have the ability to differentiate into adipocytes, chondrocytes and nerve cells *in vitro*. More recent studies have also shown the ability to differentiate into cardiomyocytes and saliva-producing glandular cells[14].

3.2 APPLICATIONS OF DENTAL STEM CELLS IN CLINICAL DENTISTRY

3.2.1 Regeneration of dental tissues

Currently, the treatment for caries diseases, for example, is characterized mainly by the removal of carious tissue and its replacement by a synthetic material for the restoration of dental form and function[15]. In some studies, it has already been possible to use a solution of different growth factors to form an odontogenic environment, capable of inducing the differentiation of DPSCs into functional odontoblasts for the formation of a regular dentin-pulp complex[16].

Still, other studies have shown the use of mesenchymal stem cells with the use of certain growth factors and also biomaterials for the formation of the dental organ, which was later successfully transplanted into an immunocompromised host with the necessary blood supply. In all studies, the formation of enamel and dentin was evidenced[6].

In a certain research, a three-dimensional culture method of for the growth of teeth in the jaw of the rat was used. Thus, epithelial and mesenchymal cells were seeded sequentially in a drop of collagen gel and then implanted in the dental cavity of adult rats. With this technique, the dental germ produced formed a tooth with all dental structures, such as odontoblasts, ameloblasts, dental pulp, blood vessels, crown, root and even periodontal tissues, such as the periodontal ligament and alveolar bone[17].

In the case of pulp damage, usually irreversible, there is the possibility of Endodontic Regeneration Therapy (ERT), which consists of replacing inflamed or necrotic pulp tissue through tissue regeneration in cases of endodontic treatments. In RET, there is the transplantation of stem cells of dental origin (DPSCs, SCAPs, SHEDs and PDLSCs) combined with growth factors and biomaterials within the root canal, resulting in the formation of the dentin-pulp complex resulting from the differentiation of these stem cells into odontoblasts. The ideal pulp regeneration process should not only form the same structure as the natural dental pulp, but also restore its function, with the formation of blood vessels and innervations[18][19].

3.2.2 Regeneration of periodontal tissues

Traditionally characterized as infectious inflammatory diseases resulting from the interaction of the oral biofilm and the inflammatory and immune response of the host to combat microorganisms. However, this response can be harmful to periodontal tissues, causing a progressive loss of tissue at the site of injury[20].

The unique anatomy and composition of periodontal tissues results in a complex regeneration process. Current treatment techniques focus on the control of the microbiota at the site, reduction of inflammation and removal of injured tissues for the regeneration of periodontal tissues with the

formation of a long junctional epithelium binding tissue, which does not provide a strong connection between the dental root and the adjacent gingival connective tissue[20][21].

With this, several processes related to tissue regeneration have been studied, one of them being tissue engineering based on the use of stem cells that with certain conditions, differentiate into cells of periodontal tissues, thus restoring their function. Stem cells from the periodontal ligament PDLSCs gain more visibility, given their ability to differentiate into cementoblasts and osteoblasts[21]. In addition, studies have shown that stem cells from the periodontal ligament can be inserted into sites of periodontal defects without adverse immunological or inflammatory consequences[22].

Stem cells derived from the dental follicle (DFCs) were able to form periodontal tissue with occasional blood vessels, and are also considered for the treatment of periodontitis and reconstruction of the insertion period[23].

3 CONCLUSION

Based on the articles studied, it is clear the range of options for obtaining and using dental stem cells, playing an essential role in regenerative dentistry. Therefore, it is necessary to continue the rigorous research on the subject so that more and more therapeutic possibilities for injuries in the field are discovered. In addition, the importance of the dentist in obtaining and processing the cells from dental elements extracted in procedures is notorious, so that there is no biological waste of these cells with enormous potential. Cell Processing Centers must continue to fulfill their important role of cultivating, processing, storing and delivering stem cells under conditions where they are capable of being used in properly regulated advanced therapies.

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Assessment of access to health products, technologies and services among the BRICS through their health indicators and their participation in global health policy

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ABSTRACT
In the WHO Constitution, the preamble states that the health of all peoples is fundamental to the attainment of peace and security, and that the achievement of any state in promoting and protecting health is of value to all. Thus, the global health issue is part of all discussions of global diplomacy in the 21st century. Since 2001, identified as the main countries in their regions, Brazil, Russia, India and China have grown in economic terms in addition to adopting activist foreign policies. Identified as a geopolitical bloc since 2006, the BRICS believe they have the right to play more relevant roles in the management of the global order in the 21st century. Despite exhibiting many regional differences, the member countries of the BRICS strive to be recognized as members of the same group through some strategies such as participation in international institutions and the effort to create connections between development and foreign policy. Many analysts suggest that the BRICS are more active in global health. Recently, this group of countries increased their cooperation in the field of social development, environmental protection and health, institutionalized regular meetings of their ministers of health, with stated objectives to address emerging health threats, both for their populations and globally. Thus, we consider that the presentation of a comparative panel of health indicators of the countries that make up the BRICS is useful for researchers in the area.

Keywords: BRICS, health diplomacy, global health, health indicators.

1 INTRODUCTION

The numerous challenges of the twenty-first century seem to require a reassessment of old paradigms and the creation of innovative mechanisms to deal with the world's most complex challenges, from climate change to financial instability, through failed states and nuclear proliferation, problems of the passportless, which cannot be solved at home, require new forms of cooperation. Classified as a difficult undertaking, managing this geopolitical transition is the biggest challenge for global governance. 1

Since 2001, Brazil, Russia, India and China have been growing in economic terms (China has an economy that is equivalent to 80% of the American economy), as well as adopting activist foreign policies. Thus, they believe they have the right to play more important roles in the management of the global order in the twenty-first century. Although the acronym BRIC (Brazil, Russia, India and China) was first coined in 2001 by an economist at the investment bank Goldman Sachs, these countries

identified themselves as a geopolitical bloc in 2006. They held their first meeting in 2009, repeated annually since then, in 2010, BRIC became BRICS when South Africa was invited to participate. 1.2

Despite exhibiting many regional differences, BRICS member countries strive to be recognized as members of the same group, through some strategies such as participation in international institutions and the effort to create connections between development and foreign policy.

Although some authors question the narrative that the emerging powers alter this pre-established order since fundamental differences such as nuclear regime, financial terms, role in global trade, role in peace operations, force us to remember the limitations of the concept of emerging powers. Others seem to agree on the fact that the rise of emerging countries is irreversibly changing the international system, creating a true and inexorable trend toward multipolar age. 2.3 However, in the face of global challenges it will become increasingly important to investigate the ideas and preferences of emerging powers.1One such effort lies in increasing influence in various areas such as global health, via its domestic health and international assistance programs, and its activism in international for a.4

In order to assess the prominence of the BRICS in the global health arena, we justify the preparation of this work that includes a diagnosis of the health area and its progress in these countries, focused through the description of their health indicators and their advances in the influence of the BRICS in global health diplomacy.

2 REGIONAL HEALTH ACTIONS OF THE BRICS COMPONENT COUNTRIES THROUGH THEIR ECONOMIC INDICATORS

The BRICS have historical differences, different political structures, vary in population size, and exhibit variable progress in economic growth and social development. However, although politically, culturally and demographically diverse, these countries share specific health challenges: large populations (within the regional and global perspective), high incidence of infectious diseases, including HIV, and chronic diseases that constitute a high financial burden. From the individual nuances in the challenges in the health area, the BRICS behave as a group, in the construction of a viable system of Universal Health Care (UHC). 5,6 In this context of contrasts, the ongoing construction of the UHC offers a current comparative experimental model of a set of actions, examples of ambitious middle-income countries, trying to make their mark on the global scene. From here we will describe the socio-demographic and health indicators of each member country of the BRICS group, offering with this data, a comparison and convergence panel for readers. It is also worth remembering that health indicators are present in five items of the eight Millennium Development Goals. They are: 1-Eradication of hunger and extreme poverty; 2- Achieve primary education universally; 3- promote gender equality and increase women's power; 4- reduce infant mortality; 5- improve maternal health; 6- Fight HIV/AIDS infection, malaria, and other diseases; 7 - ensure environmental sustainability; 8-

Develop global development partnerships. This fact adds to the importance and contribution of the study of the models under construction of UHC in global governance processes. 6,7,8

2.1 BRAZIL

Brazil has a total population of 198,700 million, with 8,515,767,049 surface area in square kilometers, a population density of 23 inhabitants per square kilometer with 85% of the total population living in urban areas. It is a federal republic with 26 states, a federal district and 5564 municipalities. The current Brazilian constitution established that health was a universal right of all citizens, which led to the unified health system (SUS), financed mainly by the federal government and by the states and municipalities, through taxes and social contributions. Health services are provided by public and private providers. The private sector is dominated by a growing health insurance market, although coverage is uneven and higher in wealthier areas, covering an estimated 25% of the population (48 million people). In 2010, the Brazilian private health market was estimated at about 36 billion dollars, slightly lower than the 38 billion by public providers. Access to the health system has increased in recent years, with the introduction of the Family Health Program (PSF), which, however, has expanded substantially in the less wealthy regions of the country and does not offer easy access to secondary and tertiary health sectors. The great benefit of the FHP is well defined in primary care and prenatal programs, in popular pharmacies and in the national immunization program, in addition to the national transplant program. Individual payment (by the user himself) in the purchase of medicines and use of procedures varies between income groups. The most disadvantaged users are those from the lower middle class, who cannot afford health insurance and spend much more out-of-pocket expenses for diagnostic procedures. The private sectors are more widely used at the expense of the public sector, and evidence suggests that the size of the private sector creates unfair competition, which contributes to inequality, inefficiency and low effectiveness. Evidence also suggests that the Ministry of Health is working to correct distributive health inequalities, both of doctors and infrastructure, but faces strong opposition from medical associations. This opposition is often related to the low remuneration of the doctor and also appreciation of his career. In addition, the redistribution of these professionals to some geographic areas of the country demands complementary actions related to socio-economic, infrastructure and security development. The main challenges of Brazil to obtain universal health coverage are associated with its rapid demographic and social transition, with the increase of the elderly population and consequently of chronic diseases. Private interest groups continue to influence government decisions, and tax subsidies for private health care contribute to an expanding private sector. The government must respond to these challenges through firmer commitments to building a larger and more effective public health sector. (5.9)

2.3 RUSSIA/RUSSIAN FEDERATION

Russia has a total population of 143.5 million, with a surface area of 17,075,400 square kilometers, and a population density of nine inhabitants per square kilometer with 75% of the total population living in urban areas. It is a presidential federal republic with 83 regions. Although the Soviet Constitution was the first in the world to guarantee the right to UHC, social status, working conditions and geographical residence for all its health systems deteriorated after the collapse of the Soviet Union, despite showing improvements in recent years. The public health sector is dominant. Services covered by public funds include inpatient, outpatient care, urgent care and supplies for special groups of the population and regional budgets cover the unemployed population. Starting in 1993, employers began to contribute to mandatory health insurance for their employees at a rate of 5.1% (2011). The shortage of funding after the collapse of the Soviet Union was partially offset by increased private spending. Public facilities were allowed to charge for free complementary health services. Private consumption amounted to 40% of total expenditure in 2011, with 88% of private health consumption. Recent government policies are centered on improving and equalizing access to quality care. A national health project (2006-2013) and several regional programs focused on equalizing access, consolidating administration and increasing contributions. This reform is removing the removal of barriers for private health care providers.

Russia's challenges in achieving universal health coverage are to decrease high mortality, with the government aiming to increase life expectancy to 75 years by 2025. For this Russia needs to modernize its health system, offer effective care, but also reinvigorate its efforts in health promotion, and more homogeneous access in the various geographical regions. These efforts will require increases in resources, which do not seem to be being visualized in the fraction of GDP used for health in recent years. In addition, combining guarantees of the provision of free health care with the reality of private financing would be an additional challenge. (5.9)

2.4 INDIA

India has a total population of 1,236.7 billion, with surface area 3,287,263 in square kilometers, a population density of 416 inhabitants per square kilometer, with 32% of the total population living in urban area. It is a federal republic with 28 states and seven territorial unions. Public financing of health is only 1.04% of GDP and the user's own out-of-pocket spending is very high. In 2010, 60 million inhabitants live below the poverty line. India's mixed health system has seen a progressive decline in public health services with a dominant growth of unregulated private health plans. The National Rural Health Mission (NHRM) has been improving maternal and child health, but does not provide primary and secondary health care. Various government initiatives have made efforts to improve primary care, and even those of high complexity, still far short of the needs of the population. In 2010, a planning

mission from India set a target of an increase in public health funding to 2.5% of GDP by 2017, as well as recommending investments for health workers, creation of effective public health sector and health management frameworks, as well as access to essential medicines, participation. This development plan proposes a near doubling in public funding and adds to the NHRM an urban component. The main challenges in achieving an effective UHC are associated with not only technical but also political issues. The public sector is overly centralized, rigid, and poorly managed, and because the private sector serves the needs of much of the population, it is more regulated and is made up of both formal and informal providers. In addition, shortages of qualified personnel, paramedics, medical supplies and equipment seriously hamper India's efforts to enable universal health care. (5.9)

2.5 CHINA

China has a total population of 1,350.7 billion, with 9,669,512 surface area in square kilometers, with a population density of 145 inhabitants per square kilometer with 52% of the total population living in urban areas. They are a republic with 23 provinces, five autonomous regions, and four municipalities. The country is experiencing a huge economic, social, environmental and emergency and disease transformation. The population is demanding an increase in health services and a reduction in personal spending on their health care. The epidemic of respiratory distress syndrome (SARS) in 2003 served as a catalyst for this process of governmental health care. Three systems NRCMS (New Rural Cooperative Medicine Scheme), URBHI (Basic Health Insurance for Urban Residents) and MFA (Health Care Financial System - for Poorer Citizens), complement each other and have expanded the scope of health service benefits. However, these efforts need to be standardized and a better health care reimbursement plan added. Its biggest challenges to access to UHC, in addition to the enormous political transition at the regional and national level, include the aging of the population and the increasing prevalence of chronic diseases in these populations. Prevention actions are still very inefficient and access to health services varies from region to region. Actions to control health costs are urgently needed, so as not to jeopardize a universal access program. (5.9)

2.6 SOUTH AFRICA

South Africa has a total population of 52.3 million, with 1,221,037 surface area in square kilometres, with a population density of 43 inhabitants per square kilometre with 62% of the total population living in urban areas. It is a quasifederal republic with nine provinces.

Because of legal apartheid, considerable disparity in health indices between races remains. For example, life expectancy at birth in 2004 was 49 years, while that of whites was 64 years, and there were inequalities between geographic areas. Despite the constitutional obligation to access health rights, the system remains deeply divided with the wealthiest population with private health coverage

and the rest more dependent on inadequate resources from public sector services. The health system falls far short of what is needed for equity in care including many barriers, especially for the poor population. In addition to the few social and economic benefits available to this population, it is also a victim of the explosion of diseases such as AIDS, in addition to the shortage of health professionals among sectors of geographical areas. There is no mandatory upfront payment, little funding or tax-based, which accounts for just over 40% of total funding and large disparities in spending. The government is committed to a pathway process to UHC over a 15-year period, with three five-year phases. According to the plan, an initial phase will create efficient conditions for the equitable provision of high-quality public services by going towards improving infrastructure deficiencies, enabling essential medicines, with a particular focus on primary care, including the presence of health agents and nurses for this population, as well as the construction of hospitals and nuclei of district authorities. At a later stage, the commitment will be to establish the National Health Insurance Fund with joint action of public and private providers. The challenges are numerous, from the resistance of private providers to ongoing government plans, to the difficulty of obtaining human resources with adequate training. (5.9)

In summary, the challenge of the BRICS component countries is to a greater or lesser degree for each of the following:

1- Increase in insufficient public spending; 2- Administer the public and private mixed health systems; 3- guarantee of equity; 4- the demands for more human resources; 5- Change Management Demographics and disease charges; 6-and address the social determinants of health. The strongly contested political nature of health reform is also evident in each country.

2- Each of the BRICS has some form of national commitment to ensuring health and is engaged in driving the necessary reforms. However, everyone has some way to go. While the formation of the BRICS was initially based on macroeconomic interests, these countries exhibit the potential to exert regional and global influence and become important leaders in the realm of social policies, using their internal learning in the construction of a universal health care system. (5,8) The attached table, based on data from the World Bank, summarises the most relevant data for the evaluation and progress of the indicators. (9)

3 FOREIGN HEALTH POLICY OF CHINA, BRAZIL AND INDIA, AND ITS IMPACT ON GLOBAL GOVERNANCE

The relationship between health and foreign policy is complex. A large number of domestic ministers and agencies with potentially competing agendas compete to be heard in international

negotiations. Traditionally, foreign policy has approached health issues historically from two prominent patterns. "The first of these is through specific threats to health such as 'cross-border' cooperation to control the spread of communicable diseases that generate international problems. The second approach uses cooperation, offering health care to increase the influence of the state or ensure better relations with other states. (6.8)

Many authors have tried to introduce frameworks for analysis in this area, particularly when considering the themes of global health governance. Stuckler and McKee 6 created five metaphors as motivation for global actions in health: global health as foreign policy, as security, as charity, as investment and as public health. Lee identified four main discourses in global health governance: biomedicine, economics, human rights and security by arguing that neoliberalism is also important transcending the other four. 6,8 In a more recent analysis Kickbusch 8 outlined the central foreign policy objectives as the realization of security, the creation of economic wealth, support for the development of low-income countries, and the protection of human dignity. The author identifies three global agendas that link health to foreign policy. Is it security, covering the fear of global pandemics, bioterrorism, humanitarian conflicts and natural disasters, economic, covering the impact of health on development, the impact of outbreaks like SARS or Ebola? In the global markets and the global market in health goods and services. And social justice seeing health as a social and human right value, linked to "The United Nations Millennium Development Goals", access to medicines and primary health care and calls in high-income countries to invest in global health initiatives. Similarly, it has been examined whether these discussions of global health security are really about global health, or preferably about national security fears, particularly of industrialized countries. 10th

However, whatever classification is used, they all agree that there are different reasons for engaging in global health activities with health and foreign policy coexisting to different extents.

During the twentieth century, the United States played the catalytic role of global health actions through its foreign policy. Since its economic crisis, this role has weakened and the global system is looking for growing powers that have the means or the will to lead in global health matters. Could emerging powers like Brazil, China, India, Russia or South Africa, do it?2, 6.8

Many analysts want the BRICS to be more active on issues involving global health, although the level and form of this partnership is unclear. At what level will they align their foreign health policy? What alliances are they looking for? Will they set regional agendas different from current global health priorities?8

What has been seen so far are the movements towards increased cooperation in the field of social development, environmental protection in health, as well as the institutionalization of regular meetings of the ministers of health of emerging countries, with objectives addressing all emerging health threats at the global level. 7, 8.10

In September 2006, SR Ministers from seven countries (Brazil, France, Indonesia, Norway, Senegal, South Africa and Thailand) participated in a meeting that explored how international policy could contribute to the fight on important health issues and how the health dimension could benefit foreign policy. This meeting gave rise to the idea of the Global Health in Foreign Policy Initiative (FPGHI), resulting in 2007 in the Oslo Declaration that was classified as an icon of the importance of the study of health as a foreign policy issue, offering a stimulus for the creation of an emerging concept of "global health diplomacy". 7 This concept provides for a set of relationships, according to which health policy is used to achieve foreign policy objectives. This coalition, with regard specifically to the BRICS, is manifested by joint declarations such as the one made before the "63rd World Health Assembly 2010", and in formal structures, with meetings with heads of state and ministers of health (BRICS Health Ministers 2011; Xinhua 2011; BRICS information Centre 2013.4,8An example for the systematic understanding of the links between foreign policy motivations and BRICS engagement would be in the specific area of access to medicines and in actions towards achieving universal health coverage, in addition to including in the domestic agenda economic growth, trade, foreign investment, the fight against poverty and the creation of social protection. These last agenda items are considered of great importance, since for the BRICS there is no simple correlation between health and wealth. The rapid growth of their economies has led to major problems, such as rapid urbanization, high rates of urban poverty, air pollution, inclusion of new habits and lifestyles, in addition to higher life expectancy at birth and the consequent increase in the elderly population and decrease in the fertility rate. Political solutions and huge investments seem to be needed at both the national and global levels to overcome these challenges. By 2035, 35% of the world's population will live in China or India, which leads the World Health Organization to conclude that through domestic actions on issues such as universal health coverage, the BRICS will be able to effectively affect the global health agenda. These movements could offer a means to achieve better health conditions for all, improve international relations, and promote health as a human right and a global public good.4,8,10

However, from the evaluation of the health indicators of each country individually, we observe that for each of them it has a more or less long path, with numerous challenges to follow. From an individual point of view, the countries that make up the BRICS present specific difficulties in conducting this process.

The social and political environment, as in the case of women in China and India, the high prevalence of alcohol abuse among middle-aged men and women in the Russian Federation, and high prevalence of HIV infection in South Africa interfere with mortality rates. The Russian Federation has the highest average income, but is among the worst in health, and has evolved little in the last 20 years. India has the lowest average income, but has managed to supplant South Africa in terms of relative health performance inequality. Brazil has a similar average income to South Africa most exhibited

improvements in health performance among all age groups. This high prevalence in South Africa has been attributed to HIV epidemic infection, continued rural poverty, and inefficient deployments of high-impact interventions. While China has half the average income of Russia, it has surpassed Russia Only the elderly remain in inequality during all these years in China. In terms of comparative performance, Brazil has the second performance in health after China, from its economic reforms and demographic transition in the mid-80s, perhaps due to the implementation of the integrated health system and family health programs. Although these initiatives do not fail to present their setbacks and shortcomings, they have contributed to substantial improvements in health performance and health equity in Brazil. In positive terms, Russia has embarked on important actions in its commitment to combat non-communicable diseases, and China has a short-term goal of increasing the value of its health investment to $1.31 trillion, followed in this effort by South Africa, which also announced in 2014 a substantial increase in its health spending. India launched the world's largest food subsidy plan in 2013 worth $22 billion a year. These investments clearly highlight the possibility of a positive impact on the post-2015 global health agenda, which enables the use of global health as a "Soft Power" in the pursuit of the objectives in the international policy of each BRICS component country. 6,8,10

In terms of geopolitical position, the BRICS align themselves with the countries of the developed world as partners and not as donors, adhering to the principle of non-interference, establishing regional and global networks through financial aid, but mainly in the exchange and cooperation in the form of technological resources and knowledge transfer. Although in economic terms, sustaining health prominently in foreign policy is becoming more difficult because the international economic context and domestic fiscal crises adversely affect governments, societies, international organizations and non-state actors. Adding to this, it is known that health has been neglected in foreign policy and diplomatic practice although global health is an urgent foreign policy issue of our time. Some authors suggest that diplomats need to acquire more specific knowledge in this area by increasing the level of trust needed between established and emerging powers for diffuse reciprocity to work sufficiently. 4.8

In summary, the academic analysis of the BRICS (more than the BRICS countries individually) shows that it has increased its influence in the last five years, but it remains very little understood. In a recent Hammer 2 review they did not find much evidence that BRICS influence global health, although they are more active and vocal, leading movements such as universal health coverage (UHC) or in the production of generics. However, the challenge would be to harness that momentum and convert political will into action. This momentum, overcoming the multiple obstacles, could become fundamental actions of the BRICS in global health diplomacy by defining priorities for an integrated post-2015 agenda privileging global governance on issues that revolve around the health sector, in particular trade, intellectual property, climate change and food and water security. 4,6,8,10

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ANNEXES

Table I-Comparison and progress of the * BRICS Socioeconomic and Health Indicators**

1990 and 2010

	Brazil	Russia	India	China	South Africa
Expectation	**1990**	**1990**	**1990**	**1990**	**1990**
of life at birth	66,7	67,6	58,7	69,5	61,8
	2010	**2010**	**2010**	**2010**	**2010**
	73,2	67,6	65,7	74,9	55,2
Mortality	**1990**	**1990**	**1990**	**1990**	**1990**
maternal	120,0	74	600	120	250
(100000 born	**2010**	**2010**	**2010**	**2010**	**2010**
alive)	56	34			
			200	37	300
Rate of	**1990**	**1990**	**1990**	**1990**	**1990**
mortality below					
of the 5 years (by	58,8	27,3	114,2	48,9	62,3
1000 born					
alive)	**2010**	**2010**	**2010**	**2010**	**2010**
	16,8	12,5	63,4	15,9	52,6
Prevalencia do HIV					
in adults between 15-	0,3%	0,8-1,4%	0,3%	<0,1 %	17,3%
49 years(%,year) (2011)					
Density of					
physicians (per 1000	1,76(**2009**)	4,3(**2006**)	0,65(**2009**)	1,46(**2010**)	0,76(**2011**)
individuals./year)					
Probability of death between 30-70 years of chronic diseases (2008)	20%	32%	27%	21%	27%
Water and Sanitation	**1990**	**1990**	**1990**	**1990**	**1990**
Prevalence of	16,7	1,0	74,5	7,1	13,2
open	**2010**	**2010**	**2010**	**2010**	**2010**
defecation	4,0	1,0	50,8	0,8	7,0
Population Rural	**1990**	**1990**	**1990**	**1990**	**1990**
	26,1	26,6	74,5	73,6	48
(% total	**2010**	**2010**	**2010**	**2010**	**2010**
population)	15,7	26,6	69,1	50,8	38,5
Health Expenditures (% of total GDP) 2010	**9,0**	**5,1**	**4,1**	**5,1**	**8,9**

The social function of the principle of insignificance and its applicability by the police authority

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ABSTRACT
This scientific article aims to analyze the social function of the principle of insignificance and its applicability within the scope of the police authority. The principle of insignificance is a doctrinal and jurisprudential construction that seeks to exclude the typicality of behaviors that, despite formally qualifying as criminal offenses, are considered socially irrelevant. The present research was based on a bibliographic review, pertinent legislation and analysis of judicial decisions related to the theme. The study highlighted the importance of the principle of insignificance as an instrument to contain the punitive power of the State, avoiding the criminalization of conducts with low social impact and focusing the resources of the criminal justice system on more relevant cases. In the context of the action of the police authority, the applicability of the principle of insignificance gains relevance, since it is the responsibility of these bodies to carry out preliminary investigations and apply precautionary measures. The approach of insignificance by the police authority can avoid the initiation of unnecessary criminal proceedings, directing the efforts of the judiciary towards the repression of more serious conduct. The study pointed out that the application of the principle of insignificance by the police authority requires a careful and sensitive analysis of the particularities of each case. It is essential to consider factors such as the absence of relevant injury or danger, the minimal offensiveness of the conduct, the inexpressiveness of the legal injury and the absence of social disapproval. The results obtained indicate that the proper application of the principle of insignificance by the police authority contributes to a more efficient and fair performance, avoiding overloading the penal system and preserving the social function of Criminal Law. However, the importance of solid and up-to-date training for professionals in the area of public security is highlighted, as well as the adoption of objective and clear criteria in the analysis of cases.

Keywords: Principle of insignificance, social role, criminal law.

1 INTRODUCTION

The social function of the principle of insignificance and its applicability by the police authority are topics of great relevance and interest in the field of Law and, in particular, for the criminal sciences. The principle of insignificance, also known as the principle of trifle, aims to prevent the criminalization of conduct of low impact or minimal harm to the legal good protected.

In the context of Criminal Law, it is essential to understand the scope of this principle and how it can be applied by the police authority in the exercise of its attributions. The social function of the principle of insignificance lies in avoiding unnecessary and disproportionate criminal prosecution in the face of minor offenses, thus ensuring the efficiency and rationality of the penal system.

In this article, we seek to analyze the social function of the principle of insignificance, exploring its origin, legal basis and the criteria established by doctrine and jurisprudence for its application. In addition, we will examine the importance of the performance of the police authority in the correct identification of situations in which the principle of insignificance can be invoked, contributing to a fairer and more efficient performance of the criminal justice system.

It should be noted that this principle is the result of the historical evolution of legal science, because as is known, in past periods of history illicit conduct was punished with excessive force and disproportion. Only with the passage of time and much effort was it possible to arrive at the current legal format of the country. What is currently perceived is that the laws that govern the Brazilian legal system are fairer and proportional, in addition, the bias of decarceration existing in the Magna Carta and therefore in other areas of public law is notorious.

Through this research, it is intended to contribute to the deepening of knowledge about the social function of the principle of insignificance and its applicability by the police authority, providing a reflection on the limits of the penal system and the importance of a proportional approach and focused on the effectiveness of the criminal process.

2 MATERIAL AND METHODS

The method employed in the current article is the logical-behavioral-investigative form. The inductive method was used to identify the fragments of knowledge, so that, when they are related, they become a whole. Bibliographic research was carried out in books, in jurisprudential collections and in legislation in general.

3 RESULTS AND DISCUSSIONS

This scientific article aims to analyze the social function of the principle of insignificance and its applicability by the police authority. Based on extensive bibliographic research and jurisprudential

analysis, relevant results were obtained that contribute to the understanding of this principle in the context of the criminal justice system.

The results of the research indicate that the social function of the principle of insignificance is to limit the punitive action of the State, directing the resources of the justice system to cases of greater severity. This principle seeks to avoid the criminalization of conduct of low social impact, whose punishment is not proportional to the objectives of the penal system.

With regard to the applicability of the principle by the police authority, the results reveal that there is an important role played by this institution in the preliminary analysis of the typicality and insignificance of criminal conduct. The police authority plays a fundamental role in the evaluation of the materiality and authorship of the crimes, in line with its functional attribution also identifies situations in which the principle of insignificance could be applied.One of the main discussions raised by the results obtained is the need for respect for the competencies of each agency, considering that the police authority does not have formal legitimacy to decide on the insignificance of the conduct of the subjects.

It is essential that there is, initially, a legislative change in the police competence, allowing it to have greater freedom for discretionary application, increasing its list of competences in this matter. It should be noted that, currently, it is impossible for a body to exceed its legal competence and at the same time, not to render null and void the investigative and criminal process.

In addition, the results highlight the importance of a collaborative action between the police authority and the Public Prosecutor's Office, aiming at a joint and judicious analysis of the cases. The exchange of information and dialogue between these institutions are essential for the correct application of the principle of insignificance, preventing conduct of low social impact from being unnecessarily brought into the criminal justice system.

However, the results also reveal some challenges related to the applicability of the principle of insignificance by the police authority. The lack of clear and uniform guidelines can lead to divergent interpretations and legal uncertainty in their application. In addition, social pressure and the need for quick results can negatively influence the analysis by the police authority, leading to a greater number of cases referred to the criminal justice system.

Thus, the results obtained point to the importance of a legislative improvement in order to ensure an adequate and uniform application of the principle of insignificance. In addition, the relevance of dialogue between the actors of the criminal justice system is highlighted, seeking mutual understanding and the construction of clear guidelines for the analysis of the applicability of this principle.

3.1 CONCEPT OF THE PRINCIPLE OF INSIGNIFICANCE

The principle of insignificance, also known as the principle of trifle, is an important concept of criminal law that seeks to limit the intervention of the State in cases where the fact practiced by the agent is of minimal relevance or has low social impact. This principle is based on the idea that the penal system should deal only with the most serious conducts, leaving aside those that do not cause significant damage or that do not represent a concrete threat to the protected legal assets.

