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Letter to the editor

Dr. Inácio de Barros Melo Neto[1]

The number 8 of the Annals of Olinda Medical School celebrates the seventh anniversary of the Faculdade de Medicina de Olinda (FMO) and the conclusion of the third class. This launch also comes after the evaluation of the course that placed the FMO among the 25% of the best-evaluated medical schools in the country, with a score of 4.35.

Although we are humbled by the results obtained in external evaluations issued by the National Institute of Studies and Research (Ministry of Education), this achievement does not close our eyes to the understanding that we need to continue improving and building a cutting-edge space for medical training.

Thus, we envision investments in teaching staff training, support for the students, and structural reforms to improve our course with bold and innovative proposals. One of these proposals will be the construction of the Maria Institute, which will initially support individuals with Down syndrome but will later expand to other conditions. The institute will enable the disclosure of essential information to parents and guardians of these individuals, and will keep the patients connected with the FMO through outpatient, therapeutic, psychological, and psycho-pedagogical care. In addition, the institute will promote research from a digital platform with expertise in the area.

All this effort allows for the expectation of an even more productive year, with the Annals of Olinda Medical School as an institutional spokesperson for the production of knowledge through research and extension interventions beyond the faculty. We hope to contribute to the training of socially referenced, reflective, and independent physicians in the exercise of their profession.

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Letter from editor

Prof. Paulo Sávio A. Goes, PhD.

The Number 8 of the Annals of Olinda Medical School represents the institutional effort of the faculty in producing knowledge in the field of medicine. The new submission rules and layout of our portal facilitate the dialogue between authors and our journal, increasing the products and the agility of editorial processes.

Another factor that encourages us is the collective commitment of authors, evaluators, and managers in preparing the journal for international indexing, which requires the gradual update of our content and the building of a bibliographic collection with its own identity but with a universal character.

In this issue, readers will be presented with a set of original articles, case reports, systematic and narrative reviews, as well as experience reports and reviews. Besides the quality of all studies, the systematic review “Mortality in patients with metabolic syndrome during the COVID-19 pandemic” stands out as it evidences the need to remain vigilant in relation to the disease that caused irreparable harm to human beings.

Last, our belief in science is renewed by the production of knowledge as an indispensable tool for the construction of society and as a key element for our civilizing process. The Annals of Olinda Medical School remains an important instrument for training and strengthening the principles of learning: teaching, research, and extension.

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MORTALITY IN PATIENTS WITH METABOLIC SYNDROME DURING THE COVID-19 PANDEMIC: A SYSTEMATIC REVIEW

Mortalidade em pacientes com síndrome metabólica durante a pandemia da COVID-19: uma revisão sistemática.

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ABSTRACT

The COVID-19 pandemic, the most significant health crisis, was a serious public health issue worldwide. Metabolic comorbidities, such as type 2 diabetes mellitus, hypertension, and obesity, characterized metabolic syndrome and have been associated with increased severity and mortality in COVID-19. The systematic review, conducted following PRISMA statements, investigated the association between mortality in patients with COVID-19 and metabolic syndrome. Cohort, case-control, and cross-sectional studies available in the MEDLINE (EBSCO), Cochrane Library, PubMed, and SciELO databases were included. The search strategy was limited to studies in English, Spanish, and Portuguese from January 2020 to March 2021. Among the 14 studies included, most were published on the MEDLINE (EBSCO) database (64.3%), in English (93.0%), and were cohort studies (57.0%). About 60.0% of the patients were male, with a mean age of 58 years. About 20.0% of patients presented hypertension (25.8%), obesity (20.5%), and type 2 diabetes mellitus (19.1%). The mortality rate was 12.5%, and the occurrence of metabolic syndrome was associated with increased mortality in patients with COVID-19. Further research is needed to elucidate the pathogenic mechanism involved, particularly in hypertensive, diabetic, and obese males, and the development of severe COVID-19.

Keywords: complications and mortality, coronavirus infections, glucose metabolism disorders, metabolic syndrome

RESUMO

A pandemia da COVID-19, responsável pela maior crise sanitária da atualidade, constitui um grave problema de saúde pública mundial. Comorbidades metabólicas, a exemplo da diabetes mellitus tipo 2, hipertensão arterial e obesidade, caracterizam a síndrome metabólica e têm sido associadas às formas graves da doença e óbito. Investigamos a mortalidade em pacientes com COVID-19 e a sua associação com doenças metabólicas. Trata-se de uma revisão sistemática seguindo a recomendação PRISMA. Foram considerados estudos de coorte, caso-controle e corte seccional. As bases de dados MEDLINE/EBSCO, Cochrane Library, PubMed e SciELO foram consultadas por meio das estratégias limitadas aos idiomas inglês, espanhol e português, no período entre janeiro de 2020 e março de 2021. A partir dessa busca, foram observados 14 artigos. A maioria deles foi publicada na plataforma MEDLINE (64,3%), em inglês (93%), do tipo coorte (57%). Em torno de 60% da população dos estudos selecionados, foi constituída por homens, e a média de idade foi de 58 anos. Observou-se que aproximadamente 20% da população total dos estudos apresentava hipertensão (25,8%), obesidade (20,5%) e diabetes (19,1%). A taxa de mortalidade entre eles foi de 12,5%. A presença de comorbidades metabólicas configurou como um dos fatores associados à mortalidade em pacientes com COVID-19. Estudos futuros são necessários para

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determinar com precisão o mecanismo patogênico que envolve esses pacientes, especialmente homens hipertensos, diabéticos e obesos, e o desenvolvimento das formas graves da infecção por COVID-19.

Palavras-chave: Síndrome metabólica, Infecção por coronavirus, Transtornos do metabolismo da glicose, Obesidade, Complicações e mortalidade

INTRODUCTION

In early 2020, reports from China described a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused coronavirus disease 2019 (COVID-19). Initially centered in Wuhan, the virus triggered an epidemic in China and rapidly escalated into a global pandemic[1]. By May 2022, the World Health Organization indicated 357,682 new cases and 523,786,368 confirmed cases of COVID-19, including 6,279,667 deaths worldwide[2].

The novel coronavirus was identified by the Chinese Center for Disease Control and Prevention in respiratory secretion, explaining its transmission via droplets and aerosols[3]. The disease could be asymptomatic in a significant number of patients or symptomatic, whose symptoms include fever, headache, shortness of breath, myalgia, fatigue, and invasive pneumonic infiltrates in both lungs, as shown by chest X-rays. In some cases, gastrointestinal symptoms, such as diarrhea, also occurred[4].

Comorbidities were associated with the development of severe COVID-19, with obesity, diabetes mellitus, hypertension, and advanced age being the most frequent risk factors among hospitalized patients with severe clinical outcomes and higher mortality[3,5,6,7]. Additionally, the comorbidities presented similar metabolic alterations that influenced the progression and prognosis of COVID-19[8,9]. Thus, the study aimed to investigate the mortality of patients with COVID-19 and its association with metabolic diseases.

METHODS

The systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements[10,11].

Study screening and selection strategy

The systematic review included observational (cross-sectional, case-control, and cohort) and interventional (randomized clinical trials) studies involving humans, available in MEDLINE (EBSCO), Cochrane Library, National Library of Medicine (PubMed), and Scientific Electronic Library Online (SciELO) databases. The search strategy was limited to studies in English, Portuguese, and Spanish from January 2020 (the first studies on COVID-19) to April 2021. The Medical Subject Headings and the Health Sciences Descriptors tools were used as keywords for selecting search terms. The Boolean operators AND and OR refined the search strategy through several combinations. The initial keywords included SARS-CoV-2, COVID-19, coronavirus, metabolic syndrome, metabolic disease, obesity, mortality, hypertriglyceridemia, and diabetes. The eligible studies were identified using the keyword combinations: [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR covid-19 OR coronavirus AND obesity], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND mortality AND metabolic syndrome], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND mortality], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND mortality AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND diabetes], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND obesity AND diabetes], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND mortality AND diabetes], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND diabetes AND metabolic syndrome OR metabolic disease], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia],

[SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND obesity], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND mortality], [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND mortality AND obesity], and [SARS-CoV-2 OR 2019-nCoV OR COVID-19 OR coronavirus AND hypertriglyceridemia AND diabetes].

Short communications, case reports, editorials, and narrative and systematic reviews related to metabolic syndrome and COVID-19 were not included in the review. Additionally, analytical observational studies with duplicated interventions or with undefined criteria for the definition of SARs-COV-2 infection or metabolic syndrome were excluded.

The methodology of all studies was critically assessed, and the PRISMA statements were followed to meet the systematic review criteria[10,11].

Data extraction

The title and abstract were assessed during the initial search, followed by the full-text assessment based on the inclusion and exclusion criteria. The AXIS tool was used to verify the methodological quality of the study design of the included studies. AXIS is a modified assessment tool for cross-sectional studies to systematically evaluate studies and investigate their reliability. The assessment of the studies was conducted independently by the researchers involved in the study.

Two researchers analyzed the studies and extracted data, including study identification (author, year, research location, and study design), data collection characteristics (assessment duration, source of information, and methods for confirming COVID-19 diagnosis), and main outcomes. The researchers were previously trained to ensure consistency in the analysis, and discrepancies were resolved through discussion or consultation with a third researcher.

Terms definition

Based on the Diabetes International Federation, metabolic syndrome was defined as the presence of obesity (body mass index ≥ 30 kg/m²) and at least two additional factors, such as hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg) and type 2 diabetes mellitus12.

SARS-CoV-2 infection was defined by a positive result from RNA detection via reverse transcription-polymerase chain reaction (RT-PCR) test, following the World Health Organization recommendations13.

Data processing and analysis

Data were stored in a custom database created for the research. The analysis included all studies that present a measure of association (e.g., odds ratio and relative risk). A p-value with a significance level of 5% was adopted.

Results:

A total of 170 studies were identified in the MEDLINE (EBSCO), Cochrane Library, PubMed, and SciELO databases. Before the initial screening, 113 studies were excluded due to duplicity or failure to meet the inclusion criteria. Among the 57 studies selected for screening, 43 were excluded due to undefined criteria for SARS-CoV-2 infection or metabolic syndrome, resulting in 14 studies. The selection process is presented in Figure 1.

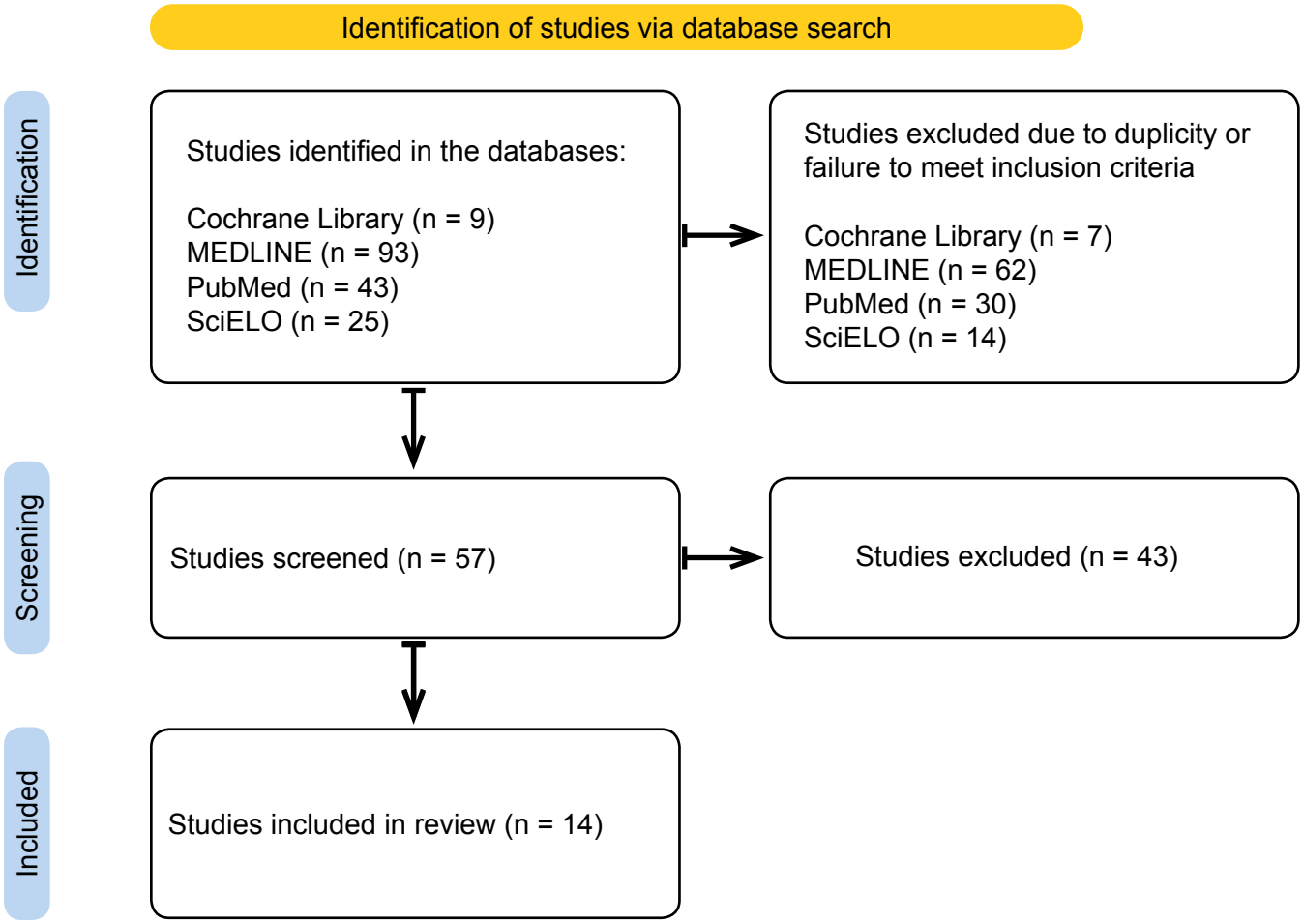

Figure 1. Flowchart of the systematic review of the studies identified in databases, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements. n: number of studies.

General characteristics of the studies and investigated population

Table 1. Selected studies: database, location, language, study design, and objectives.

Authors/Year	Database	Country	Language	Study design	Aims
Ciceri F et al. (2020)[14]	Pubmed	Italy	English	Cohort	To describe clinical, demographic, radiologic, and laboratory characteristics, clinical outcomes, and mortality risk factors of patients with COVID-19 in a university hospital in Milan, Italy
Pantea Stoian A et al. (2020)[15]	Pubmed	Romania	English	Cross-sectional retrospective	To investigate the association between mortality and comorbidities, gender, age, and hospital-acquired pneumonia using statistical methods
Ruíz-Quiñonez JA et al. (2021)[7]	Medline	Mexico	English	Cross-sectional retrospective	To assess the demographic and clinical characteristics, and pharmacological treatment of patients who died from COVID-19 in southern Mexico
Rodríguez-Zúñiga MJM et al. (2020)[16]	Scielo	Peru	English	Cohort retrospective	To describe the main factors associated with mortality in a cohort of patients hospitalized with SARS-CoV-2 pneumonia in a public hospital in Lima, Peru
Akbariqomi M et al. (2020)[17]	Pubmed	Iran	English	Cross-sectional retrospective	To describe clinical and epidemiological characteristics, and outcomes of hospitalized patients with COVID-19 with or without diabetes mellitus
Monteiro AC et al. (2020)[18]	Medline	USA	English	Cohort retrospective	To describe the development of respiratory failure in COVID-19 and explore factors associated with the risk of invasive mechanical ventilation.
Thomson RJ et al. (2020)[19]	Medline	United Kingdom	English	Cohort	To understand the characteristics of hospitalized patients in intensive care units in the United Kingdom to inform clinical decision-making, research, and planning for future waves of infection
Kaeuffer C. et al. (2020)[9]	Medline	France	English	Cohort	To identify predictive risk factors for severe COVID-19 and mortality in France
Ebinger JE et al.(2020)[20]	Medline	USA	English	Cross-sectional retrospective	To determine the demographic and clinical characteristics associated with increased severity of COVID-19 infection
Rodríguez-Molinero A et al. (2020)[21]	Medline	Spain	English	Cohort	To analyze the relationship between COVID-19 prognosis, disease presentation, pre-existing pathologies, and chronic treatments
Kammar-García A et al. (2020)[22]	Medline	Mexico	English	Cross-sectional retrospective	To assess the impact of comorbidities on the mortality rate and the occurrence of adverse events in patients with SARS-CoV-2 in Mexico
Nachega JB et al. (2020)[23]	Medline	Congo	English	Cohort retrospective	To describe clinical, laboratory characteristics, and outcomes of hospitalized patients with COVID-19 and differentiate them from other non-African patients
Wang S et al. (2020)[24]	Medline	China	English	Cohort retrospective	To describe the clinical characteristics of patients with COVID-19 in Fujian Province, China
Saldías Peñafiel F et al. (2020)[25]	Scielo	Chile	Spanish	Cross sectional	To describe the clinical characteristics, risk factors, and predictors of hospitalization in adult patients treated for acute respiratory infections associated with SARS-CoV-2

USA: United States of America

Table 2. Selected studies: sample size, number of male patients, mean age, obesity, systemic arterial hypertension (SAH), type 2 diabetes mellitus (T2DM), and mortality

Authors/Year	Sample size	Male n (%)	Age (Mean)	Obesity n (%)	SAH n (%)	T2DM n (%)	Mortality n (%)
Ciceri F et al. (2020)14	410	299 (72.9%)	65	78 (19%)	203 (49.5%)	61 (14.9%)	95 (23.2%)
Pantea Stoian A et al. (2020)15	432	282 (65.3%)	67	53 (12.3%)	162 (37.5%)	153 (35.4%)	432 (100%)
Ruíz-Quiñonez JA et al. (2021)7	185	95 (51.3%)	59	81 (43.8%)	110 (59.4%)	112 (60.5%)	185 (100%)
Rodríguez-Zúñiga MJM. et al. (2020)16	122	86 (70.5%)	56	122 (100%)	16 (13.1%)	21 (17.2%)	45 (36.6%)
Akbariqomi M et al. (2020)17	595	401 (67.4%)	55	176 (29.6%)	172 (28.9%)	148 (24.9%)	65 (10.9%)
Monteiro AC et al. (2020)18	112	75 (67%)	61	41 (36.6%)	61 (54.5%)	73 (65.2%)	41 (36.6%)
Thomson RJ. et al. (2020)19	156	112 (71.8%)	62	89 (57%)	81 (51.9%)	52 (33.3%)	38 (24.3%)
Kaeuffer C et al. (2020)9	1045	612 (58.6%)	66	351 (33.6%)	548 (52.4%)	264 (25.3%)	195 (18.7%)
Ebinger JE et al. (2020)20	442	256 (57.9%)	53	71 (16.1%)	161 (36.4%)	84 (19%)	11 (2.5%)
Rodríguez-Molinero A et al. (2020)21	418	238 (56.9%)	65	74 (17.7%)	217 (51.9%)	99 (23.7%)	79 (18.9%)
Kammar-García A et al. (2020)22	13.842	7989 (57.7%)	47	2793 (20.2%)	2969 (24.4%)	2502 (18.1%)	1302 (9.4%)
Nachega JB et al. (2020)23	766	500 (65.27%)	58	39 (5.1%)	194 (25.3%)	107 (14%)	102 (13.3%)
Wang S et al. (2020)24	199	105 (52.8%)	46	7 (3.5%)	31 (15.6%)	15 (7.5%)	1 (0.5%)
Saldías Peñafiel F et al. (2020)25	1022	507 (49.6%)	41	36 (3.5%)	128 (12.5%)	46 (4.5%)	3 (0.3%)

n: number of patients; %: percentage; SAH: systemic arterial hypertension; T2DM: type 2 diabetes mellitus.

Tables 1 and 2 present the main characteristics of the selected studies and the studied population, respectively. Most studies were published in the MEDLINE (EBSCO) (64.3%), in English (93.0%), and used a cohort (57.0%) and retrospective design (64.3%). The studies were conducted across four continents, excluding Oceania, with the Americas (43.0%) and Europe (36.0%) being the most represented. All studies aimed to describe the clinical and epidemiological characteristics of patients with COVID-19 and factors associated with mortality, including comorbidities defining metabolic syndrome (Table 1). About 60.0% of the study population were male. The mean age ranged from 41 to 67 years, with 58 years in most studies. About 20.0% of the patients had hypertension (25.8%), obesity (20.5%), and type 2 diabetes mellitus (19.1%). The mortality rate was 12.5% (Table 2), and the prevalence of metabolic comorbidities was associated with mortality in patients with COVID-19 (Table 3)..

Table 3. Selected studies: Association of metabolic comorbidities and mortality in COVID-19 patients

Authors/Year	Sample size	Mortality n (%)	Obesity n (%)	OR (CI 95%)	SAH n (%)	OR (CI 95%)	T2DM n (%)	OR (CI 95%)
Ciceri F et al. (2020)[14]	410	95 (23.2%)	78 (19%)	-	203 (49.5%)	-	61 (14.9%)	-
Pantea Stoian A et al. (2020)[15]	432	432 (100%)	53 (12.3%)	1.3* (0.84 - 2.01)	162 (37.5%)	2.09 (1.56 – 2.81)	153 (35.4%)	0.70 (0.49 – 0.99)
Ruíz-Quiñonez JA et al. (2021)[7]	185	185 (100%)	81 (43.8%)	-	110 (59.4%)	-	112 (60.5%)	-
Rodríguez-Zúñiga MJM et al. (2020)[16]	122	45 (36.6%)	122 (100%)	1.01 (1.01 – 1.05)	16 (13.1%)	1.68 (1.09 – 2.56)	21 (17.2%)	-
Akbariqomi M et al. (2020)[17]	595	65 (10.9%)	176 (29.6%)	-	172 (28.9%)	-	148 (24.9%)	-
Monteiro AC et al. (2020)[18]	112	41 (36.6%)	41 (36.6%)	5.82 (1.74 – 19.48)	61 (54.5%)	2.28* (0.68 – 7.61)	73 (65.2%)	1.71* (0.55 - 5.37)
Thomson RJ et al. (2020)[19]	156	38 (24.3%)	89 (57%)	3.06 (1.16 – 8.74)	81 (51.9%)	-	52 (33.3%)	-
Kaeuffer C et al. (2020)[9]	1045	195 (18.7%)	351 (33.6%)	1.4* (0.7 – 2.5)	548 (52.4%)	0.6 (0.3 – 0.9)	264 (25.3%)	1.7* (1.0 – 2.7)
Ebinger JE et al. (2020)[20]	442	11 (2.5%)	71 (16.1%)	1.95 (1.11 – 3.42)	161 (36.4%)	1.19* (0.71 – 1.99)	84 (19%)	1.77 (1.03 – 3.03)
Rodríguez-Molinero A et al. (2020)[21]	418	79 (18.9%)	74 (17.7%)	0.09* (0.19 – 3.66)	217 (51.9%)	1.59* (0.74 – 3.43)	99 (23.7%)	1.71* (0.90 – 3.26)
Kammar-García A et al. (2020)[22]	13.842	1302 (9.4%)	2793 (20.2%)	-	2969 (24.4%)	-	2502 (18.1%)	-
Nachega JB et al. (2020)[23]	766	102 (13.3%)	39 (5.1%)	2.30 (1.24 – 4.27)	194 (25.3%)	1.00* (0.62 – 1.61)	107 (13.9%)	1.10* (0.66 – 1.81)
Wang S et al.(2020)[24]	199	1 (0.5%)	7 3.5%)	-	31 (15.6%)	3.43 (1.05 – 11.1)	15 (7.5%)	6.93 (1.64 – 29.2)
Saldías Peñafiel F et al.(2020)[25]	1022	3 (0.3%)	36 (3.5%)	-	128 (12.5%)	-	46 (4.5%)	-

n: number of patients; SAH: systemic arterial hypertension; T2DM: type 2 diabetes mellitus; OR: odds ratio; CI: confidence interval.

DISCUSSION

COVID-19 disease, currently dispersed, has caused more than six million deaths worldwide[2], becoming a severe public health issue. Some comorbidities, such as hypertension, type 2 diabetes mellitus, and obesity, have been associated with severe forms of COVID-19[7,9]. The pathophysiology of cardiometabolic comorbidities associated with COVID-19 remains unclear in the literature; however, endothelial dysfunction has been noted among these conditions[26]. Besides the vascular endothelium, the angiotensin-converting enzyme 2 has also been targeted due to its high expression in cardiac and respiratory tissues, potentially contributing to the occurrence of symptoms and complications[26,27].

The mortality rate among the analyzed studies was 12.5%, consistent with retrospective studies conducted in Iran, Mexico, and Congo[17,22,23]. About 75.0% of the included studies, which presented a significant odds ratio ranging between 3.43 and 1.68, showed a positive association between the presence of hypertension and mortality in patients with COVID-19[15,16,24]. Dysregulated blood pressure in this population, evidenced by high systolic and diastolic blood pressure (139 mmHg and 89 mmHg, respectively)[28], increases inflammatory response and oxidative stress29 due to elevated levels of cytokines, proteins, and circulating free radicals. Given the crucial role of endothelial cells in vascular homeostasis and organ perfusion, the relationship between endothelial dysfunction and the development of severe COVID-19 is particularly relevant.

However, a cohort study involving 1,045 patients in France identified an inverse association between hypertension and mortality due to the protective effect of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, which were used by 60% of study patients9.

In Brazil, obesity was the main comorbidity associated with death in patients under 60 years, regardless of COVID-19 serological status [30]. Furthermore, in patients with positive COVID-19 serology, obesity was also associated with increased mortality[16,18-20,23]. A possible explanation was the increased oxidative stress caused by the synthesis of inflammatory substances (e.g., interleukins and adipocytes) due to excessive fat deposits, particularly in the abdominal region[31]. Combined with COVID-19, this condition exacerbated the inflammatory effect[32] and impacted the morbidity and mortality of patients with obesity. Furthermore, adipose tissue was considered a potential site for the SARS-CoV-2 replication and elimination[23, 33].

The impaired glucose metabolism during chronic hyperglycemia, due to insulin resistance, damaged various target organs essential for maintaining homeostasis, such as blood pressure, lipid metabolism, and the alveolar gas exchange, already impaired by COVID-19[34]. Hyperglycemia also hampered the innate immune response and adaptative lymphomonocytic cellular immunity, which are crucial in the immune reaction to COVID-19 and other opportunistic pathogens[35]. Smith et al.[6] analyzed the clinical characteristics of hospitalized patients with COVID-19 and observed orotracheal intubation, mainly in patients with diabetes mellitus. This finding corroborated the association between impaired glucose metabolism and worse outcomes in hospitalized patients with COVID-19[6], which was also described in the present study[20,24]. However, a study with Romanian patients described a protective effect (OR = 0.70; CI 95% = 0.49 – 0.99) related to mortality, possibly biased by the inclusion of patients with type 1 diabetes mellitus and unspecified diabetes mellitus[15]

Mortality in patients with COVID-19 was high when associated with metabolic comorbidities, such as hypertension, type 2 diabetes mellitus, and obesity. Metabolic syndrome is a complex disorder characterized by central fat deposition and insulin resistance[36]. In this context, a direct association seems to exist between the inflammatory process related to metabolic comorbidities and the immune system, leading to an impaired ability to combat infections and their complications. Prospective studies are needed to accurately determine the pathogenic mechanism, particularly in hypertensive, diabetic, and obese males, and in the development of severe COVID-19.

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CONSEQUENCES OF THE COVID-19 PANDEMIC ON ANXIETY AND DEPRESSION: A DESCRIPTIVE AND CROSS-SECTIONAL STUDY

CONSEQUÊNCIAS DA PANDEMIA DA COVID-19 NA ANSIEDADE E DEPRESSÃO: UM ESTUDO DESCRITIVO E TRANSVERSAL

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ABSTRACT

Objective: To describe the consequences of anxiety and depression caused by the coronavirus disease (COVID-19) pandemic in the general population. **Methods:** This descriptive, cross-sectional, and retrospective study used the database provided by a questionnaire applied via Google Forms® between September 2021 and February 2022. The study was disclosed on social media, and a quick-response code of the questionnaire was fixed in the environments of the Faculdade de Medicina de Olinda. The software STATA/SE 12.0 and Excel 2010 were used for data analysis. **Results:** A total of 357 participants were evaluated; most had depressive symptoms, such as sleep difficulties and irritability. Regarding anxiety symptoms, the most recurrent were sleep difficulties, difficulty concentrating, and fatigue. Anxiety and depression were correlated with the COVID-19 pandemic, which worsened the condition and functionality of the participants in daily activities. **Conclusion:** The COVID-19 pandemic impaired mental health, leading to a high prevalence and worsening of anxiety and depression symptoms in the general population during this period.

Keywords: anxiety; COVID-19; depression; mental health; pandemic.

RESUMO

Objetivo: Descrever as consequências na ansiedade e na depressão ocasionadas pela pandemia da COVID-19. **Métodos:** Estudo transversal, descritivo e retrospectivo, realizado por um questionário no banco de dados do Google Forms entre o período de setembro de 2021 a fevereiro de 2022. A divulgação da pesquisa foi por meio de redes sociais e QR code do questionário fixado nos ambientes da Faculdade de Medicina de Olinda. Foram utilizados os softwares STATA/SE 12.0 e o Excel 2010. **Resultados:** Foram avaliados 357 participantes, a partir dos 18 anos, que, na maioria, apresentavam sintomas depressivos, como “dificuldade para dormir” e “irritabilidade”. Quanto aos sintomas de ansiedade, a maior prevalência foi de “problemas de sono”, “dificuldade de concentração” e “fadiga’. Houve correlação da ansiedade e depressão com a pandemia da COVID-19, com impacto direto no agravamento de sua condição e na funcionalidade em atividades diárias. **Conclusão:** Esse estudo verificou que reflexos negativos na saúde mental estão associados à pandemia da COVID-19, identificando a predominância e piora de sintomas de ansiedade e depressão nos participantes durante o período pandêmico.

Palavras-chave: Saúde mental; COVID-19; Ansiedade; Pandemia; Depressão.