On the subject, Capez (2022, p. 27) adds:

> If the purpose of the criminal type is to protect a legal good, whenever the injury is insignificant, to the point of becoming incapable of harming the protected interest, there will be no typical adequacy. It is that in the type are not described conducts incapable of offending the protected good, which is why damages of no amount should be considered atypical facts.

One of the main scholars who addresses the subject is the renowned Brazilian jurist Luiz Flávio Gomes. In his work "Criminal Law - General Part", Gomes (2015) emphasizes the importance of the principle of insignificance as an instrument of humanization of criminal law and highlights that its application is directly linked to the principles of fragmentarity and minimal intervention.

Brazilian legislation does not provide an explicit definition of the principle of insignificance, but it is possible to find a basis in the Criminal Code. Article 20 of the aforementioned Code provides that "the agent who, by his will, practices the act in a state of necessity, in self-defense, in strict compliance with legal duty or in the regular exercise of law, does not commit a crime." This legal provision points to the need to consider the relevance of the fact to the configuration of the crime.

It is important to emphasize that the application of the principle of insignificance requires a careful analysis of the concrete case, taking into account the proportionality between the conduct and the punitive reaction of the State. In addition, it is necessary that the agent has not practiced the fact habitually, seeking to benefit from impunity.

The Criminal Law has a subsidiary character, that is, it must act only when the other spheres of Law are not efficient for the control of public order. Because of this characteristic, the minimum intervention of Criminal Law is imposed, and this should be triggered only in cases of greater relevance and transcendence for the life of society in general, as in the case of crimes of robbery and homicide, and it is not up to this branch of law to deal with insignificant conduct, which offend minimally a protected legal good, As can be seen, for example, in the theft of a pen.

3.2 THE SOCIAL FUNCTION OF THE PRINCIPLE OF INSIGNIFICANCE IN THE DECRIMINALIZATION OF LOW-IMPACT CONDUCT

The social function of the principle of insignificance in reducing the criminalization of low-impact conduct is a relevant topic in the field of criminal law and criminal procedure. Several legal scholars discuss this issue, such as Luiz Flávio Gomes, Fernando Capez and Guilherme Nucci, bringing analyses and reflections on the importance of this principle in the selectivity of the penal system, both in the pre- and post-procedural phase.

One of the renowned authors who address the subject is Fernando Capez in his book Curso de Direito Penal - Parte Geral (2022, p.27):

> In the Democratic State of Law, it is necessary that the conduct considered criminal actually has the content of a crime. Crime is not only what the legislator says it is (formal concept), since no conduct can materially be considered criminal if it does not somehow endanger fundamental values of society. From dignity are born the other guiding and limiting principles of Criminal Law.

Capez (2022) explores the principle of insignificance as a fundamental guarantee of the individual, highlighting its role in protecting fundamental rights and limiting criminal intervention disproportionate to the crime committed. Moreover, it maintains that all the guiding principles of law derive from the principle of the dignity of the human person.

That is, when applying the law, the judge must be careful to select, among all criminal conducts, only those that, in fact, cause irreparable social damage or endanger fundamental values of society. In the words of the author (2022, p.27), "the function of the norm is the protection of legal goods from the solution of social conflicts, which is why the conduct will only be considered typical if it creates a situation of real danger to the collectivity."

Still on the subject, the prestigious author Paulo César Busato (2015) analyzes the applicability of the principle of insignificance from a procedural perspective, emphasizing the sequelae left to the individual who enters the state punitive system, no matter how small the illicit conduct practiced by it:

> [...] a criminal law obedient to the idea of minimal intervention, a true welfare state, must take into account the process of progressive replacement of the dimension of sociability that the convict suffers and the resulting social damage. Not only for the convict, but for all the people who have to live with someone whose capacity for sociability is impaired (BUSATO, 2015, p.181).

The context of the illicit act committed by the subject is analyzed in a comprehensive way, not limited only to the illicit act itself, it is necessary to pay attention to the fact that once prosecuted, no matter how small the crime committed, the individual will suffer the consequences of this crime for the rest of his life, considering that, in addition to the criminal record, He is part of society and, as a corollary, will suffer the ills of having carried a criminal case on his back. In this same sense, Busato

(2015, p.181) highlights the importance of this principle in the fight against desocialization arising from incarceration:

> Currently, the fight against desocializing deprivation of liberty is also part of the minimum criminal law program. It should be borne in mind that short-term incarceration sentences do not produce resocialization, but, on the contrary, produce, to a greater or lesser extent, a certain amount of desocialization.

In the meantime, the author highlights the relevance and influence of the principle of insignificance in the post-procedural phase, in the phase of execution of the sentence, as well as the importance of this principle in the applicability of less stringent sanctions and alternatives to the dreaded custodial sentence, allowing the criminal subject not to be segregated from society and, subsequently, making it impossible to reinsert.

3.3 THE APPLICABILITY OF THE PRINCIPLE OF INSIGNIFICANCE IN THE PRE-PROCEDURAL PHASE

The applicability of the principle of insignificance in the pre-procedural phase is a controversial and relevant topic in the context of the current legal system. In this initial stage of the criminal process, the police authority plays a fundamental role in the analysis of conduct and in making decisions related to the continuation or not of investigations. According to the understanding enshrined in the book "Criminal Investigation by the Judicial Police" authored by legal scholars Hoffmann, Machado, Anselmo, Gomes and Barbosa (2016, p.9),

> Brazil has adopted a system of preliminary investigation conducted by the Civil Police and the Federal Police, with the police inquiry presided over by the police chief being the main form of search for the truth beyond a reasonable doubt. It is precisely through criminal investigation, conducted with exemption and independence, that the State investigates criminal offenses, allowing the accountability of the perpetrators, on the one hand, and on the other, avoiding unfounded accusations. In this path, the police chief is projected as the first state authority to preserve the fundamental rights, not only of the victims, but also of those investigated themselves, being the state agent who has the most intimate contact with the institutes of the investigative phase.

In the pre-procedural phase, the application of this principle assumes singular importance, since the police authority has the responsibility to analyze the circumstances of the fact and decide if there are sufficient elements to initiate the criminal process, using the police investigation to carry out the proper investigation. On the nature of the police investigation adduces Guilherme Nucci (2021, p.184):

> The police investigation is a preparatory procedure for criminal proceedings, of an administrative nature, conducted by the judicial police and aimed at the preliminary collection of evidence to ascertain the practice of a criminal offense and its authorship [...] its primary objective is to serve as a ballast for the formation of the conviction of the representative of the Public Prosecutor's Office (*opinio delicti*), but also to gather urgent evidence, that may disappear after the crime has been committed.

In the context of the investigation of crimes by the judicial police, the consideration of the insignificance of the action can lead to the non-initiation of criminal proceedings, saving resources of the justice system and directing them to cases of greater relevance. Nucci states that "nothing prevents the delegate, upon receiving a concrete case, in front of him, to draw up (or not) the arrest warrant in flagrante (or initiate an investigation), to detect an insignificant offense and, therefore, not to draw up the record or not to initiate the investigation (2021, p. 203)."

However, the application of the principle of insignificance in the pre-procedural phase is surrounded by challenges and controversies. One of the main challenges is the definition of objective criteria to assess the insignificance of a conduct, since it is necessary to establish clear and consistent parameters to avoid subjective or arbitrary interpretations.

In addition, the police authority must take into account not only the quantitative aspect of the injury, but also other relevant elements, such as the absence of social dangerousness of the agent, the absence of criminal records, the condition of the victim and the reparation of the damage caused. These aspects may influence the decision not to initiate criminal proceedings on the basis of the principle of insignificance. Capez (2022, p. 28) explains the most commonly used requirements in the application of this principle:

> The Federal Supreme Court has already established jurisprudence, stating that the assessment of the material relevance of the criminal typicality and the consequent application of the principle in question must take place through the concomitant satisfaction of some requirements, which are: (i) the minimum offense of the agent's conduct; (ii) the absence of social dangerousness of the action; (iii) the low degree of reproach of the behavior; (iv) the inexpressiveness of the legal injury caused.

It is observed that there is a need to analyze a series of requirements that, together, can characterize the insignificance of the agent's conduct. Busato (2015, p. 179) makes a rereading of these requirements, explaining them in a simpler and easier to perceive way:

> [...] The requirements for assessing the hypothesis of incidence of the principle of minimum intervention are: (a) the recognition that the case reflects an attack on a legal good fundamental to the development of the victim in society; (b) that this attack was serious enough to warrant the ultimate instance of criminal social control taking action. This severity, in turn, must be measured taking into account: (b.1) the class of violation performed, in view of its social tolerability; (b.2) the intensity of the damage to the legal property of the victim in view of his personal conditions; (b.3) whether the use of criminal law, in the concrete hypothesis, is not merely symbolic, in the face of the best and most effective possibility of solving the social problem by another means.

Complementing the understanding, Capez (2022) points out that only one of the above requirements cannot be taken into account:

> Thus, it is already pacified that one should not take into account only and only the value subtracted (or intended to subtract) as a parameter for the application of the principle of insignificance, even because, otherwise, obviously, the attempted modality of various crimes

> would cease to exist, as in the example of simple theft itself, as well as the figure of privileged theft would disappear from the legal system (CP, Art. 155, § 2). In fact, the criterion of material typicality must take into account the importance of the legal good possibly achieved in the specific case. (2022, p. 28)

However, it is important to emphasize that the application of the principle of insignificance in the pre-procedural phase does not prevent the Public Prosecutor's Office or the Judiciary from subsequently questioning its incidence and deepening the analysis of the conduct during the procedural phase. On the continuation of investigations after the closure of the investigation, Nucci (2021) informs that

> The closure of the investigation does not have definitive effect and the situation may be reviewed at any time, including because new evidence may emerge. It happens that the police authority, according to the precept in law, regardless of the establishment of another investigation, can carry out new research, which means going out in search of evidence that arises and comes to its knowledge. (2021, p. 230)

In short, the applicability of the principle of insignificance in the pre-procedural phase requires a careful analysis by the police authority, considering the criteria established by jurisprudence and doctrine. This analysis should take into account not only the quantitative dimension of the damage, but also other relevant elements to assess the severity of the conduct, as explained.

Furthermore, with regard to the role of the police chief in the application of that principle, it is clear that it plays an essential role within the context of the application of justice. However, it is very important to discuss the extent to which it is responsible for deciding on the investigation and the continuation of the police investigation. Any action of the police authority that exceeds its attribution, as a rule, violates the procedibility of the analysis of the specific case and, therefore, will pass through the fulcrum of the Public Prosecutor's Office and the judiciary, which are responsible for discussing the recognition and legality of the application of this principle during the police investigation.

According to Gomes (2009, p.17), the police chief "cannot render a definitive decision on the insignificance of the conduct or the result", and his attribution is only to proceed with the registration of the criminal fact. Gomes points out that the delegate cannot by himself file the investigation or the detailed term, and it is up to him only to register the criminal fact and refer the criminal investigative process to the Public Prosecutor's Office so that the prosecution body proceeds with the filing, if the material atypical nature is found, and later the competent judge also so determines. It also argues that the police authority may not have files filed, and such practice is prohibited to the police chief.

According to Vidal and Britto (2020, p.21):

> The line that considers it impracticable to apply the principle of insignificance by the police chief, inadmitting that he fails to draw up the arrest warrant in flagrante or file the investigative process, maintains the absence of legal provision in this sense, the non-compliance with article 17 of the Code of Criminal Procedure, and also, that the admission of this practice would

> characterize a true violation of competences, for it would be the police chief claiming functions inherent to the Public Prosecutor and the Judge, thus extrapolating his prerogatives.

On the basis of Art. 5, § 2 of the Code of Criminal Procedure, the delegate may cease to carry out the police investigation, by legal provision that confers on him such prerogative. This is possible when the police authority is faced with facts that are atypical to unleash a criminal prosecution, however, its decision should be based on the filing of the police report.

> The application of the principle of insignificance that the establishment of the police investigation is enough for there to be an attack on what is called the status dignitatis of the investigated. The investigative procedure, by itself, represents an embarrassment that will prove unnecessary if we are faced with the absence of just cause, without gathering a set of elements that construct the authorship and materiality of the criminal offense put under investigation. (Isabelle Modesto Vidal and Cláudia Aguiar Britto, 2020. p.13)

Through this prism, it is noted that it is not possible to apply the principle of insignificance in the pre-procedural phase, precisely because most of the crimes committed are considered of high relevance to society and the law. The result of this is perceived in the large volume of cases received by the judiciary.

Regarding the analysis of the impacts on the legal system caused by the applicability of the principle of insignificance in pre-procedural terms, it should be noted that in order to have formal legitimacy of this competence, it would be necessary to have changes regarding the discretionary power of the police authority.

Thus, even before discussing the possibility of the police authority being able to resolve issues based on the principle of insignificance, it is necessary and fundamental to change the current legislation regarding its competences. For, as is known, each organ and its respective public servant has its respective functions and competences, and any action that goes beyond its limits makes the administrative act vitiated, either in the scope of legality or legitimacy.

In the meantime, according to Filocre (2017, p.67):

> The foundation of the police power of public security – and, consequently, of discretion in its exercise – is the general duty of preservation of public order – modernly taken – originating from the thought of the natural right to control the disturbances of the good order of the community resulting from individual existence. Where the police exceed in the requirement of the performance of that duty, they will be outside their scope of action and thus exorbitant of their discretionary power. Police discretion in public safety is fundamental for the legal order to defend itself against those who refuse its claim to authority. Provided that the limits of the law are respected, the public security police have a choice of the opportunity and convenience of exercising police power, in the public interest. Outside the limits established by law, arbitrariness in police action is established. The specific purpose of the public security police is to control the dangers arising from crime. Such control, in protective terms, consists primarily of actions preventing conduct hypothetically capable of producing damages – resulting from allegedly criminal practices -, or, if these are configured, aims at the public security police to restrict the damage and prevent its expansion. At the same time that the dangers that can be prevented by police must result from practices provided for by law as criminal, the police power of public security is necessarily assigned by law – a norm of competence and police attribution – and aims to achieve the ends established therein, so that

> it can be affirmed that there are no police without law or outside the law and the law, even if the police situations and measures are not, by impossibility, all of them typified.

The police competences are legally defined and based on the national order, the same understanding applies to the competences of the body responsible for the criminal action that is the Public Prosecutor's Office and the one responsible for the decision of the case that is the court. Thus, there is nothing to talk about in the possibility of an organ exceeding its legal competence and even then, such an administrative act does not harm the continuity of the legal process. For Di Pietro (2021, p. 168) "The competence and the procedure must also observe the relevant legal norms".

In addition, the author adds:

> Like any administrative act, the police measure, even if it is discretionary, always runs into some limitations imposed by the law, as to the competence and form, the ends and even with respect to the motives or the object; as to the latter two, even if the Administration has a certain amount of discretion, it must be exercised within the limits set by law. (DI PIETRO 2021, p. 168).

It remains evident, according to the understanding of the aforementioned authors, that the competences of each body must be legally respected. In the example of the closure of the police investigation, Article 28 of the Code of Criminal Procedure states that "once the closure of the police investigation or any information of the same nature is ordered, the Public Prosecutor's Office shall communicate to the victim, the investigated person and the police authority and forward the case to the ministerial review body for homologation purposes, in the form of the law." That is why the order and the democratic rule of law are also observed. That is, even though the police authority is competent to preside over the police investigation, it is the Public Prosecutor's Office that decides to dismiss it.

4 CONCLUSIONS

For a correct analysis of the principle of insignificance, some highlights about the criminal typicality should be made. Initially, the traditional doctrine analyzed the typicality under the formal prism, where it was verified merely the subsumption of the agent's conduct to the norm typified in the legal system. With the evolution of the studies of the sciences of criminal law, in the face of the protection of the fundamental rights of the human person, embodied in the principle of non-retrogression, the current modern dogmatics tends, however, towards an analysis of formal typicality concomitant with material typicality. As such, it is not enough just the legal provision in the abstract plane in which it conforms to the conduct, being necessary, that such conduct also violates, in a relevant way, the legal good protected, being precisely in the field of material typicality the scope of application of the principle of insignificance.

This principle, introduced into the penal system by Claus Roxin in 1964, was established in the Brazilian legal system, and its applicability occurs in the procedural phase, given the vectors

established by the Federal Supreme Court (STF). In the meantime, the theme in question, sought to develop in the course of this study, the analysis of the likelihood of the application of the principle of insignificance in pre-procedural headquarters, by the police authority (delegate), and its reflections within the national legal system. To develop the proposed case, the assumptions and requirements for the application of insignificance to the concrete case were presented, allied to the positioning of the best doctrine, with a focus on the legal foundations.

The principle of insignificance is already settled in the country through jurisprudence and doctrines, however, there is still no legal provision, which is why it is required that the concrete case be directed to the Judiciary for its assessment and, only at this stage, the magistrate will decide whether or not the principle will be applied, evaluating the material typicality of the crime, leaving the Police Authority only the analysis of the formal typicality.

In spite of the understanding described above to be the majority in the country's legal system, a new current has been forming, where several operators of the law defend that the Police Authority is the first guarantor of fundamental rights, not only can, but should appreciate both typicities before the concrete fact, and the procedure can be promptly filed and, in this way, avoid the wear and tear that the procedural movement generates to those involved. Thus, we seek in this article to analyze and justify the applicability of the principle of insignificance by the Police Authority, in pre-procedural terms, in its possible reflections within the social context and also in the celeumas pointed out in the current legal system itself with regard to this theme.

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Synthesis and determination of the Sun Protection Factor of a cosmetic gel-cream based on norbixin

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ABSTRACT
This work aimed to determine the Sun Protection Factor (SPF) of a cream-gel based on norbixin through spectrophotometry. Samples of gel-cream A and B were prepared at a concentration of 0.2 µL/mL and the absorbances were measured in the UVB region and the SPF was calculated using the equation used in the Mansur method. The absorption spectrum of each cream-gel was obtained using the origin program. Gel-creams A and B showed absorption in the UVA and UVB region and also in the long UVA region, therefore, they presented photoprotective characteristics. Regarding the Sun Protection Factor - SPF, both the cream-gel A and the cream-gel B were considered photoprotective by ANVISA. Norbixin increased the Sun Protection Factor - SPF and this potentiation was proportional to its concentration. Therefore, the use of norbixin in photoprotective products proved to be effective, favoring an increase in the photoprotection of the formulations.

Keywords: Norbixin, sun protection factor, spectrophotometry.

1 INTRODUCTION

Ultraviolet radiation is a source of energy needed by humans; it is responsible for the synthesis of Vitamin D in the skin. This vitamin acts on bone repair and proper cellular and neuromuscular functioning, however, too much exposure to these ultraviolet radiations can bring harm to health (Lima; Shah; Lima, 2020).

According to Sonda (2011) factors such as genetic characteristics and excess solar radiation, as well as lack of photoprotection, lead to the development of melanoma (cancer with a high mortality rate).

According to the National Cancer Institute (INCA) it is estimated that in Brazil, skin cancer, being the most common, is responsible for 30% of the recorded cases of tumors. It is estimated for

each year of the triennium 2020 – 2022, the emergence of 177 thousand new cases of non-melanoma skin cancer (INCA, 2020).

In this sense, the application of sunscreens is indispensable to protect the skin against the harmful effects of ultraviolet radiation. One of the alternatives is the production of sunscreens based on natural plant products (Santos *et al*., 2021).

Several natural products have been used against the increase of the deleterious effects of the sun, through natural topical formulations associated with chemical filters, with the intention of protecting the skin in the Ultraviolet region (Munhoz, 2012).

Norbixin is a carotenoid derived from annatto. Some natural antioxidants, such as vitamins, polyphenols and carotenoids, are being used in the area of cosmetics in photoprotective formulations due to their photoprotective and antioxidant characteristics (González; Fernandez; Gilaberte, 2008).

Given this context, the present work describes the synthesis and determination of the sun protection factor (SPF – UVB) *in vitro* of a cosmetic gel-cream based on norbixin, obtained by means of spectrophotometry.

2 DEVELOPMENTS

2.1 ULTRAVIOLET RADIATION

The sun's rays are essential to humans, since they are responsible for the activation of vitamin D and melanin production. However, too much exposure to this solar radiation can trigger many skin diseases, such as cancer and premature photoaging. The effects on the skin come from the formation of free radicals which, in turn, are formed through the interaction between UV radiation and reactive oxygen species (Lodyga *et al*., 2015; Wang *et al*., 2017).

Ultraviolet radiation is divided into three regions, according to the position occupied in the electromagnetic spectrum. The first region is the UVA (400 – 320 nm) which is responsible for the production of skin pigmentation and formation of free radicals, in addition to being able to induce skin cancer. It is subdivided into UVA I – long (400 – 340 nm) and UVA II – short (340 – 320 nm) (Nichols; Katiyar, 2010).

The second region is UVB (320 290 nm), which is associated with premature aging of cells, DNA damage as well as sunburn. Finally, the UVC region (290 – 100 nm), which have shorter wavelengths and high energies, are therefore extremely harmful to humans. However, most of it is absorbed by the atmosphere, so almost no UVC radiation reaches the Earth's surface (Mbanga *et al*.; 2014).

2.2 SUNSCREENS

To slow down or prevent damage to the skin induced by ultraviolet rays is necessary for its photoprotection. Sunscreens are topical formulations made with the purpose of protecting the skin against ultraviolet radiation and have as their main active ingredient sunscreens. These are classified into inorganic and organic (Santos *et al*., 2018).

Inorganic sunscreens act by reflecting and scattering ultraviolet radiation. They have low irritability and are widely used in products for sensitive and children's skin. This provides safe photoprotection (O'donoghue, 2007).

In turn, organic filters act by absorbing ultraviolet rays, transforming them into radiations with lower energies and that are not harmful to the body. They are formed mainly by aromatic compounds (Flower; Davolos; Correa, 2007).

For a sunscreen to be effective, it is necessary that it presents photostability, is not toxic and broad-spectrum, that is, it must act in the UVA and UVB region. However, some actives used in sunscreens can cause undesirable side effects such as thyroid alteration and endocrine disorders (Ruszkiewicz *et al*., 2017).

Another worrying factor about the photodegradation of organic sunscreens is the effect of their derivatives on the environment (Santos *et al*, 2012). According to studies done by Fent *et al* (2010) some substances resulting from the photodegradation of sunscreens have been found in the aquatic environment.

With this, the study for substances that cause less damage to health has grown. In addition to having photoprotective characteristics, they may also have antioxidant activity. In this way, natural actives have stood out in the cosmetics market in sunscreens (Saewan; Jimtaisong, 2015).

2.3 DETERMINATION OF THE SUN PROTECTION FACTOR

The Sun Protection Factor -SPF is one of the many ways used to analyze the safety of a photoprotector. Through the SPF it is possible to verify the absorption in the UVB region (Brasil, 2012). There are *in vitro* methods that are simple, low cost and fast.

Mansur *et al* (1986) proposed a methodology based on spectrophotometric methods for the *in vitro determination* of the Sun Protection Factor (SPF). This methodology, in addition to being used to determine the Sun Protection Factor of formulations, also helps in the quality control of products with photoprotection (Zocoler *et al,* 2019).

2.4 UVA/UVB RATIO AND CRITICAL WAVELENGTH ΛC

Another way to examine the photoprotection capacity of a sunscreen is through the FP-UVA, which checks the absorption of radiation in the UVA region. The *in vitro method* used for the evaluation

of FP-UVA is spectrophotometry. By means of spectrophotometry it is possible to determine the UVA/UVB Ratio and the Critical Wavelength (λc) (Diffey, 1994).

According to Donglikar; Deore (2017), the UVA/UVB Ratio corresponds to the ratio between the integrated areas of the curve in the UVA and UVB range and aims to evaluate whether the protection provided by the photoprotector is broad spectrum.

According to Brasil (2012), The critical wavelength (λc), is the wavelength that originates in 290 nm and refers to 90% of the area of the integrated curve between 290 and 400 nm, is also determined in *vitro* by scanning spectrophotometry.

3 METHODOLOGIES

3.1 RAW MATERIAL AND BASE FORMULATION

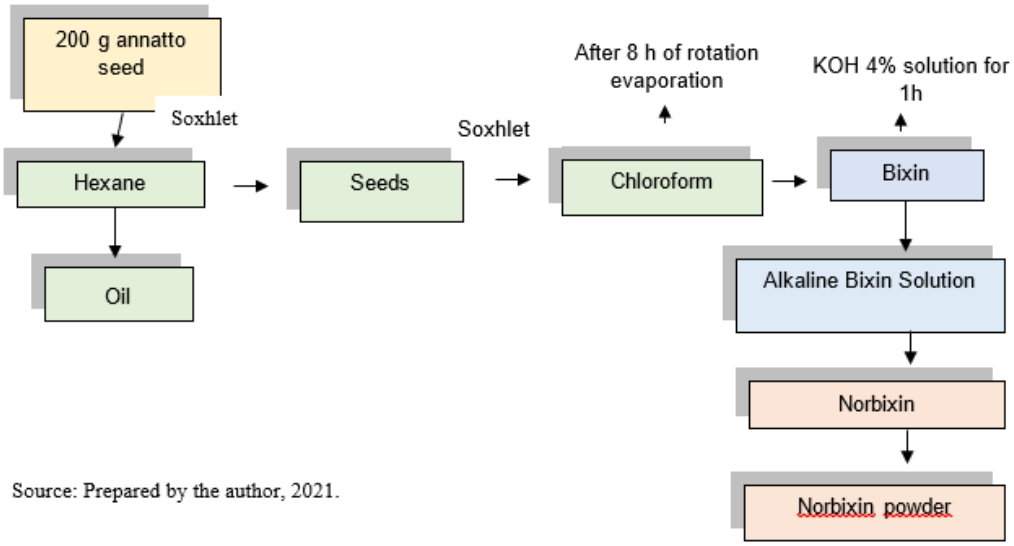
The annatto seeds were purchased in the central market and the basic formulation for the incorporation of chemical filters and norbixin was acquired in a compounding pharmacy in the city of Teresina-PI.

3.2 NORBIXIN EXTRACTION

200 g of annatto seeds were weighed and kept in reflux for a period of 8h in hexane in a Soxhlet system. The oily fraction obtained was separated from the seeds. Then the seeds were placed in reflux with chloroform for a period of 8 h, thus obtaining bixin (Barbosa-Filho, 1998).

A 4% KOH solution was added to bixin in constant agitation at 700C for 1 h. Subsequently, HCl was added for the precipitation of norbixin. The solution was washed with water and vacuum filtered and dried in the oven for 24 hours.

Figure 1: Norbixin Obtaining Flowchart



Source: Prepared by the author, 2021.

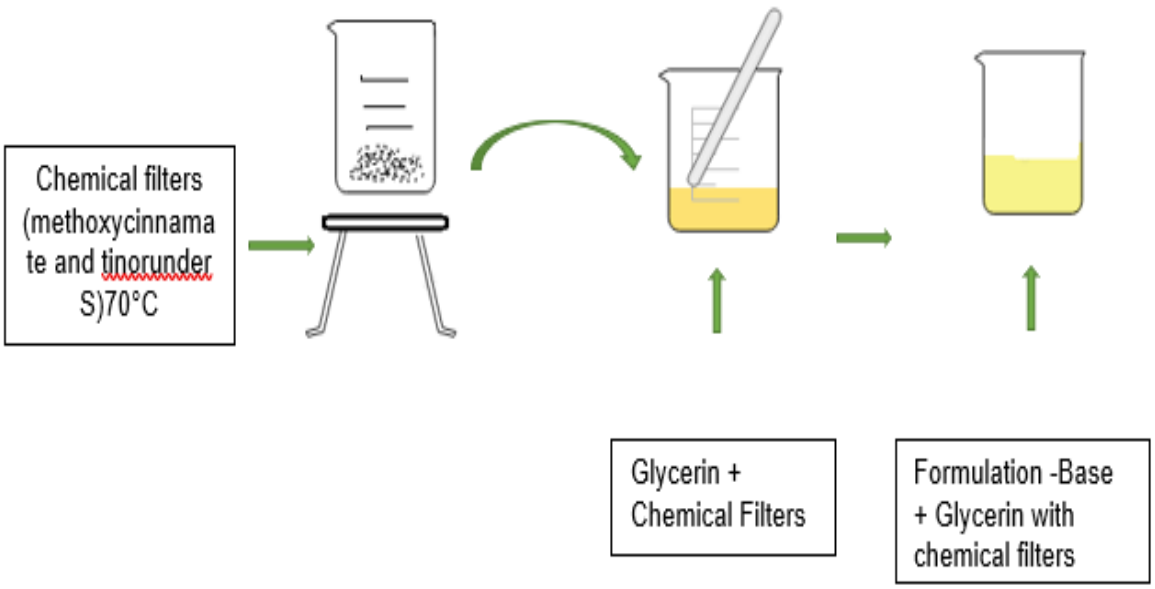
The spectrophotometric evaluation of absorption of the cosmetic formulation occurred in the spectrum of ultraviolet radiation following the method of Mansur *et al* (1986). Thus, scans from 290 to 320 nm were performed, at intervals of 5 nm, and absorbances were read at the end of time.

The UV Spectrophotometer UV-1800 SHIMADZU equipment (Figure 3) was used with quartz cubettes of 1 cm optical path to obtain the reading. The values obtained were multiplied by a correction factor, and by the normalized weight values that are constant (Table 1) and applied in the equation of Mansur *et al (*1986) to determine the in vitro sun protection factor *(*Figure 4).

3.3 PREPARATION OF COSMETIC FORMULATION

Initially, the chemical filters methoxycinnamate (3.5 %) and tinorsob s (2.5 %) were heated to 70^0 C. Then they were added to a beaker with glycerin (6%) and homogenized. To this mixture of chemical filters and glycerin was incorporated the gel-cream and norbixin at 2% and 4%.

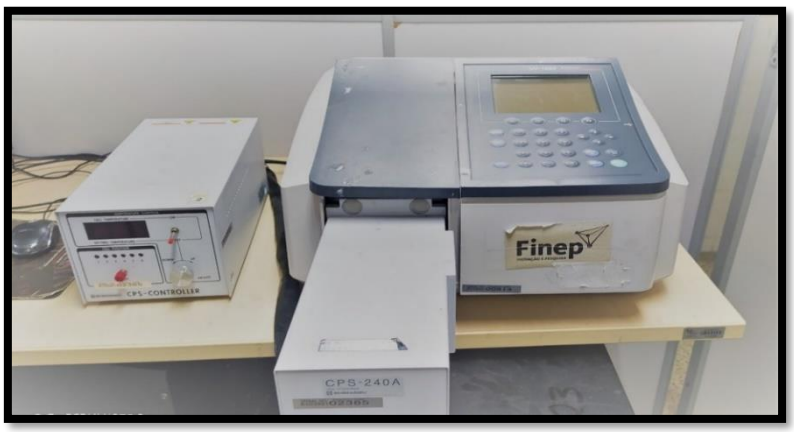
Figure 2 – Preparation of gel-creams



Source: Author, 2021. EdrawMax Program

3.4 DETERMINATION OF THE SUN PROTECTION FACTOR (SPF) OF THE COSMETIC FORMULATION

Figure 4- Equation used in the Mansur met



Source: Prepared by the author, 2021.

Table 1 - Erythemogenic effect (EE) versus radiation intensity (I) relationship according to wavelength λ (nm)

Wavelength λ (nm)	EE (L) x I (L)
290	**0,0150**
295	**0,0817**
300	**0,2874**
305	**0,3278**
310	**0,1864**
315	**0,0839**
320	**0,0180**

Fonte: Velasco *et al.,* 2011.