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the new severe acute respiratory syndrome coronavirus 2 (SARS--CoV-2) that impairs the nervous system; this disease was declared a pandemic by the World Health Organization in March 2020[1,2].

In 2020, mental and psychosocial health problems increased in the context of public health, with depression rates sevenfold higher in the general population. This incidence is directly related to the rapid increase in the number of

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COVID-19 deaths and the social distancing imposed by the government[1].

Psychological consequences may emerge as direct effects of the pandemic, not only in those with COVID-19 but also in the general population due to its high impact on mental health[3].

Therefore, this study aimed to estimate the consequences of the COVID-19 pandemic on the prevalence of depression and anxiety symptoms in the general population.

METHODS

This descriptive, cross-sectional, and retrospective study used data from an online questionnaire developed by the authors of this study (i.e., students of the Faculdade de Medicina de Olinda [FMO]), which was applied between September 8, 2021, and February 18, 2022. The questionnaire was created using Google Forms® and included questions about sociodemographic characteristics, changes in lifestyle, mood, health conditions, and access to health services during the COVID-19 pandemic.

The sample was obtained using a non-probabilistic method. Participants were invited via social media, and each researcher sent the questionnaire to 20 random individuals, ensuring stratification by gender, age group, and contact with SARS-CoV-2. Participants were asked to invite others from their social media, following a "virtual snowball" sampling method. Additionally, a quick-response code for the questionnaire was fixed in the environments of the FMO to increase disclosure.

The software STATA/SE 12.0 and Excel 2010 were used for data analysis. Data were calculated considering only valid responses (i.e., questions answered). The results are presented as tables and charts with their absolute and relative frequencies.

This study was approved by the research ethics committee of the FMO and the national research ethics commission (No. 48107821.6.0000.8033), affiliated with the National Health Council. The informed consent form was presented in Google Forms®. The participants proceeded with the questionnaire after being informed about the study and agreeing to answer it.

RESULTS

A total of 357 participants were included. Most were female, young adults, and adults; over half of the participants did not contract COVID-19; a quarter was diagnosed with COVID-19 and had mild symptoms; a small percentage was not diagnosed but had symptoms; and less than 1% were hospitalized because of the disease (Table 1).

Table 1. Sociodemographic data of participants

Variable	n	%
Age (years)		
18 to 29	181	50.7
30 to 39	99	27.7
40 to 59	62	17.4
60 or older	15	4.2
Gender		
Female	237	66.4
Male	117	32.8
Prefer not to say	3	0.8
Had COVID-19		
Yes, diagnosed by a doctor and had mild symptoms	94	26.3
Yes, I needed to be hospitalized	3	0.8
Think I had it, but I was not diagnosed by a doctor	50	14.0
No, I did not had COVID-19	210	58.9

n: number of participants; COVID-19: coronavirus disease.

Slightly more than half of the participants reported anxiety or depression or both, but most were not diagnosed by a doctor. Less than a quarter had the diagnosis for more than two years, and an even smaller number received a diagnosis recently (within the last two years) (Table 2).

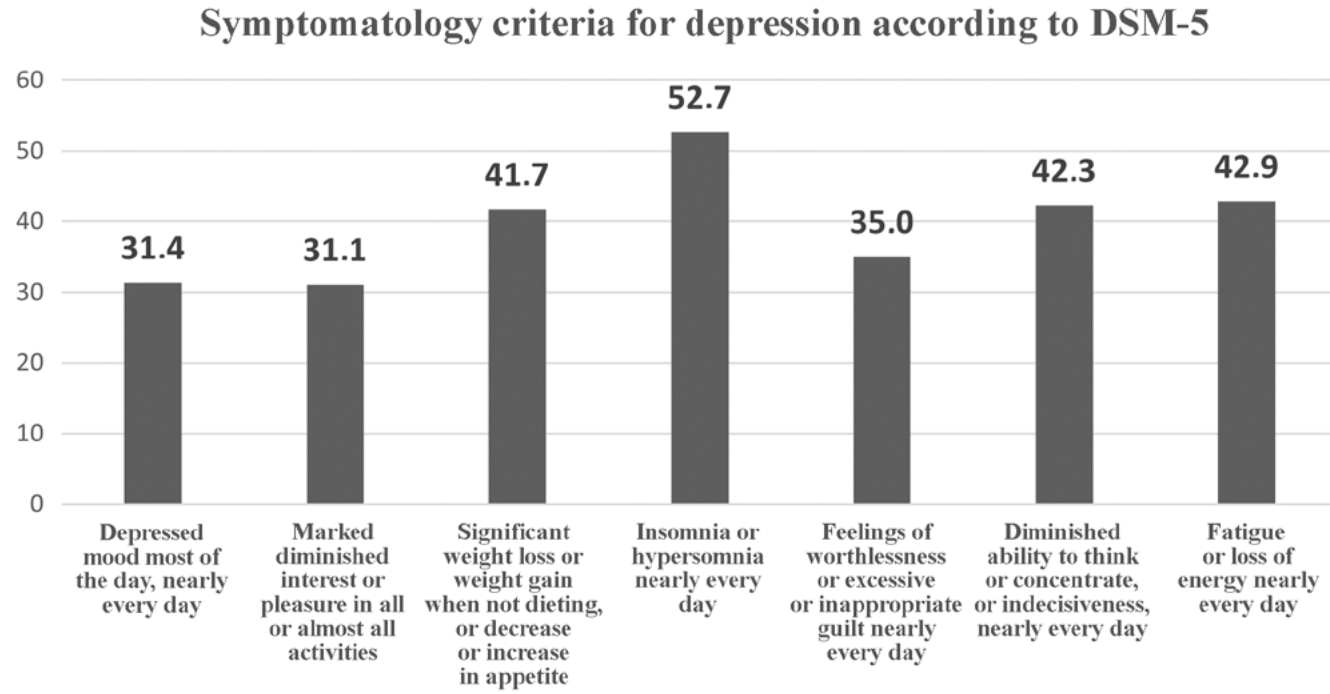
Table 2. Pre-existing mental diseases

Variable	n	%
Have anxiety or depression (or both)		
Yes	191	53.5
No	119	33.3
Unable to answer	47	13.2
Diagnosed with anxiety or depression (or both) by a doctor		
Yes, have a diagnosis (for more than two years)	75	21.0
Yes, have a recent diagnosis (in the last two years)	53	14.8
No, never diagnosed	229	64.2
The pandemic worsened your pre-existing anxiety or depression (or both)		
Yes	165	46.2
No	72	20.2
I do not have the diagnosis	120	33.6

n: number of participants.

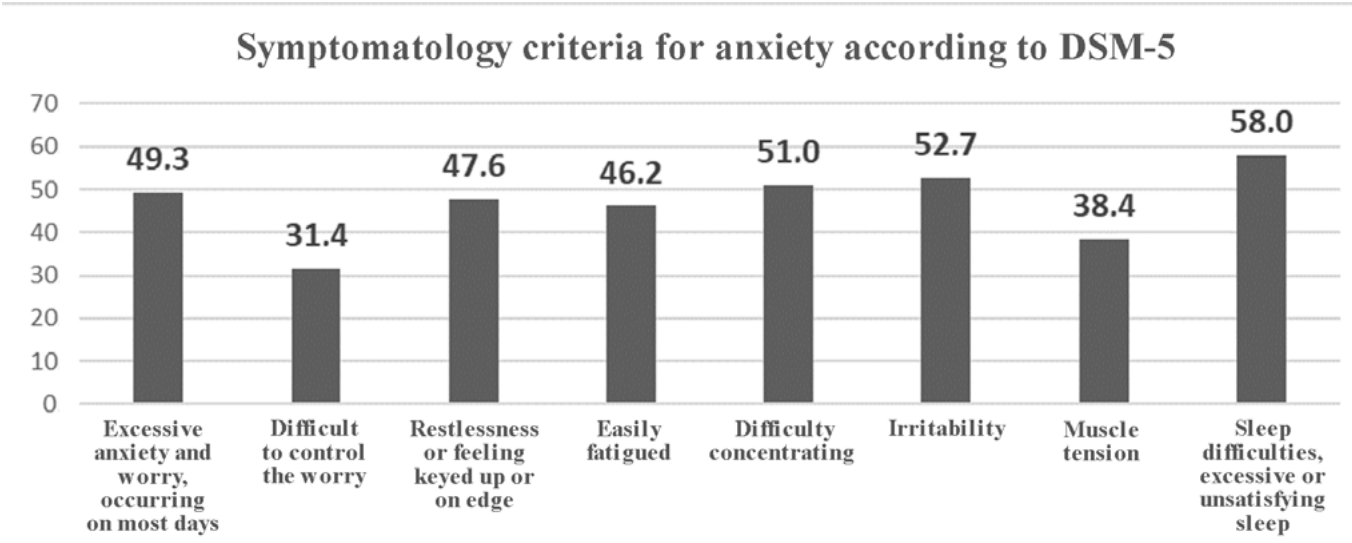
Diagnosed or not by doctors, almost half of the participants who reported a pre-existing condition indicated that the pandemic worsened their anxiety or depression (or both) (Table 2).

During the COVID-19 pandemic and social distancing, insomnia or hypersomnia nearly every day was the predominant depressive symptom from the Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5), followed by fatigue or loss of energy nearly every day (Figure 1).



DMS-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition)

According to the DSM-5 criteria, the most anxiety symptoms reported were sleep difficulties, excessive or unsatisfactory sleep, followed by irritability and difficulty concentrating (Figure 2).



DMS-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition).

Most participants felt that these behavioral changes impaired their daily activities. However, most did not seek professional support or follow social distancing properly, mostly because of the need to work or study. Sources of information more often used during the pandemic were newspapers and television, followed by the internet, family or friends, and radio (Table 3).

Table 3. Behaviors during the COVID-19 pandemic

Variable	n	%
The adopted behaviors are impairing your daily activities		
Yes	184	51,6
No	99	27,7
Maybe	74	20,7
Are you following social distancing guidelines		
Yes, I stayed isolated at home	111	31,1
No, I need to go out to work or study	216	60,5
I am not following social distancing	30	8,4
Professional support during the pandemic		
Yes, I had professional support	91	25,5
No, I cannot afford it	52	14,6
No, I did not seek professional support	214	59,9
Source of information		
Newspapers and television	279	78,2
Internet (WhatsApp, Facebook, Instagram)	235	65,8
Radio	69	19,3
Family or friends	148	41,5

n: number of participants.

DISCUSSION

The increased number of confirmed COVID-19 cases worldwide and deaths in March 2020 led the World Health Organization to implement restrictive measures, such as social distancing, lockdowns, and the mandatory use of masks to control the peak of virus transmission. These measures resulted in moderate or severe psychological impact of depressive and anxious symptoms in 53.8% of the participants, corroborating the results of a Chinese study with 1,210 participants from 194 cities in 20204.

Another 2020 study5 with 500 participants in Hong Kong used the Patient Health Questionnaire-9 (PHQ-9), a 9-item tool that evaluated major depressive disorder symptoms, and the Generalized Anxiety Disorder 7-item (GAD-7) questionnaire, which evaluated the main symptoms of generalized anxiety disorder according to the DSM-IV for suspected depressive and anxious conditions. The study indicated a prevalence of 19.0% for major depressive disorder symptoms and 14.0% for generalized anxiety disorder. Additionally, 25.4% reported that their mental health has worsened since the outbreak of the COVID-19 pandemic.

The situation of women during social distancing was also emphasized. Historically, women have been responsible for domestic activities and associated with lower-prestige occupations. This situation intensified during social distancing, which has overwhelmed women because of the increased domestic demands, resulting in a high probability of developing mental disorders[6, 7].

In this study, 66.4% of the participants were female, which suggests a greater concern among women regarding mental health and eventual symptoms6. However, this finding is insufficient to estimate if they were the most affected during the pandemic.

The predominant age group that responded to the questionnaire was 18 to 29 years old (50.7%). This finding can be justified by the interrruption of extracurricular actitivies performed by most participants from this age group, besides their greater access to rapid and sometimes false information via social media[8].

Although 58.9% of the participants reported that they had not been infected with COVID-19, 26.3% were diagnosed and had mild symptoms and 14.0% had symptoms but did not receive a diagnosis. These data reveal that depressive and anxious symptoms increased among participants, regardless of the COVID-19 diagnosis (Table 2 and Figures 1 and 2).

The most frequent symptoms presented in Tables 1 and 2 may result from the uncertainties of the pandemic, unemployment, risk of infection, and fear of death of family members and oneself6. Compared with the pre-pandemic period, the incidence of these symptoms significantly increased after the outbreak of the pandemic (Figures 1 and 2).

The COVID-19 pandemic was a key factor in the incidence and worsening of depressive and anxious symptoms due to subjective (e.g., the uncertainty and fear of death) and objective factors (e.g., the severity of symptoms and transmissibility of the virus)[9].

When analyzing the depressive and anxious behaviors, 51.6% of the participants experienced disruptions in their daily activities. Among the variables, social distancing caused routine changes. Despite this, 60.5% of participants did not follow social distancing guidelines as they needed to go out for work, including essential services, or study or both[10, 11].

Since mental health issues increased during the COVID-19 pandemic, participants were asked about professional support; 59.9% did not seek professional support, and only 25.5% received care. Participants with pre-existing mental diseases who required care tended to clinical worsening and had difficulties accessing psychotherapeutic services. Besides the closure of clinics[12], individuals had difficulties recognizing the need for help to treat and identify potential mental diseases. In addition, individuals were afraid of being diagnosed with depression or anxiety and socially labeled as mentally ill[13].

Many studies warned about the social harm of fake news during the COVID-19 pandemic. In this study, 78.2% of the participants relied on newspapers and television as sources of information, and 65.8% used the internet. The abundance of fake news hinders access to legitimate, trustworthy sources11. Therefore, the

internet, as a means of information with a wide circulation of news, sometimes false, affects reliable sources. This excess of information can be a precipitating factor for anxiety[15].

CONCLUSION

COVID-19 is an infectious disease that has caused significant harm to mental health. This study evaluated the consequences of the COVID-19 pandemic on depression and anxiety symptoms in the general population and identified that the psychological reflexes were associated with the pandemic due to stressors factors, such as social distancing, lack of psychotherapy support, and fake news exposure. Moreover, the occurrence and severity of depression and anxiety increased during this period. Given the psychosocial damages evidenced during the pandemic, public health measures focused on mental health (i.e., combating psychophobia) are needed to ensure access to psychosocial care network and support of individuals in psychological distress by qualified professionals. Restraints the dissemination of fake news are also a measure of mental health promotion.

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TRANSVERSE SINUS DRAINAGE DOMINANCE PATTERNS: MORPHOLOGICAL STUDY IN CEREBRAL ANGIOGRAPHY EXAMS

Padrões de dominância de drenagem do seio transverso: estudo morfológico em exames de angiografia cerebral

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ABSTRACT

Objective: To investigate the pattern of dural sinus drainage dominance based on the anatomical variations of the transverse sinus (TS) observed in digital cerebral angiography exams. **Methods:** This cross-sectional retrospective study with non-probabilistic convenience sampling analyzed 83 exams of 2D digital brain angiography. **Results:** The percentages of dominance patterns of TS in males were 32.43% (n = 15), 8.11% (n = 3), and 59.46% (n = 22) for the right, left, and symmetric, respectively. In females, the percentages of dominance patterns were 32.61% (n = 15), 6.52% (n = 3), and 60.87% (n = 28) for right, left, and symmetric, respectively. Considering all individuals, the symmetrical dominance presented the highest percentage (about 60.24%). **Conclusion:** The most prevalent TS drainage pattern identified was symmetrical, regardless of gender. When dominance was identified, the right pattern was the most prevalent. The most prevalent variation was left transverse sinus hypoplasia. Rare variations (e.g., TS agenesis) were also found. No differences were identified between genders.

Keywords: Anatomic variation, cerebral angiography, surgery, transverse sinuses

RESUMO

Objetivo: Investigar o padrão de dominância de drenagem sinusal dural por meio da ocorrência de variações anatômicas do seio transverso (ST) em exames de angiografias digitais cerebrais. **Métodos:** Trata-se de um estudo do tipo transversal, observacional e retrospectivo, com amostragem do tipo não probabilístico por conveniência, realizado por meio da análise de 83 exames de angiografia digitais cerebrais em 2D. **Resultados:** No sexo masculino, o padrão de dominância do ST direito foi encontrado em 32,43% dos casos; já do ST esquerdo, em 8,11%; e o padrão simétrico, em 59,46%. No sexo feminino, os percentuais foram de 32,61%, 6,52 e 60,87 para os padrões de dominância direito, esquerdo e simétrico do ST, respectivamente. Para todos os indivíduos, o maior percentual foi o de padrão simétrico do ST: cerca de 60,24%. **Conclusões:** O padrão simétrico de drenagem do ST foi o de maior ocorrência, independentemente do sexo do indivíduo. Quando uma dominância foi identificada, o padrão direito foi o mais prevalente. A hipoplasia do ST esquerdo foi a variação mais recorrente. Foram encontradas variações raras, como a agenesia do ST. Não foram identificadas diferenças entre os sexos.

Palavras-chave: Angiografia cerebral, Cirurgia, Seios transversos, Variação anatômica.

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INTRODUCTION

The dural sinuses are venous channels covered by endothelium located between the inner and outer layers that compose the dura mater; the former continues with the spinal dura mater, and the latter adheres closely to the skull bones, behaving as a periosteum[1].

The blood from the superficial and deep cerebral veins, meninges, and calvarium is drained into the dural sinuses and conducted to the internal jugular veins, forming the main drainage route of the cranial cavity[2].

Understanding the anatomy of the cranial venous sinuses is crucial in the field of neurosurgery and radiology, especially in surgical planning and treatment of neurological diseases to prevent complications[3,4,5,6,7,8,9].

The dominance of cerebral venous drainage needs to be analyzed before surgeries for several neurosurgical diseases, as well as for cervical surgeries5. Therefore, the analysis of venous sinuses by angiography is generally indicated as the best preoperative assessment for diseases involving the major sinuses[10].

In this perspective, the present study aimed to investigate the pattern of cerebral drainage dominance based on anatomical variations of the transverse sinus (TS) observed in digital cerebral angiography exams.

METHOD

This cross-sectional retrospective study was conducted between June and August 2022 using non-probabilistic convenience sampling.

The study was conducted at the Faculdade de Medicina de Olinda by analyzing 83 digital 2D cerebral angiography exams of individuals of both genders, aged between 11 and 90 years, hospitalized in a private hospital in Recife. All exams were performed with a similar standard by the same radiology team and analyzed by the chief radiologist of the team.

As inclusion criteria, the examinations should have incidences in profile, oblique, and posteroanterior and present a clear visualization of cerebral venous anatomy. Those that did not have the three incidences analyzed, or procedures that avoided the visualization of vascular venous anatomy were excluded. Initially, cerebral digital angiographies were selected.

Then, the RadiAnt DICOM Viewer (Medixant, Poznan, Poland) was used to analyze the angioarchitecture of the deep cerebral venous system in a paired manner by the researchers. The study variables were (1) sinus diameter; (2) presence of hypoplasia; (3) laterality; (4) age; (5) gender; (6) presence of anatomical variation; and (7) presence of associated diseases.

The measurement of the TS was acquired in pixels and converted to millimeters and was obtained by averaging the distance between the edges on both sides.

The sinus could be classified as dominant (i.e., when its measurement was > 50% compared with its contralateral side), symmetrical (i.e., when the difference in measurement was < 50% compared with the contralateral side), or absent (i.e., when no drainage or increase compared with the contralateral was observed).

Data were organized into spreadsheets, tabulated, and processed by the PASW STATISTICS (IBM Corp, NY, USA) 17.0 software. Data analysis was conducted descriptively; qualitative variables were described in absolute and relative values, and their association was verified using contingency tables and Fisher's exact test. The established confidence interval was 95%.

This study was approved by the research ethics committee of the Faculdade de Medicina de Olinda (no. 43998421.0.0000.8033).

RESULTS

The mean age of the individuals was 55.28 years (range: 11 to 90 years and standard deviation [SD] = 17.36). The mean age was 54.11 years for males (range: 11 to 89 years and SD = 20.16) and 56.22 years for females (range: 19 to 90 years and SD = 14.89). The distribution by gender was 55.42% female (n = 46) and 44.58% male (n = 37). Findings regarding the dominance of TS considering gender are shown in Table 1.

A prevalence of right TS dominance was evidenced in both genders compared with the left side. The percentages of dominance patterns of TS in males were 32.43% (n = 15), 8.11% (n = 3), and 59.46% (n = 22) for the right, left, and

symmetric, respectively. In females, the percentages of dominance patterns were 32.61% (n = 15), 6.52% (n = 3), and 60.87% (n = 28) for right, left, and symmetric, respectively.

Considering all individuals, the percentages of TS were 32.53% (n = 27), 7.20% (n = 6), and 60.24% (n = 50) for the right, left, and symmetrical dominance patterns, respectively (Table 2).

This data pattern suggests three interesting aspects: (1) considering all individuals, the symmetrical drainage pattern of the TS is more prevalent than the right and left drainage patterns; (2) the right drainage pattern of the TS is more prevalent than the left drainage pattern; and (3) the symmetrical, right and left drainage patterns of the TS are similar between genders. Thus, Fisher's exact test was used to verify these aspects, which revealed that the prevalence of the symmetrical pattern was higher than in the right and left patterns in all individuals (p = 0.003). The right pattern was not more prevalent than the left dominance patterns (p = 0.086), and the drainage patterns (left and right) were not similar between genders (p = 0.830) (Tables 1 and 2).

Additional findings

Left TS hypoplasia appeared in 24.32% (n = 9) of males and 26.09% (n = 12) of females. Left TS agenesis was observed in 8.11% (n = 3) of males and 6.52% (n = 3) of females. On the other hand, right TS hypoplasia was perceived in 5.41% (n = 2) of males and 6.52% (n = 3) of females. Right TS agenesis was found in 2.7% (n = 1) of cases but only in males.

Individuals with morphological changes in the left TS had a mean age of 57.92 years (median = 58.00) in males and 56.87 years (median = 55.00) in females. The mean age of individuals with morphological changes in the right TS was 73.67 years (median = 81.00) for males and 48.33 years (median = 54.00) for females. Last, the mean age of individuals who presented a pattern of symmetric sinus dominance was 49.36 years (median = 48.50) for males and 56.71 years (median = 56.00) for females.

DISCUSSION

Devoid of muscle tissue, the venous sinuses of the dura mater drain the blood and cerebrospinal fluid circulating through the brain toward the internal jugular veins. The TS originates at the confluence of the sinuses and is located in the posterior portion of the skull, typically as bilateral structures. They curve anteriorly and laterally from the internal occipital protuberance, running along the edges of the tentorium cerebelli to the petrous part of the temporal bone, where they receive blood from several areas of the brain, such as the temporolateral surface, basal surface, and temporal and occipital lobes to be drained into the sigmoid sinus[2,11-14]. The TS also receives blood from the anastomotic vein of Labbé, when present, and communicates with extracranial veins via mastoid emissary veins[2,15]. Some TS parts (or a complete side) may be absent or present isolated hypoplasia, and this sinus can also be distinguished from sinus occlusion by the absence of collateral vein dilation and associated parenchymal hemorrhage[2].

The present alterations of the TS were considered anatomical variations to avoid confusion with pathological changes and to highlight the relevance of the analytical, evaluative, and observational nature of this study[11].

The cerebral venous system has a complex anatomy that may present several anatomical variations, and the TS may be subjected to some of them. Therefore, understanding these variations is important during surgeries[16]. During the embryological period, many procedures can occur due to this structure being predisposed to developing variations[17].

As the telencephalon grows, the confluence of sinuses shifts to a more inferior craniocaudal position. This process seems to be related to a tilt of the lateral portions of the TS, which become less prominent. During embryological development, the region of the confluence of sinuses increases and reduces the caliber of its structures, which may result in hypoplasias, irregularities, absences, and asymmetries of structures in this region, especially the TS[17].

The age group seems to influence some TS variations. Studies indicated a higher prevalence of TS hypoplasia in the age group above 60 years and a lower prevalence around the third decade of life[13].

Some studies demonstrate a higher prevalence of hypoplasia of the TS in males than females. Literature also suggests that females may present a higher prevalence of symmetry of these vessels[18]. Conversely, the present study did not identify a significant relationship between gender and the prevalence of TS hypoplasia. The TS symmetry was the most prevalent finding in both genders. Therefore, most individuals did not present significant morphological alterations. This finding may derive from morphological characteristics of the studied population or the sample size, which may have induced statistical tendencies, justifying the need for further observational studies.

CONCLUSION

The understanding of the morphofunctional findings, including the pattern of dominance of dural drainage and the anatomical variations found in this study, is important for clinical and surgical practice, such as in the diagnosis and treatment of pathologies of the cerebral venous sinuses and neurovascular surgeries.

Although variations in the normality of the dural sinuses are common, anomalies of these structures are rare, which raises a warning since most are associated with complex vascular malformations or congenital brain malformations.

The most common drainage pattern of the TS in the studied population was symmetric, regardless of gender. When dominance was identified, the right pattern was the most prevalent. Left TS hypoplasia was the most recurrent variation, and rare variations (e.g., agenesis) were found. No differences between genders were identified.

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Table 1. Dominance of the transverse sinus according to gender.

Gender x TS Dominance	Right		Left		Symmetrical or without dominance		Total	
	N	%	N	%	N	%	N	%
Male	12**	32.43	3**	8.11	22**	59.46	37	100
Female	15**	32.61	3**	6.52	28**	60.87	46	100
Total	27	32.53	6	7.23	50	60.24	83	100

N: number of individuals. TS: transverse sinus. %: percentage. Significant values ($p < 0.05$) – Fisher's exact test.

**No statistical significance was observed in the relationship between sex and TS dominance ($p = 0.830$).

Table 2. TS Dominance.

TS Dominance	Right		Left		Symmetrical or without dominance		Total	
	N	%	N	%	N	%	N	%
Total	27**	32.53	6**	7.23	50*	60.24	83	100

N: number of individuals. TS: transverse sinus. %: percentage. Significant values ($p < 0.05$) – Fisher's exact test

*No statistical significance was observed between the symmetrical drainage pattern when compared with the right and left patterns ($p = 0.003$).

** No statistical significance was observed between right and left dominance drainage patterns of the TS ($p = 0.086$).

MORPHOLOGICAL AND MORPHOMETRIC OF THE THYROID FORAMEN OF THE LARYNX AND ITS CLINICAL-SURGICAL IMPLICATIONS

MORFOLOGIA E MORFOMETRIA DO FORAME TIREOIDIANO DA LARINGE E SUAS IMPLICAÇÕES CLÍNICO-CIRÚRGICAS

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ABSTRACT

Introduction: The thyroid foramen is an opening in the posterior portion of the cartilage. Knowledge about the vascular and nervous structures and possible anatomical variations (e.g., the thyroid foramen) of the neck region is important for the success of surgeries. From this perspective, the present study aimed to investigate the incidence, morphometry, and morphology of the thyroid foramen of the thyroid cartilage in cadaveric human larynges, and discuss its clinical-surgical implications. **Methods:** A total of 100 human larynges were selected from the collection of cadaveric parts of the Department of Anatomy at the Federal University of Pernambuco, which allowed the visualization of the cartilaginous skeleton of the larynx, especially the thyroid cartilage. **Results:** Of the 100 selected larynges, 2 presented the thyroid foramen, indicating an incidence of 2%. Conclusion: The thyroid foramen had an incidence of 2%, a circular format, and measured 7.00 mm in the laryngeal cartilage with unilateral presentation and 0.45 mm (left) and 0.50 mm (right) in the bilateral presentation. The present study provided important morphological and morphometric data on this anatomical variation, which should be addressed during surgeries in the neck region.

Keywords: Morphology, morphometry, thyroid foramen.

RESUMO

Introdução: O forame tireoidiano é uma variação anatômica caracterizada por uma abertura na porção póstero-superior da lâmina da cartilagem tireoide da laringe. Ter conhecimento anatômico sobre as estruturas vasculares e nervosas da região do pescoço e saber da existência de variações anatômicas, tais como o forame tireoidiano, são de vital importância para o sucesso cirúrgico. Nessa perspectiva, o presente estudo teve como objetivo investigar a incidência, a morfometria e a morfologia do forame tireoidiano da cartilagem tireoide em laringes humanas cadavéricas e discutir as relações cirúrgicas e clínicas decorrentes dessa variação anatômica. **Método:** Foram selecionadas 100 laringes humanas do acervo de peças cadavéricas do Departamento de Anatomia da Universidade Federal de Pernambuco que permitissem a visualização do esqueleto cartilaginoso da laringe, em especial, da cartilagem tireoide da laringe. Resultados: Das 100 laringes, 2 apresentaram o forame tireoidiano, configurando uma incidência de 2%. **Conclusão:** O estudo embasou a importância do conhecimento anatômico sobre o forame tireoidiano. Observou-se uma incidência de 2% desse forame. Ele era circular, medindo 7 mm na cartilagem laríngea com apresentação unilateral e 0,45 mm e 0,5 mm no lado esquerdo e direito, respectivamente, na apresentação bilateral. Ademais, este estudo apontou importantes dados morfológicos e morfométricos dessa variação anatômica, que não deve ser negligenciada no momento de procedimentos na região do pescoço.

Palavras chaves: Forame tireoidiano, Morfometria, Morfologia.