Figure 4- Equation used in the Mansur method

$$FPS\ espectrofotométrico = FC\ .\ \Sigma_{290}^{320}\ EE(\lambda).Abs\ (\lambda)$$

Source: Prepared by the author, 2021.

Where:

HR = Correction factor (equal to 10);

EE = Erythematogenic effect of wavelength radiation (λ);

I = Intensity of the sun at wavelength (λ);

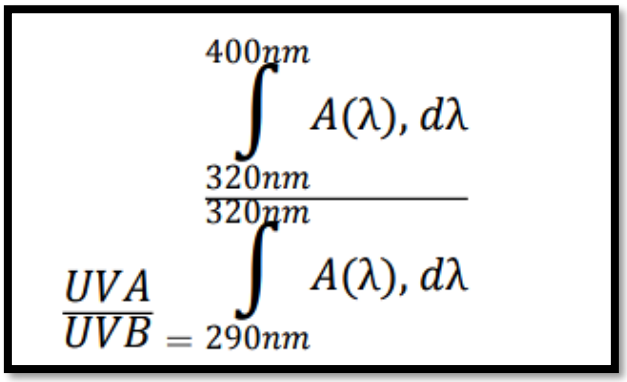
Abs = Absorbance of the sample in solution at wavelength (λ).

The tests were performed in triplicate, using pyrrolidone as white.

3.5 UVA/UVB RATIO AND CRITICAL WAVELENGTH (ΛC)

The UVA/UVB ratio was calculated through the ratio of the areas under the UVA curve in relation to the UVB curve (Springsteen *et al*., 1999), according to the equation shown in Figure 5 and with the aid of the Origin 7 program. The two gel-creams were classified according to the Boot's Star Racing System related to the UVA/UVB ratio as shown in Table 2.

Figure 5 – Equation for the calculation of the UVA/UVB Ratio



Source: Springsteen *et al*., 1999.

Table 2 - Boot's Star Rating System related to UVA/UVB ratio

UVA/UVB Stars Ratio Description
0.0 to < 0.2 - very low
0.2 to < 0.4 * moderate
0.4 to < 0.6 ** Good
0.6 to < 0.8 *** Superior
0.8 to < 0.9 **** Maximum
≥ 0.9 ***** Ultra

Source: Adapted from Velasco *et al,* 2011.

The critical wavelength was measured *in vitro* by scanning spectrophotometry and quantified using the Origin 7 program. It originates in 290 nm and corresponds to 90% of the area of the integrated curve in the region between 290 and 400 nm (Brasil, 2012).

4 RESULTS AND DISCUSSION

4.1 DETERMINATION OF THE SUN PROTECTION FACTOR - SPF

The Sun Protection Factor and the absorption spectra of gel-cream A and gel-cream B and are shown in Table 3 and Figure 6, respectively. It is observed that both the gel-cream A and the gel-cream B present absorption in the UVA and UVB region, thus indicating photoprotective activity of the ultraviolet region.

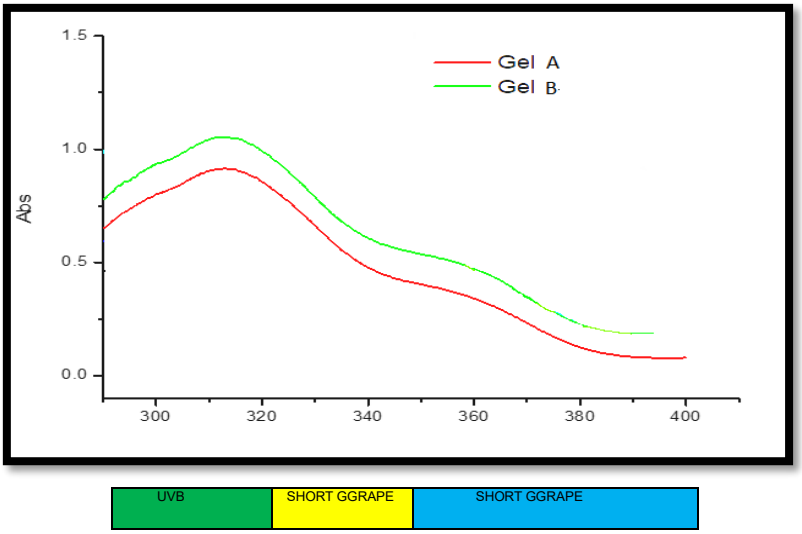
According to Rai *et al* (2012), a photoprotector is efficient when it absorbs both in the UVA region and in the UVB region indicating a product with broad-spectrum protection.

Table 3 – SPF of gel-cream A and B

Cosmetic Formulation	Gel-cream A (2% norbixin)	Gel-cream B (4% norbixin)
FPS	8,3	9,6

Source: Prepared by the author, 2021.

Figure 6 – UV/Vis absorption spectrum of gel-cream A and B



Source: Prepared by the author, 2021.

Figure 6 shows that the highest absorption peaks for the two gel-creams are between the UVB and short UVA regions. However, there is also significant absorption in the long UVA region. According to Ribeiro (2010), this region of the long UVA is directly associated with photoaging and skin cancer, being a difficult region to be reached by some chemical filters.

Regarding the Sun Protection Factor – SPF, it was found in Table 3 an increase in SPF in gel-cream B indicating that the SPF boost effect was intensified with the increase in norbixin concentration.

Considering the resolution RDC º 30 of June 1, 2012 of the National Health Surveillance Agency - BRAZIL (2012), for a product to be classified with photoprotector it must present the minimum value of SPF of 6 (six). Therefore, observing the results of Table 3, it can be said that gel-cream A and B fall into the category of photoprotectors.

Currently there is a tendency to use natural products in sunscreens in order to intensify the effect of synthetic chemical filters and thus increase the Sun Protection Factor (SPF) (Munhoz *et al*, 2012).

4.2 DETERMINATION OF UVA/UVB RATIO AND CRITICAL WAVELENGTH

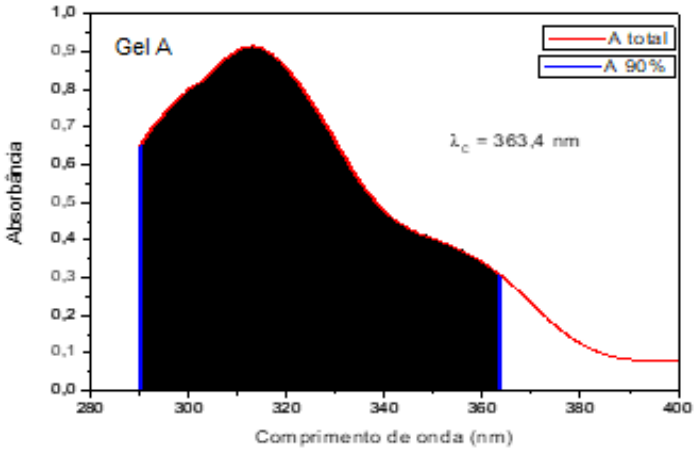
Based on the data obtained in Table 4 and shown in graphs in Figure 7 and 8, it can be said that the two gel-creams showed a good UVA/UVB ratio, and the gel-cream B had the best rate. They presented a UVA/UVB ratio ≥ 0.9 and according to the Boots Star Rating System they are considered as five stars and with ultra protection in relation to UVA radiation (Boots the chemists, 2004).

Table 4 – UVA/UVB Ratio and Critical Wavelength (λc) of gel-cream A and B

Formulations	UVA/UVB ratio	λc (nm)
Gel-cream A	1.12	363.4
Gel-cream B	1.3	370.6

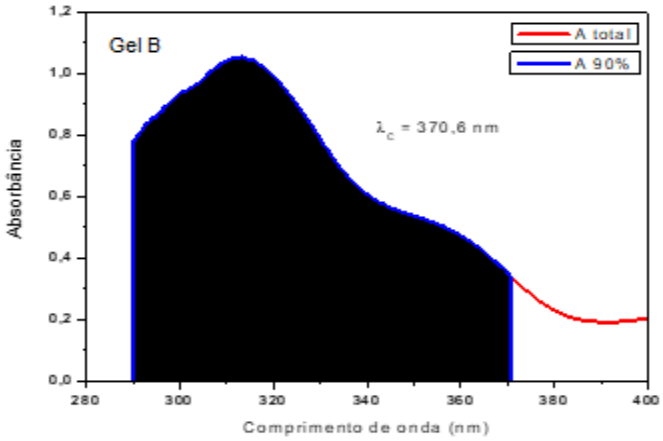
Source: Prepared by the author, 2021.

Figure 7 - Graph of the critical wavelength (λc) of the gel-cream A



Source: Prepared by the author, 2021.

Figure 8 - Graph of the critical wavelength (λc) of the gel-cream B



Source: Prepared by the author, 2021.

Table 4 showed an increase in the UVA/UVB ratio proportional to the concentration of norbixin. This result shows that norbixin favors the absorption of radiation in the UVA region, increasing the area under the curve that corresponds to the UVA region. According to Donglikar; Deore (2017) a UVA/UVB ratio closer to 1 demonstrates more effective protection against ultraviolet rays.

The gel-cream B (4% norbixin) showed the best results both in relation to the UVA/UVB ratio (1.3) and the critical wavelength λc (370.6 nm) achieved all parameters defined by ANVISA.

According to the Resolution of the Board of Directors, RDC No. 30 of June 1, 2012 of ANVISA, a product is considered photoprotector if it presents a critical wavelength λc of at least 370 nm and the longer this wavelength, the better its efficiency in photoprotection (Brasil, 2012).

5 CONCLUSIONS

In this work two gel-creams with different concentrations of norbixin that presented photoprotective properties were synthesized.

Gel-cream A and B have demonstrated absorption in the UVA and UVB region and also in the long UVA region that is difficult to achieve by synthetic chemical filters.

Regarding the Sun Protection Factor – SPF, both gel-cream A and gel-cream B are considered photoprotectors by ANVISA. For the critical wavelength (λc), only the gel-cream B can be considered photoprotective.

Norbixin increased the Sun Protection Factor – SPF and this potentiation was proportional to its concentration.

Thus, the use of norbixin in photoprotective products has been shown to be effective, favoring the increase of photoprotection of formulations.

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SEVEN publicações acadêmicas

Social representations elaborated by mothers on the care of the child with congenital heart disease in the hospital

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ABSTRACT
This article discusses part of the results of a multi-method research of Doctoral Thesis.
The study aims to describe the social representations of mothers about the care of their children with congenital heart disease. Descriptive guided by the Theory of Social Representations (SRT), developed in two stages. The first stage had 88 mothers to apply the sociodemographic questionnaire and the Test of Free Association of Words (TALP), which contained as inducing stimuli: heart disease, caring for the child with heart disease and mother-child relationship in the hospital. Eight mothers participated in the second stage for the semi-structured interviews. It was carried out in a reference hospital in the North and Northeast of the country in the treatment of congenital heart disease linked to the Secretary of Health of the State of Ceará. The data collected through TALP were transcribed and processed by the Trideux software, version 5.3. The statements obtained from the interviews were organized based on Bardin's content analysis. The data obtained by both techniques (TALP and interviews) were categorized and substantiated with RRT, emerging the following categories: Social representations of mothers about the moment of diagnosis: apprehension of a new reality; Social representations of mothers about maternal care in the hospital routine and social representations about maternal feelings. The results showed that maternal representations are related to the importance of understanding the child's diagnosis with clear information, that maternal care in the hospital is carried out with feelings of pain, despair, worry, insecurity and difficulties and is overcome through love and faith, which makes it special and that the mother-child relationship is adapting to the new reality in the hospital experience and with the experience of other mothers and health team. Therefore, apprehending the social representations of these mothers about the care of their children with congenital heart disease in the hospital is a path in search of quality care to the mother-child dyad, in which it is necessary to awaken in these mothers the value they have when caring for their children in the hospital. It is important that the health team understands the maternal social representations to plan interventions that can alleviate the suffering and support them in the care throughout the hospitalization.

Keywords: Representations, social psychology, care; mother, heart disease, congenital.

1 INTRODUCTION

The birth of a child is an indescribable moment for mothers, so they devote time and energy preparing this reception: they choose the name of the child and plan the trousseau, gradually building an identity for this child that is still being generated.

However, when this period is accompanied by the discovery that your child has a congenital heart disease, suffering, anguish and fear are inevitable, implying moments of joy, but also of pain and uncertainty, especially the frustrated desire for a perfect pregnancy. The constant fear of the loss of the child, who carries an often-serious disease and who requires hospitalizations for surgical interventions and painful procedures, sometimes for long periods of hospitalization in Intensive Care Units (ICU), which imply limitations in their activities of daily living, disadvantages in their psychomotor development, suffering due to separation from the family and uncertainty about the future.

Upon receiving the diagnosis of congenital heart disease (CHD) from the child, the mother experiences a period of transition that requires decisions and attitudes towards the new situation that is imposed on her. This process brings with it the fact of having in your arms a child with a serious disease and permeated with uncertainties. However, the hospitalization of the child in the ICU causes a strong family impact, contrasting with what was idealized in pregnancy, especially by the mother (Silva, 2019).

Although the arrival of a child, in general, represents great joy, receiving in the arms a child with a serious disease, with a Congenital Cardiac Malformation (CCM), is a great challenge for this woman who is faced with new responsibilities, fears and insecurities of caring for a child with serious health problems.

Congenital heart disease can be defined as any disorder in the structure or function of the cardiocirculatory system and can be identified since embryogenesis or at any stage of life, being one of the most frequent malformations and the one with the highest morbidity and mortality (ROSA *et al*., 2013).

They are anomalies resulting from anatomical defects in the heart or circulatory network that compromise its functions. They are considered as diseases with complex chronic health conditions, due to their common characteristics, such as temporality and continuity of care, symptom control and longitudinality of care, interruption and incorporation of life routines. (MOREIRA *et al*, 2017)

Pinto Júnior *et al.* (2015), highlight an incidence between 8 and 10 cases of congenital heart disease per 1,000 live births in Brazil, a total of 23,834 new cases/year of which: 2,565 cases would be distributed in the North region, 6,669 in the Northeast region, 9,470 in the Southeast region, 3,169 in the South region and 1,962 in the Midwest region.

Early neonatal mortality is equivalent to about 60% to 70% of infant mortality, with 10% of these deaths resulting from congenital heart disease (AGUIAR *et al*., 2018).

Braga *et. al*, 2017 conducted an observational ecological study, evaluating the trend of mortality from cardiac malformations in Brazil, based on the Mortality Information System (SIM), whose data are managed by the Ministry of Health, and processed by the Unified Health System Information System (DATASUS). In the study, a trend was observed in the reduction of cases of mortality due to

congenital heart disease in Brazil, pointing out as the main cause the probable underreporting and underdiagnosis in the neonatal period.

Due to the complexity of heart disease and its treatment, the family needs to adapt to an arduous routine of care, with frequent visits to medical appointments and recurrent hospitalizations. There are several transformations of this family, especially for the mother, who in the vast majority assumes the demands of care that become part of their daily lives.

The Social Representations (SR) relate new knowledge and ideas that are presented to the subject, and consists of the shared interpretation of a group of mothers about the care of the child with CHD and thus can direct their attitudes, behaviors and conducts in the hospital routine. Social representations are generated in social environments through interpersonal relationships from symbolic exchanges. In this cntexto, Moscovici (2013) considers culture, language and communication, values, ideological and historical context, social insertion of subjects - their position and group affiliation. Thus, these relationships share the construction of this knowledge, which explains the complex human subjectivity.

As for the formative process of SR, there is anchoring and objectification. Anchoring consists of making the unknown or new object familiar from a pre-existing thought system. The objectification corresponds to materialize the abstract, makes concrete the object of SR through a network of meanings and association with reality (JODELET, 2001; MOSCOVICI, 2003).

In this perspective, the mothers' social representations about the care of their child with congenital heart disease can be understood as a collective interpretation of the reality lived and spoken by that social group, directing behaviors and communications. In this way, the collective itself penetrates as a determining factor, within individual thought (MOSCOVICI, 2013). Given this statement, SR can be re-signified, enabling new practices and social knowledge.

With the experience of the researcher in a cardiopediatrics unit, it is believed to be at a time when it is necessary to obtain knowledge of how the mothers there accompanying with their children in Cardiopediatrics Units (ward and ICU), experience this experience, through their own perceptions or constructed from the experiences of other mothers in the hospital. This is possible, since in the social environment of these subjects, through their relationships and communication, beliefs, opinions, feelings about caring for their child with congenital heart disease in the hospital are conveyed.

In this sense, the objective was to apprehend the social representations of mothers who care for their children with congenital heart disease in the hospital. This study becomes relevant since, in possession of these social representations, it will be possible to understand the needs and feelings experienced by these mothers, unveil the meanings of maternal care in the hospital and from then on, be based to re-signify them, and thus provide better care and assistance to the dyad in a cardiology unit.

2 METHODOLOGIES

This is a descriptive study using multimethods, anchored in the Theory of Social Representations (Moscovici, 2013). Data were collected in the cardiopediatric hospitalization units of a public hospital, located in the city of Fortaleza, Ceará, Brazil, from October 2020 to April 2021.

The selection of the mothers, participants of the research, occurred with the support of the team of the pediatric service of the hospital and individually, being clarified, by the researcher, about the objectives, justification and relevance of the study, guaranteeing them the confidentiality and freedom of participation without prejudice to their care in the unit. After the clarification phase, with acceptance and the signing of the Terms of Free Consent Clarification – TCLE, the data collection period began. It is noteworthy that this study included mothers aged 18 years or older, accompanying their children from 0 to 3 years with congenital heart disease, hospitalized in the cardiopediatrics unit and who were in a position (guidance and communication preserved) to participate in the research. The exclusion criteria were the following: babies who were not in clinical conditions, that is, hemodynamically stable for maternal care and mothers who presented some alteration that could make communication unfeasible, such as mental disorders and/or another morbid condition in a way that compromises participation in the research.

In the first part of the sample, a form was used to trace the sociodemographic profile of the mothers and a technique to apprehend the social representations of the participants, with an instrument, called: Test of Free Association of Words (TALP), applied with 88 mothers.

Subsequently, eight of these 88 mothers answered the semi-structured interview with a guiding question: ***How is it for you to take care of your child in the hospital?*** This combination of techniques had the intention that the different methodological perspectives complement each other to integrate and know the consensual universe of the mothers about the care of their child with congenital heart disease, which made it possible to enter into the maternal subjectivity and to know the meaning of their experience in the hospital environment.

The mothers responding to the TALP were selected by intentional criteria from a sample of 88 mothers. For the elaboration of the TALP chose three inducing stimuli: ***heart disease,*** *caring for my child with heart disease and Mother-child relationship* ***in the hospital*** previously defined by the researcher, taking into account the characteristics of the interviewed subjects as well as depending on the object of the SR to be researched. In addition to the opinion variables (inducing stimuli), three fixed variables were chosen, such as: maternal age (IDA), religion (REL) and marital status (SCI). This type of attachment made it possible to establish groups of social actors who have common and non-consensual SR about maternal care for children with CHD in the hospital.

After the application of the test, the evoked words were transcribed in their entirety and organized in a database and processed in *the* Trideux 5.3 software, which allowed an interpretation based on the Correspondence Factor Analysis (CFA). (Cibois, 1998).

The interviews were analyzed from the perspective of qualitative analysis, with the application of the resources of the techniques of thematic content analysis (Bardin, 2011), to the data from the open questions and grounded with the framework of the Theory of Social Representations.

The categories obtained from the analysis of the two techniques received the following names: Social representations of mothers about the moment of diagnosis: apprehension of a new reality; Social representations of mothers about maternal care in the hospital routine and social representations about maternal feelings.

The research was submitted to and approved by the Research Ethics Committee (CEP) of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes, with opinion 4346177 and CAAE 39059920.7.0000.5039 and developed in accordance with Resolution 466 of 2012 of the National Research Ethics Commission that regulates research with human beings (BRASIL, 2012), together with the consent of the institution where the research was conducted.

Anonymity was guaranteed by the alphanumeric identification of the testimonies, whose letter M stands for mothers followed by the numeral (1 to 8) identifying them also by names of precious stones in dedication to the brilliance of these women: M1 Bright, M2 Sapphire, M3 Ruby, M4 Emerald, M5 Turquoise, M6 Amethyst, M7 Tourmaline, M8 Jade.

3 RESULTS AND DISCUSSIONS

3.1 CHARACTERIZATION OF THE STUDY PARTICIPANTS

Regarding the eight mothers interviewed: two had only one child, one mother had two children and the other seven children and four mothers had three children, all started prenatal care, however three of them did not go to all appointments due to the fear of being infected by the new Coronavirus. Five had cesarean section and three had normal deliveries in the hospital.

It is worth mentioning that the Ministry of Health recommends that at least six or more consultations be performed (Correa MD *et. al, 2018) and that studies by BRITO VRS* et al, *2010* highlighted the prevalence in the establishment of fetal diagnosis between 21 and 25 weeks made possible through diagnostic tools fetal echocardiography, Doppler and obstetric ultrasound during prenatal care; allowing to plan therapeutic medications pre and post immediate delivery as well how

Of the eight mothers interviewed, two had children diagnosed with Hypoplasia of the Left Heart, and the children were aged 2 months and 5 months. Two mothers with children with Tetralogy of Fallot aged 1 year and 1 month and 1 year and 5 months, one with Truncus Arterial Type I aged 1 month and 20 days, the other with a child with Arterial Truncus Type II aged 7 months, a child with

Unspecified Malformation of the Heart at 6 months of age, and finally, a child aged 1 year and 5 months with a diagnosis of ventricular septal defect.

Congenital heart disease is a malformation arising from the development in the intrauterine period, that is, the individual is already born with a cardiac dysfunction. In Brazil, it is considered the second leading cause of death in children under one year of age, with 1 case occurring in every 100 live newborns, whose 1/3 of these babies underwent surgery. Technological advancement enabled greater survival, as many were no more than 5 years old (Santos, 2020; Barreto, 2017).

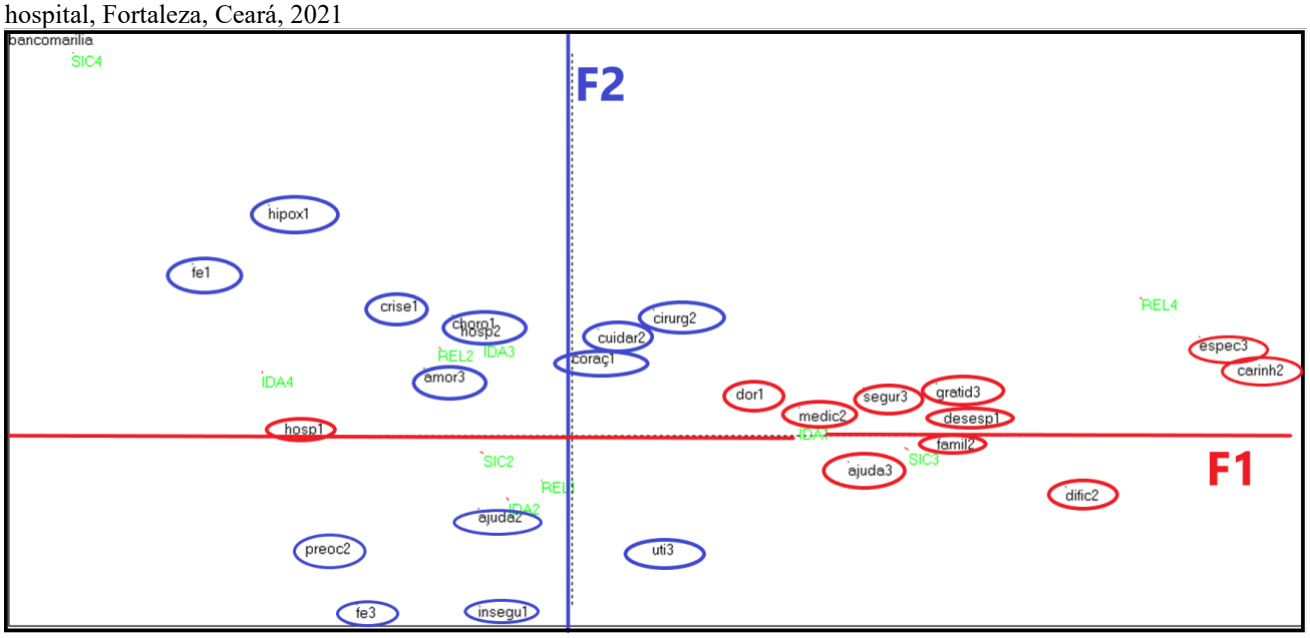
Regarding the sociodemographic data of the caregiver mothers, two of them were from Fortaleza – capital and four came from the interior of Ceará, followed by two from the State of Piauí – Teresina. As for marital status, four married, three in stable union and one single. Regarding schooling, six mothers had incomplete elementary school and two completed high school. Regarding occupation and income, four mothers define their occupation as housewives and have no income, the other four are in the formal labor market: two cleaners, with income below the minimum wage; an elderly caregiver and another pharmacy consultant, both with an income of one minimum wage. On religion, four defined themselves as Catholic and the others as evangelical.

3.1.1 Factorial analysis of correspondence of the evocations issued by the talp of the caring mothers to the child with congenital heart disease

The evocations obtained through the TALP were processed in *the Trideux* 5.3 software and interpreted according to the Correspondence Factor Analysis (CFA). For each inducing stimulus, 384 different words were evoked, totaling 1058 words.

This factor map determines the most frequent and most significant evocations for the three inducing stimuli. Chart 1 represents the two axes, axis F1 (horizontal axis) and axis F2 (vertical axis). Factor 1 is represented by the color red, where the most consensual representations of the social actors of this study are found and explained 24.6% of the variance, while Factor 2, represented by the color blue, highlights the idiosyncrasies of the representations and demonstrated a variance of 17.5% making a total of 42.1% of variance or significance in the total of responses evoked. The fixed variables are represented by the color green, in which IDA refers to maternal age, REL to religion and SIC to marital status. The numbers 1, 2 and 3 that accompany the evocations are equivalent to the corresponding inducing stimulus.

Graph 1: Factorial plan of the Social Representations of caregiver mothers to the child with congenital heart disease in the hospital, Fortaleza, Ceará, 2021



Regarding stimulus 1 *heart disease,* in the F1 axis, horizontal, the most representative words and their correspondence by factor (CPF) on the right side were: pain (CPF:28), despair (CPF:52) evoked by mothers with maternal age between 19 and 25 years and on the left side: hospital (CPF:53) evoked by women aged 40 to 46 years and represented by the marital status of stable union.

For the mothers, stimulus 1*, heart disease,* which is confirmed with the diagnosis of congenital heart disease of the child, was anchored to feelings such as pain and despair and was objectified in the hospital, because these feelings were meanings materialized in the experience of hospitalization (objectification). The words pain and despair were revealed as representations at the moment they discovered the heart disease in the child, the moment of diagnosis and the experience of hospitalization.

A study by Menezes et al (2020) obtained similar results and states that the initial reaction to the child's CHD diagnosis as an unexpected event, provoking negative feelings and behaviors, such as fear, worry, isolation and even rejection to the child.

Given the strangeness of the diagnosis, the words mentioned in the F2 axis, vertical, in relation to the same inducing stimulus 1 *heart disease*, the most representative words in the upper pole were: hypoxia (CPF:142), it was associated, still, to this stimulus the words: faith (CPF :45), crying (CPF: 33) and heart (CPF: 25) evoked by women aged 33 to 39 years and with evangelical religion, anchors used in moments of uncertainty in the face of the discovery of heart disease, clinical prognosis, promoted during the hospitalization process and in the lower pole: insecurity (CPF:43) evoked by women with maternal age from 26 to 32 years, married and Catholic.

This axis brings important elements regarding the representation of the child's heart disease, makes it possible to identify and understand the meaning of having in the arms a child with a serious

heart disease, feelings of insecurity are potentiated when the child presents signs in his body that demonstrate how fragile he is and requires care. The word hypoxia as the most evoked by mothers represent the fear of the child having some crisis and dying at any time, these feelings are objectified in crying. However, the experience of caring for the child with CHD succinct feelings of faith, which leads the mother to construct new meanings, to review her expectations in the face of the new reality

Given this, studies reveal that mothers emphasized the heart as a complex organ, essential for survival and, therefore, a cause for greater concern when compared to other diseases. By associating the heart with life, the child's need for cardiovascular surgery puts the mother in contact with the possibility of death, favoring ambivalent feelings between the fear of the loss of the child during surgery and the expectation of cure. (MENEZES, L. T. *et al*, 2020)

Regarding the inducing stimulus 2*, taking care of my child with heart disease,* in the F1 axis on the right side, the most representative words were: affection (CPF: 95) and difficulty (CPF:52) associated with medications (CPF:31) and family (CPF:29) corresponding to maternal age from 26 to 32 years and marital status of stable union.

In the F2 axis, for the same inducing stimulus in the upper quadrant in relation to age between 33-39 years and evangelical religion, the main words were: surgery (CPF:48), hospital (CPF:39) and care (CPF:44) while in the lower quadrant we found the words help (CPF:34) and concern (CPF:25) as more representative.

Schneider; Medeiros, 2012 state that hospitalization changes the way a family lives, since one is in an unknown place, often in a city far from their home, with a sick child who demands special care. However, the care of the child with heart disease is anchored by the family, which although many of them face alone a routine of caring for the child in the hospital, away from their relatives' facing threats of surgery, medication administration, supported by technological structures (accesses, probes, drains, etc.) are objectified by the difficulty and concern, but also by the affection mainly exercised by the team and other mothers from shared experiences as a network of support.

Regarding the inducing stimulus 3*, mother-child relationship in the hospital,* in the axis F1 right pole, the main evocations were: special (CPF: 85) and help (CPF: 74) associated with safety (CPF:32) and gratitude (CPF :36). As for the F2 axis at the upper pole over the same inducing stimulus, the word was evoked: love (CPF:35) and at the lower pole, ICU (CPF: 34) and faith (CPF:44) with greater representativeness.

The term faith and special, besides having been evoked more readily, indicate that there is a connection between the representation of having a child with a serious illness with the spirituality that they experience from their religion, such findings corroborate the understanding of social representations anchored in religious beliefs. In this case, some mothers in possession of their religious

beliefs, believe that caring for a child with congenital heart disease is something special is a gift and love from God.

In this case, religion is understood as an organized system of beliefs, practices, rituals and symbols created to provide an approximation of the subject with a divine being; and spirituality as a personal search for answers about the meaning of life and the relationship with the sacred (KOENIG, 2001).

In this study, the social representations point to the forms of interpretation of reality according to the experiences and knowledge of the common sense of the mothers in relation to the care of the child with CHD in the hospital context, especially in the ICU. The stress and fear of taking care of the child in the ICU are perceived in a significant way by the mothers.

3.1.2 Thematic content analysis

From these evocations from the TALP and processed in *the* Trideux software, combined with the answers of the interviewed mothers, three categories emerged: Social Representations of mothers about the moment of diagnosis: the apprehension of a new reality; Social Representations of mothers about maternal care in the hospital routine and Social Representations of mothers about maternal care in the hospital routine.