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RESUMO

Introdução: O forame tireoidiano é uma variação anatômica caracterizada por uma abertura na porção póstero-superior da lâmina da cartilagem tireoide da laringe. Ter conhecimento anatômico sobre as estruturas vasculares e nervosas da região do pescoço e saber da existência de variações anatômicas, tais como o forame tireoidiano, são de vital importância para o sucesso cirúrgico. Nessa perspectiva, o presente estudo teve como objetivo investigar a incidência, a morfometria e a morfologia do forame tireoidiano da cartilagem tireoide em laringes humanas cadavéricas e discutir as relações cirúrgicas e clínicas decorrentes dessa variação anatômica. **Método:** Foram selecionadas 100 laringes humanas do acervo de peças cadavéricas do Departamento de Anatomia da Universidade Federal de Pernambuco que permitissem a visualização do esqueleto cartilaginoso da laringe, em especial, da cartilagem tireoide da laringe. Resultados: Das 100 laringes, 2 apresentaram o forame tireoidiano, configurando uma incidência de 2%. **Conclusão:** O estudo embasou a importância do conhecimento anatômico sobre o forame tireoidiano. Observou-se uma incidência de 2% desse forame. Ele era circular, medindo 7 mm na cartilagem laríngea com apresentação unilateral e 0,45 mm e 0,5 mm no lado esquerdo e direito, respectivamente, na apresentação bilateral. Ademais, este estudo apontou importantes dados morfológicos e morfométricos dessa variação anatômica, que não deve ser negligenciada no momento de procedimentos na região do pescoço.

Palavras chaves: Forame tireoidiano, Morfometria, Morfologia.

INTRODUCTION

The thyroid foramen is an anatomical variation characterized by an opening in the posterior-superior portion of the thyroid cartilage lamina. This foramen is commonly circular and may contain nerves, vessels, neurovascular bundles, and connective tissue. Among these structures, the most important are the internal branch of the superior laryngeal nerve (SLN) and the superior laryngeal arteries and veins[1,2].

The SLN is a branch of the vagus nerve (X cranial nerve) that emerges from the jugular foramen at the base of the skull and descends near the horn of the hyoid bone, dividing into the internal (or superior) and the external (or inferior) branches; the former enters the larynx after piercing the thyroid membrane and is related to the sensory innervation of the supraglottic portion. This topography can anastomose with the branches of the recurrent laryngeal nerve to form Galen's anastomosis. The external or inferior branch runs over the inferior constrictor muscle of the pharynx or pierces it with a craniocaudal and oblique trajectory until it innervates the cricothyroid muscle. This branch has a motor function and maintains the tension of the vocal folds. Anastomoses with the recurrent laryngeal nerve also exert a motor function in the thyroarytenoid and interarytenoid muscles[3].

The superior laryngeal artery is the main vessel distributed in the larynx, originating from the superior thyroid artery in most cases. This artery follows the internal branch of the SLN to irrigate the larynx. Knowing the morphology of this vessel, as well as its anatomical relationships and variations in its course, is important in surgeries, such as laryngectomy and partial laryngeal reconstructions[4,5].

The anatomical knowledge of the vascular and nervous structures in the neck region and its anatomical variations, including the thyroid foramen, is important for the success of surgeries. In addition, physicians and specialists (e.g., otolaryngologists, neurosurgeons, and head and neck surgeons) need to be aware of the existence and importance of this foramen[1,2].

Thus, the present study aimed to investigate the incidence, morphometry, and morphology of the thyroid foramen on the thyroid cartilage in human cadaveric larynges and discuss its surgical-clinical implications.

METHOD

This study was conducted at the Department of Anatomy of the Federal University of Pernambuco. A total of 100 human larynges were selected from the collection of cadaveric parts.

Dissected human larynges were analyzed to allow the visualization of their cartilaginous skeleton, particularly the thyroid cartilage. In some

cadaveric parts, the blocks of viscera from the cervical region (larynx-pharynx-trachea-esophagus) needed to be dissected: the sternohyoid, omohyoid, sternothyroid, and thyroid muscles were separated and removed from the larynx. After this procedure, the specimens were ready to be included in the study.

The blocks of viscera of the cervical region were not included; they were only superficially dissected without the possibility of further dissection. Therefore, the laryngeal skeleton or dissected larynges in axial, coronal, and sagittal planes (hemilarynx) were not visualized. Dissections in the sagittal plane were maintained if they occurred in the posterior region. The cadaveric parts were fixed in 10% formalin.

The study was divided into three stages: (1) screening and selection of human laryngeal specimens; (2) investigation of the presence of the thyroid foramen in the selected larynges; and (3) morphological description of the thyroid foramen. After the screening, 100 larynges were included in the study.

RESULTS

Of the 100 selected larynges, 2 presented the thyroid foramen (Figures 1 and 2), corresponding to an incidence of 2%. Regarding its location and laterality, one larynx presented the thyroid foramen in the posterior-superior portion of the thyroid cartilage lamina unilaterally (right side), and the other presented the thyroid foramen on the same portion but on both sides symmetrically. The thyroid foramen interrupted the oblique line in both cases and was located near the superior tubercle of the thyroid cartilage of the larynx.

The thyroid foramen was circular in both larynges, and measured 7.00 mm in the unilateral presentation and 0.45 mm (left) and 0.50 mm (right) in the bilateral presentation. The content passing through or occupying the thyroid foramen could not be determined because the larynges were already dissected.

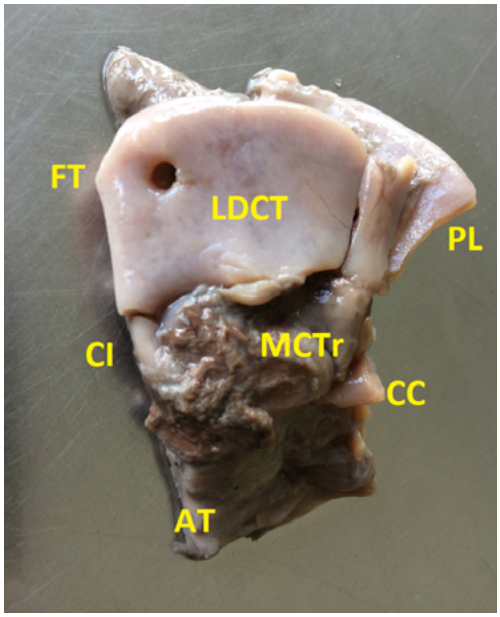

Figure 1. Unilateral thyroid foramen. LP: laryngeal prominence. RLTC: right lamina of the thyroid cartilage. TF: thyroid foramen. CTM: cricotracheal membrane, CC: cricoid cartilage. TR: tracheal rings. IH: inferior horn.

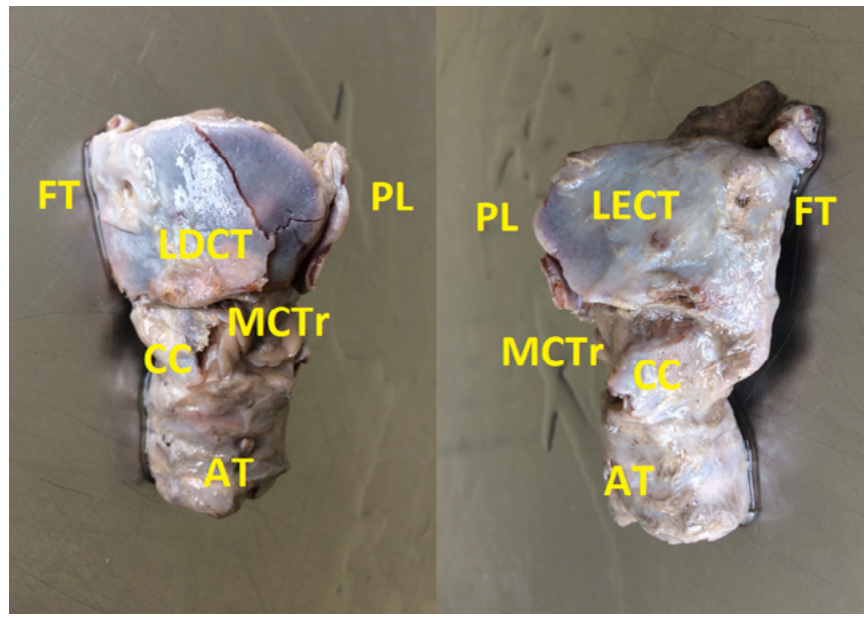

Figure 2. Bilateral thyroid foramen. A: Right lateral view. B: Left lateral view. LP: laryngeal prominence. RLTC: right lamina of the thyroid cartilage. LLTC: left lamina of the thyroid cartilage. CTM: cricotracheal membrane. CC: cricoid cartilage. TR: tracheal rings. TF: thyroid foramen.

DISCUSSION

The thyroid foramen, characterized by an opening in the postero-superior region of the thyroid cartilage lamina, was first described by Segond in 1847. Its incidence is controversial since it varies according to ethnic study. Yalçın et al. (2018) reported clinical and anatomical relevance of the thyroid foramen; the authors found an occurrence of 2% to 57% in adults. They also observed a relative prevalence of the unilateral presentation of the thyroid foramen compared with the bilateral presentation[2], which was not observed in the present study.

The development of the thyroid cartilage lamina begins around the first trimester of gestation and is characterized by the presence of quadrilateral plates and a foramen; the latter closes during the later stages of fetal development in most cases. The literature proposed two theories to explain the embryological origin of this anatomical variation: the first suggests that a disruption in the union of cartilaginous tissue between the fourth and sixth pharyngeal arches may leave this foramen open. The second proposes that the presence of neurovascular content interferes with the proper chondrification of the thyroid lamina, causing the variation[1,2,6].

The thyroid foramen can be circular, oval, crescent-shaped, or, rarely, irregularly shaped. The dimensions vary according to the study, with diameters ranging from 0.50 to 9.00 mm in men and from 0.45 to 6.50 mm in women7. In the present study, the gender could not be analyzed because the larynges were already dissected, limiting its determination. The area occupied by the foramen is proportional to the caliber of the elements that pass through it and varies from 3.2 mm^2 (when nerves pass through the foramen) to 13.8 mm2 (when neurovascular arrangements pass through the foramen)[1].

The thyroid foramen may be filled with neural, vascular, neurovascular, or connective tissue, and these contents must be known to better understand the possible clinical-surgical implications[1].

In the vascular group, the possible structures are (1) isolated superior laryngeal artery; (2) superior laryngeal artery and vein; and (3) anastomosis between a branch of the superior laryngeal artery and cricothyroid vessels. In the neural group, the possibilities are (1) external branch of the SLN; (2) external branch along with an internal branch of the SLN, externally or internally to the larynx; and (3) double neural anastomosis between the external and internal branches of the SLN (proximal loop) and external branch of the SLN and inferior laryngeal nerve (distal loop). In the neurovascular group, the possible structures are (1) superior laryngeal artery and anastomosis between the internal and external branches of the superior laryngeal nerve; and (2) similar to type 1 but nonspecific vessels passing by the foramen. Last, the thyroid foramen may be only filled with connective tissue[1,6,8].

The superior laryngeal artery irrigates the larynx and anastomoses with the inferior laryngeal artery, being one of the crucial vessels in laryngeal irrigation. In most cases, the superior laryngeal artery arises from the superior thyroid artery. These vessels are usually identified by piercing the thyroid membrane; however, they can pass anomalously by the thyroid foramen. Rusu et al., in their morphological study of 50 adult human larynges, identified that the superior laryngeal artery originated from the superior thyroid artery in 68% of cases, while the remaining 32% arose directly from the external carotid artery[4,9].

Devadas et al. reported the importance of anatomical knowledge regarding variations related to the superior laryngeal artery in partial laryngectomy, laryngeal reconstruction surgeries, and transplants. This knowledge can also assist in radical dissections in the neck region, reducing postoperative complications[9].

The external branch of the SLN is responsible for the motor innervation of the cricothyroid muscle and is closely related to the superior thyroid artery. This branch is located at a varied distance from the superior pole of the thyroid gland: 60% pass more than 1 cm above the superior pole, 17% pass less than 1 cm above this pole, and 20% pass below the described plane; the latter presents the highest inherent risk of iatrogenic injury10. The recommended steps to maximize the identification and preservation of the SLN are the sectioning of the sternothyroid muscle, with careful dissection of the cricothyroid space and caudal retraction of the

superior pole of the gland to expose the superior thyroid vessels. Then, controlled retraction of the vascular pedicle to expose the SLN (external branch), which will be found on the surface of the cricothyroid muscle. If identification is not possible, the vessels of the superior pedicle should be individually ligated to prevent injury[11]. The literature described the iatrogenic injury to the SLN after thyroidectomy, with incidence ranging from 0% to 58%[12].

Dekhou et al. reported clinical repercussions of injury to the SLN, such as loss of the ability to elevate vocal frequency due to loss of motor innervation of the cricothyroid muscle and increased risk of aspiration due to loss of the laryngeal cough reflex. The risk of nerve damage in surgeries derives, among other reasons, from its proximity to arteries, such as the superior thyroid artery[13].

CONCLUSION

The anatomical knowledge about the thyroid foramen is important since the structures that may be contained within it should be preserved in different surgeries. The thyroid foramen was circular in both larynges, and measured 7.00 mm in the unilateral presentation and 0.45 mm (left) and 0.50 mm (right) in the bilateral presentation.. The data are similar to those of previous studies but differ depending on the location of the study. This study also provided important morphological and morphometric data on this anatomical variation, which should be addressed in surgeries involving the laryngeal cartilage and structures directly related to it.

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PATENT FORAMEN OVALE: CURRENT CONCEPTS ON THE MAIN THERAPEUTIC METHODS

FORAME OVAL PATENTE: CONCEITOS ATUAIS SOBRE OS PRINCIPAIS MÉTODOS TERAPÊUTICOS

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ABSTRACT

The foramen ovale is a structure present in the fetal period that allows a contour of the non-functional pulmonary circulation of this period. This foramen remains in about 20% to 25% of the population, and it is renamed as patent foramen ovale, which can have clinical repercussions. This study reported a case of patent foramen ovale and discussed the main updates for managing patients with this condition. In recent years, renowned institutions have reviewed evidence from studies to define the principles needed in the decision-making and management of these patients. Interdisciplinarity in decision-making aiming for proper management is crucial, and individual risk must consider the clinical, anatomical, and imaging characteristics of the patient.

Keywords: Anatomy; atrioventricular communication; fetal heart; foramen ovale.

RESUMO

O forame oval é uma estrutura presente no período fetal que permite um contorno da circulação pulmonar não funcionante desse período. Em cerca de 20% a 25% da população, esse forame permanece, sendo chamado de forame oval patente, e pode trazer repercussões clínicas. O presente estudo visa relatar um caso de forame oval patente e discorrer sobre as principais atualizações no manejo de pacientes portadores dessa condição. Nos últimos anos, renomadas instituições revisaram evidências de estudos a fim de definir os princípios que devem ser seguidos na tomada de decisão e do manejo desses pacientes. A interdisciplinaridade na tomada de decisão visando o manejo adequado é incontestável, e o risco individual deve levar em conta fatores como características clínicas, anatômicas e de imagem do paciente.

Palavras-chave: Anatomia; Comunicação atrioventricular; Coração fetal; Forame oval.

INTRODUCTION

The foramen ovale is a normal interatrial communication of the fetal circulatory system, present in the interatrial septum and formed by the fusion of the primum and secundum septa, which allows a contour of the non-functional pulmonary circulation in the fetal period[1,2]. In about 75% of the population, this foramen closes after birth due to increased blood flow to the lungs and elevation of pressures on the left side of the heart3. However, the foramen ovale remains beyond early childhood in 20% to 25% of the population, which may have clinical repercussions; when this occurs, it is named patent foramen ovale (PFO).