3.2 SOCIAL REPRESENTATIONS OF MOTHERS ABOUT THE MOMENT OF DIAGNOSIS: THE APPREHENSION OF A NEW REALITY

In the first category, it was evidenced that the moment of diagnosis of the child's heart disease is the moment of apprehension of a new reality and changes in a relevant way the life of this mother, to which it will assume a different meaning, a situation that presents itself in a complex way and that requires adaptations, considering that the child's heart disease often brings a slow and reserved prognosis. The process of discontinuity of the dreamed baby, of the perfect child, begins, and then it is realized that they are facing the unknown;

It was difficult to receive this diagnosis from my daughter, when she was born, she was referred to the hospital of Messejana, when I was told that it was cyanosis of the extremity and her disease was tetralogy of Fallot. From there began my suffering with her. I came to take an exam and I didn't go out anymore. After a few days she went for surgery. He had the surgery at 8 months, spent 15 days in the ICU. And I've been told she's going to have to have other surgeries. M3 Ruby

Receiving the news that my daughter had heart problems was difficult, I went into shock, I cried a lot. She has the diagnosis of Hypoplasia of the Left Heart Because I soon thought that she would not resist. M5 Turquoise

The discourses apprehended were significant in their content to the extent that the apprehension of this new reality was verified in the discovery of the diagnosis and in the course of the hospital experience. Faced with the unknown, mothers begin to seek an understanding for the new, the one that needs to be known (heart disease), and thus use the available resources to access them.

This category brings important elements regarding the representation of the child's heart disease. It makes it possible to identify and understand the meaning of having in your arms a child with a serious heart disease, as well as feelings of insecurity potentiated when the child presents signs in his body that demonstrate how fragile he is and requires care. The word hypoxia as the most evoked is anchor represented by mothers as to the fear, they have of the child having some crisis and dying at any time, these feelings are objectified in crying.

However, the experience of caring for the child with heart disease succinct with feelings of faith, which leads the mother to construct new meanings, to review her expectations in the face of the new reality. It is prudent to note, however, that some statements bring in their content these representations:

The moment I received this news (diagnosis) I was floored because I had never heard about this disease, Tetralogy of fallot. The doctors explain, but there's a lot of complicated stuff that I don't understand. I know it's a disease that needs to fix the heart with surgeries. He had seizures (hypoxia) and turns purple. I have faith that we're going to get through this. M8 Jade

Then they were referred to the messejana and the diagnosis was large VSD. It was one scare after another. I knew he had heart disease, but I didn't imagine he would have to stay in hospital for so long, have surgery. It was hard for me, but for him it's been worse. These were days of crying, fear and insecurity. I was looking at him all the time, I think I spent a couple of days without sleep, afraid of him feeling bad and dying. Having a seizure (hypoxia) Because a child with a heart problem is said to die in his sleep. My faith and hope grow every day. M6 Amethyst

3.3 SOCIAL REPRESENTATIONS OF MOTHERS ABOUT MATERNAL CARE IN THE HOSPITAL ROUTINE

In the most complex cases of the disease, hospitalization of the child in a Cardiopediatric Therapy Unit (PICU) is common. Studies by Azevedo, Hemesath & Oliveira (2019), demonstrate, that

the hospitalization of the child in the Pediatric ICU is a frightening experience, marked by several feelings, for having to deal with unknown and unexpected situation, beliefs associated with the possibility of death of the child

Hospitalization brings a different dynamic to the mother, with a sick child who demands special care, in an unknown place, often in a city far from her home, family, friends and work.

Studies by Silva (2019), reaffirm that the most reported feelings were sadness, impotence and fear of death, all of these noted at the beginning of hospitalization, which tended to be replaced by feelings of satisfaction and joy when perceiving the development of the child, returning to be seen the negative feelings with the verification of the temporal extension of hospitalization.

However, the care of the child with heart disease is anchored by the family, which although many of these mothers face alone a routine of caring for the child in the hospital, far from their relatives facing threats of surgeries, medication administration, supported by technological structures (accesses, probes, drains, etc.) are objectified by the difficulty and concern, but also by the affection mainly exercised by the team and other mothers from shared experiences as a support network, presented in the following statements:

A new challenge, learning to care and live one day at a time. Everything is different, the worry is constant. The simplest thing becomes complicated. The bath, the diaper change, eating through her mouth, until her breathing I watch, I take care of her so she doesn't cry, doesn't get angry and doesn't get tired. There are the medications. She managed to run out of oxygen. Every day a victory. M5 Turquoise

At first, I didn't want to do anything, take care of it, you know? But the professionals were helping me, guiding me. How to bathe, how to hold on his lap, how to change the diaper, put on the clothes, put on the correct way for him to sleep. Each one comes and helps me, corrects me. Because he wasn't like the other children, he has a developmental delay, he's 6 months old, but he looks like a 1-month-old baby. So, for me like he was born the day he came into my lap, we were getting to know each other. M4 Emerald

Studies conducted by Siqueira and Dias (2011) regarding the maternal perception about the experience and learning of the care of a premature baby, bring the reflection of mothers on the importance of being trained during the period that their children were hospitalized and how important these teachings were about care also in the home environment.

In the following discourse, the mother reveals the importance of receiving support and guidance on how to care for the child with CHD in the hospital and at the same time the fear and suffering of

taking their children home and performing the care without the supervision of the multidisciplinary team, as mentioned in the discourses:

I didn't want to take her home now; I'm confused and I don't think I'll be able to take care of her like I have to. There are the medications. She's a special kid, I'm still learning and getting to know my daughter. It's only been 20 days since I've been with her, I'd take a professional of yours away with me. My family will help me, but for them it will also be difficult. M7 Tourmaline

Medina *et al*. (2018), state that the lack of protagonism in relation to decision-making about the care provided to the child without the consent of health professionals can, in some cases, make them feel excluded from the care process.

Even though I stayed with him in the ICU, I was distressed because I knew he was under my responsibility. Even so, the team helped me in the early days. I was nervous about his discharge. I was afraid he would pass out, throw up, cry. I was afraid to bathe, to take him out of bed, I was afraid to change his position and hurt his heart. It was distressing, but he was discharged from the first surgery and we went home. M6 Amethyst

Deepening the knowledge about the Social Representations of mothers about maternal care in the hospital routine, made it possible to understand how groups and human beings think and relate to this phenomenon in its complexity, (JODELET, 2001), as a model that allows the possible mediation between the participants, who relate from a certain logic of conducts. It is in the movement of interpreting the meanings of this experience of how mothers take care of their children, understanding it as feedback between mother and team.

However, as they passed through the course of hospitalization, they adapted to the hospital routine, the routine of caring for the child and overcoming fear and insecurity. This daily experience of care brought the mother-child bond closer together and strengthened.

The team helps a lot. I wouldn't make it without the pros. But I feel very alone, I'm very afraid to take care of her, to do something that might hurt her, afraid of losing the probe, the accesses, the oxygen, fear of everything. The team goes by and guides me, reassures me, I know that if she feels bad, she has the doctors to help. I'm learning how to take care of her. M7 Tourmaline

I'm looking forward to this moment, the high. I've learned a lot from the professionals. Because the care of such a child is different from a normal child. It's very delicate. He's not doing things from a kid

his age; he has a developmental delay. He looks more like a newborn. But I'm still more relaxed. When he takes home, he will meet his brothers and the whole family. I learned here to respect God's timing!! M2 Sapphire

It is noticed in this study that mothers find difficulties in caring for their child with CHD in the hospital, often attributed to the devices that remain in the child, such as the orogastric tube, accesses, the nasal catheter, drains, electrodes, mainly related to their feelings and their limitations; however, they manage to overcome them, because they demonstrate above all faith and courage to overcome the obstacles encountered.

3.4 SOCIAL REPRESENTATIONS OF MATERNAL FEELINGS

The representation is not limited to a simple opinion, but constitutes a structured thought that serves as the basis for what one thinks. It is the product of a group, which gives it its social character. These representations guide the behavior and understanding of the daily life of the world in which we live. They function as organizers of the attitudes and practices of the groups that originate them and organize the expectations of the subjects about the object in order to meet them (JODELET, 2001).

For the mothers in the study, having faith is an essential requirement to face the difficulties of their child's disease, the hospitalization process itself, the ICU, the surgeries, in short, all the mishaps faced.

She's everything to me, I'm proud of her being such a strong child to survive heart surgery. She showed me what it's like to love a real person. I love my daughter so much; she is special and I have faith that God will heal her. I believe it!! M3 Ruby

He (my son) taught me that I need to have more faith and believe in God. I have gratitude to God for my son M4 Esmeralda

The term faith and special, readily evoked by the mothers, indicate that there is a link between the representation of having a child with a serious illness with the spirituality that they experience from their religion, such findings corroborate the understanding of social representations anchored in religious beliefs.

The expressions of the mothers in the word's faith, gratitude, special and love refer in their speeches to the confrontation and the possibility of healing the child's problem, as daily anchors, as emotional support and strength to face reality and find meaning in everything.

4 CONCLUSIONS

From the beginning, there was the intention to approach these mothers and apprehend the SR, which made it possible to reveal important aspects in which they were recorded not only in the interviews, but that went beyond the verbal, from the sharing of an arduous routine and allowed the researcher to recognize maternal care in her daily life in the hospital.

From the results presented, it was possible to perceive how mothers represent the care of a child with heart disease in the hospital. Thus, the construction of networks of meanings that are created and shared in the hospital scenario is noted.

Therefore, the representations apprehended here are re-elaborated productions from the experience that each mother has when caring for her child with congenital heart disease in the hospital, that is, her a priori knowledge of this social object, which is acquired through the group to which she belongs is transformed and receives new clothing as a result of this experience.

In this study, it made it possible to enter the subjective world, the world of social representations that pointed to the forms of interpretation of reality according to the experiences and knowledge of the common sense of the mothers in relation to the care of their child with CHD in the hospital context.

Thus, it is stated that, in general, when representing heart disease (stimulus 1), caring for the child in the hospital (stimulus 2) and mother-child relationship in the hospital (stimulus 3), the mothers highlight the importance of facing the diagnosis of CHD as the first step to understand and apprehend this new reality, either through information, which is often based on a technical language. And even if inserted in the daily life of this child in the hospital with which he has no familiarity, a limitation to his understanding is sometimes accentuated, prevailing a superficial relationship with the medical and multidisciplinary team.

It is perceived that initially, the team assumes the care of the child, due to his clinical condition, the need for technological instrumentalization for intensive support, causes a distance between the dyad, limiting the approach of the mothers to the care of their child.

Understanding the SR elaborated by the mothers is an important step to support them in the care of this child in the hospital, respecting their initial feelings; pain and despair. The importance of help from health professionals in search of quality care to the mother-child dyad is highlighted, in which it is necessary to awaken in these mothers to the value they have when caring for their children in the hospital, a process of (re)signification in the face of the adversity faced (surgeries/hospitalization).

It is evident that the orientations by the team become adequate and effective when the professional, in possession of these SR, interacts with the mothers and develops orientations based on maternal experiences during hospitalization.

However, it is recognized the significant maternal role in the care of the child in the hospital, with actions rich in creativity and affectivity, relevant aspects for development, in which they act directly on the emotion, love, affection, solidarity that will in turn mobilize numerous bodily and emotional processes contributing to an increasingly harmonious mother-child relationship, important aspects for the development of a child.

EMPLOYEES

FROTA, M.X.F participated in the conception and design, analysis and interpretation of the data, writing of the article and relevant critical review of the intellectual content and final approval of the version to be published. RODRIGUES, D.P participated in the analysis and interpretation of the data and relevant critical review of the intellectual content PINHEIRO, J.A.M and BASTOS, F.M.C, B participated in the search for sources and the review of the article.

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Remote teaching: Perception of nursing students about their training process

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ABSTRACT
This article seeks to unveil the perceptions of nursing students regarding the suspension of classroom activities and the insertion of emergency remote learning during the COVID-19 pandemic. This is a qualitative study, carried out with nursing students who experienced remote teaching in their training process; the interviews were collected from March to August 2022. Data analysis was performed using the Collective Subject Discourse methodology. As a result, seven third year undergraduate nursing students from a university in the south of the country participated in the study, all female, aged 21 to 24 years, from the analysis of the collective subject discourse were divided into two categories, between potentialities and weaknesses pointed out in the DCS. The potentialities and weaknesses of the insertion of remote emergency teaching in the perception of the students were raised from this research.

Keywords: COVID-19, remote teaching, nursing.

1 INTRODUCTION

In 2020, the World Health Organization (WHO) decreed a pandemic caused by the *Severe Acute Respiratory Syndrome Coronavirus* 2 – SARS-COV-2 virus (PAN AMERICAN HEALTH ORGANIZATION, 2020), in view of this situation, it was recommended by health authorities the use of personal protective equipment and social distancing, as a way to minimize viral transmission, modifying the face-to-face work routines, education, transportation and health services (CRODA; GARCIA, 2020).

In teaching services, through Ordinance No. 343 of March 17, 2020, there was the replacement of face-to-face classes for *online teaching, as* well as the reorganization of the academic calendar and the possibility of non-face-to-face activities for the purpose of fulfilling the workload (MINISTRY OF EDUCATION, 2020).

The suspension of face-to-face teaching activities generated the obligation for teachers and students to migrate to the *online reality*, transferring and transposing methodologies and pedagogical practices typical of the face-to-face mode of learning to emergency remote teaching (MOREIRA; HENRIQUES; BARROS, 2020).

Emergency remote learning was the only option for educators to continue their students' academic training during the pandemic. In view of this, remote learning was composed of essential elements, such as the pedagogical proposal to be used, the media platforms, or technology, in addition to the preparation of the faculty, as well as the motivation, expectations and involvement of the students. It is known that these elements suffer difficulties throughout the process of remote teaching (MAGALHÃES, 2021).

In the context of nursing, educators transferred fundamental disciplines to remote teaching, but practical activities needed a face-to-face approach, which generated concern for nursing students for not being able to complete their undergraduate degree and achieve their learning objectives (BASTOS, 2020).

In this critical period of global public health, the Ministry of Education (MEC) authorized students of health courses to graduate earlier than foreseen in the academic calendar, in view of the emergence of human resources to act on the front line in the fight against the COVID-19 pandemic, so there was no possibility of delaying the training of nursing students until face-to-face teaching was reestablished (BRAZIL, 2020).

Because nursing is a profession of care practice, extremely important for the health team that works on the front line in the fight against the COVID-19 pandemic, being the largest category in quantity in health services. This challenged the possibilities of distance education, as well as the need for urgent training of new professionals, given the global shortage of nurses in the labor market due to the absences and dismissals linked to risk groups and professionals who decided to prevent themselves amid the uncertainties about the virus (WORLD HEALTH ORGANIZATION, 2020; SILVA, ORIYAM, CLARO, BORGHI, CASTRO, SALVADOR, 2021).

Based on the above, the problem addressed in the research was: What are the perceptions of nursing students about emergency remote teaching during the COVID-19 pandemic for their training process?

To respond to this problem, the objective of the study was to unveil the perceptions of nursing students about the insertion of emergency remote teaching in their health education process.

2 METHODOLOGIES

This is an exploratory study, with a qualitative approach, conducted with students of the 3rd year of undergraduate nursing at a State University in the South of the country.

25 students from the referred year were invited to participate in the study, of which seven students agreed to participate in the research. As for the inclusion criteria, we considered students in the aforementioned grade, who experienced face-to-face teaching before the pandemic and emergency remote teaching during the pandemic.

Regarding the exclusion criteria, students who were on vacation or certified at the time of data collection were also those who experienced only a face-to-face or remote teaching format.

Data collection took place in the months of March to August 2022 at a place and date previously agreed, following the current sanitary requirements of the university due to the pandemic period The collection began through the questionnaire of characterization of the students as the following variables age, income and forms of access to the internet, followed by semi-structured interviews with the following guiding question:

- What was your perception of remote learning in your training process during the pandemic?

And the ancillary issues:

- What facilities have you found during remote learning in your training process?
- What difficulties have you encountered during remote learning in your training process?

The interviews were audio-recorded via smartphone and lasted approximately 15 minutes. Then they were transcribed in full by the researchers and to ensure the anonymity of the participants, the names were replaced by the letter DE (Nursing Students), according to the order of accomplishment, DE1, DE2, so on.

Data analysis occurred through the methodological framework Discourse of the Collective Subject (CSD), which consists of a process of grouping discourses into discourses-syntheses through Key Expressions (KE), with fragments of speeches that have similar meanings translated into Central Ideas (CI) which are used to unite the fragments of the same meaning and transcribe as a single discourse (LEFEVRE; LEFEVRE, 2006).

In some cases, Anchors (AC) are used that express ideologies, generic beliefs, or theories. The final CSD represents the speech of all subjects. Aiming to reveal how people think, attribute meanings and manifest positions on a given subject (LEFEVRE; LEFEVRE, 2006).

In addition, the CSD, as a technique for the analysis of the data obtained, generates social representations with possibilities and dimensions in the understandings of the perceptions of the subjects participating in the study focused on the meanings, which allows to make the representations clearer, exemplified, detailed and justified (LEFEVRE; LEFEVRE, 2012, P. 1194).

The transcriptions of the speeches were analyzed in full in the first Discourse Analysis Instrument (IAD 1) in this data collection mechanism, it is necessary to identify the following

components of each discourse: Key Expressions (KE); Central Ideas (CIs) and the Discourses of the Collective Subject.

The development of this research complied with ethical standards and obeyed the provisions contained in Resolution No. 466/2012 of the National Health Council (BRASIL, 2013; BRASIL 2016), approved by the Research Ethics Committee (CEP) involving human beings with CAAE: 53932321.0.0000.5231.

All participants were invited to participate in the research voluntarily and, those who agreed, signed the Free and Informed Consent Form (ICF).

3 RESULTS AND DISCUSSION

Seven nursing students from the third year of graduation were interviewed, all of them female, single, without children and aged between 21 and 24 years.

Regarding the internet *connection* for remote teaching, five reported that they have access at home and two that do not. Regarding the type of connection, six reported that they connect via *Wi-fi,* one uses via cable and via cell phone. Regarding the quality of the *internet* to watch and perform the activities in the remote mode, on a *Likert scale* (0 very bad to 5 excellent) five students consider the connection good, one as great and one as bad. All students reported having an adequate environment for their studies at home, as well as having their own computer*notebook*, five did not share this resource.

To present the results of this study, the ECH from the interviews were selected, the CIs were apprehended and the DCS were constructed, which were then discussed in: "Theme 01 - Facilities of the insertion of remote teaching" and "Theme 02 - Difficulties of the insertion of remote teaching".

The following discourses were constructed from the central ideas that relate to internet access, adaptations in the environment, routine, technologies, teaching methodology and singular perceptions. Thus, through the discourses, they reveal the perceptions of potentialities and difficulties of the study group, about the insertion of remote teaching in their nursing education process.

3.1 FACILITY FOR THE INSERTION OF REMOTE LEARNING

The COVID-19 pandemic has brought numerous changes in our daily lives, due to sanitary measures and social distancing. One of the sectors affected was higher education, related to the training of human resources, so that face-to-face pedagogical activities were suspended and national regulatory bodies indicated the continuity of the school period through remote activities.

The following discourse refers to the question about the perception of the insertion of remote teaching in the process of training third-year students, still representing how it was for the student the beginning, organization and execution of remote activities, in terms of difficulties and facilities.

3.1.1 Theme 1 - Perceptions of the facilities of the insertion of remote teaching

CI 1 - Perceptions of the facilities in the insertion of remote teaching.

DSC 1: *At the beginning of the pandemic, I was very afraid, I didn't want to be around other people due to the virus (DE01), the insertion of remote learning was a solution found for the moment, and mainly because we needed to finish college. Thinking on this side, it was a good solution (DE02). The remote teaching was very practical, comfortable, by the fact of being at home, it ended up being comfortable, because when a class was over, I was already at home (DE03), you do not need to wake up so early to have to get around, take the bus, be at risk of contamination (DE02). I think it was great to make the tutorials online in small groups work very well, what often happened in the face-to-face tutorial was that it lasted an hour, there were people who spent more time on the bus than in class (DE05). Unlike the face-to-face, the online had the Google drive and class and had to review some classes, if it was recorded, post the activities and proximity to the teachers (DE01). Even with some specific content there were teachers who took some classes with dynamics in kahoot and other applications that helped in the interaction of the groups and made the classes lighter (DE03). We used WhatsApp, Classroom a lot and through the meet we made a call to study everyone together and ask questions (DE02).*

In the discourse above, statements are found that emphasize the facilities experienced in this remote context, such as, for example, adaptation to a new teaching methodology; stimulation of autonomous and group learning online; and a sense of security in preventing the COVID-19 pandemic.

With regard to the use of technological resources, it is important to reflect critically on the reality of students, their previous knowledge and the relationship between technologies as a teaching tool and learning objectives. For, only incorporating technological resources does not transform educational processes, however, it substantially modifies the context in which these processes occur and the relationships between their actors and the tasks and content of learning, thus opening the way for an eventual profound transformation of these processes (BORTOLAI, 2023).

However, it is worth highlighting how much teachers reinvent themselves in the pandemic period, even without adequate preparation (BARRETO, 2020), there is a tireless search to offer the best to their students, a fact observed, for example, in the DSC of students, how much teachers sought digital tools for greater interaction in *online* classrooms and in the process of producing classes in this format, to improve the teaching-learning process.

As a potential of the *online learning modality* stand out the synchronous moments when using inverted classroom strategies, interspersing small learning activities and making available the recording of classes in the Classroom, *allows activities in small virtual groups, with clear objectives and support to the demands of the students; asynchronous moments, aligning the activities with the*

learning objectives; video lessons (recorded or in real time) that promote personal study, individual reflection, group discussion; use of social media, given its long reach, prioritizing the development of interpersonal relationships, to comment, offer *feedback* and the sense of belonging and sense of community; and *individual or group* online reflection (AVELINO AND MENDES, 2020).

It is noteworthy that technological tools are great allies in distance teaching-learning, however, it does not replace face-to-face activities (OLIVEIRA, et al, 2020).

The sense of safety among students who have been subjected to remote learning during the COVID-19 pandemic is notorious, as social isolation measures are aimed at preventing and slowing the spread of the virus. However, even feeling "safe", there are studies that report the consequence of social isolation on mental health among students who experienced remote learning during this period. Among them, the uncertainties about learning, anxiety, insecurity about the professional future, fear of the risks of contamination and infection for themselves and family members, loss of close people, among other psychological aspects that affect life in society (CAMPOS, et al, 2022).

3.2 WEAKNESSES ABOUT THE INSERTION OF REMOTE LEARNING

Theme 2 highlights the categories of anchoring of the fragilities and/or difficulties of the students in the insertion and adaptation in the period of social isolation for the development of undergraduate activities. It was identified by the students as weaknesses in learning in the remote context, the considerable increase in the day of classes, the difficulties of connection, the inequality in the quality of the connection, the adaptations in the domestic environment and the use of technological equipment to accompany the classes.

3.2.1 Theme 2 - Perception of the weaknesses of the insertion of remote teaching

CI 1 - Weaknesses of remote teaching.

DSC 2: *In the beginning of online it was a little troubled, because it really was out of nowhere that they said it would be remote learning, and then basically from one day to the next it already started, so it was a somewhat difficult adaptation process (DE04). Thinking about nursing online was almost impossible (DE01), especially in the third year, a period with a lot of technique and practical classes (DE2). There are some points that cause insecurity (DE01), as in this process we had many contents in classes of many hours in a row with few intervals (DE03), there was a moment that I could not focus and absorb the content and follow the activities, I had difficulty because I am a distracted person, and after many theoretical classes had the practical part with the internships and it was very tiring, and when we went to the internship I no longer remembered the classes (DE06), such as, for example, the mechanical ventilation class with the ventilatory parameters that was online, and I do not remember anything, the class was very tiring, I reviewed in the internship field on the way back to the classroom*

(DE04). The bad side was the internet connection that was sometimes unstable, sometimes it was not enough to support the applications, it had a fall, but came back with many periods of instability, and there were times that depended on the computer, the weather, even more that when it rained the internet was terrible. (DE07), at home we use the notebook more, but there is the computer with the cable, and it is all shared as everyone was at home had to take turns to follow the classes (DE04). And there were cases that the connection of the teachers was also bad, it happened to crash, fall and not come back, and it took time to start the class, which overloads some modules (DE02). There was the part of keeping the camera on and many teachers demanded it, and there were days when the connection was bad, or I didn't want to call, it was uncomfortable because I had the movement of the house, the routine of my family, the demands of the children and with everyone at home there was sound interference, and the privacy of the family (DE05).

It is observed from these discourses how the insertion of remote teaching in the students' view took place, relevant points in the sense of fragilities. In this process of adaptation to the recurrent fragilities were related to the connection to the *internet,* technological devices and domestic spaces to accompany the classes, and the new routine of the house with social isolation.

In relation to home studies, research shows the difficulty of family adaptation during the COVID-19 pandemic, in which many companies have adopted the home *office*, and schools the modality of remote or distance learning, being necessary that the family composition adapted, bringing offices and classrooms into the homes, dividing the spaces that would be of rest, for studies and work, facing the difficulty of connection and the availability of technological resources (GROSSI, et al, 2020).

Counterpoint to the moment before social isolation, there was the difficulty of technological resources reaching schools; in this pandemic context, students faced the challenge of not having enough resources to follow the virtual classes and carry out the activities online *(*AVELINO AND MENDES, 2020).

Among the academic regulations modified to mitigate the losses to the students in question, measures of agreements and evaluations were adopted during the period of suspension of face-to-face activities and the insertion of remote teaching.

The evaluation criteria were modified, allowing *individual* or small group online assessments, seminar presentations, participation and interaction in collective activities, which can be in the *chat* of the platform used to transmit the classes, and even the permanence of the camera on. Another evaluation strategy included the migration to online classrooms such as *Classroom*, which is a platform that allows the posting of files with activities, in which the teacher makes the post with the guidelines

and the deadline for posting, allowing interaction between the student, teacher and the collective, in addition to allowing file shares with greater extension (DOMINGUES, 2020).

It is worth mentioning that with the suspension of face-to-face activities, the professors of the nursing course organized themselves in order to reformulate the classes, evaluation methods, class schedule, and survey of the needs of the students such as access *to the internet*, and the equipment to follow the classes. In some cases, a *notebook and* internet payment *were provided* at home, as well as support and welcoming as a coping measure (RONDINI, et al, 2020).

4 CONCLUSIONS

It is understood that the experience of remote teaching went through the training and monitoring of teachers and students regarding the use of virtual tools, as well as the need to readjust teaching strategies, domestic and routine adaptations of the student, constant doubt in relation to a new disease, concern with the training of students, points that supported this research.

It is understood that emergency remote teaching was the best solution for the moment, despite the difficulties reported in the discourses, the students reveal the opportunity to return to the classroom and review the past contents, having the security to remain in isolation without total prejudice in the graduation.

However, it cannot be fully stated that the learning process in this period occurred without presenting gaps, requiring further research on this topic.

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Case Report: Acute cholecystitis complicared with colocystocolonic fistula

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ABSTRACT
Acute cholecystitis is an acute inflammatory disease of the gallbladder, commonly caused by lithiasis. It is more prevalent in females, and one of its risk factors is obesity. In the vast majority of cases, symptoms include intense pain in the right hypochondrium or epigastrium, which may radiate to the back, associated with nausea, vomiting, diarrhea, hyporexia, fever and jaundice. The diagnosis is made through images, such as abdominal ultrasonography, which is considered a very efficient method for these cases, or computed tomography of the abdomen and in some situations through endoscopic examination (colnoscopy). The treatment is surgical. The patient in the case report in question had a cholecystocolic fistula, which is a rare complication of biliary lithiasis, which has variable and nonspecific clinical manifestations, and its diagnosis is often made incidentally in the perioperative period of its underlying cause. The most indicated treatment is cholecystectomy with closure of the fistula by videolaparoscopy.

Keywords: Colecystitis, etiology, symptoms, fistula, diagnosis, treatment.

1 INTRODUCTION

Acute cholecystitis is an acute inflammatory disease of the gallbladder, commonly caused by lithiasis. It is more prevalent in females (4:1), and has as risk factors obesity, advanced age (greater than or equal to 50 years), multipartum and childbearing age. Gallstones affect 10 to 15% of the population in developed countries, and presents as calculous cholecystitis in 20% of symptomatic patients, and there may be clinical evolutions that vary according to severity. More than 90% of cholecystitis cases are associated with cholelithiasis, and when affected in the elderly, they present higher mortality. On the other hand, cholecystocolic fistula is a rare complication of gallstones, in

which its clinical manifestations are variable and nonspecific, and its diagnosis is often made incidentally in the perioperative period of its underlying cause. (1,9,11)

Symptoms include severe pain in the right hypochondrium or epigastrium observed in 74 to 96% of patients, and may radiate to the back, associated with nausea, vomiting, diarrhea, hyporexia, fever and jaundice, and these signs and symptoms were identified in 60 to 87% of cases. Cholecystocolic fistula is a complication of chronic cholecystitis that occurs in less than 15% of patients, with a prevalence of around 80% in elderly over 60 years of age and females, who present exuberant symptoms, associated or not with intestinal obstruction. (2,4)

The diagnosis is made through images, such as abdominal ultrasound, which is a method considered very efficient for these cases or computed tomography of the abdomen and in some situations by means of endoscopic examination (colonoscopy). However, as the clinical manifestations are nonspecific, it contributes to the preoperative diagnosis being made in only 7.9% of the patients and thus, the detailed description of the real complication will be performed in a furtuitous way during the intraoperative period to treat the underlying cause. (7,8)

Mirizzi syndrome is a rare complication in which a gallstone becomes lodged in the cystic duct or neck of the gallbladder, which results in compression of the common bile duct and its consequent obstruction, which causes jaundice. This syndrome is classified into 5 groups, according to the degree of biliary tract involvement, being: I) extrinsic compression of the common common bile duct or the common hepatic duct by a calculation in the vesicular infundibulum or cystic duct; II) presence of cholecystobiliary fistula with a diameter less than 1/3 of the circumference of the common hepatic duct/choledochus; III) cholecystobiliary fistula with a diameter greater than 2/3 of the circumference of the common hepatic duct/choledochus; IV) cholecystobiliary fistula that affects the entire circumference of the common hepatic duct/choledochus; V) any type, if there is presence of cholecystoenteric fistula, being Va: without biliary ileum and Vb: with biliary ileum. (10)

For those patients who are classified as type I of Mirizzi syndrome, partial or total cholecystectomy is recommended. For type II, cholecystectomy with fistula closure or choledochoplasty with suture of the fistulous orifice in the remaining wall of the gallbladder is performed. If there is cholecysto-choledochal fistula (types II, III and IV), laparotomy by the conventional route is imperative, since biliary drainage needs to be performed simultaneously. (12, 13)

The treatment is surgical, and cholecystectomy with closure of the fistula by videolaparoscopy is the most indicated choice, because it courses with shorter hospital stay and better postoperative period, in relation to laparotomy. It consists of unclogging the intestine by removing the stone, with or without resection of the intestine. Due to necrosis, perforation, and ischemia, removal of the intestinal segment may be necessary. In addition, a check for the presence of other stones in the rest of the small

intestine is made, since the occurrence is from 3 to 16% of cases. Recurrence is 5 to 20% in patients treated only with the removal of obstructive stones. (3,7,8)

2 CASE REPORT

A 57-year-old female patient was admitted to the Santa Casa de Presidente Prudente with a previous history of cholelithiasis, awaiting surgery for two years. However, two months ago, the pain in the right hypochondrium increased in intensity, and accompanied by nausea and several episodes of vomiting, which made her seek the hospital more than 3 times. He reports that, two days ago, the pain became unbearable and he began to present a fever of 38 degrees. She also had diarrhea and three episodes of bilious-looking vomiting. He did not report fecal acolia or jaundice.

Personal history: hypertensive patient, makes use of losartan and hydrochlorothiazide. Diabetic, with irregular use of medication. He has no history of previous surgery. No habits and vices.

On physical examination, the patient presented pain in the right hypochondrium, with positive Murphy's sign and positive BD.

The patient presented ultrasound of the abdomen demonstrating acute cholecystitis (Figure 1).

Laboratory tests showed urea of 35 mg/dL, creatinine of 1.5 mg/dL, sodium of 139 mEq/L, GOT of 505 U/L and TGP of 497 U/L. The blood count revealed leukocytosis of 27,690 /mm3, hemoglobin of 11.8 g/dL and platelets of 309,000 /µL.

Laparoscopic cholecystectomy was performed (Figure 2). During the procedure, a cholecystocolonic fistula was identified and it was decided to convert to open surgery. An open cholecystectomy with colon raffia was then performed. The patient presented good evolution of the condition, with diet in the second postoperative period, discharged in the fourth postoperative period, returning to the outpatient clinic well and without complaints.

Figure 1- Ultrasonography of the abdomen with calculus in the infundibulum, but does not show inflammation with fistula.

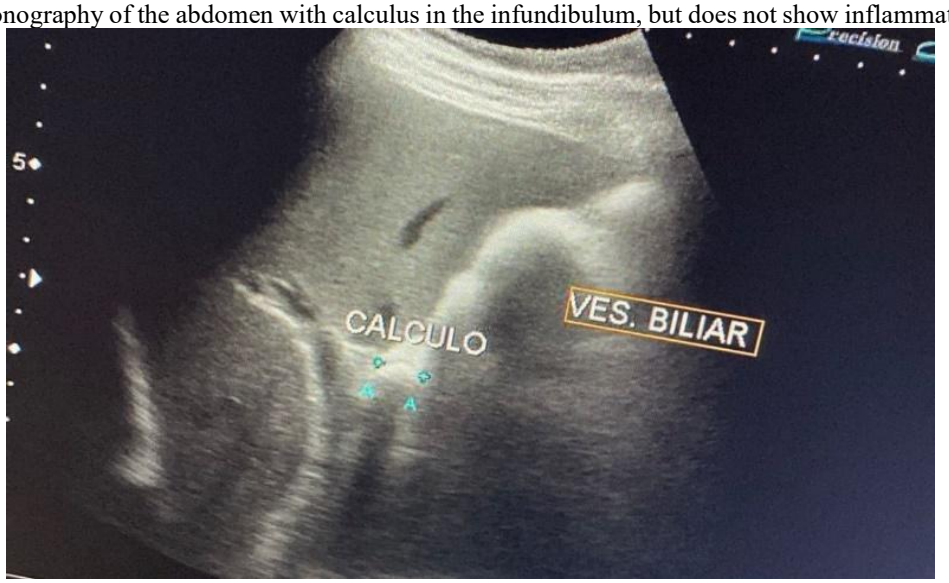
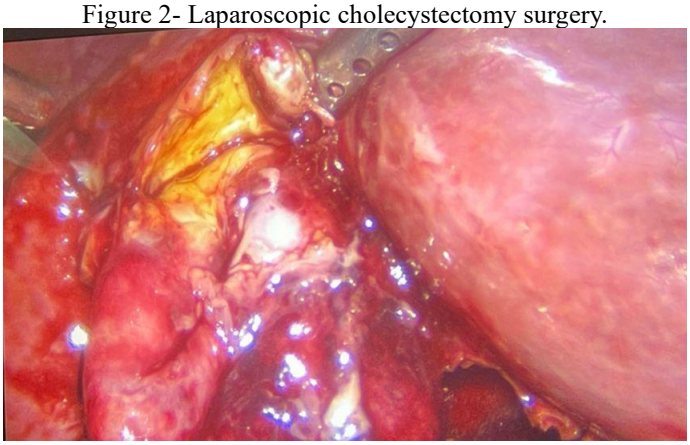


Figure 2- Laparoscopic cholecystectomy surgery.



3 DISCUSSIONS

In the first analysis, it is worth highlighting the difference between cholelithiasis and cholecystitis. Cholelithiasis is a gallstone that generates biliary colic. Cholecystitis is the inflammation of the gallbladder that most often results from an obstruction of the cystic duct in 95% of cases and is usually associated with previous pictures of cholelithiasis. This association occurred with our patient who had been waiting for surgery for cholelithiasis for 2 years. Due to the delay in performing cholecystectomy, this calculus was persistently impacted and biliary stasis occurred, causing damage to the gallbladder and, thus, generating its inflammation**.**

Acute cholecystitis, then, can be described as an inflammatory pathological process, occurring, for the most part, associated with a picture of lithiasis. Friction of the stone in the cystic duct or infundibulum can cause obstruction and distension of the gallbladder, characterizing biliary colic. This process triggers the increase in the production of prostaglandin and lisolectin (mucosal irritant), initiating the inflammatory process. In this case, inflammation with fistula was identified in laparoscopic cholecystectomy surgery, which quickly converted to open surgery.

Risk factors associated with a higher incidence of gallbladder disease and gallstones are: female gender, obesity, hormonal exposure, diabetes, liver disease, age over 40 years, and weight loss. The present case reports a patient at high risk of acute cholecystitis, because she is female, has diabetes (uses medication, but irregularly) and is over 40 years old.

To confirm the diagnosis, the patient's symptoms and laboratory and imaging tests should be analyzed. The clinical picture is characterized mainly by epigastric pain of strong intensity radiating to the back, nausea and vomiting, persistent pain for more than 12 hours, positive response to Murphy's maneuver, tachycardia and elevated temperature. Laboratory tests show leukocytosis, increased direct bilirubin, elevated amylase, and elevated alkaline phosphatase. In imaging exams, ultrasonography identifies gallstones and is therefore the most indicated exam, however radiography, computed tomography and magnetic resonance imaging are important for the exclusion of differential diagnoses.

The introduction of ultrasound has brought a revolution in the field of gastroenterology, especially in the study of the liver and bile ducts, due to its simple, precise and non-invasive form of analysis. Ultrasonography has no contraindications or harmful effects, and the preparation of the patient is simple and can be performed at the bedside, even in cases of critically ill patients. This technique has a sensitivity of more than 90% in the detection of gallbladder stones, being able to diagnose even small stones with a diameter of up to 2 mm, regardless of the number of them.

However, it is important to emphasize that the quality of the exam and, consequently, its sensitivity may be impaired in obese, distended or intraperitoneal adhesion patients. In our case, ultrasound of the biliary region identified calculus in the infundibulum, but without inflammation with fistula. This calculation was enough to diagnose acute cholecystitis, since it was responsible for biliary colic, referred to as pain in the right hypochondrium.

Our case belonged to the group with the highest prevalence (woman, diabetic, over 50 years of age), with a previous history of cholelithiasis and presented the clinical picture and results of tests that confirmed the diagnosis of cholecystitis. Thus, the chosen approach was laparoscopic cholecystectomy surgery.

Laparoscopic cholecystectomy surgery was first performed in 1987 in France, two years after the first laparoscopic cholecystectomy in Germany, and performed in Brazil in 1990. Laparoscopic cholecystectomy has been shown to be 3superior to conventional (open) surgery in several aspects. This minimally invasive approach offers several advantages, including less surgical aggression, shorter hospital stays, and faster return to social and work activities.

When performing laparoscopic cholecystectomy, the surgeon makes small incisions in the abdominal region and inserts a laparoscope and special surgical instruments to remove the gallbladder.

Cholecystectomy is indicated in patients with cholelithiasis associated with acute cholecystitis. In general, a patient with acute cholecystitis is hospitalized, the patient is hydrated and electrolyte replacement is done intravenously and fasting is established.

In addition to faster recovery, laparoscopic cholecystectomy also offers a lower risk of infections, less blood loss during the procedure, and a lower incidence of postoperative complications such as adhesions and incisional hernias.

However, there is a high proportion of cases in which it is not possible to carry it out. About 10 years ago, situations such as pregnancy, previous abdominal surgery, intolerance to increased intra-abdominal pressure, intestinal obstruction, coagulopathy, obesity, cirrhosis, intolerance to general anesthesia, choledocholithiasis and acute cholecystitis were considered as absolute contraindications of laparoscopic cholecystectomy.

In addition, in some patients, when there are technical difficulties (anatomical visualization, extensive inflammation, adhesions, bile duct lesions, retained bile duct stones and uncontrolled

bleeding, complications inherent to laparoscopic dissection), it is necessary to convert from laparoscopic surgery to open surgery. Studies have shown that this conversion is done in 1.5 to 19% of patients. In the case reported, a cholecystocolonic fistula was identified. Cholecystocolic fistula is a rare complication resulting from the chronic local inflammatory process, its diagnosis often made during the intraoperative period and, thus, being performed the conversion to open cholecystectomy.

If surgery is not a viable option for the patient, percutaneous cholecystostomy may be an effective diagnostic and therapeutic alternative, with an improvement rate of about 90% of cases. Especially in elderly and unstable patients, in whom surgery presents significant risks, percutaneous cholecystostomy can be performed under local anesthesia. Combined with the use of antibiotics, this approach can improve the acute picture of the condition, and subsequently cholecystectomy (surgical removal of the gallbladder) can be performed after a period of 3 to 4 months. Our patient did not fit the criteria of percutaneous cholecystostomy.

Thus, the patient presented good evolution of the picture, even having undergone open surgery and being in the risk group. He returned to the outpatient clinic without any apparent complaints and currently continues his life normally without abdominal pain.

4 CONCLUSIONS

We conclude that acute cholecystitis complicated with colocystocolonic fistula requires early diagnosis and appropriate surgical treatment, the access route depends on the fitness of the surgeon, in the minimally invasive option, conversion to open surgery may be necessary in some cases and postoperative follow-up is essential to ensure an adequate and uncomplicated recovery.

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SEVEN publicações acadêmicas

Food consumption behavior during the Covid-19 pandemic

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ABSTRACT
The article presents the results and impacts on the population's food consumption behavior during the Covid-19 pandemic. Changes in routine, psychological aspects and the contribution of the media in this period form crucial points in the decision-making process in choosing food. A bibliographic review of articles on the subject and quantitative research carried out on the Google Forms platform, published by the WhatsApp application, was carried out. The questionnaire presented a sample of 82 respondents from the city of São Paulo, with the objective of ratifying the inclinations presented in the bibliographic review and assisting in the reflection on which prevention strategies can be developed to combat inappropriate habits during the pandemic. The questions were divided into three blocks, punctuating sociodemographic, psychographic and behavioral aspects, totaling 15 questions. The survey showed that a total of 84% of respondents changed their eating routines totally or partially, in addition to indicating a high level of anxiety in the period, leading to the choice of foods harmful to health.

Keywords: Covid-19, behavior, consumption, food.

1 INTRODUCTION

A brief news story in the Hong Kong Journal about the city of Wuhan on the fateful day of November 17, 2019 about a case of a mysterious pneumonia would be able to change the course of humanity forever. The first cases of the disease, identified as severe acute respiratory syndrome, began to worry authorities officially in December of that year.

In March 2020, Brazil went into a state of alert following the announcement of the WHO (World Health Organization) about the pandemic that the world would face with the new coronavirus in circulation, called Sars-Cov-2. The disease caused by the virus, known as Covid-19, brought a new way of living, thinking and acting, so the daily life of the population changed drastically as it suffered an almost immediate impact after the painful news.

The restrictions of circulation, alteration in the routine and the psychological transformations in this period bring changes to the behavior of food consumption. The intense news about the pandemic and advertising in this period are also factors that have altered consumer perception, making him act on impulse when choosing certain foods.

Justo (2020) described in his research on the perception of the nutritionist and eating habits in the pandemic that the population tends to buy more processed and ultra-processed foods, as they are less perishable, practical and cheaper than fresh foods. The author also reports that psychological issues such as anxiety can lead to exaggerated and impulsive consumption of food.

The objective of this study is to report the impacts of covid-19 on food choice, pointing out possible changes in human behavior during the phase of social distancing, as well as observing which psychosocial aspects are relevant and that determine these consumption preferences. Therefore, the proposal of the article becomes relevant to understand how the pandemic was able to change the eating routine of Brazilians and what possible consequences may be linked to the health of the population.

2 REVISIONS BIBLIOGRAPHICAL: THE IMPACTS OF COVID-19 IN FOOD CONSUMPTION BEHAVIOR

It is necessary to understand, first, what aspects are linked to the daily choices of consumers in the context of product purchases in general, even before the emergence of the pandemic. For Bragaglia (2010), there would be three main motivations: the consumer opts for the product that brings him emotional pleasure, he can also choose something that provides him with satisfaction in relation to the functionalities of the merchandise and he can still consume products by the status that the brand provides, with the objective of being inserted in a group of society. From the latter, advertising is pointed out as an expressive factor in consumer engagement.

When dealing with the consumption of food, it is clear that even in the face of any crisis, this commodity is the last that the population will stop buying. From this view, other factors are part of the set of motivations that lead the population to opt for certain foods, in this case the space-time relationship, because over the years great transformations in the daily life of private life have led to a behavior in favor of convenience, mainly due to the lack of time, leading the population to prefer fast and processed foods. The convenience and speed in meals are valued, increasing the consumption of sandwiches, chocolates and soft drinks, in addition to the media playing an important role in this relationship, since the meal is transformed by advertising in sign, capable of inducing the purchase (ORTIGOZA, 2008).

According to Simoni (2018, p.5):

> Food consumption consists of the set of foods chosen by an individual in a given period. These choices depend on the consideration of social, cultural and psychological factors and are related to the environmental conditions, history, personality and values of each individual. Such choices are not always made consciously, but are based on the desire to meet physiological needs and/or specific desires.

Still, Ortigoza (2008, p.91) reveals:

> It is necessary to consider, then, that the production of some forms of commerce also ends up creating new consumption habits, new behaviors and hence new consumers. Hunger as a biological necessity is masked in certain types of trades and manipulated exaggerations occur and even if there is freedom of choice, the consumption of food loses its coherence.

When studying behavioral issues, it is evident that psychology has a fundamental role in understanding the desires and impulses present in everyday eating habits. The social context and experiences shape the thought and consequently the action (SILVA; MEADOW; SEIXAS, 2016).

According to Skinner (1982, p.43), it is possible to observe through Behaviorism the construction of habit in function of stimuli that occur in the environment in which we live:

> When a behavior has a type of consequence called reinforcement, it is more likely to occur again. A positive reinforcer strengthens any behavior that produces it: a glass of water is positively reinforcing when we are thirsty, and if we then fill and drink a glass of water, we are more likely to do so again on similar occasions. A negative reinforcer invigorates any behavior that reduces or makes it cease: when we take off a shoe that is tight the reduction of the grip is negatively reinforcing and increases the likelihood that we will act like this when a shoe is tight.

Emotions undergo evaluation about positive and negative situations and are transformed throughout the events, and this factor is the object of study that evaluates the relationships between emotions, consumer behavior and influence on the purchase process. When studying the purchase process, emotive factors are determinant for the choice of affective, pleasurable and experimental products (SIMONI, 2018).

Covid-19 can also change the way the world's population relates to food, as panic and the consequent stockpiling of food causes people to buy more processed food, i.e., non-perishable, replacing all categories of fresh food, affecting the quality of the diet. Convenience products, unhealthy food and snacks in general are examples of merchandise with a longer shelf life and that are part of the choices in this period of isolation. (HASSEN; BILALI; ALLAHYARI, 2020).

In this sense, for Silva et al. (2020, p.2), during the quarantine period, two important strands were identified that point to human behavior and food choices. The imperative of the term "stay at home" (which includes the routine of digital education, work, limitation of outdoor physical activities) and the stock of food (due to the restriction of circulation) can result in factors such as: anxiety, stress, boredom and a so-called "emotional eating", which leads to an excess consumption, mainly of foods rich in fats and sugars, ingesting these products stimulates the production of serotonin in the body, which is known to reduce stress and anxiety.

Still, Durães et al. (2020, p.3), point out that cortisol levels, elevated due to stress, increase the feeling of hunger for foods called comforting for the body, in this case sugary and fatty foods. This desire for food includes the emotional, behavioral, cognitive (thinking about food) and physiological

(salivation) axes. The researchers also again address serotonin, which is responsible for the positive effect on mood. Already mentioned earlier, this neurotransmitter is stimulated, mainly, by the consumption of carbohydrates.

Another relevant point to be considered for this study is that according to Megin (2020, p.47), boredom and behaviors linked to addiction are present in people who are quite active and who had their routine changed abruptly, linking this boring feeling to less ability to deal with negative issues, making these consumers feel angry, dissatisfied and frustrated, contributing to activities that distract them, influencing the choice of food, being more likely to eat high-energy food.

In China, during the initial phase of Covid-19 in the country, there are reports from researchers about the psychological impacts on the population, demonstrating high levels of stress, anxiety and depression and how these feelings affect decisions about consumption. Drastic changes can trigger a series of negative feelings for the fear that the disease spreads in society (HASSEN; BILALI; ALLAHYARI, 2020).

Also in China, it was possible to observe in an online survey of 2,272 Chinese in 27 provinces and municipalities on eating habits during the pandemic, where an increase in the consumption of coffee, vegetables, water, fruits and grains was observed. These choices are linked to health concerns and also as a way to prevent Covid-19, as this questionnaire also showed a drop in the consumption of fish, shrimp and crab, chicken meat, cattle meat, sugary drinks and snacks (DURÃES, et.al., 2020).

Silva et.al (2020, p.11) point out the following research conducted in Italy:

> A survey conducted with the Italian population through the analysis of 1,932 questionnaires showed, among the various results, in particular, an increase in the consumption of "comfort foods", especially chocolate, ice cream, desserts and snacks, given that 42.7% attributed this increase to the attempt to control anxiety levels. About 21.2% of respondents increased their consumption of fresh fruits and vegetables. Only 33.5% of those who reported reduced consumption attributed this change in diet to lower availability and access to these items.

Therefore, it is possible to verify that the level of reach of processed and industrialized foods are also a considerable point in this relationship of consumption during the pandemic, since the research conducted in Italy, found that there was an increase in the consumption of pasta, flours, eggs, milk and frozen, and a reduction in the consumption of in natura foods, such as vegetables and fruits, as these have affected the means of production and distribution during the pandemic scenario.

In a recent survey titled "Consumer Agency, Food Consumption Behavior and the Novel Corona Virus (COVID-19) Outbreak," the U.S. and Canada, for example, showed the habit of freezing fruits and vegetables, which can lead to an imbalance in sales, also influencing unhealthy eating. On the other hand, Qatar (a country located on the Arabian Peninsula) showed a reverse behavior, as there was an increase in the consumption of fresh foods, combined with health care, in addition to a low

spread of negative emotions such as worry, nervousness, depression and fear (HASSEN; BILALI; ALLAHYARI, 2020).

In Brazil, it is possible to verify in the research done by Datafolha (2020), an approach conducted with people between 18 and 55 years old, belonging to all social classes and regions of Brazil, revealing that packaged snacks or salty cookies were the leaders of consumption in the period, comparing with the analysis made in 2019 on these same products. Second place went to margarine, ketchup and other industrialized sauces (AGÊNCIA BRASIL, 2020).

It is worth remembering that visual stimuli are also important for consumer decision-making. For Jenkins (2008 apud ABREU; ALVES, 2021, p.49): Information and communication technologies contribute to changes in the social and cultural sphere and create new consumption habits, transforming the media and the way of communicating, which becomes bilateral. In this way, it is inevitable that the way of consuming the means that and there is interaction with the content will change,

First, we look at the advertising landscape, which grew during this period of isolation and benefited from social networks to disseminate various contents, including fast food and similar food products. Calls such as that of the fast-food chain Burger King: "Which of these menu items would you isolate yourself with?" aired in April 2020, was created to provide comfort in a period of uncertainty (IWASAWA, 2020).

In the opinion of Bortoleto (2020), a nutritionist at Idec (Brazilian Institute for Consumer Protection), the trend of consuming processed foods should continue "given that at this time the policies adopted so far to promote healthy eating during the pandemic have been very timid and there has been an increase in advertising and appeal, both for convenience, as for the convenience of the consumption of ultra processed foods"

Contrary to the positioning and scarce communication about healthy eating, the big brands of processed foods stand out in the pandemic by using social networks to create content and persuade the public with messages of an affective nature. The company Seara, for example, uses social media such as Facebook and Instagram to publish campaigns and ways to enjoy the moments at home, creating a link with special recipes in the style of do it yourself. On dates

For example, the phrase "This Easter, be with the one you love, even if you are not close. Discover what you can prepare at home this Sunday on our website", accompanied by an emotional soundtrack and families gathered by video conference, encourages the consumer to cook at home in a practical way (ABREU; ALVES, 2021).

A survey conducted by USP, between June and September 2020, through social networks, newspapers, television and radio, evaluated Brazilian women, through an online questionnaire, from different social classes and nutritional states about the current moment, affected by the psychological impacts in relation to habits and food choices. The questionnaire conducted with 1,183 women, among

demographic, socioeconomic and psychological questions, indicated that they began to cook more, left the diet aside, decreased trips to the supermarket and adopted the delivery system more often. The latter showed a 174% growth in demand during this period. The questions about the psychological aspects dealt with the reasons that led the participants to choose certain foods such as: hunger, desire, health, social convention). Homemade foods and sweets showed greater demand among the requests. (USP JOURNAL, 2020).

In addition to the advertising stimulus, the perception about the media during the pandemic also presented a bias about how negative news can affect behavior. A study conducted and published in the scientific journal Proceedings of the National Academy of Sciences, points out that Brazilians tend to react more strongly to bad publications, even before the pandemic took hold in the country. (CORRÊA, 2019).

Therefore, the growing wave of publications about the coronavirus has an important part in the impulse food purchase decision process, since negative news readings can trigger sadness and stress, causing consumers to seek the so-called "emotional eating", which is based on processed, sugary and high-calorie food options.

Next, table 1 shows the significant number of news published by government on Facebook, Instagram and Twitter. The search also shows the on health and the public's shares in relation to the first months of the year 2020.

Table 1

GOVERNMENT	JANUARY	FEBRUARY	MARCH	MARCH X JANUARY
ACTIONS	1.424.177	2.057.367	2.566.310	80%
CONTENT	3.995	5.013	5.363	34%
ACTIONS BY POST	356	410	479	34%
SHARES	224.565	344.773	617.982	175%
HEALTH	JANUARY	FEBRUARY	MARCH	MARCH X JANUARY
ACTIONS	703.534	726.277	802.357	14%
CONTENT	807	812	858	6%
ACTIONS BY POST	873	894	935	7%
SHARES	14.282	24.799	20.758	45%

Source: CAMPOS, 2020. Available at: https://www.comscore.com/por/Insights/Blog/Consumo-of-the-social-networks-in-Brazil-during-the-Coronavirus-pandemic. Accessed on: 04/18/2021.

Analyzing or frame is possible check one crescent numbe from sharing government-related content and health-related topics, especially in the month of March, when the new coronavirus was beginning to be prominence throughout the country. Constant and informative publications on the of the pandemic in Brazil and in the world have had a direct impact on the feelings of the population and

a climate of uncertainty was about to be installed in the routine of the Brazilian. The number of news sharing about the government has skyrocketed 175% from January to March in 2020. Health news, on the other hand, jumped by 45% between the same months. The actions in the networks carried out by the government, increased 80% in the first quarter and health care grew by 80% 14%. This panorama reveals that during this period there has already been a change in the news consumption behavior and greater audience engagement in relation to to government and health information.

3 METHODOLOGIES

In addition to the literature review on the subject, where the results of several analyses carried out in Brazil and other countries on the impacts on food consumption behavior in the face of Covid-19 were also presented, a quantitative survey was proposed for respondents from the city of São Paulo. A questionnaire was used, diagrammed through Google Forms, which was disseminated through the WhatsApp application. The measurement of the results and crossing of data for analysis were performed with the aid of Tableau Public software. All interviewees were recruited voluntarily and knew from the introduction of the questionnaire what the objective of the study would be. Individuals were also selected for convenience so that they were readily available.

The research included a total of 15 questions, which addressed sociodemographic, psychographic and behavioral issues. There were seven multiple-choice questions that involved gender, age, marital status, number of children, school level and income. In addition to three questions related to the eating routine and the types of food consumed at the time, using the multiple choice and also the four-point Likert scale, mentioning the possibilities such as: totally agree, partially agree, totally disagree and partially disagreement. Finally, five questions about feelings and motivations were proposed, using only the Likert scale, in this case.

Therefore, a pre-test was conducted with 10 respondents so that the questions were clear, coherent and easy to interpret, detecting possible noises and problems that could affect the results. Then, the research was adjusted and applied efficiently among adult men and women. The questionnaire generated a total of 82 samples for analysis and subsequent results pointed out by Tableau with data downloaded from Google Forms. The results were shown between tables and graphs, indicated by percentage and frequency.

4 FINDINGS

4.1 SOCIODEMOGRAPHIC CHARACTERISTICS

Table 1 shows the results of the sociodemographic questions, indicating 62 respondents, where 76.8% were women and 23.2% were men. Ages vary, indicating the majority of 28% between 45 and 59 years, followed by 22% from 25 to 30 years, 17% between 31 and 37 years and finally, an average

of 10% in the scales of 18 to 24 years; 38 to 44 years old and over 60. In addition to the age group, the majority of 54.9% are married, followed by 37.8% single and 7.3% divorced.

Table 2

Variable	Answer options	Frequency	Percentage
Gender	Male	19	23,20%
	Female	63	76,80%
Age group	18-24	10	12%
	25-30	18	22%
	31-37	14	17,10%
	38-44	8	9,80%
	45-59	23	28%
	> 60	9	11%
Marital status	Married	45	54,90%
	Single	31	37,80%
	Divorced	6	7,30%
Number of Children	1	11	31,40%
	2	18	51,40%
	3	6	17,10%
School Level	Middle school	18	22%
	Graduation	32	39%
	Graduate	29	35,40%
	Masters	3	3,70%
Income	1-3 minimum wages	13	15,90%
	3-6 minimum wages	27	32,90%
	6-9 minimum wages	25	30,50%
	9-12 minimum wages	10	12,20%
	12-15 minimum wages	2	2,50%
	> 15 minimum wages	5	6,10%

Source: Own author.

Table 1 also shows a profile with the majority being part of the middle class, identified among classes B, C and D, which make up 78.1% of the respondents. This parameter is associated with the sociodemographic table of the IBGE (2020). It is also possible to verify that 78% have higher education and some kind of specialization. Therefore, the research is segmented to a portion of the population that has easy access to the internet, through which this research was disseminated, in addition to the total understanding of the content exposed, knowing how to correctly interpret the questions.

4.2 BEHAVIORAL CHARACTERISTICS

Table 2, on the other hand, shows the behavior of food consumption in the face of COVID-19. Scoring if there were changes in the eating routine, changes in food choices and which products are being consumed more by the respondents. It is possible to observe that a large part of the public, totaling 84.1%, totally or partially altered the feeding routine during the pandemic. Regarding the change in food choice, 78.1% believe they have changed their choices totally or partially. Finally, it was possible to choose which products (more than one option) are on the rise in the current routine of each participant, sweets led reaching 58% of the responses, followed by fast food with 47.60%.

Table 3

Variable	Answer options	Frequency	Percentage
Changed the eating routine	Totally Agree	31	37,80%
	Partially agree	38	46,30%
	Strongly disagree	4	4,90%
	Partially disagree	9	11%
Changed the choice of food	Totally Agree	30	36,60%
	Partially agree	34	41,50%
	Strongly disagree	6	7,30%
	Partially disagree	12	14,60%
What foods have you been consuming the most	Fast Foods	39	47,60%
	Sweets	48	58,50%
	Vegetables, Vegetables and Fruits	25	30,50%
	Animal Protein	46	56,10%

Source: Own author.

4.3 PSYCHOGRAPHIC CHARACTERISTICS

To conclude the research, it was necessary to understand the feelings of the participants regarding the pandemic and what psychological and social aspects can influence food choices. Next, in table 3, it is possible to verify the level of anxiety of the respondents, represented by the Likert scale from 1 to 4, and 56.1% appear at the highest level (4), followed by 29.3% by the intermediate level (3), 9.8% by the median level (2) and only 4.9% do not feel anxious, represented by the level (1).

Table 4

Variable	Answer options	Frequency	Percentage
On a scale of 1 to 4, how anxious do you feel in this time of pandemic?	1	4	4,90%
	2	8	9,80%
	3	24	29,30%
	4	46	56,10%
My emotions are tied to the type of food product I consume.	Totally Agree	27	32,90%
	Partially agree	37	45,10%
	Strongly disagree	10	12,20%
	Partially disagree	8	9,80%
I believe that the daily news about the pandemic can induce me to a compulsive behavior of food consumption.	Totally Agree	30	36,60%
	Partially agree	29	35,40%
	Strongly disagree	16	19,50%
	Partially disagree	7	8,50%
I believe that the consumption of industrialized foods can bring a feeling of momentary comfort in these pandemic times.	Totally Agree	29	35,40%
	Partially agree	39	47,60%
	Strongly disagree	5	6%
	Partially disagree	9	11%
Do social media posts from fast food restaurants make you consume these	Totally Agree	19	23,20%

foods more often?	Partially agree	42	51,20%
	Strongly disagree	11	13,40%
	Partially disagree	10	12,20%

Source: Own author.

Most respondents totally or partially agreed that day-to-day emotions influence the type of food product consumed, totaling 78% of incidence. This inclination is directly linked to the issue of the high level of anxiety linked to the concept of "emotional eating", which is about choosing foods rich in fat that are able to bring a sense of momentary comfort to those who consume, since 35.4% of respondents totally agree with this statement and 47.6% partially agree.

Regarding access to news about Covid-19 and subsequent consequences regarding human behavior, it is evident the expressive agreement of 73% on the influence of the media and the feeling of the public that translates the bad moment into immediate needs, bordering on compulsivity, seeking comfort in food, most often with high fat and sugar content, being harmful to health. In addition to the reports on the pandemic, the advertising of foods harmful to health on social networks also aroused a more frequent consumption, generating a partial agreement of this statement of 51.2% and a total of 23.2%.

5 FINAL CONSIDERATIONS

After the bibliographic study with the notes of several countries, including Brazil, on the behavior of the population regarding the issue of food choices during the Covid-19 pandemic, it was possible to ratify this information through the questionnaire conducted for this article, which comprised the social, psychographic and behavioral aspects as strands for the study of the proposal. It was found, as the survey indexes showed, that most of the respondents had their eating routines affected by the pandemic, perceived a high level of anxiety in the period, as well as a compulsive eating behavior linked to visual stimuli observed in the media, driven by fast-food advertisements or with negative news from communication channels.

The number of searches for foods harmful to health increased in Brazil, unlike the questionnaire conducted with 2,272 Chinese, where the population reported that the reason for the increased intake of healthier products and an active change in eating habits was to prevent Covid-19 (DURÃES, et.al., 2020).