A hypothesis states that strokes are associated with PFO since they involve the passage of paradoxical emboli by this foramen. The mean diameter of the PFO (4.9 mm) allows the passage of emboli large enough to occlude the middle cerebral artery (3 mm) and the main cortical branches (1 mm). Paradoxical emboli are clots or embolic particles that originate in the venous circulation and pass into the arterial circulation via a right-to-left shunt. Apparently, its size increases with age, and its incidence decreases at older ages[2,5].

In some affected patients, PFO is often asymptomatic and may be responsible for blood clot-related disorders. Among the several associa-

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ted conditions, congenital heart disease, stroke, transient ischemic attacks, migraine, and obstructive sleep apnea can be highlighted. Many patients with PFO are asymptomatic and are only considered for diagnosis after cryptogenic stroke or transient ischemic attack[6,7]. About 40% to 50% of patients who had a cryptogenic stroke, which does not have a well-defined etiology, had PFO. Thus, these conditions may be associated. Moreover, the presence of PFO, along with atrial septal aneurysms, is a significant predictor of the recurrence of stroke[3,4].

PFO diagnosis must be considered in patients with dyspnea and low arterial saturations without other known causes, young patients with cryptogenic stroke, transient ischemic attacks, or associated congenital heart diseases. In these cases, the test used to detect right-left shunts and the PFO are transthoracic echocardiography or transesophageal echocardiography[6,7]. Although the study of microbubbles with transesophageal echocardiography imaging is the gold standard, the semi-invasive nature limits its widespread use. Other resources that can be adopted are transcranial Doppler and transthoracic echocardiography[4].

From this perspective, this study aimed to report a case of PFO and discuss the main updates for managing patients who have this condition.

CASE REPORT

The present study was conducted at the Department of Anatomy of the Federal University of Pernambuco. During the dissection of the digestive system in the department, the presence of PFO was noted in one of the systems.

Initially, the thoracoabdominal region of a cadaver fixed in 10% formalin was opened. For the dissection of the heart and great vessels, the pericardial cavity was opened with a cruciform incision, rebutting the four flaps. Then, the inferior vena cava and the pulmonary vena cava were sectioned at the level of their entry into the pericardium, the pulmonary trunk, 2 cm above the valve, and then the superior vena cava when penetrating the pericardium. Last, the aorta was sectioned 5 cm above its valve, and the heart was removed.

With a dermographic pencil, incision lines were drawn on the outer surface of the heart. The first line started from the superior to the inferior vena cava, passing parallel and anteriorly to the terminal groove of the right atrium. The second line started in the aorta artery and went towards the coronary sulcus, close to the origin of the posterior interventricular artery, passing equidistantly between the pulmonary veins.

Then, a section was performed along the lines drawn, opening the right and left atria of the heart. In the right atrium, the terminal crest, the absence of the inferior vena cava valve, and the coronary sinus valve were identified. The foramina of the minimal cardiac veins, the interatrial septum, the oval fossa, the limbus of the oval fossa, and the PFO were observed. In the left atrium, in the interatrial septum, PFO was detected in the oval fossa.

For morphometry, a digital caliper was used to measure the diameters of the PFO, which presented a maximum potential diameter of 5 mm.

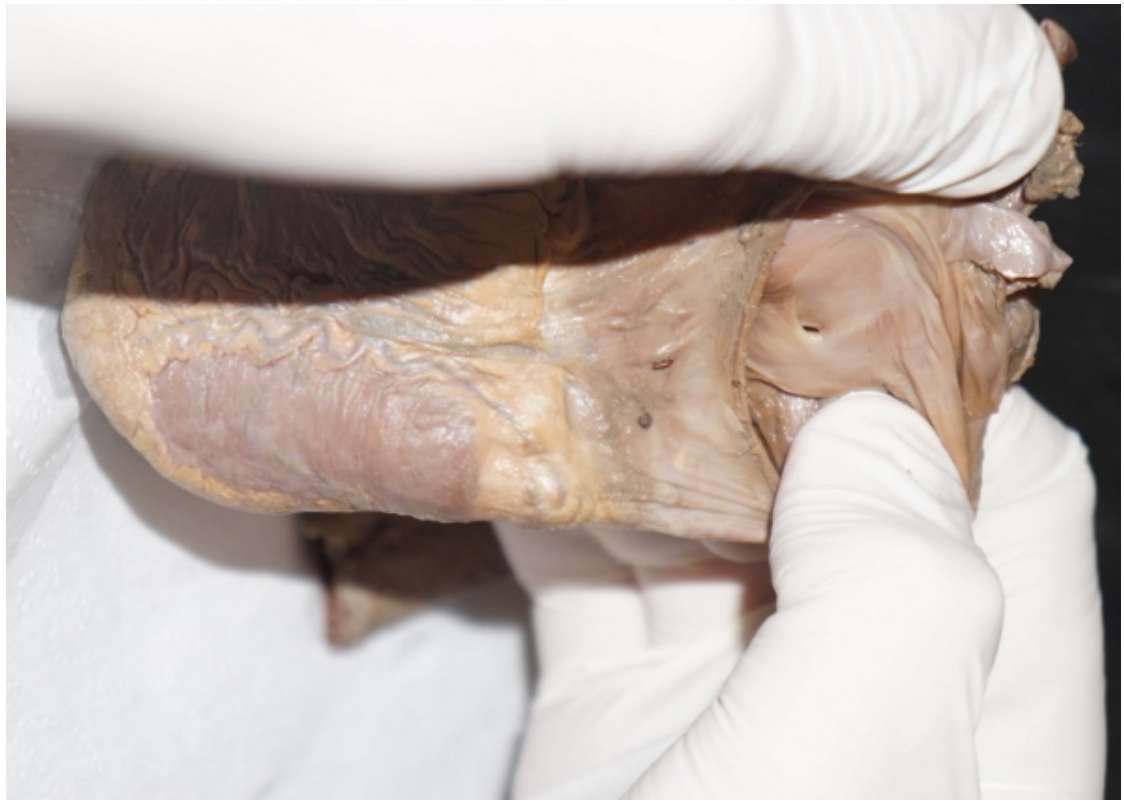

Figure 1. Left atrium open. Interatrial septum with presence of patent foramen ovale in the oval fossa.

DISCUSSION

The presence of PFO is associated with some clinical conditions. In recent years, well-known institutions, such as the European Association of Percutaneous Coronary Interventions, have reviewed evidence from studies to define the principles needed in the decision-making and management of patients with PFO[8,9].

PFO may be associated with cardiovascular events of the left circulation to various organs, causing ischemia and leading to significant clinical repercussions.

At the initial approach to patients with repercussions (e.g., thromboembolism), two aspects guide decision-making[7]: the first is to verify whether the PFO has significant relevance in the clinical event; the second is to identify the probability of the occurrence of this event. Treatment will be targeted according to these aspects.

The FOP must be closed if a high correlation between the foramen and the clinical event is identified. In cases with low probability, drug therapy should be considered. As for patients with intermediate probability, targeted clinical judgment is required in decision-making.

Regarding the clinical management of patients with PFO, it is crucial to adopt interdisciplinary and targeted interventions, as well as insert patients during the process. A 12-lead electrocardiogram, cardiac telemetry, or 24-hour Holter is recommended[7].

The treatment options in patients with PFO who suffered associated thromboembolism encompass antiplatelet agents, oral anticoagulants, PFO closure via percutaneous procedure, and surgical closure. Of these, percutaneous closure has the highest success rates, in which complete closure of the PFO occurs in up to 93% of patients followed for one year. On the other hand, a surgical closure is not advised in these cases[7].

One of the possible complications associated with PFO is the formation of gaseous emboli related to decompression sickness, which is typical of populations that perform diving. The association between these conditions has been discussed in the literature. Controlling risk factors in these populations by avoiding the formation of emboli can prevent paradoxical embolism, regardless of the presence of PFO, since

the decision to close the emboli is individualized[8].

Lifestyle modifications, such as smoking control, adequate body weight, and hydration before and after diving, may prevent decompression sickness. On the other hand, the closure of the PFO can be proposed for patients who cannot implement these measures, and studies have evidenced the decreased incidence of this pathology[8].

Literature suggested a correlation between migraine and PFO after a higher prevalence of this foramen was identified in patients with migraine, especially with aura. However, closing the PFO as a routine treatment is not recommended for these patients. Due to data controversies, PFO closure should be considered only in clinical trials or compassionate use in the case of migraine with aura[8].

The method used and the accuracy of the diagnosis may result in varied incidences and diameters of the PFO, despite some studies reporting reduced diameters of the PFO as age advances. No consistent data correlated PFO with race and sex. A limitation of this study is the lack of epidemiological data on the individual[2].

Last, this study described a case of PFO with a potential maximum diameter of 5 mm. This data is compatible with the passage of emboli that is capable of occluding cerebral branches, such as the middle cerebral artery and large cortical branches, given the greater causal association between strokes with the largest PFO diameter and atrial septal hypermobility.

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TRITICEAL CARTILAGE: MORPHOLOGY AND CLINICAL-SURGICAL IMPLICATIONS

CARTILAGEM TRITÍCEA: MORFOLOGIA E IMPLICAÇÕES CLÍNICO-CIRÚRGICAS

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ABSTRACT

The triticeal cartilage is a small structure present in the thickness of the lateral thyrohyoid ligaments. Clinical-surgical implications may be related to this structure. The present study reported a case of the presence of triticeal cartilage and discussed its prevalence, distribution, and function. During dissection, a small cartilaginous nodule named triticeal cartilage was observed in the left lateral thyrohyoid ligament. Some studies suggest that the triticeal cartilage strengthens the lateral thyrohyoid ligament. However, a well-accepted theory suggests that this cartilage has no function in humans. Considering laterality and prevalence, the data found in the literature vary according to the population studied.

Keywords: anatomy, cartilage, surgery, larynx

RESUMO

A cartilagem tritícea é uma pequena estrutura presente na espessura dos ligamentos tireo-hióideos laterais. Implicações clínico-cirúrgicas podem estar relacionadas a essa estrutura. O estudo visa relatar um caso de presença da cartilagem tritícea e discorrer sobre sua prevalência, distribuição e função. Durante a realização de uma dissecação, foi observado, no ligamento tireo-hióideo lateral esquerdo, um pequeno nódulo cartilaginoso denominado cartilagem tritícea. Alguns estudos sugerem que essa cartilagem serve para fortalecer o ligamento. Entretanto, uma teoria bem aceita sugere que a cartilagem não possui função em nossa espécie. Em termos de lateralidade e prevalência, os dados encontrados na literatura variam de acordo como a população estudada.

Palavras-chave: Anatomia; Cartilagem; Cirurgia; Laringe.

INTRODUCTION

Triticeal cartilage is a small circular or fusiform structure present in the thickness of the lateral thyrohyoid ligament, commonly extending between the upper horn of the thyroid cartilage and the greater horn of the hyoid bone. This structure has varied prevalence in the population, is not constant in individuals, and can be unilateral, bilateral, or absent. When present, the cartilage usually does not undergo involution according to age[1-3].

Embryologically originating from the fourth and sixth pharyngeal arches, laryngeal cartilages begin to develop around the 12th week of pregnancy and are relevant to the clinic and surgery. Although uncertain, some functions have been related to this anatomical structure. Apparently, triticeal cartilage supports the lateral thyrohyoid ligament and may be related to muscle attachment[2]. This structure is related to clinical implications, such as false diagnoses of hyoid fractures, and can sometimes be subjected to pathological calcifications[3].

Few studies investigated the triticeal cartilage[1]. Thus, this study aimed to report a case of the presence of triticeal cartilage and discuss its occurrence, distribution, and function, correlating with possible clinical and surgical implications.

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CASE REPORT

This study was conducted at the Department of Anatomy of the Federal University of Pernambuco. During a laryngeal dissection course, six blocks of viscera from the cervical region (larynx-pharynx-trachea-esophagus) belonging to the department were dissected.

During the dissection, the blocks were initially diffused with each other (Figure 1). Then, the sternohyoid and omohyoid muscles were sectioned and folded for better visualization of the outer surface of the thyroid cartilage blades. On these surfaces, an oblique line was observed starting from the upper thyroid tubercle, located next to the root of the upper horn of the thyroid cartilage, directing downward and forward to the lower thyroid tubercle at the lower edge of the cartilage blade. In this line, the insertion of the sternothyroid muscles and the origin of the thyrohyoid and lower pharyngeal constrictor muscles were observed.

After rebounding part of the extrinsic muscles of the larynx, the thyrohyoid membrane and the median thyrohyoid ligament were exposed. Examining the cartilaginous skeleton of the larynx laterally, the lateral thyrohyoid ligaments were observed, small fibrous cords that formed the posterior edges of the thyrohyoid membrane and extended vertically from the tips of the upper horns of the thyroid cartilage to the posterior vertices of the larger horns of the hyoid bone. In one of the dissected larynges in the thickness of each left lateral thyrohyoid ligament, a small cartilaginous nodule named triticeal cartilage (cartilaginous nucleus) was observed (Figure 2).

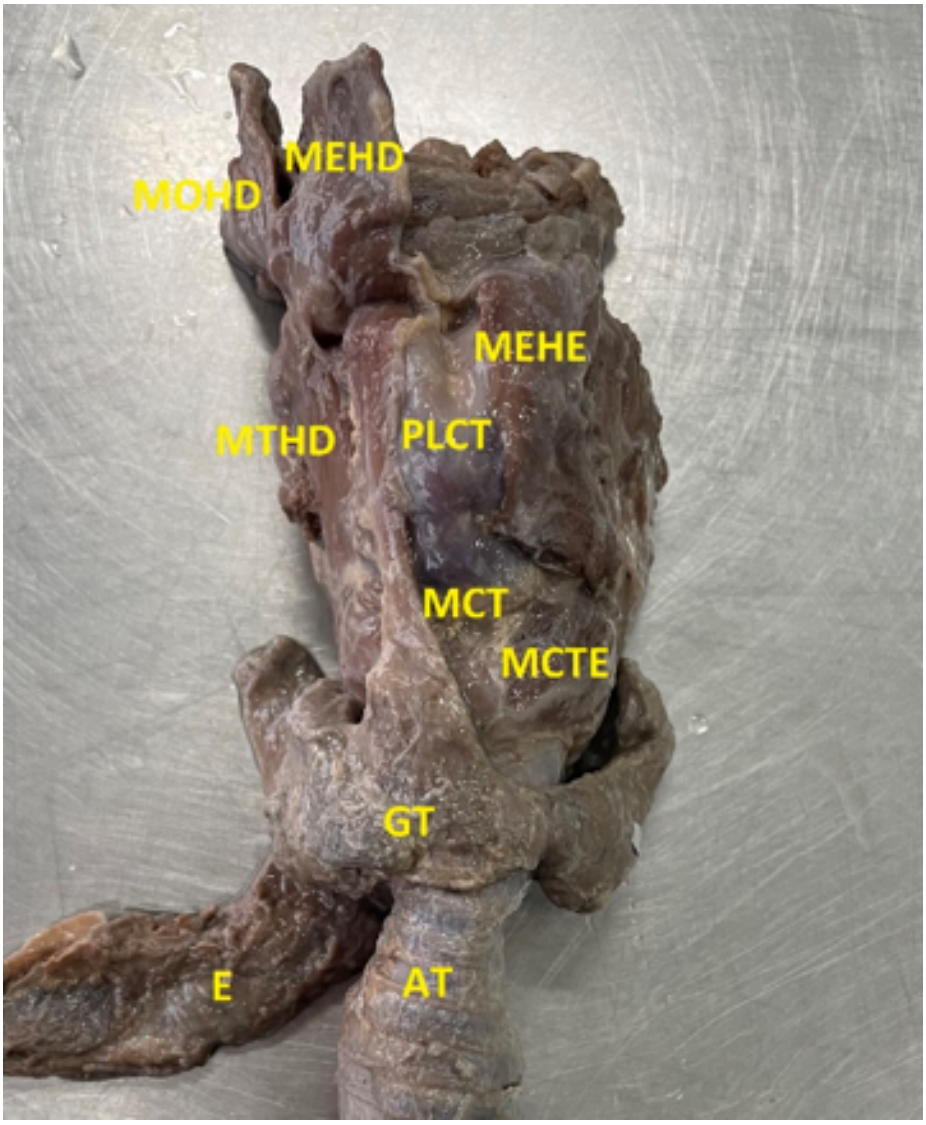

Figure 1. Visceral block of the cervical region (larynx-pharynx-trachea-esophagus) with diffused structures. Anterior view. E: esophagus. TR: tracheal rings. TG: thyroid gland. LCTM: left cricothyroid muscle. CTM: cricothyroid membrane. LPTC: laryngeal prominence of thyroid cartilage. RTHM: right thyroid-hyoid muscle. LSHM: Left sternohyoid muscle. ROMH: right omohyoid muscle. RSHM: Right sternohyoid muscle.

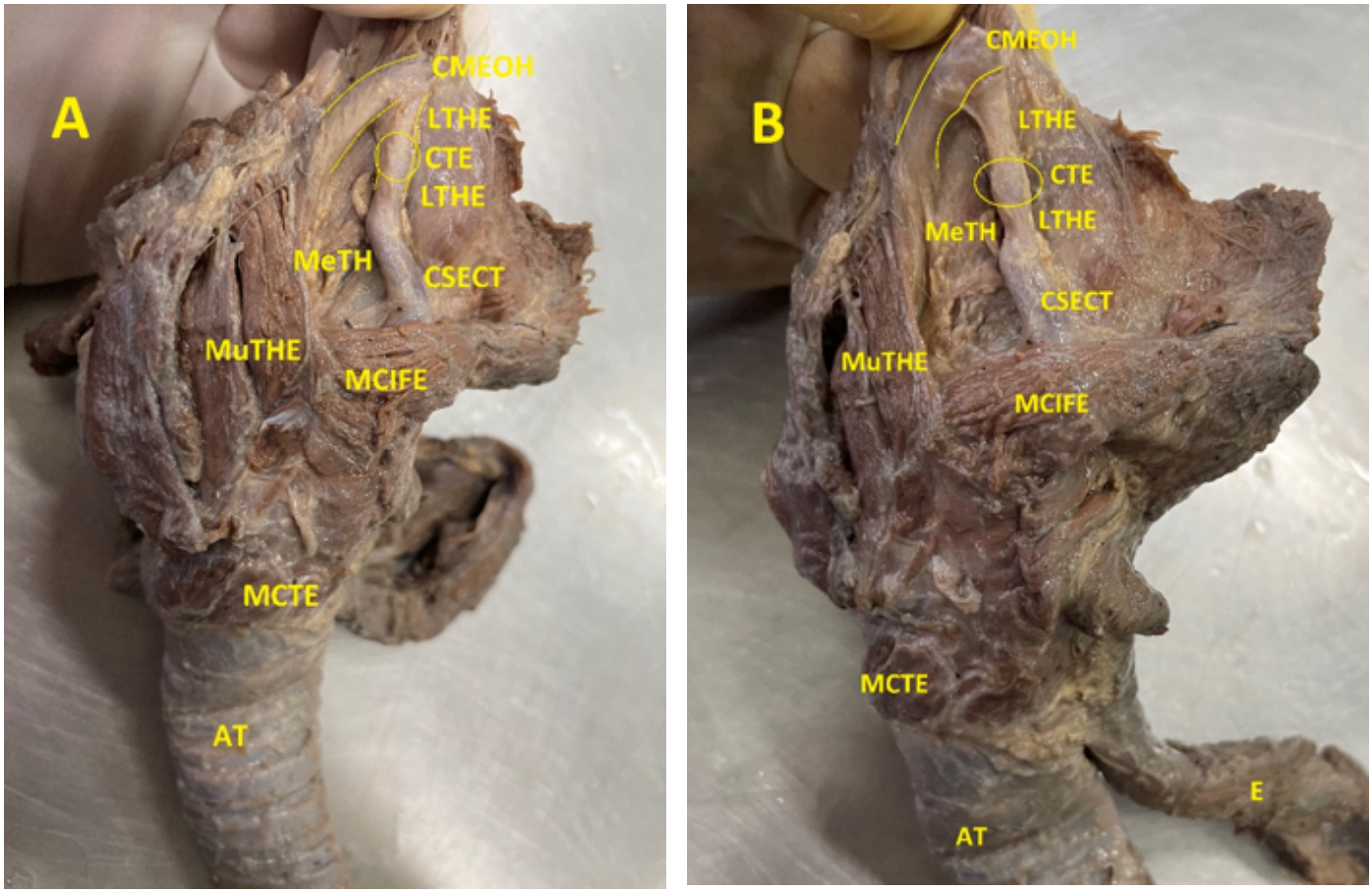

Figure 2 (A and B). The visceral block of the cervical region (larynx-pharynx-trachea-esophagus) was dissected. Anterior view. E: esophagus. TR: tracheal rings. LCTM: left cricothyroid muscle. ICMLO: inferior constrictor muscle of the left pharynx. LTHM: Left thyroid-hyoid muscle. THM: Thyrohyoid membrane. LUHTC: left upper horn of the thyroid cartilage. LTHL: left thyrohyoid ligament. LTC: left triticeal cartilage. LMHHB: left major horn of the hyoid bone.

DISCUSSION

The triticeal cartilage, histologically composed of hyaline cartilage, can be found at the level of the third and fourth cervical vertebrae near the bifurcation of the common carotid artery4. Its prevalence varies greatly according to study and population(8% to 68%), and its length, width, and volume vary between 1.54 and 22.20 mm, 1.34 and 6.07 mm, and 3.7 and 389.0 mm^3, respectively. Generally, the higher the length, the greater the volume. In addition, men are more likely to have larger triticeal cartilages than women[1-3].

Around the 12th week of fetal development, the processes of chondrification and ossification of the laryngeal structures begin, which separates the superior horn of the thyroid cartilage from the greater horn of the hyoid bone. Apparently, a common variation in this process includes the formation of triticeal cartilage[5,6].

Considering laterality, the presentation of triticeal cartilage is more unilateral than bilateral. However, the data found in the literature varies according to the population studied, and the bilateral presentation may be more frequent in some cases. As for sex, some studies reported a higher prevalence in men, and others did not find significant differences between sexes[1,4].

The function of the triticeal cartilage is not a consensus in the literature. Some studies suggested that triticeal cartilage strengthens the lateral thyrohyoid ligament. However, individuals without this cartilage did not present deficiency or disadvantages compared with those who had it[1-4]. The literature also suggested that triticeal cartilage may have muscle fibers that connect it with the tongue[6]. A well-accepted theory states that this cartilage has no function in humans[1-4].

Similar to other laryngeal cartilages, the triticeal may be subjected to calcification or ossifica-

tion[1]. One relevant clinical repercussion is when poor knowledge about the anatomical aspects of the triticeal cartilage leads to the misdiagnosis of fractures of the upper horn of the thyroid cartilage, usually associated with strangulation[7].

When triticeal cartilage is present, the internal laryngeal nerve, a branch of the superior laryngeal nerve, runs along its lateral surface; this relationship requires awareness in anterior cervical spine surgeries and carotid endarterectomy because the nerve can be compressed during the placement of retractors, leading to potential dysfunction and increased risk of aspiration[6].

Due to its location near the bifurcation of the common carotid artery, studies showed the importance of comprehending and identifying the triticeal cartilage since it can be mistaken with the atherosclerotic processes and lead to false diagnoses[2].

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DOWN SYNDROME AS A GENETIC RISK FACTOR FOR ALZHEIMER'S DISEASE: AN INTEGRATIVE REVIEW OF MOLECULAR MECHANISMS

SÍNDROME DE DOWN COMO FATOR DE RISCO GENÉTICO PARA A DOENÇA DE ALZHEIMER: UMA REVISÃO INTEGRATIVA DOS MECANISMOS MOLECULARES

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ABSTRACT

Objectives: To explain why Down syndrome (DS) is considered a risk factor for Alzheimer's disease (AD) by describing the genetic markers involved in this relationship.

Methodology: The following descriptors were used in the Virtual Health Library and PubMed databases in English and Portuguese: "Down syndrome", "trisomy 21", "Alzheimer's disease", "dementia", "mongolism", "aging", "Alzheimer's dementia", "risk factors", and "genetics". Of the 45 studies found in the PubMed database, 15 were selected for review.

Results: The enhanced life expectancy of individuals with DS has been increasing the risk for AD incidence in this population. This progression, the genetic risk factors from trisomy 21 (especially the complete form), and extra copies of genes (e.g., amyloid-β precursor protein) increase the risk for developing AD by triggering events, such as excess production of the amyloid-β peptide.

Conclusion: Trisomy 21 and its genetic and molecular effects are the main factors for the onset of AD, showing the need for further studies to elucidate the genetic relationship between AD and DS.

Keywords: Down syndrome, Alzheimer's disease, risk factors, genes.

RESUMO

Objetivos: Explicar os motivos da síndrome de Down ser considerada um fator de risco para a doença de Alzheimer, por meio da descrição dos marcadores genéticos envolvidos nessa relação.

Metodologia: Foram feitas buscas na Biblioteca Virtual em Saúde e na PubMed, com uso destes descritores, em inglês e português: "síndrome de Down", "trissomia do 21", "doença de Alzheimer", "demência", "mongolismo", "envelhecimento", "demência por Alzheimer", "fatores de risco" e "genética". Dentre os 45 artigos recuperados, 15 foram selecionados, todos referentes à PubMed.

Resultados: O aumento da expectativa de vida das pessoas com síndrome de Down trouxe uma maior probabilidade para a incidência da doença de Alzheimer nesses indivíduos. Essa evolução se juntou aos fatores de risco genéticos advindos da trissomia, em especial da sua forma total, e às cópias extras de genes, a exemplo do gene da proteína precursora β-amiloide, elevando ainda mais a probabilidade de desenvolvimento dessa doença, por desencadear eventos como o excesso do peptídeo β-amiloide.

Conclusão: A trissomia do cromossomo 21 e os seus efeitos genéticos e moleculares são agentes basilares no amplo surgimento da demência pela doença de Alzheimer, comprovando-se a necessidade de mais estudos que elucidem a relação genética entre essa patologia e a síndrome de Down.

Palavras-chave: Síndrome de Down, Doença de Alzheimer, Fatores de risco, Genes.

CC BY

INTRODUCTION

Down syndrome (DS) is the most common condition among intellectual disabilities, affecting between 5 and 8 million people worldwide[1]. The advances in multidisciplinary care related to DS increased the life expectancy of these individuals and the risk for dementia due to Alzheimer's disease (AD), which has an 80% prevalence in individuals with DS aged over 65 years[2].

In this context, DS is considered the main genetic risk factor for early-onset AD. Also, AD is the leading cause of dementia, characterized by short-term memory loss and subsequent loss of other cognitive abilities due to reduced neuronal activity[3].

According to the 2013 Guidelines for Care of People with Down Syndrome[4], among the genetic causes of an extra chromosome 21, 95% occur due to simple trisomy, 3% to 4% due to Robertsonian translocations, and 1% to 2% due to mosaicism. This etiological variety contributes to the diverse phenotypic presentations of DS.

Despite the phenotypic variability, the primary cause of mortality in individuals with DS is AD and its complications5 since this neuropathology is caused by an activation of several genes located on chromosome 21, which are triplicated in DS. For example, the amyloid-β precursor protein (APP) is cleaved into amyloid-β (Aβ) peptide when its gene is excessively produced, accumulating and forming amyloid plaques responsible for the pathogenesis of AD[6]. However, several other genes also participate in the onset of AD7, such as superoxide dismutase type 1 (SOD1) and dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A)[8]. Also, AD was described in all adults with DS aged around 40 years, evidencing the relationship between AD and DS[5].

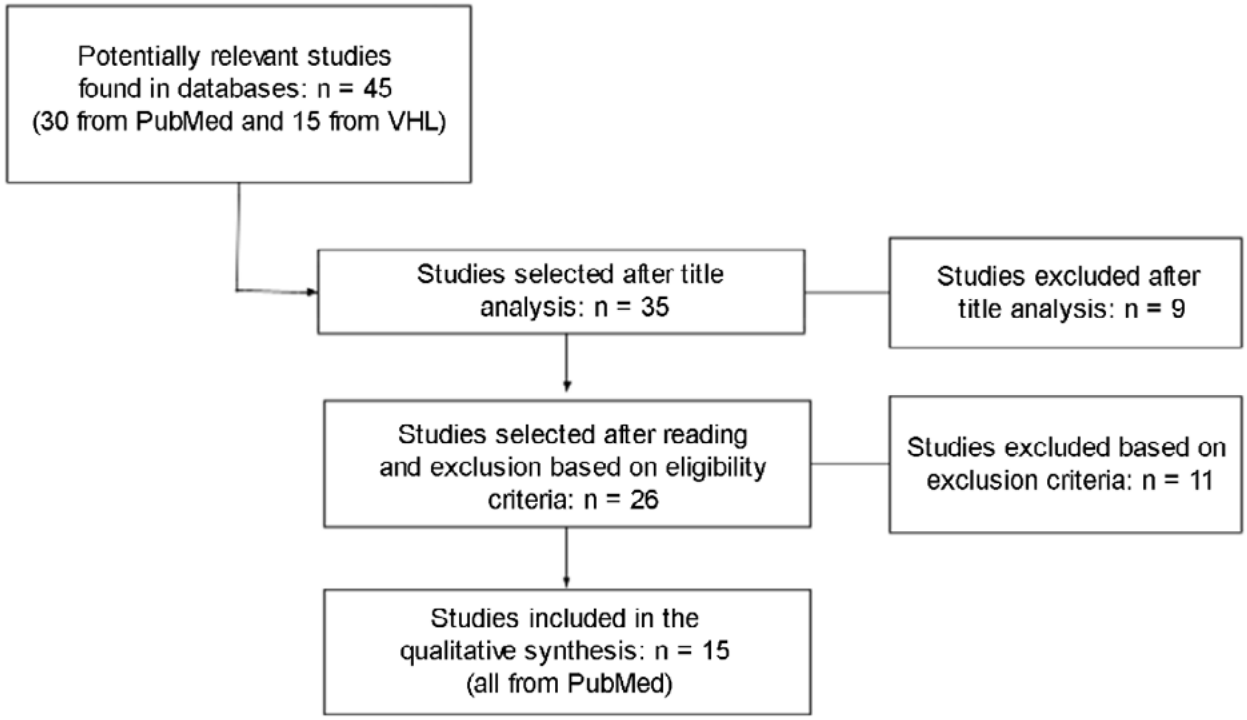
DS is considered the main genetic risk factor for AD due to their physiological similarities. Consequently, the advancing age of adults with DS (especially between 60 and 69 years) increased the number of AD diagnoses, estimated as 54.5% of cases in this age group[9]. Both diseases have a noticeable genetic relationship, highlighting the need for more studies on their similarities. Therefore, this review aimed to explain why DS is considered a risk factor for AD and the importance of data on this topic to prove their shared molecular aspects.