It is necessary to take care of health to prevent diseases, especially in this delicate time, where a pandemic is ravaging the world. Studies on the Brazilian population and the relationship with eating behavior, especially in this period of fragile health, draw attention and raise an alert about the complications that may arise, especially at a time when the immune system needs to react and poor food choices from day to day can interfere negatively. The article helps to reflect on the dangers that

Brazil may be following and which prevention strategies can be developed later, helping to combat inappropriate habits

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Discussing health in high school: Coronary artery disease (CAD) and its relationship with gene, sedentary lifestyle and nutrition

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ABSTRACT
The work in question is related to the "XXIII Scientific Exhibition" held at the School of Basic Education linked to the Regional Integrated University – URI where academics guided by the regent of the discipline of Biology encourage high school students to carry out scientific work that provides opportunities for research, scientific development and protagonism. The relevant points of the work are in the research and understanding carried out between the relationship of genetic and environmental factors and their actions in the development of coronary artery diseases (CAD); in addition to the perception regarding the learning opportunities of this work for high school students. To this end, the bibliographic research was carried out from the search of articles published between 2021 and 2022 found in the "PubMed" database, being discarded articles whose objective and the results/conclusion were not consistent with the central idea of the work. In relation to the research, it was concluded that genes are important factors for the possibility of the development of such diseases, however, a good diet and the practice of physical exercises appear as limiting factors for CAD to manifest themselves, considering their influence on the body, since it is proven that the genes contribute very little to the action of coronary diseases. In relation to the protagonism of the student, it was observed that the research provided scientific knowledge, opportunity to dialogue with academics, incentive to research understanding that it is an essential factor for the development of criticality, autonomy, competence and learning in a significant way.

Keywords: Genes, cardiovascular diseases, middle school, role.

1 INTRODUCTION

The real and significant learning should be related to the daily life of the adolescent, in this way the schools use tools for the students to understand the importance of scientific research, making the relation of the contents developed in different disciplines with those seen in the Universities and with the National High School Examination (ENEM).

These tools are related to "Scientific Initiation Exhibitions", which aim to provide the development of protagonism through research and investigation, experiencing concrete, creative and

innovative experiences, appropriating scientific concepts and values in their own observations, as well as promoting the socialization of the results researched.

This research should contribute to instigate and improve knowledge, starting from the following premise:

> When talking about research there is a question that needs to be clarified in principle: the concept "research" is not univocal and it is from it that we begin by defining our understanding and emphasizing that doing research is not an exclusive activity of doctors, professionals of academia, scientists, among others, but constitutes a task of launching new discoveries from something that intrigues us, worries us (NOGARO; CERUTTI, 2016, p.67).

Thus, this research aimed to work with coronary artery disease (CAD), a disease that develops in the arteries that supply the heart, called coronary arteries, which is addressed in high school textbooks, studied in health courses, common in everyday conversations of adults, which occurs due to a process called atherosclerosis, in which atheroma (fat) plaques are deposited in the arteries, obstructing the blood passage and forming atherosclerotic plaques (SWEIS, 2020; JIVAN 2020).

The initial idea was based on the possibility of establishing the relationship between the factors that influence the development of CAD, highlighting the action of multiple genes, obesity, dietary factors, sedentary lifestyle, hypertension, smoking and the high index of low-density lipoprotein (LDL).

To have this perception, we sought research in Genetics that make it clear that genetic inheritance can help the development of diseases, but there are a range of pathogens that are more linked to external factors and not to genetic action, being called multifactorial (MARCHESI, 2020).

This literature review presents the relationship of CAD with genetic and environmental factors; in addition to discussing the importance of scientific research in high school and the different opportunities that this work can bring to the student.

2 THEORETICAL FRAMEWORKS

To understand the relationship that exists between genes, the environment and daily life, we chose a disease that brings many questions, which is expressed in textbooks and manifests itself in family conversation circles, CAD. It becomes essential to demonstrate to the community the importance that genetics or lifestyle have on the health of the population.

Thus, Gottlieb et al (2007), demonstrate that genes play an important role in the formation of CAD, however, it is of primary attention to highlight the action of these other factors, which alone do not represent so much danger, but when joined can cause catastrophic results in the health of the individual. Genetics does not determine the expressiveness or otherwise of CAD, as the genetic contribution in such a disease is relatively low, considering that it is not a syndrome. However, it still plays a risk factor, as it may influence the development of this pathogenesis in a silent way.

One should question how much this relationship is part of everyday life, because in times of processed foods or "*fastfoods*" would be a way to contribute to adolescents understanding the importance of healthy lifestyle habits, making choices that can make a difference in adult life. Diet comes in as one of the main factors to consider when dealing with the onset of CAD. The intake of HDL and LDL are agents that are directly related to CAD, because LDL is the cholesterol that accumulates in the walls of the coronary arteries, thus causing the development of fat plaques called atheroma (HENNING, 2021).

To avoid fat plaques, it is necessary to take care of the diet, which is the main focus to prevent the development of CAD, a fact envisioned by Khera and Kathiresan (2017). In this context, the consumption of unprocessed foods becomes crucial for health, as processed foods have a high content of saturated fats, when compared to unprocessed foods, a fact observed in the studies of Sekhar et al. (2021).

Scientific initiation work can contribute to discussions about the health of adolescents, to the development of habits and attitudes, to the choice in relation to diet or the option of practicing physical exercises, because we live in times when childhood obesity is increasingly fierce. We should still discuss health in its different nuances, because we experience the time of valuing the body by the media, a fact that can have serious consequences for an adolescent. Providing discussion or instigating knowledge regarding CAD may be a stimulus for changing habits.

In this context, Moss collaborates (2015, p.16) "Our culture has turned against cigarette advertising campaigns, but we do nothing while food companies do exactly the same thing. And we could say that the damage to public health caused by a poor diet is comparable to that caused by tobacco."

Another factor to be discussed refers to the lack of regular practice of physical exercises, because the exercises are part of a clinical process that is called "cardiac rehabilitation". This process consists of the practice of exercises, the change of behavior in relation to the disease, psychological support to the sick and education about the risk factors for CAD, as advocated by Yamamoto *et al.* (2010).

Changes in lifestyle, such as inadequate eating patterns associated with sedentary lifestyle, alcohol abuse and smoking, contribute to the occurrence of the development of diseases. In relation to food, the most prominent change is the supply of industrialized foods, with high energy density, at the expense of saturated fats and simple carbohydrates, to the detriment of natural foods, which have lower caloric value and are sources of micronutrients and fiber (DE JESUS; HADDAD, 2017).

3 METHODOLOGIES

The XXIII Scientific Initiation Exhibition, involving interdisciplinarity, the community and the media, took place from October 29 to 31, 2022 and had as its theme: "Transforming our world: the 2030 agenda for Sustainable Development". The high school students chose their advisors and the school supervision provided *the template for article production*, banner *template* for presentation and choice of the board, formed by university professors who evaluated the work. After the choice of the guiding professor, there was an invitation for an academic of the VI semester of the Medical Course of the University of Rio Grande (FURG) and an academic of the VIII semester of the Nursing Course of URI, to act as co-advisors.

The bibliographic review work was performed through queries in the *PubMed* database, through the combination of the keywords *"coronary artery disease*", "polygenic risk*", "*diet" and "exercise". For the work, a group of *WattsApp* was created where the academics assisted by the regent professor and professor of the University guided the student researchers; in addition to face-to-face meetings. Articles and papers published between 2021 and 2022 were selected. In the first search, 7 papers that corresponded to the descriptors were chosen and, after reading the objectives and abstracts of these, 5 papers were selected to compose this review. In addition, a study from 2017 was used, considering its relevance and correspondence with the objectives of this work. For the discussion, a table was made that describes the selected works and their contributions; in addition to taking into account the testimonials of student researchers at work and their relevance to learning.

4 RESULTS AND DISCUSSIONS

Initially, (table 1) the result of the research related to CAD, the selected articles and their main information will be demonstrated. Afterwards, the testimonies of the students involved in the research will be presented, with the respective analysis.

Table 1 - Presents the article, authors, objective and conclusion.

Article	Authors	Goal	Conclusions
Genetics of Coronary Artery Disease: Discovery, Biology and Clinical Translation	KHERA, A. V.; Kathiresan, S., 2017.	Understand the genetic factors of CAD, the role of human genetics in catalyzing drug discovery efforts for CAD, and the promises and challenges of integrating genetic information into routine clinical practice.	It was noticed that genetic factors such as hypercholesterolemia have a strong action on CAD, and familial hypercholesterolemia is the main monogenic factor of CAD. It is believed that family genetic analysis, focusing on LDL cholesterol levels, promotes an easy mapping of a possible CAD, opening avenues for early treatments.
Obesity and Obesity-induced Inflammatory Disease contribute to	HENNING, R. J., 2021.	Research and relate obesity with the formation of	Visceral adiposity is a severe chronic inflammatory condition that contributes to vascular

Atherosclerosis: A Review of the Pathophysiology and Treatment of Obesity		atherosclerosis, studying the means that this overweight is related to the development of CAD. As well as researching ways to slow down the effects that obesity can cause, and perhaps ways to treat it	atherosclerosis. Obese patients produce the adipokines leptin, resistin, interleukin and chemotactic proteins that attract monocyte and macrophage to the adipose tissue causing inflammation and platelet aggregation responsible for endothelial dysfunction and myocardial fibrosis. Weight loss with diet and exercise, medications and bariatrics will be able to reduce inflammatory adipokines, oxidative stress and abnormal lipid metabolism. A multidisciplinary approach with obese patients that involves lifestyle changes, pharmacological or surgical interventions is essential. Research on inflammatory and anti-inflammatory adipokines should be continued to facilitate the understanding of adipokines with cardiovascular diseases.
Monogenic and Polygenic Models of Coronary Artery Disease	MUSE, E. D. *et al.*, 2021.	Review and analyze how advances in genomic sequencing have broadened the understanding of monogenic and polygenic contributions to CAD and how these insights can be utilized in order to to create polygenic risk estimates, to improve risk stratification for diseases such as CAD.	CAD, being an inherited disease, is being increasingly mapped by the advancement of genomic medicine, which allows to more accurately identify people genetically susceptible to this condition. With this it is possible to act early and in a personalized way in the prevention of CAD.
Food for Thought or Feeding a Dogma? Diet and Coronary Artery Disease: a Clinician's Perspective	SEKHAR, A. *et. al.*, 2021.	Provide an overview of nutritional studies evaluating the association of dietary saturated fat and meat intake with the development of CAD and discuss the implications of recent data.	Trans fats and processed meats are directly related to increased cardiovascular risk. Unsaturated fat is preferred, but there are limitations in studies as to the outcome of saturated fat consumption. It is also noticed that a high intake of refined carbohydrates, which have a high glycemic index, is associated with the worst data on cardiovascular diseases.
Association between Food and Nutrients Intakes and Coronary Plaque Vulnerability in Patients with Coronary Heart Disease: An Optical Coherence Tomography Study	WANG, W. *et al.*, 2021.	To explore how food intake is linked to the treatment of CAD and its association with coronary plaque vulnerability, the main mechanism for the progression of coronary heart disease, by means of	It has been demonstrated that dietary factors are associated with the vulnerability of atherosclerotic plaque. Salt intake is the main dietary risk factor for plaque vulnerability. On the other hand, the consumption of vegetables, fruits, dietary fiber, folate and vitamin C are dietary protection

		OCT (optical coherence tomography).	factors and are inversely related to plaque vulnerability.
Exercise Training and Interventions for Coronary Artery Disease	FÉRNANDEZ-RUBIO, H. *et al.*, 2022.	Perform a brief specific analysis of the results that patients with CAD can achieve by performing endurance, strength, or inspiration muscle training.	Physical exercise is an effective therapy for the primary and secondary prevention of CAD, attenuating some pathophysiological processes and promoting improvements in functional capacity and muscle strength. The study shows that the most important parameter to be considered seems to be the total caloric expenditure, and not so much the modality itself.

Source: Prepared by the authors.

It should be considered that 2 selected articles bring the discussion of the relationship of CAD with genetics. Khera *and* Kathiresan (2017) demonstrate the importance of understanding genetic factors as a challenge to integrate this content into clinical practice, noting that hypercholesterolemia has a strong action on CAD and Muse *et al.*, (2022) observe that CAD is a hereditary disease, hence the importance of understanding nutrigenomics.

We understand that discussing the action of the gene in the organism is a very intriguing factor, because genes have as characteristic penetrance and expressiveness, factors that can undergo oscillations, contributing to the understanding of epigenetics, which according to Moalem (2016) is characterized as the study of how genetic traits 'can change and be changed in a single generation, and even be passed on to the next generation. Following this reasoning we understand that the environment will be able to act on the expressiveness of the gene:

> Some genes are activated by external triggers or random factors. In this process, proteins act as master sensors, turning genes on or off, or even combinations of genes. Like the score of a symphony, the genome contains the information for the development of these proteins, which often causes this score to be described differently, suffering the influence of the environment (KEAN, 2013, p.56).

Another fact demonstrated by Moalem (2016, p.69) consists in understanding that "your thoughts are always impacting your genes, which need to change over time to align your cellular machinery within the expectations you have set and the experiences you have experienced."

Along these lines, Muse *et al.* (2021) observe that CAD is increasingly related to genomic medicine, which according to Romboli and Viola (2017) consists of the science that studies the influence of nutrients on the expression of genes and their products on the alteration of the phenotype, that is, on the information of gene expression, which allows the understanding of the influence of food components on metabolic routes.

And they also contribute by stating that about 80% of cases of cardiac coronary disease, 90% of cases of type 2 diabetes and 1/3 of cancers can be prevented by changes in eating habits and maintenance of an ideal body weight, associated with physical activity (ROMBOLI; VIOLA, 2017). As for environmental factors, the selected authors report that visceral adiposity is a determining condition for inflammation of the arteries (HENNING, 2021). Each one-point increase in the Body Mass Index (BMI) of an overweight individual causes a 10% increase in the risk of atherosclerosis and CAD (WANG *et al.*, 2021).

They report that trans-fat and processed meats are directly related to increased cardiovascular risk (SEKHAR *et. al., 2021), that dietary factors are associated with the vulnerability of atherosclerotic plaque, especially salt intake (WANG* et al., 2021), that consumption of vegetables, fruits, dietary fiber, folate and vitamin C are dietary protective factors and are inversely related to plaque vulnerability (WANG et al., 2021).

It is observed that nutrition is directly related to CAD, but this is not the only factor. Férnandez-Rubio *et al.* (2022) emphasize that physical exercise is an effective therapy for the primary and secondary prevention of CAD, attenuating some pathophysiological processes and promoting improvements in functional capacity and muscle strength. It is noted that all selected authors make it clear that nutrition and lifestyle habits are directly related to CAD. Risk factors are obesity, high cholesterol (LDL), high blood pressure, smoking and alcohol. Therefore, a change in life habits, and not only in food, can promote better quality of life; in addition to having an impact on the factors that contribute to chronic diseases (SARTI; TORRES, 2017).

A healthy diet generates enormous impacts on the control and prevention of various diseases, but it needs to be complete and varied, in order to provide not only the essential nutrients as the bioactive substances that will improve the functioning of the body (SALVADOR, 2017). It should still be considered that it is we who invented our lifestyle, and it is within our power to change it. We do not need to wait for the invention of a magic pill or a low-calorie potato chip, it is already clear that the changes that will minimize the risks to CAD, depends on each one. These changes include: not smoking, exercising regularly, limiting total calorie intake, alcohol, salt, saturated and trans fats, sugar, soft drinks, processed foods, among others (DIAMOND, 2014).

As with most complex diseases, an individual's risk of developing CAD is modulated by the interaction between genetic factors and lifestyle (KHERA *et al.*, 2017), and some of the most eminent risk factors for this disease are chronic elevation of blood pressure, hypercholesterolemia, diabetes, age, obesity, smoking and sedentary lifestyle (FÉRNANDEZ-RUBIO *et al*., 2022).

Regarding the perception of the students, the transcript of the testimony of those involved in the research follows:

"Our scientific initiation show stood out among the other works, because we were able to conclude our main objective with excellence - to demonstrate that CAD does not have a great influence due to genes, having a higher probability of development from external factors, such as sedentary lifestyle. This experience provided us with a greater knowledge in the area of Biology, as well as corroborated to understand how scientific research occurs. I am very grateful to Professor Cisnara Amaral and the academics Eduarda and Luana, who helped and collaborated with the accomplishment of our work with quality and in a pedagogical way. Finally, I would like to say that I was pleased to receive the outstanding work award, which certainly rewarded all the effort that my group put into this work." A.M.A

"I am passionate about work and studies on medicine and the human body, I love learning and being able to pass on what I know to people and, in some way, help them. Producing the Scientific Exhibition was fantastic! I had the opportunity to venture into clinical cases and other literature reviews, which made me understand the dimension that is human life. I realized that the more we study, the more we have to learn and when done in a group, we have the possibility to discuss our findings and thus learn from each other. Even though I was a teenager, I found myself at times having discussions above my age group and with extremely important topics. The work done made me realize not only how laborious and rewarding scientific work is, but it made me sure of the profession I want to pursue!" E.F.M

"The scientific initiation show that we held, with the supervision and assistance of Professor Cisnara Amaral and the academics, was extremely impactful in terms of presenting a new reality. The methods proposed for the research carried out differed greatly from the classic school models, being a more scientific and reliable approach to the reality of scientific research. To realize, then, that our effort and hard work in carrying out this work was rewarded, with the award of outstanding in the activity, was extremely rewarding, encouraging me even more to carry out external research, in the areas of my personal interest, as well as increasing my taste for reading and researching things hitherto unknown to my person." J.P.S.S.

It is noted that the research provided scientific knowledge, since the reference and the discussion took place in partnership with the academics of health courses and the guiding professor. It provided the opportunity for interdisciplinarity, as it demonstrated the importance of English for academic knowledge, orality for the presentation of the work and the perception in relation to the rules of a scientific study. In "liquid times", we need new ways of thinking about education, since the challenges of teaching grow with the changes in the world pointing to the creation of a teaching culture

that has research as an educational principle to overcome the reproductionism and accumulation of contents transmitted in a little significant way (NOGARO; CERUTTI, 2016).

Nogaro and Cerutti (2016, p.68) also contribute "stripping ourselves of the "academic" sense, clothed in the pomp of research, becomes necessary for it to be incorporated into the practice of the teacher of basic education and in the life of the student".

It should be emphasized the change in habits that may cause in relation to diet and physical exercises, determining factors to avoid CAD; the mastery of concepts studied in Genetics that do not make much sense, and that related to a disease can establish parameters that stimulate learning. Learning with comprehension is more likely to promote transfer than simply memorizing information from a text or lecture (WIGGINS; McTIGHE, 2019).

In relation to the orality and presentation of the work, it is observed that it gained as "featured work" (figure 1) a fact that will serve as a stimulus to students to understand the importance of research, using knowledge in their daily lives, making analogies, reflective thinking, autonomy to make decisions and criticality in relation to life habits. In addition to the recognition that genetics or environmental factors are related, that everything in our body is related, including our perceptions and thoughts. That we experience times of choices, which can affect positively or negatively on our health and that of our families.

Figure 1 – Certification and outstanding award medal.



Source: Personal archive of the authors.

5 FINAL CONSIDERATIONS

In relation to research on CAD and environmental factors, it is perceived that a complexity of factors related to each other can lead to the expression of the disease. Among the environmental factors,

the lifestyle gains prominence, especially in relation to the consumption of fats, unbalanced diet, sedentary lifestyle and obesity. The high consumption of fats, especially trans and saturated fats, and refined carbohydrates with a high glycemic index, favor the creation of atherosclerotic plaques, which are responsible for causing CAD. Similarly, salt intake is the main dietary risk factor for plaque vulnerability, unlike the intake of fruits and vegetables that have an inverse action.

It is noted that sedentary lifestyle and obesity lead to the accumulation of fatty plaques in the arteries, causing CAD. People with obesity produce adipokines and some proteins that attract monocytes and macrophages to adipose tissue, causing inflammation and aggregation of atheromatous plaques. Another problem associated with obesity is a sedentary lifestyle. With the practice of physical exercises, the atheroma plaques can undergo a regression, increasing the blood passage in the arteries and decreasing the risks of the disease.

Still, it is noticeable the genetic influence on the development of CAD, but it is proven that genes have little action in the development of these diseases, because they have variable expressiveness and act by binding and disconnecting proteins, and suffer demonstrably the environmental action.

In relation to the contribution to high school students, it was observed that the practice of scientific initiation can corroborate to sharpen the taste for research, interdisciplinarity, academic experience, significant learning, protagonism in relation to habits and attitudes, scientific literacy, mastery of contents that make little sense, choices regarding diet and physical exercise as a prerequisite for health.

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The profile of patients with neoplastic wounds and nursing care: A cross-sectional study

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ABSTRACT
Objectives: to identify the clinical characteristics of patients with neoplastic wounds admitted to the palliative care unit and discuss nursing care applied to this patient. Methods This is a cross-sectional, prospective and descriptive with quantitative approach. Data collection was performed at the palliative care of the National Cancer Institute (INCA IV), located in Rio de Janeiro January-RJ. Results: for the analysis of the characteristics a sample of 35 was evaluated patients who were hospitalized in the ward at the time of the research. In relation to the gender variable did not present statistically significant difference in males and female, as for the age variable, there was a clientele over 60 years of age, with low performance status (impaired functional capacity), very advanced, especially in patients with female breast carcinomas and Head and Neck Carcinomas in males. In the evaluation of the wound, it is observed the importance of knowing the clientele in order to follow the care planning. From the profile found, advanced staging is a complicating factor because the more profoundly increased the risk of bleeding and impairment of nerve endings, which demands conducts to control pain and hemorrhage. And as for the odor, it's It is important to note that this symptom is one of the most bothersome for patients and. Therefore, to minimize it is important an effective control of the local microbiota, the proper management of cleaning solutions, coatings and environmental aromatizers.

Keywords: Wounds and injuries, oncology nursing, palliative care.

1 INTRODUCTION

The neoplastic wound presents in about five to ten percent of patients with advanced cancer in the last six months of life. These lesions may arise from primary tumors or even metastases, mainly present in the age group of 60 to 70 years [1,2]

Patients with wounds carry with them great stigma, from late-stage and exposed cancer on the skin. The injury causes damage to the quality of life of the patient, due to the exophytic characteristics, mainly such as pain, odor and exudate [3,4], affecting the daily life due to the great demand for care

concomitant with the social and psychological impacts. Social isolation, for example, is associated with the strong, nauseating odor characteristic of the tumor. [5]

It is possible to observe that palliative nursing care goes far beyond wound care, it is about providing care based on the multiple dimensions of the individual (physical, psychic, social, spiritual and family of the patient), in order to improve their quality of life during their last days, since the patient who lives with advanced oncological disease and presents neoplastic wound has a high degree of vulnerability in the dimensions that integrate him as a being human. [2] The palliative view envisions no cure, but quality of life and the promotion of comfort.

A better understanding of the characteristics of patients with wounds and the evidence is important to support nursing care in oncology, especially for patients in palliative care with cancer. The literature is still scarce on this theme.

The delimitation of the objective of the study envisages to analyze the clinical characteristics of the patient with neoplastic wound hospitalized in the palliative care unit and its implications for oncological nursing care. To support the study, the following questions are asked: what are the implications of the clinical profile of patients with neoplastic wounds in palliative care for oncology nursing care?

2 METHOD

This is a cross-sectional, prospective and descriptive study with a quantitative approach. Data collection was carried out over three months, in the hospitalization sector of the palliative care unit of the National Cancer Institute (INCA IV), based in the neighborhood of Vila Isabel, in the city of Rio de Janeiro-RJ.

The inpatient sector is composed of 56 active beds, maintaining an average operational occupancy of around 70%. Being a sector of high turnover, since the objective is that the patient recovers and returns to the conviviality of the family. But in some cases, patients end up hospitalizing and staying in the unit for end-of-life care.

This study is an excerpt from the master's thesis entitled: "The bacteriological profile and the variables associated with neoplastic wounds", concluded at the Academic Graduate Program of Sciences in Health Care of the Fluminense Federal University in February 2020.

To compose the non-probabilistic and consecutive sample, 35 patients were recruited, who fit the profile of the research. The eligibility criteria were: having a malignant solid tumor of any size; wound staging equal to or greater than 1N; admitted to the unit for at least 24 hours, aged 18 to 90 years. Exclusion criteria were: patients with tumors with active bleeding, no apparent lesion on the skin and with wounds in genitourinary areas.

The sociodemographic and clinical variables analyzed were: gender, age group, kps, types of tumors, staging and odor.

The data were submitted to simple frequency analysis, using the Excel 2010® program and compared with the literature with a view to the objective of the research

The research was conducted respecting the ethical principles of research with human beings, according to Resolution No. 466/2012 of the National Health Council. The study was approved by the Research Ethics Committees of the Fluminense Federal University School of Nursing (Opinion No. 2,810,432) and the José Alencar Gomes da Silva National Cancer Institute (Opinion No. 2,895,106).

3 FINDINGS

The study included a sample of 35 patients admitted to the palliative care unit composed of 56 inpatient beds, who met the eligibility criteria. Patients who were in end-of-life care and presented complications during collection, such as bleeding in tumor lesions, were excluded from the sample.

When the percentage of patients with neoplastic wounds was analyzed in relation to gender, there was no statistically significant variation, approximately fifty percent were female (n=18) and male (n=17).

The types of tumors found were: melanomas, sarcomas, carcinomas of the breast, head and neck and vulva. Head and neck cell squamous carcinomas presented a percentage of 43% (n=18) and breast carcinomas 34% (n=12). Still found in a lower percentage melanoma tumor (n=1), with 3% and sarcomas (n = 1), with a percentage equal to 3% and vulvar carcinomas with 7%. In the sixth-rate distribution, tumor/sex distribution table is represented below:

Table 1

Distribution of patients by age group by sex			
Age group	**Gender F**	**Gender M**	**TOTAL**
30-40	1	4	5
41-51	3	4	7
52-62	5	5	10
Over 62	9	4	13

Source: Own (2022)

The analysis of the age group was classified into 4 categories: 30-40 (n = 5), 41-51 (n = 6), 52-62 (n = 10) and above 62 (n = 15). According to Table 2:

Table 2

Distribution of tumor type by sex			
Types of tumors	**Gender F**	**Gender M**	**Total**
breast cancer	12	0	12
CEC head and neck	3	15	18
melanomas	1	0	1
sarcomas	0	2	2
Vulvares carcinomas	2	0	2
Total	18	17	35

Source: Own (2022)

Another aspect analyzed in the study was the Performance Status of each patient, through the Karnovfsky Scale (Kps). Of the results found, with KPS 10-20: 7 patients, kps of 30-40 were 22 patients and KPS of 50-60 only 6 patients.

Odor is a symptom that can be classified into three grades: I, II and III. Odor grade I is classified as weak, felt only when opening the dressing, odor grade II felt with open dressing and odor grade III classified as strong and nauseating, felt at a distance from the patient and with closed dressing. Regarding the criterion of odor presence, the 3 grades (I< II< III) were evaluated. As for the grade I odor, felt when opening the dressing, a rate of 51% was identified with the patients, followed by the grade II odor, characterized by being felt even without opening the dressing, with a percentage in 34% of the patients, and grade III, a strong and nauseating odor, in 15% of the sample).

Staging is a classification to measure the layers of skin affected by the tumor. In staging 1, the lesion presents only as a nodule without opening of the epidermis, in staging 1N there has already been rupture of the epidermis and small exposure, still very superficial. On the other hand, stages 2 and 3 have larger lesions, with involvement of the dermis and connective tissue, respectively. They already have a large amount of exudate and present odor. The most serious, however, is stage four when the lesion already affects the bone and muscle structure.[1]

For staging there was a predominance of classification 3, according to the following results follow the entire distribution of Staging: 1N (n = 4 / 11%), 2 (n = 4 / 11%), 3 (n = 19 / 54%) and 4 (n = 8/ 22%).

4 DISCUSSIONS

It is worth mentioning that one of the weaknesses of the study, time is the issue of the finitude of the patients of the unit, given that because it is a specific place totally focused on exclusive palliative care, there is naturally an impact on the recruitment of participants.

Neoplastic wounds are lesions caused by tumor cells that infiltrate the basal layer of the skin, rupture the epidermis and externalize. The accelerated cell growth leads to a deficit of local oxygenation, leading to tissue death and emergence of areas of necrotic tissue [(1)]. It then becomes a

propitious site for the growth of bacteria with worsening symptoms such as pain, odor and the presence of exudate. [1.4]

In the present study, patients hospitalized with neoplastic wounds, in relation to the gender variable, had a similar percentage, with about 50% each, with no statistical difference. The predominant tumor wounds in females are due to advanced breast cancer. Breast cancer is the most prevalent in women in the world, with approximately 2.3 million new cases estimated in 2020, which represents 24.5% of new cancer cases in women. It is also the most frequent cause of death from cancer in this population, with 684,996 deaths estimated for this year (15.5% of cancer deaths in women) (6).

Early detection is a primary factor for cure, but for this it is necessary that women over 40 years of age undergo mammography. Unfortunately, late arrival at the health service, difficulty in scheduling exams, and difficulty in obtaining treatment make it impossible to cure, and patients suffer from malignant neoplastic lesions and multiple metastases caused by breast cancer. [2.7]

The most common advanced male tumors, on the other hand, are predominantly located in the head and neck region. Head and neck tumors (PC) have an incidence of 70% in males, especially in men over 40 years of age, and are associated with risk factors such as alcohol use and smoking. Accordingly, with breast cancer cases detected early have an eighty percent chance of cure. [8.9]

As for the age of patients with neoplastic lesions, there is a predominance of the age group above 50 years. It is known that age is a predictive factor for the onset of cancer, the older the age increases the ability to have errors in cell multiplication and decreases the body's ability to identify cellular errors, destroying cancer cells. Another relevant aspect is the fact that the cancer treatment itself is more difficult in advanced ages, because chemotherapy drugs reach not only tumor cells, but also healthy ones causing effects such as renal, cardiac and pulmonary toxicity [9]. Thus, it is a difficult management of treatment to achieve a cure for the disease in patients with more advanced ages, especially if associated with multiple comorbidities.

Another aspect analyzed was the Performance Status of patients with neoplastic wound. The Karnofsky performance status scale is used to measure the ability to perform the activities of daily living of patients in palliative care, with a performance rating of 10 to 100, with 10 being the measure for dying patients, and 100 corresponding to the patient without complaints, or without any daily activity disorder. [10]

In the study, a predominance of the KPS scale was observed between 30-40, compatible with an inability to self-care, requiring a lot of assistance. The neoplastic wound is related to advanced disease mainly in the last months of life. The deterioration of KPS quantification occurs naturally with the progression of neoplastic disease. The more the KPS decreases, the greater the workload of the nursing team. In a study conducted in an oncology unit, the NAS (Nursing Activies Score) was used

to measure the workload and demonstrated an association of increased demand for nursing care with the decrease in KPS. [11]

The nursing care most present in palliative care are: control of dyspnea, control of hemorrhages, pain monitoring, gastrointestinal disorders (abdominal distention, vomiting, diarrhea or constipation), emotional support to the patient and family with monitoring of the grieving process and dressings of neoplastic wounds. [12.13]

Regarding the types of tumors most present in the formation of neoplastic wounds found in the study, we highlight the following: carcinomas, subdivided into breast carcinomas and cellular squamous cell carcinomas. Carcinomas are tumors of malignant etiology, with a high capacity for metastasis formation, when discovered late. [9] On the other hand, squamous cell carcinoma, present mainly in patients with head and neck tumors, is externalized to form wounds because they are close to the subcutaneous tissues. Similarly, breast carcinoma due to its location in the underlying epidermal tissue favors the appearance of lesions when the tumor is not treated early. [7] In addition to neoplastic wounds originating from primary or metastatic tumors as already described above, these can also occur from an accidental implantation of cells in the skin during a surgical procedure or diagnosis or even by the invasion of lymph nodes.

Tumor wounds require great expertise from nurses, because they do not follow the same principles as other lesions. This type of wound is only healed by surgery, chemotherapy and radiation therapy. Wound care focuses on minimizing the associated symptoms, which are: odor, pain, bleeding, infection, and exudate. [14,15] To perform the dressing, the INCA clinical protocol is used, in which the nurse must classify, estade, measure the degree of odor and describe bleeding, exudate and infection, and from this trace the conducts to be performed and the appropriate coverages. [1]

For example, in the study the most prevalent odor grade in the study was grade I (51%) followed by grade III (34%) and grade II (15%). This is one of the most bothersome symptoms, which can affect the patient's self-esteem and disrupt their social life, often leading to social isolation. [3] The higher the degree, the stronger the odor. The odor symptom is associated with the presence of anaerobic and aerobic bacteria, existing in the area of the lesion. Thus, the treatment of odor can be local, systemic or environmental, including: infection control with the use of topical and systemic antibiotics or natural products, removal of necrotic tissue, and use of flavorings from environments [15] In the institutional protocol the use of metronidazole for Grade III odor is recommended. [1]

Other coatings are also indicated for odor control, such as the use of silver coatings, activated charcoal and Phmb gel and liquid. The change time routine will depend on the product used being every 24 hours (e.g., metronidazole) up to 72 hours (phmb, foams impregnated with silver and activated carbon). And as a recommended cleaning solution, saline, distilled water and phmb solution can be used14.

Another important aspect is the evaluation of the microbiota that grows in the lesion through the Swab exam, in order to determine bacterial resistance and biofilm, so that antibiotics can be used more assertively. [15]

Regarding the percentage of staging, the study reflects a predominance of staging 3, which implies very advanced lesions, with deep tissue involvement and a high amount of exudate. The care of injuries in this dimension requires great expertise from the nursing team because it already compromises blood vessels and produces symptoms that are difficult to control, such as bleeding and pain. To control bleeding, it is recommended the use of cold saline, application of calcium alginate, hemostatics, and application of gauze with local adrenaline in a compressive way.

Pain should be measured before and after dressing, and it is important to perform local and systemic analgesia at all times. The exposure of nerve endings, caused by the deepening of the wounds makes the region extremely sensitive. [1] Systemic analgesics should be in accordance with the patient's need, and may be opioids or anti-inflammatory drugs. And for local use lidocaine gel with pre-dressing, remembering that you should let the product act 3 to 5 minutes before the change. [12.15]

5 CONCLUSIONS

The profile of the patients was similar in the gender variable, but an elderly clientele with low performance status stood out, which is consistent with high dependence and greater demand in nursing care.

In the evaluation of the wound, it is observed the importance of knowing the clientele to follow the care planning. From the profile, advanced staging is a complicating factor that draws attention, because the deeper the greater the risk of bleeding and impairment of nerve lesions, which require conduct for pain control. And as for the odor, it is important to emphasize, this symptom as one of the most uncomfortable for patients and therefore, an effective control should be performed, associating the identification of the microbiota present and more assertive antibiotic therapy measures

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Perception of the newly graduated nurse in nursing care during the COVID-19 pandemic: Report of experience

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ABSTRACT
Upon being hit by the Covid-19 pandemic, and in view of the evolution of the clinical spectrum caused by the new Coronavirus, the world was faced with different challenges: development of vaccines, medications, mechanical respirators and interfaces for ventilatory therapies. At the end of December 2019, in the province of Wuhan, China, health authorities identified a set of cases of pneumonia of unknown etiology, with rapid worsening and highly transmissible. After analysis of swab samples collected from patients, the causative agent was identified as a new type of coronavirus named SARS-CoV-2 with an infectious characteristic, manifesting itself with a relevant impact on the health of the population. Also known as the new SARS-CoV2 viral syndrome, COVID manifests itself in the human body at different levels of severity. It varies between asymptomatic, mild or severe cases, and mainly affects the lower respiratory tract.

Keywords: Covid-19, Nursing assistance, Graduation.

1 INTRODUCTION

Upon being hit by the Covid-19 pandemic, and in view of the evolution of the clinical spectrum caused by the new Coronavirus, the world was faced with different challenges: development of vaccines, medications, mechanical respirators and interfaces for ventilatory therapies. At the end of December 2019, in the province of Wuhan, China, health authorities identified a set of cases of pneumonia of unknown etiology, with rapid worsening and highly transmissible. After analysis of swab samples collected from patients, the causative agent was identified as a new type of coronavirus named SARS-CoV-2 with an infectious characteristic, manifesting itself with a relevant impact on the health of the population. Also known as the new SARS-CoV2 viral syndrome, COVID manifests itself in the human body at different levels of severity. It varies between asymptomatic, mild or severe cases, and mainly affects the lower respiratory tract. The clinical spectrum of SARS-CoV2, in most cases, presents itself as mild symptoms of gradual evolution, whose most evident manifestations are: dry cough,

recurrent hyperthermia and respiratory discomfort, which may or may not be associated with episodes of runny nose and nasal congestion. In view of this scenario, this article aims to report the professional experience as a recent graduate in nursing care in the Covid-19 ward.

2 WORK DEVELOPMENT

The motivation for exposing this peculiar experience of mine made me organize my report into three important moments: 1st Welcoming, Integration and adaptation of routine: moment prepared by the nursing management core with the purpose of integration and knowledge of work flows and processes of the nurse in their medullary and multidisciplinary activities. This step provided approximation and communication between the professional categories active in assisting Covid-19 patients. 2nd Training: newly graduated nurses are offered training in the various thematic segments of greater application and routine in the service: gowning and undressing, biosafety measures, SARS, notification forms; blood gas collection. 3rd Assuming the scale: a very challenging stage in the face of very dynamic and peculiar shifts of patients with a Covid-19 profile, but with important clinical scenarios of significant learning.

3 RESULTS

Faced with this opportunity, I was able to immeasurably develop different cognitive, psychomotor, and communication skills for the development and reach of important skills worked on in my academic and scientific training, positioning myself to develop as a more technically prepared and humanized professional to exercise with excellence , ethics and professionalism to nursing care.

4 FINAL CONSIDERATIONS

In this sense, it is concluded that the opportunity of the first job in a reference hospital that values welcoming and multidisciplinary integration makes an impactful difference for the initial progress of the newly graduated nurse, in the eagerness for cognitive and practical improvement and for the search for an ethical, humanized and competent professional.

Critical analysis of palliative surgical therapy for advanced thoracic esophageal cancer

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ABSTRACT
Although malignant neoplasm of the esophagus is a disease with a high incidence, its diagnosis is often still delayed. This fact combined with excessive weight loss due to dysphagia and the association with car-diopulmonary diseases resulting from excessive tobacco use, makes these patients have a difficult clinical control, which explains that more than 50% of them require palliative treatment. The ideal scenario would be to perform procedures that provide an adequate quality of life and with satisfactory rescue of swallowing, without the need for frequent hospitalizations and with a low rate of complications. Thus, this chapter aims to discredit the indications and results of palliative methods and especially shunt surgeries, discussing the technique of isoperistaltic gastric tube of great healing (GIT). In the Department of Surgery of Hospital PUC Campinas, 143 patients with unresectable esophageal squamous cell carcinoma (T4b) were studied, and all of them had clinical conditions to be submitted to GIT. In the early postoperative evaluation, 64p (44.7%) presented systemic complications, with pulmonary infection being the most frequent; 51p (35.6%) presented local complications, with dehiscence of the cervical esophagogastric anastomosis being the most frequent. 13p (9.1%) died due to postoperative complications. Of the 112 patients who were properly followed, 91 (81.2%) presented good palliation with this procedure, with adequate swallowing rescue. Chemoradiation was performed after the TGI in 82 patients, with a mean survival of 3 years in 63 patients (76.8%). With these results, it is possible to conclude that despite the postoperative morbidity not being negligible, the TGI can be performed safely, especially after the advent of mechanical suture, because it offers adequate palliation and survival. In addition, this procedure has the advantage of simultaneously providing good drainage of the esophagus and stomach, and thus potentially avoiding esophageal mucocele.

Keywords: Sphageal cancer, palliative therapy, surgical therapy, isoperistaltic gastric tube.

1 INTRODUCTION

1.1 GENERAL CONSIDERATIONS

The malignant neoplasm of the esophagus continues to be a very frequent affection, occu-pando the third place among the most frequent tumors of the gastrointestinal tract and the eighth most prevalent in the world (1,2,3,4). Recent studies demonstrate that these tumors have had an increase in the order of 10% per year, causing approximately 400,000 annual deaths and being the sixth cause of death by cancer (5,6,7).

In Brazil it is the seventh most common malignant neoplasm with an estimated 13,550 new cases in 2018, highlighting its highest incidence in the South and Southeast regions of the country (8.9).

Almost always the diagnosis is delayed, because dysphagia, the main symptom, occurs only when 50% or more of the esophageal lumen is filled by the tumor lesion. The delayed diagnosis, the excessive weight loss due to dysphagia and the association of cardiopulmonary diseases resulting from excessive tobacco abuse, make the carrier of this condition a patient of difficult clinical control, having the physician who assists him few therapeutic possibilities (3,4,10,11,)

And this comes to reflect in the indication of esophagectomy, because although this surgical procedure still remains to the present day the best indication of therapy for potential cure of this condition, due to the advanced stage of the disease in most cases and the great nutritional clinical impairment that is present in patients, makes only 30 to 40% of them can perform this treatment, which makes the prognosis very unfavorable (1,5,11,12,13).

Thus, it is necessary to perform a palliative treatment in more than 50% of patients with this neoplasm. The ideal situation should have procedures that provide more adequate quality of life and that satisfactorily re-taurasar swallowing, without the need for new hospital admissions and with lower rates of complications (14,15,16,17.)

Choosing the best therapeutic option respecting these principles is a difficult decision, since all methods have limitations and often contraindications due to the high potential for morbidity

1.2 PALIATION METHODS

In a practical way, palliative therapy can be classified into two groups:

1.2.1 non-surgical

The methods currently recommended are endoscopic techniques being indicated:

Patients who have indication of definitive chemoradiation, but who present severe dysphagia in the initial evaluation and thus requiring this intervention previously (5,18) _

Failure in the resolution of dysphagia palliation by initial therapy (5,18)

Recurrent dysphagia due to locoregional failure (5,18)

Recurrent dysphagia due to benign stenosis in patients who have had success with chemoradiation (5,18)

Patients with clinical comorbidities, mainly cardiovascular and pulmonary that contraindicate surgical treatment and/or chemoradiation. (5,18)

Of the endoscopic methods recommended, the self-pansible metallic endoprosthesis stands out, which, although costly, has shown very adequate results, with satisfactory rescue of swallowing, low morbidity index and average survival of 6 to 10 months in most of the series that have used it (19,20).

The use of endoscopic dilatation, alcoholization, and laser has little application nowadays, because in addition to the low resolution, there is a need to be performed several times, increasing the potential for morbidity (18,20,21,)

1.2.2 Cirurgical

Palliative surgical therapy is indicated mainly in patients with satisfactory clinical conditions, but who present irrese-caveal tumors. It can be performed by the following procedures:

a) Gastrostomy and Jejunostomy: this type of procedure performed alone should be remembered only to be discarded as a palliative method of choice in the treatment of advanced esophageal neoplgh easy to perform, and can even be performed with local anesthesia, it does not bring any relief of symptoms presented by patients with this unresectable condition. The patient is punished by the presence of a probe fixed to the abdominal wall that invasively, presents extravasation of digestive contents around it, as well as exuberant growth of granulation tissue. The patient continues without feeding through the mouth, besides being predisposed to aspiration of saliva to the tracheobronchial tree, due to the permanence of the esophageal obstruction. Thus, the method does not provide any quality of life, not contemplating the principles of an adequate palliative therapy. In addition, complications such as invariably aspiration bronchopneumonia, abdominal wall dehiscence, bleeding, digestive fistula with consequent mortality potential and low survival are frequently associated (5,22, 23)

Thus, the studies reported in the literature serve only as a historical review, since they are from the 1960s, 1970s and early 1980s, when the endoscopic methods presented today were not yet evident. Meniconi (22), in a literature review with 967 patients submitted to this type of procedure, reports complications ranging from 15 to 50%, with a mortality rate of up to 33% with survival time generally, not exceeding 90 days in most of the patients studied and without having rescued a satisfactory quality of life.

Thus, gastrostomy/jejunostomy are nowadays exceptional procedures, and is restricted only to unresectable cancer of the cervical esophagus or as the first time of another palliative procedure or not.

b) Resection: for several years it has been demonstrated that the best form of palliation of the patient with advanced unresectable neoplasm of the esophagus, but with low clinical comorbidity, is esophageal resection, because in addition to preventing the course of esophageal disease, tumor hemorrhage, aspiration pneumonia, fistula to the respiratory tree and mediastinitis, it also provides adequate relief of dysphagia, a fact rarely observed with any other palliative method (1,2,4,5,24). It also allows an increase in survival with better quality of life (11,15,25).

Over the years, several series of the literature have demonstrated that palliative resections present higher morbidity than curative ones, with emphasis on the work of Muller et al (26). These authors in an extensive review managed to gather 13,061 curative and 16,024 palliative resections, demonstrating that the deadness associated with the curative procedure and that associated with the palliative procedure was significant of 11 and 18%, respectively. This fact was also demonstrated by Law et al (24) who reported 9% mortality for curative resections and 20% for palliative resections.

However, in recent years with the most appropriate postoperative care, with teams trained and accustomed to surgical procedures in the esophagus, there was a decrease in morbidity and mortality (14,15,19,23).

In addition, with the evolution of radiotherapy and chemotherapy, it has been possible to adjust greater survival to these patients, on average 24 months, in relation to those who did not undergo any type of treatment. (2,5,11,13).

Thus, palliative resection has its representation well consolidated, although it offers survival below the ideal. It offers, however, an adequate quality of life by making the patient swallow by the natural way

c) Shunt Surgeries: the indication of this method occurs for patients who have advanced tumors with wide invasion of the mediastinum.

However, because it is a medium to large surgical procedure, it is necessary that such patients have satisfactory clinical and nutritional conditions, a fact that is very uncommon when the stage of the disease is advanced.

This fact was well demonstrated in the experience of AQUINO et al (27), that of 318 inoperable/irresectable patients of the series of 789, only in 34.9% it was possible to perform some type of shunt surgery. In the other 2/3, another type of non-surgical palliative treatment or even no procedure was performed due to the poor clinical conditions of the patients.

The most commonly used viscera are:

c-1) Jejunum- reconstruction idealized by WULLSTEIN (28) and ROUX (29), in cases isoplated for more than one hundred years and not being routinely used nowadays. The biggest obstacle to its use is the difficulty for the jejunum to reach the cer-vical region without tension or ischemia.

However, patients with tumors of the distal third of the esophagus that present dissemination by contiguity to the aorta and / or spine can have their swallowing rescued by the esophagojejunal laterolateral derivation, above the tumor zone, by abdominal route with median frenotomy (30).

The literature is scarce in relation to this type of procedure, highlighting the review performed by MENICONI (22), which in 93 patients who presented unresectable cancer of the distal third of the

esophagus and submitted to this type of procedure, demonstrated 30% of morbidity, with 25% of death in the immediate postoperative period and average survival of 6 months.

c-2) Put to the past, palliative colonic interposition is very old, because already in 1911, KEELING & VULLET (22) already recommended this type of reconstruction in patients with advanced unresectable tumor of the esophagus. The few patients reported died due to the limited resources of the time.

In turn, even today, this procedure has little publicity, because it is large, with extensive mobilization of the cervix, multiple anastomoses and many complications.

MENICONI (22), demonstrating the experience of the Esophageal Surgery Service of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (USP) in 13 patients, in which this procedure was performed with palliative intent, evidenced a high incidence of complications with 23% of deaths, 38% of anastomotic fistulas and 15% of pulmonary complications. Thus, it concluded that such a procedure should no longer be performed, due to the high morbidity rate. POSTLETHWAIT (31) also had the same opinion after evaluating the high rate of complications in 690 patients in whom this type of reconstruction was performed.

Thus, the use of coloplasty for palliative treatment of patients with advanced esophageal neoplasia nowadays should be viewed with great caution and parsimony, being indicated only as an exception, when there are no technical conditions for performing another type of reconstruction.

c-3) Stomach-in this type of procedure, several authors recommend that the cervical and abdominal esophagus be buried, with transposition of the stomagus by retrosternal route, believing that this abbreviates the surgical act (5,22,25,31,32).

However, because it acts most often in patients with precarious nutritional conditions and clinical morbidities, this procedure presents a series of local or systemic complications, such as dehiscence of the proximal and distal stump of the esophagus, fistula of the cervical esophagogastric anastomosis and pulmonary infection.

MENICONI (22), in a literature review, demonstrated that in 483 patients submitted to this procedure, there was variable morbidity from 27 to 63.3% and mortality from 4 to 37%, with a mean survival of 7.5 months, but most patients presented satisfactory swallowing.

Another fact that has always been discussed was the possibility of this procedure producing mucocele, with potential mediastinitis due to the complete exclusion of the esophagus, although the reviewed studies do not present any consistent casuistry that proves this fact (14,22, 31,32,33). To prevent this complication, some authors have recommended the drainage of the thoracic esophagus with tubular probe, which is also not free of complications, such as the exit of the tube with consequent media-tinitis and peritonitis and with fatal evolution in most patients (22, 27,31).

Based on these facts, some authors, mainly from the Chinese school, led by WONG et al (34), recommended the use of the surgery proposed by Kirschner, already in 1920 for benign stenoses of the esophagus secondary to the ingestion of caustic agen-tes. The procedure consists of transposing the stomach to the cervical region, anastomosing the cervical esophagus and draining the abdominal esophagus by a jejunal loop to Billroth II or Roux-en-Y, and thus allowing the drainage of the esophageal contents and thus preventing the potential development of mucocele in the thoracic esophagus.

In Brazil, this type of procedure is little valued. It is noteworthy only the work of BRANDALISE et al (35), which in 13 patients analyzed, presented a morbidity rate of 40%, mortality of 15.3% and average survival of 8.5 months.

AQUINO et al (27), studied 17 patients with unresectable esophageal cancer submitted to total gastric transposition, and in three of them with the Kirschner procedure also demonstrated that such procedure presents a high morbidity index. 47% of the patients had complications, most of them in the cardiopulmonary sphere, and three patients died due to clinical and/or local complications. Regarding palliation, this was adequate in 70% of the patients, who reported satisfaction with the surgical act because they were able to rescue swallowing, although with an average survival of seven months.

Due to the non-negligible morbidity rate and the new techniques of the present day, palliative total gastric transposition is not indicated as the first option for surgical treatment, being an exception in those patients in whom it is not possible to perform other procedures.

c-4) Gastric tube of great curvature- was developed in order to solve the dysphagia of patients with esophageal strictures. Its principle was to minimize the complications that commonly affect surgical procedures on the esophagus, intending to be simple and with low morbidity and mortality.

The great advantage is that it simultaneously makes a good drainage of the esophagus and stomach, thus avoiding the potential esophageal mucocele.

Historically, BECK & CARREL (36) demonstrated in cadavers and experimental animals the continent gastrostomy, using a tube made from the great gastric curvature irrigated by the left gastroepiploic artery. They also glimpsed the possibility of esophagoplasty from this long tube of great curvature

Subsequently, CARTER et al (37), in experimental animals, demonstrated the possibility of the construction of the gastric tube of great curvature nourished by both the left and right gastroepiploic artery. They began to name them according to the sense of the peristaltimum: the one nourished by the right gastroepiploic artery and with a free end close to the gastric body-fundus junction, a tube of great isoperistaltic gastric curvature; on the other hand, the one nourished by the left gastro-epiploic artery

and free extremity near the gastric junction pyloric antrum, tube of great anisoperistaltic gastric curvature.

In clinical experience, GRAVILIU (38) in 1951 reported having performed the first gastric tube of great anisoperistaltic curvature in cervical shunt with success in the treatment of esophageal stenosis

Later HEIMLICH (39), demonstrated his experience with gastric tube of great anisoperistaltic curvature in cervical shunt in the treatment of esophago-goplasties that failed with the use of stomach, colon, jejunum or even prostheses. There were 67 patients submitted to this procedure with only 3 deaths.

Almost at the same time POSTLETHWAIT (40), in the United States refers to the use of the gastric tube of great curvature in the isoperistaltic direction in the treatment of a benign stenosis and in 29 malignant neoplasms irresecacaveisi of the esophagus with 13% of mortality

In Brazil, SPERANZINI (41) refer to the first national experience in the palliative treatment of esophageal neoplasia by the gastric tube of great curvature, isoperis-taltico in cervical derivation. Of the 13 patients submitted to this procedure, none of them presented mortality.

From this time, and especially with the advent of mechanical suture, both linear and circular, made several authors began to demonstrate greater experience with this procedure, for being fast, simple and with acceptable morbidity (14, 19,27,42,43,44)

2 SURGICAL TECHNIQUES

The surgical technique involves the creation of a tube using a large gastric curvature about 2.5 cm wide, with preservation of the right gastroepiploic vessels.

To obtain this tube, the stomach is divided into a line parallel to the great curvature, extending from the bottom to the gastric antrum, with the aid of a cutting linear mechanical suture

The sectioned stomach resembles a "V", the part of which corresponds to the small curvature drains the distal esophagus in relation to the tumor

The reconstruction of the transit is performed by transposition of the isoperistaltic tube by retrosternal route, being performed in the cervical region the manual anastomosis in two planes or circular mechanics.

In all patients, jejunostomy is performed for enteral feeding, remaining until the release of the enteral diet.

AQUINO et al (14) in report of their experience in 112 patients submitted to retrosternal transposition of the gastric tube of great curvature with palliative intent, demonstrated that such procedure was advantageous. This is because although this procedure was not free of complications, these were well acceptable in view of the profile of the patient in which it was acted, with advanced neoplasia, with 25.7% of systemic complications and 34% of sites, these being mainly related to the

dehiscences and stenoses of the cervical esophagogastric anastomosis. They also demonstrated that dehiscence was significantly more incident with manual suture (31/83p- 37.3%) than with mechanical suture (4/29-13.8%).

In order to increase survival, recently, it has been demonstrated even by technically minimally invasive the advantages of performing palliative surgery prior to radiotherapy and chemotherapy, because patients rescuing swallowing, present with better nutritional status, and thus can prevent complications of radiotherapy and chemotherapy (45,46,47)

And this had already been demonstrated by AQUINO et al (27) that evaluating 36 patients submitted to chemoradiation after transposition of the palliative gastric tube, obtained an average survival of 18 months in 80.5% of the patients, and for the patients in whom after the realization of the gastric tube was not performed the chemo-radiation, this survival was 39.5%.

Some authors have also demonstrated in recent reports that in patients submitted to exclusive chemoradiation for palliative purposes, because they have advanced tumors, there is often regression of the local stage of the disease to the me-diastinal level, and thus it is possible to perform salvage esophagectomy. (3,4,13,48,49)

AQUINO & LEANDRO-MERHI (50), also demonstrated the validity of salvage esophagectomy. Of the 82 patients who underwent radiotherapy and chemotherapy after the previous preparation of the palliative gastric tube, in 37 there was tumor regression, and rescue esophagectomy was performed by thoracotomy. Although 2 patients died due to postoperative complications, in the others the so-brevida was well adequate in relation to time: from 36 to 48 months in 26 patients and 3 patients evolving to death due to metastatic disease with variable time from 9 to 15 months after salvage surgery

3 EXPERIENCES OF THE SURGERY SERVICE OF PUC CAMPINAS BRAZIL HOSPITAL

In the period from January 1993 to December 2022, 1,614 patients were diagnosed with squamous cell carcinoma of the esophagus, and the isoperisataltic gastric tube of great curvature with palliative intent was performed in 143 of them for having unresectable tumors (T4b), but with clinical conditions of being submitted to this type of procedure. In the early postoperative evaluation, 64 patients (44.7%) presented systemic complications, mainly cardiovascular and pulmonary, 51 patients (35.6%) local complications, with the fistula of the cervical esophagogastric anastomosis being the most frequent and 13 patients (9.1%) died due to complications.

Of the 112 patients in whom a follow-up was performed, in 91 (81. %) the isoperistaltic gastric tube provided a good palliation, because these patients adequately rescued swallowing, with ingestion of even solid foods.

Regarding the mean survival, of the 112 patients evaluated, they presented different evolutions according to the association of complementary treatment or not:

In 30 patients in whom no complementary treatment was associated with the palliative surgical procedure, the median survival was 14 months.

In 45 patients in whom chemoradiation was associated after the palliative surgical procedure, the median survival was 29 months

And in the 37 patients in whom palliative surgery, in addition to chemoradiation, rescue esophagectomy by tumor regression was associated, the median survival was 42 months.

4 FINAL CONSIDERATIONS

The indication of the best palliative surgical therapy is a difficult decision, due to the great impairment of the general condition of patients with advanced esophageal neoplasia. So some items should be emphasized:

a) Need for adequate selection of patients, since more than 50% of them are not able to undergo any surgical procedure, due to clinical comorbidities, especially cardiopulmonary, in addition to impaired nutritional status

b) Need for adequate selection of the palliative surgical procedure, because although all have potential for complications, the isope-ristaltic gastric tube of great curvature seems to provide the lowest morbidity index, besides having a fast and safe preparation, especially after the advent of mechanical suture, offering palliation and survival well adequate

c) Association of radiotherapy and chemotherapy after palliative gastric tube in well-selected patients, as it seems to offer a higher survival rate, in addition to being able to provide the performance of rescue esophagectomy.

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University integration and epidemiological surveillance in fighting Covid-19

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ABSTRACT
Mass testing of the population is a strategy to face the Covid-19 pandemic, as it allows knowing the situation of transmission of the virus, to design policies for action. However, the few existing tests in health services were available only for severe cases and for health professionals, especially in the first months of the pandemic. In Santa Maria, starting in June, rapid tests were made available free of charge. However, the Municipal Health Department of Santa Maria (SMS) did not have enough staff to apply the tests to a large number of people notified as suspects, since the beginning of the pandemic. These people consulted the health service with mild symptoms, and were placed in domestic isolation for 14 days, but it was not possible to seal the diagnosis. In view of this, SMS asked for support from UFSM for the Mutirão to carry out rapid tests, held in Parque da Medianeira on July 11. It integrates the action, the analysis of the database, the identification, through telephone calls, of people who have already been tested and their notification, subsequent testing actions in basic health units and continuous processing of surveillance data. These stages extend during the pandemic. The elucidation of the list of suspects will make it possible to clarify the real magnitude of the pandemic in the city of Santa Maria by including mild cases of the disease in the official data. In addition, it will provide a service to people who still have doubts about their health situation.

Keywords: COVID-19, COVID-19 Test, Public Health.

1 INTRODUCTION

Covid-19 is an infectious respiratory disease caused by the New Coronavirus, Sars-Cov-2, discovered in December 2019, following an outbreak of pneumonia of unknown etiology in Hubei province, Wuhan municipality, China (SRIVASTANA, 2020). Sars-Cov-2 is one of seven human infecting viruses that can result in anything from an asymptomatic infection to severe acute respiratory syndrome, which often leads to death due to multiple organ failure (KUMAR, 2020).

The clinical presentation of Covid-19 includes non-specific signs and symptoms such as runny nose, cough, fever, fatigue, myalgia, dyspnea, headache, ageusia and anosmia. The initial picture of a flu-like syndrome can lead to misdiagnosis, with the patient getting worse and facilitating the transmission of the virus. The presence of comorbidities that can favor the development of these complications, increasing the severity of the disease, such as uncontrolled systemic arterial

hypertension, diabetes, coronary heart disease, hepatitis B, cerebrovascular diseases, chronic obstructive pulmonary disease, neoplasms, chronic kidney disease and immunodeficiency diseases. According to studies in China, the ages most affected are middle-aged or elderly (SHARMA, 2020).

The incubation period for Sars-Cov-2 is between 2 and 11 days (KUMAR, 2020). The virus is transmitted from person to person, through aerosols present in sneezing, speech, coughing or droplets in feces, in a highly contagious way, which would explain the rapid spread of the virus across the planet (YADAV, 2020). Another mode of transmission is through fomites (SHARMA, 2020).

Covid-19 positive individuals should remain in isolation for at least 14 days, monitoring any possible worsening of symptoms. Surveillance should contact the people with whom the infected individual has had contact, in order to trace cases (PADHI, 2020). The gold standard for diagnosis is the RT-PCR laboratory test, which detects viral RNA in the body and should be carried out within the first 7 days of symptoms. After this period, a rapid serological test is recommended, which identifies immunoglobulins in the body (IgM and IgG) through blood collection (PADHI, 2020).

In January 2020, the World Health Organization declared Covid-19 a Public Health Emergency of International Concern and, in March, a pandemic. Thousands of cases have spread to more than 196 countries. As of July 5, there were 11,125,245 confirmed cases and 528,204 deaths from Covid-19 worldwide, of which 1,539,081 cases and 63,174 deaths occurred in Brazil. Cases continue to increase worldwide (WHO, 2020).

The household-based study that has been evaluating virus infection in nine cities in RS (Epicovid-RS) showed that prevalence is low, but has been increasing. In the first three surveys, between mid-April and the end of May, it increased almost fivefold, from 0.048% to 0.22% (PR 4.6; 95%CI 1.01-21.03%) (HALLAL, 2020; SILVEIRA, 2020). In the last survey, on June 26 and 17, the prevalence increased to 0.47% (GOVERNO DO RIO GRANDE DO SUL, 2020). When the person drawn for the sample was positive, 35% of the residents of the household were also positive. (SILVEIRA, 2020) This study pointed to an underestimation of the official data in relation to the prevalence of infection found in the survey, which varied from 12 to 2 times, the lowest being in the last survey (GOVERNO DO RIO GRANDE DO SUL, 2020).

The occurrence of Covid-19 cases in Santa Maria follows the same upward trend as the state, as well as deaths. According to data from the municipality's Epidemiological Bulletin, as of July 4, 684 cases of Covid-19 have been reported, 17 deaths have occurred as a result and 302 cases have been cured (PREFEITURA DE SANTA MARIA, 2020).

Faced with the Covid-19 pandemic, several governments have enacted preventive measures aimed at containing the spread of the virus, such as isolation and social distancing, raising awareness among the population, hygiene at both the individual and collective levels, the use of masks, etc (SRIVASTAVA, 2020).

Mass testing of the population is another strategy for tackling the Covid-19 pandemic, as it provides a better understanding of the virus transmission situation in order to propose policies for action (WHO, 2020). However, the Brazilian Ministry of Health has invested very few resources and efforts to offer tests to the population. As a result, the few tests available in health services (both public and private) were only available for severe cases and for health professionals, especially in the first months of the pandemic.

In Santa Maria, starting in June, an initiative by the Labor Prosecutor's Office funded RT-PCR tests and the RS State Health Department funded rapid tests. However, the Santa Maria Municipal Health Department (SMS) didn't have enough staff to administer the tests to the large number of people who have been stuck since the beginning of the pandemic. In other words, these are people who have consulted a health service with mild symptoms, have been placed in home isolation for 14 days, but for whom it has not been possible to seal the diagnosis because there was no test available at the time. They were therefore notified as "suspected Covid-19 cases" by Epidemiological Surveillance (ES).

As a result, the SMS asked the Department of Collective Health and the UFSM Health Observatory for support in carrying out this action. It turned out that at the time, the VE had only four workers working on the Covid-19 pandemic, a 20-hour doctor, a coordinator, a nursing technician and a 40-hour biomedicine resident. This project was therefore designed in partnership with the SMS.

The rapid test used in this action is the WONDFO SARS-CoV-2 Antibody Test, which is approved by the Brazilian National Surveillance Agency (ANVISA). It is based on the principle of lateral flow immunoassay for the detection of IgG/IgM antibodies against SARS-CoV-2 in human whole blood, serum and plasma (WONDFO, 2020). Estimates from four validation studies of this test show sensitivity of 84.8% and specificity of 99.0%, with 95% confidence intervals of 81.4-87.8% and 97.8-99.7%, respectively (SILVEIRA, 2020).

The elucidation of the list of EV suspects made it possible to include mild cases of the disease in the city of Santa Maria in the official data. It has also provided clarification for people who until now have had doubts about their health situation. The University, through extension, has contributed to this moment of public calamity by making available the experience and work force of its teachers in organizing these public health events and in training and encouraging students in this dialogical interaction with society to carry out this action.

In this context, this article aims to describe the process of the Mutirão action developed by the University and VE; show the reduction in the list of cases notified by health services as suspected of Covid-19, in the municipality of Santa Maria, RS, and describe the profile of users who attended the Mutirão to perform the rapid tests.

2 METHODS

This section presents the steps used in the process at the Mutirão in Parque da Medianeira to test users and the preliminary analysis of the profile of the users who attended. The description is structured into five items that describe the work process of the VE and the University.

a) Analysis and Cleaning of the EV Database

Information on COVID-19 is sent to VE via e-SUS Notifica and Sivep-Gripe. The former contains outpatient information and the latter hospital data and deaths. VE then gathered these two databases and converted them into EXCEL software so that the DSC could check all the information. Several variables provided information, so a single variable was created indicating whether the individual had already been tested or had a test result. The other individuals would be eligible for the Mutirão collection.

b) Pilot study

Based on this list of names and phone numbers from VE, two medical students were trained to contact these people and invite them to take the rapid test at VE's COVID-19 Center. The aim was to test the time needed for the calls, acceptability and adherence to the event. The standardized telephone text was as follows: "Good morning! My name is x and I'm calling from the VE COVID Center. I'd like to speak to Mr. ... Your name is on the list of suspects with COVID-19. Have you been tested? IF YOU HAVE: Please can you send the results by Whatsapp or email? IF YOU HAVE NOT: I would like to invite you to take a rapid Coronavirus test. We'll take a drop of blood from the tip of your finger, using sterile materials. We'll do the test and the result will be available in fifteen minutes. It will show whether you have had contact with the virus. Could you come on day x, address x? Before I make your appointment, I need to ask you if you have any symptoms such as fever, sore throat, cough, difficulty breathing, smell or taste anything less, diarrhea, vomiting? Your test will be carried out at x hours. Can this be the time? Bring an identity document. Don't forget to wear a mask. IMPORTANT: The tests are only for people who have already been notified."

Therefore, the calls followed the script above, which explained the action and questioned the presence of symptoms. Scheduling took place by block of hours, with 3 exams per hour for each examiner. The calls were made to people with symptoms for more than 15 days, in reverse chronological order, in order to schedule 50 people for testing at VE's Covid-10 Center.

c) Totaling up the suspect lists and retracing the phone calls

The list of suspects was evaluated at two points in time, and the variables and values checked. The same procedure used in the pilot study was replicated at this point. This list was divided into ten parts so that each volunteer was responsible for their calls. A single spreadsheet was created in Google Drive (online) with names, telephone numbers and addresses so that the volunteers could note the users' appointments appropriately.

Based on the pilot study, the Health Department made ten telephone lines available for VE. Training was once again carried out by DSC teachers with students, Multiprofessional Residency Residents and Health Professionals. Telephone calls were made to each number at least three times, in alternating shifts. The work was carried out in the EV with adequate distancing. Telephone contact with suspected cases was also aimed at identifying people who had already been tested for Covid-19 in private services, such as RT-PCR or rapid tests. The person was asked to send the test result to an EV email or Whatsapp.

d) Training for the Mutirão in Parque da Medianeira

Based on the accumulated experience, training was provided for the main event of this action, which consisted of the Mutirão held in Medianeira Park. The team with experience in administering questionnaires and rapid tests received additional training on the afternoon of July 10, with the following program:

The Mutirão took place on Saturday, July 11, 2020, from 9 a.m. to 5 p.m., in the Festival Hall of the Basilica of Our Lady of Medianeira Park. The team arrived at 8 am to organize and test. The idea was that if anyone tested positive, they would be excused from the action.

The press reports were careful to emphasize that the action would only accept those notified by appointment, to avoid people inadvertently going to the park looking for tests. Family members of those who tested positive would be contacted by VE afterwards for tests.

Scheduling took place on Saturday, July 4, at the Covid Center. 10 telephone lines and 10 computers were made available, with a team of 10 schedulers. They received prior training the day before to standardize the approach, increasing the appeal and optimizing time. Scheduling continued throughout the week, with two phone lines available.

The Mutirão's capacity was planned to handle 480 exams. Scheduling was done by block of hours (3 people per hour per examiner), to avoid waiting times and organize the flow of people in the park. The people who had been booked went to the tables at the established times, the rapid test was administered and an interview was carried out while they waited for the results.

The team present on the day of the Mutirão included:

- **Coordination**: carried out by four people (two representatives from the SMS and two from the DSC

- **Reception**: located at the main gate to the park, with the task of checking the names of those on the list to allow them to enter the park. It was made up of five people: two from the SMS (checking the lists) and three people from the Traffic Department - the municipality's Urban Mobility Department (organizing the flow of cars and people).

- **Examiners**: 20 examiners/interviewers: Multiprofessional residents (3), EpicovidRS Research (17), FISMA (7), totaling 27 examiners (7 reserves).

- **Support**: the joint effort team had two types of support - Report Support and Guidance Support, with five people in each role. Laudo Support were senior health professionals who visually validated the test result. Before releasing the user, the examiner would call the Report Support to validate the result. The reports had guidance on the results and were signed and stamped by the VE. One Report Support attended to four examiners. The Guidance Support supported the examiners if the user needed more time to obtain information about the new Coronavirus and Covid-19 (symptoms, prevention, testing, etc.) and also helped with the reception and organization of people at the tables.

The infrastructure for prior action:

- **Flow of cars and people in the park**: Motorized users parked obliquely to the main entrance and entered unaccompanied heading for the ballroom. Exit at the back of the park.

- **Location for the tests**: Party Room with windows and balcony adequately sheltered users and examiners, maintaining adequate distance due to the pandemic and protection due to the cold weather.

- **Toilets**: Users, next to the Basilica. Staff, next to the ballroom.

Biosafety for users and staff was provided for with the following precautions: The room had space that allowed adequate distancing of 1.5m minimum between people, for examinations and circulation. The examiners wore Personal Protective Equipment (disposable gloves changed after each examination, disposable double surgical masks changed every 2 hours, face shields and disposable lab coats). The material used was sanitized with 70° alcohol after each exam (pen, clipboard, etc.). The tables were protected by kraft paper, changed every 2 hours or if contaminated. Liquid soap and a paper towel were available for washing hands, as well as 70° alcohol for sanitizing.

The user received the report with the results of the rapid test. A specific report was produced for the Mutirão, including a brief explanation of the meaning of the positive and negative test results in the one that already existed at the SMS. It was also pre-signed and stamped by a professional from the municipality's VE, in order to speed up the work at the Mutirão. Visual validation was carried out by a senior health professional (Laudo Support) before the result was released.

While waiting for the test result, information was collected using a questionnaire with data of interest to VE: presence of comorbidities related to Covid19, symptoms at the time of notification and adherence to social distancing. The project team processed and analyzed this information, registering a specific research project to analyze secondary data. In view of this, this support is indispensable, given the shortage of workers in the municipality's ES sector. This will ensure that research and extension are inseparable.

For those users who tested positive, a questionnaire was administered to investigate the people who lived in their household, for future investigation and follow-up by VE. If any of these people were

accompanying the user at the time of testing, they were invited to take the rapid test and answer the questionnaire. In the event of positive results, the case was referred to VE for further notification.

e) Profile of users who attended the joint effort

A standardized questionnaire was administered to all users during the group testing, with questions pertinent to COVID-19, as well as information on age, gender and schooling. These questions were double-typed and analyzed using Epi-info version 7.0. The analyses were descriptive.

3 RESULTS

Initially, from the initial July list of 4659 individuals with suspected COVID-19 symptoms, 58 had positive tests (26 rapid tests and 32 RT-PCR) and 1566 negative rapid tests, 1174 had already been tested but had no results entered and 5 had died from COVID-19. That left 1,856 eligible for the calls. So, at this point there has been a big reduction in the number of suspects.

The pilot study was then prepared. At this stage, the Covid Center provided a telephone line from Monday to Thursday, in the afternoon, so that two academics trained by DSC teachers could make contact with the suspects.

A total of 271 calls were made, of which 36 had already been tested, 16 still had symptoms - so couldn't attend, 17 were repeated names, 2 had moved city and 5 were refusals. In the end, it was possible to schedule 50 people to be tested on June 19, in the afternoon (1-5pm). Of these, 45 were tested by the five trained examiners - UFSM undergraduate and Multiprofessional Residency students - and five (11.1%) were positive for Sars-Cov2.

The assessment made after the pilot study was completed was that it was necessary to remove repeated names from the VE list, ask the municipality's laboratories to send negative reports to VE, increase VE's telephone lines and extend call times.

During the week before the Mutirão, starting on Saturday, July 4, at least three calls were made to each number on the notification register and a time was scheduled in a Google Drive spreadsheet. This technique allowed the ten schedulers to work simultaneously. On Saturday the 4th, and over the next week, approximately 1,500 calls were made to the Covid Center. Ten telephone lines and ten computers were made available, with a team of ten schedulers. They received training the day before to standardize their approach, increasing their appeal and optimizing their time. Scheduling continued throughout the week, with two phone lines available.

Of the users eligible (n= 1856) for the calls, approximately half of them could not be contacted because the phone number was not answered (370), the phone was set to voicemail (280), switched off (139), the number was incomplete/wrong or outside the coverage area (56) or there was no phone (6). In addition, 75 telephone numbers did not correspond to the name notified, 192 had already undergone

tests, 10 were living in other cities, 35 were refused, 69 were repeated names, 19 still had symptoms and 120 asked to call at another time.

People who had already been tested were encouraged to send their results to VE by email or Whatsapp, which was created specifically for this purpose as part of this project. These means of communication were checked daily by a Multiprofessional Resident linked to this project. The data was passed on to the EV for the following actions in the notifications: the tests that were in accordance with the standards of the Ministry of Health and the State Department of Health and had positive results were reclassified as confirmed cases and removed from the list of suspects. Cases with negative RT-PCR were excluded from the list of suspects. Cases with negative rapid tests will remain on the suspect list, due to the low sensitivity of the tests (around 85%).

Of the 192 who had already been tested, 90 sent in their results, of which 9 were positive RT-PCR tests, 57 were negative RT-PCR tests, 6 were positive rapid tests and 18 were negative rapid tests.

On the day of the Mutirão, 243 users showed up. Of these, 5 showed antibodies to Sars-Cov2.

Table 1. Profile of users who attended the Pilot and the Mutirão to reduce suspected cases. Santa Maria, RS, 2020.

FEATURES	**N**	**FREQUENCY**
SEX		
male	107	44,3%
female	136	56,0%
COLOR		
white	194	79,8%
other	49	20,2%
AGE GROUP		
0-19 years	31	12,8%
20-59 years	181	74,5%
60 years or older	31	12,8%
CIVIL STATUS		
married	145	60,4%
others	95	39,6%
SCHOOLING		
up to incomplete secondary education	77	32,0%
up to incomplete higher education	105	43,6%
up to post-graduation	59	24,5%
WORKS IN HEALTH		
yes	35	14,4%
SMOKING		
yes	28	11,5%

Table 2. Reported morbidity of users who attended the Pilot and the Mutirão to reduce suspected cases. Santa Maria, RS, 2020.

FEATURE	**N**	**FREQUENCY**
OBESITY (BMI > 30)		
yes	56	25,7%
DEPRESSION		
yes	60	24,7%
LUNG DISEASE		
yes	57	23,6%
HIGH PRESSURE		
yes	55	22,8%
HIGH CHOLESTEROL		

yes	47	19,5%
HIGH BLOOD SUGAR		
yes	26	10,7%
HEART DISEASE		
yes	20	8,3%
KIDNEY DISEASE		
yes	9	3,7%
IMMUNE DISEASES		
yes	6	3,0%
CANCER		
yes	7	2,9%
DERRAME		
yes	4	1,7%

Table 1 shows the distribution of users who were present for Covid-19 testing. More than half were women. Around 80% were aged between 20 and 59, most of them had white skin and were married. Among the users, 43% had up to incomplete higher education. At the time of testing, 14% worked in the health sector. Smoking was present in 11%, as was diabetes. High blood pressure was found in a fifth of cases, as was high cholesterol. Around 8% had heart disease. In addition, around 4% had some kind of kidney disease and 23% had lung disease. Stroke affected 1.7% of cases and a history of cancer 3%, as did the presence of some kind of immune disease. A quarter of users had experienced depression, obesity and other health problems.

- User profileIn the dNTa

4 DISCUSSIONS

Data collection at all stages required careful processing of the different forms, from scheduling the pilot event, identifying tests that had already been carried out, checking and cleaning the list of suspects, typing up interviews, and notifying new cases based on tests sent or identified during the Mutirão.

It was necessary to check the names on different lists and type in the new information to update the VE data. As already mentioned, the municipality's VE staff is scarce, and given the overload of the pandemic, it needs reinforcements, which this project complements with scholarship holders and volunteers, on some scale.

We also identified the importance of training on how to properly fill in the telephone number on notifications, as approximately half of the sample could not be contacted because the number was incorrect.

Throughout the process, it was possible to reduce the number of cases reported as suspicious for EV.

The plan is to schedule other actions to carry out rapid tests at basic health units (UBS) where there is a higher concentration of suspected cases, or at the Covid Reference Center.

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The discussion of menopause in community: Providing opportunities for knowledge and concepts

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ABSTRACT
We live in times that taking care of esthetics has become a standard in society, but there is still a lack of information regarding the cellular and metabolic dysfunctions that occur in the climacteric and menopausal phase. Thus, an Online Journey on Menopause was held during Esthetics and Cosmetics of the Regional Integrated University of Alto Uruguay and the Missions/URI, with the objective of providing opportunities for the protagonist women over 40 years of age, enabling discussions related to hormones and their consequences in the body. To this end, a partnership was made with the Academic League of Health and Environment (ALHE), registration in the event through the University's website and contact with the volunteer speakers, namely: Biologist, Pharmacist, Doctor and Psychologist. To discuss the results, the Grounded Theory (GT) was chosen. It was noted that the activity had 75 registrations, that there was participation of women through interaction in the chat during the lectures, that the feedbacks received demonstrate that discussing menopause, providing opportunities for knowledge sharing and inserting academic knowledge in the community are primary prevention actions capable of enabling autonomy, criticality and protagonist action of mature women.

Keywords: Menopause, Primary care, Health.

1 INTRODUCTION

1.1 THEORETICAL FRAMEWORK

1.1.1 Physiological and metabolic aspects of menopause

It is noted that the concept related to menopause has become a taboo in society. Women at this stage of life tend to denialism, because they believe that they will be attesting to the bankruptcy of life as a productive woman. This difficulty may be directly related to the beauty standards imposed by the media and the large number of rejuvenation techniques.

Obviously, such techniques help women, providing opportunities to pass through this period with more empowerment, but it is essential that women also take possession of concepts and meanings, understanding the physiological mechanisms that occur in this phase. Fonseca (2015) notes that climacteric women are tormented by society, as there are still beliefs about this phase of life related to body aging.

Aging is not only linked to hormonal changes, but also involves social, economic, physiological and psychological aspects. However, it is important to note that:

> Hormonal fluctuations lead to changes, not only in reproductive function, but in other important body areas. It is worth noting that amenorrhea can also be of induced cause, resulting from the removal of parts of the female reproductive system, for example. Thus, the arrest of ovarian activity induces a chronic inflammatory character, increasing the susceptibility of women to various diseases (LINS et al.2020, p.12019).

Still collaborates Fonseca (2015) the intensity of symptoms is influenced by sociocultural factors, psychological, marital, family and professional situation. Linked to this, the woman in this phase lives the myth of the loss of sexual desire, it is believed that this factor is related to the stereotyped social view about the role of the woman (wife and mother) that may negatively interfere in the vision about herself and in her relationship with people and the world (VALENÇA; NASCIMENTO FILHO and GERMANO, 2010).

Thus, it is essential that these women have access to health information to understand this period, re-signifying this phase of life. Thus, it is essential to discuss what the absence of hormones will cause in the body and what are the prospects for this new phase of life. In this context Amaral et al (2022) observe that health promotion activities about menopause are moments that need to be in evidence, as they provide knowledge, engagement, discussions and curiosity, contributing to changes in habits, ensuring the crossing of this period with more tranquility.

Carvalho, Cohen and Akerman (2017) understand that promoting health helps protagonism, as it becomes a way to prevent diseases and seek improvements in the life of the community. This will be the purpose of this work, to provide discussions in conversation circles, instigate curiosity, share knowledge to demystify taboos, contributing so that in addition to an impeccable aesthetic, women are equipped with scientific knowledge about one of the most important phases of their lives.

1.2 UNDERSTANDING BETWEEN THE BIOCHEMICAL ASPECTS OF MENOPAUSE AND AESTHETIC IMPACTS

The biological process of menopause is the end of spontaneous menstruation that occurs by changing the structure of the ovarian follicles, while there is a reduction in the secretion of estrogen and progesterone. It will usually occur in the lives of women along with the aging process, possibly occurring between 40 to 58 years. After the "start" the woman finds herself in a new hormonal

environment impacting her body daily. Some exogenous factors can anticipate the effects of menopause, use of specific medications, smoking and overweight, factors that potentiate the effects of menopause (ANTUNES; MARCELINO and AGUIAR, 2003).

Among the many effects that can be observed, it turns out that the loss of collagen is one of the most common complaints of this phase. This process may impact women's lives, but it is necessary to have knowledge about this process and how to minimize this impact.

The drop in the level of estrogen has an important relationship with reduced collagen, decreased sebaceous secretions, loss of elasticity and consequently atrophy of the skin, in addition to deficiency in the healing process and emergence of expression lines. The connection of the visible appearance of skin changes with the fall of estrogen secretion is linked to the estrogen receptors present in the dermal fibroblast, keratinocytes, in addition to the direct action on the mitochondrial membrane potential (SHU; MAIBAC, 2011)

Evidence also points out that the thickening of the skin is associated with a drop in the level of estrogen in the body, presenting deficiency that varies between 15 to 30%, in addition to changes in vascularization and quality of extracellular matrix, there is a loss of elasticity. This hormone is also responsible for increasing the hyaluronic acid content and hydration of the skin, resulting in loss of elasticity (HALL; PHILLIPS, 2005).

It is known that this loss of collagen will occur anyway, but the Brazilian Society of Dermatology (BSD) points out specific care to minimize skin damage in this phase such as: use of sunscreens and adequate sun exposure, increased water consumption, healthy diet rich in proteins and fatty acids, use of exfoliating in the skin care routine twice a week. Other recommendations include avoiding tobacco, using firming lotions not only on the face but neck and neck, ingesting phytoestrogens with proper medical guidance to further slow the damage, and using moisturizing, antioxidant and amino acid masks to maintain skin integrity (WDS, 2023).

It is believed that the understanding of physiology and its relationship with nutrition and physical activity can help women in relation to the pressure exerted by the media; in addition to strengthening skin care, because it is understood that the meaning of beauty for women, may not occur only from one perspective, but as a result of experiences, customs and myths (ALBARELLO et al, 2016).

Wittt and Schneider (2011) report that body image is the way the individual sees himself. The media and industry will be responsible for creating desires and reinforcing standardized images; thus, it is observed that the most striking behaviors are related to the habit of dieting, consuming dietary products and seeking aesthetic procedures (WITT; SCHNEIDER, 2011). Thus, it is essential that women appropriate knowledge, making choices that can help the passage of this phase more naturally.

2 METHODOLOGY

The activity is related to the discipline of Biological Processes of the Course of Aesthetics and Cosmetics of EAD URI, this discipline has as one of the curricular components the sex hormones, senescence and epithelial tissue, so it was proposed the II Online Journey where hormonal issues and their relationship with physiology and metabolism were discussed; the use of aromatherapy to minimize these impacts; Hormone Replacement Therapy (TRP) and health women's psychology.

To this end, the teachers partnered with the Academic League of Environment and Health (LiASM), since in 2022 the league held the I Online Journey, with the theme in question. Registration took place through the University's website, free of charge, where enrollees were directed to a group of *WattsApp*. The lectures took place on July 3 and 4, from 7 pm to 10 pm via *google meet*. The event was publicized through the social networks of the professors involved and LiASM, on the city's radios and newspapers and through the University's website (Figure 1).

The speakers worked voluntarily and had the participation of Biologist, Pharmacist, Physician and Psychologist. For the analysis of this activity, we opted for the Grounded Theory (GT), a type of interpretative research that seeks to produce an overview about the activity performed and its importance for the subject, in order to build small and medium-sized theories to explain social processes. According to Cassiani, Caliri and Pelá (1996) in this research the investigator looks for processes that are happening in the social scene, starting from a series of hypotheses to explain a phenomenon.

About the research still corroborate Strauss and Corbin (2022) the main requirement is search for a guided investigation that understands the meaning of the relationships and interactions between social phenomena and the understanding of reality and human action, identifying the emotion that is generated based on experiences.

The experience of the activity allowed us to understand the importance of the experience with the elaboration of categories that exemplify the context of the extension activity, thus constructing the central category, entitled: You are in menopause, so what?, delimiting 3 categories of analysis: demystification of taboos and concepts; empowerment and conscious vision, women's protagonism. The categories are illustrated in an explanatory theoretical scheme in the results and discussion.

Figure 1 – Folder of information about the lectures of the Journey.

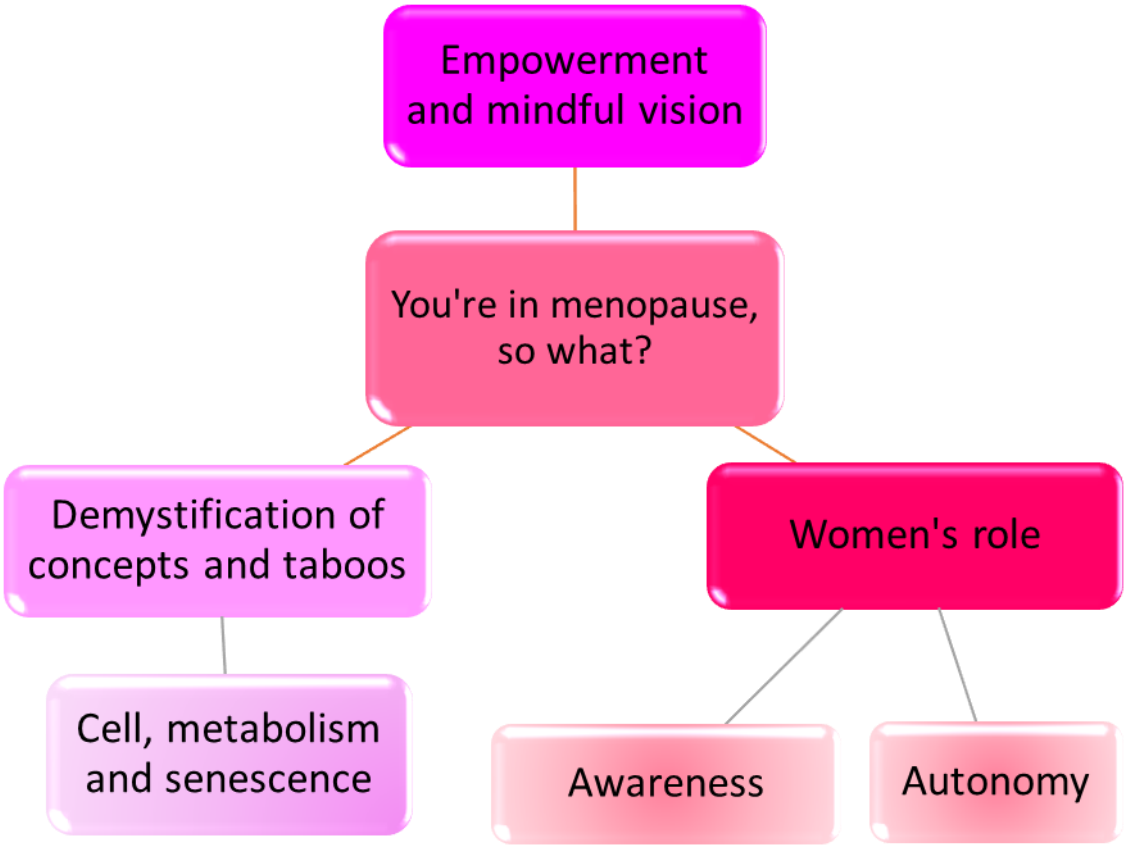


Source: Prepared by the authors.

3 RESULTS AND DISCUSSION

The discussion begins by presenting the central category (Figure 2) constructed from the GT of the study and the categories of analysis constructed from the perception of the researchers about the activity performed.

Figure 2 – Central Category presented from the GT of this study and categories of analysis.



Source: Prepared by the authors.

It is perceived that extension activities that prioritize women's health, promote primary health care, helping women over 40 years to determine a time to discuss menopause and the processes that lead to cellular senescence. It is believed that there are still taboos in relation to this period, because many women deny this phase of life, prioritizing a single symptom that would be the "hot flashes"; but studies show that estrogen, one of the hormones produced in the ovaries is related to lack of lubrication, intestinal problems, problems associated with the absorption of vitamin D and osteoporosis, stroke and infarction, accumulation of abdominal fat, loss of collagen, among others.

Corroborate Alves et al (2015) the integrity of women's health, in addition to cultural, social, psychological and emotional factors, can help the transformations in your body, with diverse symptoms, strange, incomprehensible and often difficult to be verbalized, highlighting the hot flashes, cold sweats, insomnia, sadness, emotional instability, changes in sexual habits, skin, body fat distribution and silhouette.

Thus, the integrity of health is constituted by a sum of factors, thus, it is essential to understand these factors, as an aid to the acceptance of this phase of life. It is noted that the media is an impact factor in this phase, because it coexists with numerous rejuvenation techniques, which mitigate the impacts. But the lack of studies and works on menopause, the lack of dialogues makes women have scant notions about the period, paying attention only to the "loss of collagen" or "Hot Flashes", visible

symptoms, forgetting the other silent symptoms that the body is releasing. Maron et al. (2011) already identified the absence of information and the scarcity of studies referring to this period, believing that the information would be essential for women to be able to identify the symptoms of this phase of life.

In relation to category 2 called: Empowerment and conscious vision, it is believed that some women realize that scientific knowledge will make a difference in their lives, this fact was perceived during the activity, because we had 75 registrations in the II Journey. And during the first day of activity, we had 56 women who were *online* and on the second day we got to 48 women. Although we did not get the presence of all, it is observed that we had a great success, because for 2 days this group of women was interested in discussing this phase of life, demystifying one of the biggest taboos of this phase which is the Hormone Replacement Therapy (HRT). It is noticed that, in general, women have little knowledge about HRT, with numerous beliefs in false information, which combined with the lack of guidance, generates insecurity, especially in relation to the conditions of use, contraindications and available alternatives (BELIZÁRIO et al., 2021).

Given this situation, it is of paramount importance that different therapeutic forms are investigated to mitigate climacteric symptoms, since many women are in risk groups in relation to HRT. Therefore, women who for some personal, psychosomatic or physiological incompatibilities are unable to perform a traditional hormone therapy can adhere to Complementary Integrative Practices (ICPs), including aromatherapy. It is known that this practice has been standing out intensely, due to the use of the properties of essential oils (volatile concentrates extracted from vegetables).

Several studies have shown that the use of essential oils individually or in association, through inhalation and body/facial massage, promoted statistically significant improvements in sleep quality, self-esteem, anxiety, skin aspects, vasomotor symptoms, sexual function, reduction of hot flashes and increased estrogen levels. Therefore, aromatherapy can be used by menopausal women as an alternative therapy, with noticeable benefits, in addition to being a simple, non-invasive and safe method (MAIA et al,2021; BALTOKOSKI; NASCIMENTO and SILVA, 2022).

These discussions enhance primary health promotion. Primary prevention is the best strategy to prevent the development and control of risk factors that favor the establishment of heart disease. In this sense, these discussions promote awareness regarding healthy diet and physical activity, paramount factors to achieve optimal cardiovascular health, since this is a phase of great risk for heart disease (EL KHOUDARY et al., 2020).

Category 3 is related to "Women's Protagonism: autonomy and awareness". It is noted that we can only have autonomy from the moment we understand the physiology of the organism and its relationship with metabolism. Thus, it is necessary to disseminate scientific knowledge to understand that: "aging does not have to be, as has been thought for so long, a slippery one-way street towards

disease and decadence. We will all age, but how we age depends a lot on the health of our cells (EPEL; BLACKBURN, 2017, p.18,19).

Thus, it is necessary to demystify the culture of aging, as an unproductive and finished form. It is necessary to pay attention to culture as a producer of categories of thinking, feeling, acting and expressing. It articulates concessions, conflicts and resistance. It is the space of the expression of subjectivity (MINAYO, 2014).

And to assist the discussion here are reports received after the end of the activities:

> *"I wanted to listen twice as long, I had no idea how much estrogen influences the body, because I only hear about hot flashes. Gratitude to you."*
>
> *"Discussing this phase of my life was fundamental because I am becoming very depressed, especially with the changes in the body and face. Understanding that there are exits was phenomenal. Thank you, teacher!"*
>
> *"At first I thought it would be silly, kind of a waste of time, but I confess to you that I was very pleased. It is a very difficult time, we lack reading, we do not understand anything and we are still ashamed to talk about this phase. I'm grateful to you, who provided us tonight with discussions with different types of professionals."*
>
> *"Thank you, thank you and thank you for thinking about the women who are tormented every day by beauty standards, who are terrified without understanding what is happening, who are ashamed to accept and discuss this phase."*
>
> *"I thank the teachers for their concern with women's health, the event was very good, it brought information, discussion and maturity in relation to the moment we experienced."*

The reports make clear the satisfaction, the opportunity and the awareness in relation to the moment experienced. Amaral et al. (2022) report that health promotion activities offered to women over 40 years of age about menopause are punctual moments that need to be in evidence, as they provide knowledge, engagement, discussions and curiosity, contributing to changes in habits, ensuring the crossing of this period with more tranquility.

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