METHODS

This integrative literature review was conducted based on a compilation of primary sources using the Virtual Health Library and PubMed databases. The following descriptors and their variations in Portuguese and English were used for the searches: "Down syndrome", "trisomy 21", "Alzheimer's disease", "dementia", "mongolism", "aging", "Alzheimer's dementia", "risk factors", and "genetics".

The following inclusion criteria were used for screening: (a) studies in English and Portuguese; (b) DS and AD as central topics; (c) genes affected by trisomy 21 and related to AD; and (d) epidemiological data on dementia in individuals with DS. Studies not meeting the inclusion criteria (a) and (b), lacking information on the genetic aspects of DS and its influence on AD, without pathophysiological markers for AD, or published more than nine years ago were excluded. After the search, 45 studies were found; 15 were selected from the PubMed database

Figure 1. Flowchart of study selection for the integrative review.



VHL: Virtual Health Library.

RESULTS AND DISCUSSION

Chart 1. Integrative chart with the selected studies.

DOWN SYNDROME AS A GENETIC RISK FACTOR FOR ALZHEIMER'S DISEASE: AN INTEGRATIVE REVIEW OF MOLECULAR MECHANISMS					
No.	Title	Author/Year	Objective	Results	Conclusion
01.	"Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis"	WILCOCK D., GRIFFIN W., 2013.	To explain the neuroinflammatory responses in the brains of individuals with DS during fetal development and their relation to EOAD.	The APP of Aβ plaques is the main genetic factor linking DS to AD, and its gene is located on chromosome 21. Also, glial cells increase, resulting in the overexpression of a product from chromosomes 2 (interleukin-1) and 21 (S100B). Thus, cytokines may regulate the EOAD in individuals with DS.	Many genes positively regulate the immune responses of microglial cells, while others promote the overexpression of pro-inflammatory proteins.
02.	"Down syndrome and Alzheimer disease: common pathways, common goals"	HARTLEY D. et al., 2015.	To explain the common pathogenic mechanisms between DS and AD and the goals for diagnosing and treating AD in individuals with DS.	Most adults will develop AD around the age of 40 years, which is mainly characterized by early deposition of Aβ peptides in extracellular plaques and brain vessel walls. Later, neurofibrillary tangles accumulate, especially in the hippocampus, entorhinal cortex, and neocortex.	The care for individuals with DS has been improving along with their life expectancy. However, this improvement increased the risk for AD since most genes associated with AD pathogenesis are located on chromosome 21. Therefore, individuals with DS should be included in AD biobanks, and clinical trials involving this population might provide valuable insights.
03.	"A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome"	WISEMAN F. et al., 2015	To present an overview of the clinical and pathological characteristics of AD in individuals with DS compared with other forms of AD to highlight shared genetic, pathogenic, and protective mechanisms and discuss future research topics.	DS is associated with a high risk for EOAD, mainly justified by the presence of three copies of the APP gene. The APP leads to an accumulation of Aβ in the brain when excessively cleaved. Also, the distribution and biochemical composition of Aβ plaques and neurofibrillary tangles in individuals with DS, EOAD, or LOAD are similar. A rare form of familial EOAD can also be observed, which is caused by the duplication of the APP trait from small internal duplications of chromosome 21, leading to three copies of the APP gene.*	Many questions still need to be answered regarding the relationship between DS and AD, especially mechanisms responsible for the late onset of dementia compared to duplication of APP, how changes in neurodevelopment affect neurodegeneration, and the possible gene(s) on chromosome 21 that protect against dementia.

04.	"Is apolipoprotein E4 an important risk factor for dementia in persons with Down syndrome?"	ROHN. T. T. et al., 2015.	To assess the potential risk and frequency of the APOE4 allele in individuals with DS through a literature review.	Three of the studies concluded that carrying the APOE4 allele did not increase the risk of developing AD dementia in individuals with DS. One of these studies included young individuals with DS, which may have biased the results toward a null effect. Of the ten studies, six showed a potential risk for AD dementia or increased mortality in individuals with DS with APOE4, and Deb et al. documented a tendency of risk for AD (not statistically significant). Two studies (Deb et al. and Coppus et al.) also conducted a meta-analysis of all previously published similar studies. Zigman et al. found that individuals with DS without dementia who had at least one APOE4 allele were approximately five-fold more likely to die than those with APOE3 allele. Prasher et al. showed a risk ratio of 5.9 in individuals with DS without dementia who had at least one APOE4 allele compared with a risk ratio of 1.0 for the APOE3/3 group. Thus, the APOE4 allele may lead to early mortality in individuals with DS, independent of dementia risk.	DS has a complex etiology and is considered a model for EOAD due to the triplication of the APP gene on chromosome 21. Thus, adults with DS above 40 years old have neuropathological criteria (including senile plaques) consistent with AD and are more likely to develop dementia than the general population. Considering the similarities between these two conditions, risk factors for AD may also increase the risk for dementia in DS. Also, the APOE4 allele represents the most critical genetic factor for LOAD, with 65% to 80% of all individuals with AD carrying at least one allele. However, results on whether the APOE4 gene has the same potential risk for dementia in DS are conflicting. The presence of the APOE4 allele may increase the risk of dementia in individuals with DS despite the lower risk than for AD. Several studies supported an increased risk for mortality in individuals with DS with the APOE4 allele, independent of dementia risk.

05.	"Telomere longitudinal shortening as a biomarker for dementia status of adults with Down syndrome"	JENKINS E. C. et al., 2015	To verify whether the progression of cognitive and functional declines due to AD reduces the telomere. Sequential changes in telomere length were examined in five individuals with DS (three women and two men) during the transition from preclinical AD to MCI-DS (N ¼ 4) or dementia (N ¼ 1).	Consistent telomere shortening was observed over time. Telomere lengths before clinical decline were similar to those of adults with DS who did not experience clinical decline. However, telomere lengths after the transition to MCI-DS or dementia were similar to those of adults with DS who developed MCI-DS or dementia.	The rapid conversion to clinical practice may improve diagnostic accuracy for individuals with DS developing AD, contributing to better planning to support needs. Negative results in individuals with symptoms mimicking dementia may encourage the search for the cause of these symptoms and effective treatment.
06.	"Down syndrome, increased risk of dementia and lipid disturbances"	KLOSOWSKA A. et al., 2017.	To highlight the importance of understanding the early development of dementia, obesity, and metabolic disorders in individuals with DS, which may lead to brain tissue degeneration, cerebrovascular disorders, and a significant impact on the quality of life of these individuals and their families.	Over 70% of individuals with DS up to 55 to 60 years old showed early signs of dementia consistent with those of AD. These signs were primarily due to the complete or partial triplication of various genes on chromosome 21 (e.g., APP, SOD1, CBS, DYRK1A, and SYNJ1). These genes influence the cascade of Aβ peptide production, which is negatively correlated with HDL. Also, HDL suppresses Aβ peptide production by reducing cellular cholesterol through activated cholesterol efflux mediated by ABC transporters. *	Although many studies have analyzed lipid and lipoprotein levels in individuals with DS, few related these markers to memory impairment, which could be useful for better understanding the pathological mechanism of dementia.

07.	“Aging with Down syndrome: the dual diagnosis: Alzheimer disease and Down syndrome”	CIPRIANI G. et al., 2018.	To explore the dementia in DS.	Most individuals with DS aged between 35 and 40 years exhibited characteristic neuropathological changes of AD. However, only a small portion of this group developed clinical dementia around the age of 50, and the initial signs may differ compared with the general population. *	Adults with DS had a high risk for AD, and the development of dementia may differ from the observed in the general population. Therefore, failing to recognize it may delay the diagnosis and interventions, affecting cognitive decline, behavioral, and emotional aspects. Many studies have attempted to standardize the assessment of individuals with DS and AD, but a gold standard for diagnosis is still lacking.
08.	“Association of dementia with mortality among adults with Down syndrome older than 35 years”	HITHERSAY R., STARTIN C., STRYDOM A., 2019.	To explore the association of AD dementia with mortality and factors associated with dementia in adults with DS.	Of 211 adults with DS, 96 (45.5%) were women, and 66 (31.3%) had a clinical diagnosis of dementia. The crude mortality rate for individuals with dementia was five-fold higher than for those without dementia. In the latter group, epilepsy onset after 36 years old was associated with mortality. *	Most adults with DS who died had dementia and were affected by some associated factors that were not found in the individuals with DS (e.g., APOE genotype). These findings highlighted the need for clinical trials on treatments to prevent or delay dementia in individuals with DS.

09.	“Dementia in Down syndrome: unique insights for Alzheimer disease research”	LOTT I., HEAD E., 2019.	To assess the similarities and differences between the pathological cascades underlying DS and AD, providing a platform for the common exploration of these two conditions.	Post-mitotic somatic mutations resulting in mosaicism may represent a risk factor for AD in individuals with and without DS, suggesting a common topic that could be investigated in future research. Some individuals developed AD due to the duplication of a small region of chromosome 21, which includes APP (Dual-APP). Pathogenic mechanisms in these individuals may parallel those in individuals with DS and AD. An additional copy of APP was present in Dual-APP and DS with AD, contrasting with conditions where other genes (e.g., PSEN1 or PSEN2) are mutated, and APP processing was changed independently of genetic copy number. Dual-APP shared some common traits with DS, including early onset of dementia (average age of 52 years for Dual-APP), AD, and increased prevalence of cerebral amyloid angiopathy. Individuals with Dual-APP presented no phenotypic characteristics of DS. Although most individuals with DS had AD, variability in dementia prevalence was more pronounced in DS than Dual-APP, whereas cerebral amyloid angiopathy was less prevalent in DS than Dual-APP. These phenotypic differences between DS and Dual-APP provided a platform for better understanding the roles of genes on chromosome 21 (except for APP) in AD pathogenesis.	DS allows the monitoring of temporal events and pathways of important mechanisms for AD throughout life. Research areas include similarities and differences in molecular markers of pathogenesis, targets for therapeutic intervention, predictive studies, evolution of significant clinical biomarkers, and course of APP throughout life and its relation to dementia onset in the brains of individuals with DS. Thus, systematic large-cohort studies should be developed in the population with DS.

10.	"Down syndrome, Alzheimer disease, and cerebral amyloid angiopathy: the complex triangle of brain amyloidosis"	CARMONA--IRAGUI M. et al., 2019.	To review the available evidence on various aspects of cerebrovascular disease in DS, focusing on cerebral amyloid angiopathy and characterization of pathophysiological mechanisms by biomarkers.	The overexpression of the APP gene leads to excessive production and deposition of the Aβ peptide (main marker of AD development) and cerebral amyloid angiopathy. Individuals with DS develop neuropathological characteristics of AD by the age of 40 years, with an increased risk for cognitive impairment related to this neuropathology. The walls of leptomeningeal and cortical vessels become fragile and prone to bleeding due to progressive deposition of the Aβ peptide, defining cerebral amyloid angiopathy. *	General cerebrovascular diseases, especially cerebral amyloid angiopathy, are common in AD. AD and cerebral amyloid angiopathy are considered part of the continuum of cerebrovascular amyloidosis and are associated with DS through pathophysiological mechanisms related to amyloid. DS provides a unique opportunity to study cerebrovascular diseases in a population with a low frequency of conventional vascular risk factors. The limited evidence supported that cerebral amyloid angiopathy is the primary form of cerebrovascular disease in DS.
11.	"Signaling pathways implicated in Alzheimer's disease neurodegeneration in individuals with and without Down syndrome"	MARTÍNEZ-CUÉ C., RUEDA N., 2020.	To provide an overview of the most relevant pathways implicated in the onset and progression of AD in individuals with and without DS.	The complex scenario of AD etiopathology suggested that the development of therapies to treat this disorder should target molecular pathways involved in multiple changed events. DS can be considered a useful model for studying AD etiopathology and pursuing new therapeutic strategies due to the high prevalence and EOAD in this population and the multiple common mechanisms found in both conditions.	The complex scenario of AD etiopathology suggested that the development of therapies to treat this disorder should target molecular pathways involved in multiple changed events. DS can be considered a useful model for studying AD etiopathology and pursuing new therapeutic strategies due to the high prevalence and EOAD in this population and the multiple common mechanisms found in both conditions.

12.	“Clinical and biomarker changes of Alzheimer disease in adults with Down syndrome: a cross-sectional study”	FORTEA J. et al., 2020.	To characterize the natural history of AD in adults with DS.	A total of 388 adults with DS (347 in Barcelona and 41 in Cambridge) and 242 euploid controls (Barcelona) were recruited between February 1st, 2013, and June 28th, 2019 (Barcelona), and June 1st, 2009, and December 31st, 2014 (Cambridge). Most individuals with DS (45%) and euploid controls (67%) were female. Trisomy of chromosome 21 was present in 308 individuals with DS; 80 individuals had no genetic confirmation. A total of 72 (19%) individuals with DS had mild, 175 (45%) had moderate, and 98 (25%) had severe or profound intellectual disability. The number of adults with DS and controls differed for each biomarker method.	Individuals with DS were suitable for clinical trials of AD. Describing the natural history of AD in this population would have an immediate effect on the design of such trials.
13.	“Down syndrome and Alzheimer disease: common molecular traits beyond the amyloid precursor protein”	GOMEZ W. et al., 2020.	To highlight recent data on the origin of shared factors between DS and AD and explore the mechanisms related to cognitive impairments in DS associated with dementia.	Changes in chromosome location due to the extra chromosome 21 and epigenetic modifications may promote changes in gene expression beyond this chromosome. Similar pathological features and cellular dysfunctions in DS and AD, including impaired autophagy, lysosomal activity, and mitochondrial dysfunction, may be regulated beyond the APP overexpression.	This review highlighted recent findings on the common molecular pathways between DS and AD, emphasizing less studied aspects (e.g., mitochondrial function and epigenetic regulation).

14.	"Common genetic signatures of Alzheimer's disease in Down syndrome"	SHARMA A. et al., 2020.	To investigate the relationship between AD and DS using integrative analysis of derived genes from peptides associated with amyloid plaques in AD and DS and genes from chromosome 21, risk factors for AD, and differentially expressed genes identified using genome analysis of individuals with DS in the dorsal frontal and cerebellar cortex.	Functional enrichment analysis, characteristics of the transcription factor, and network analyses were used to assess unique and shared aspects of each gene set. Genes identified as important for DS and AD included SOD1, SYNJ1, S100B, ACSM1, APBA2, APLP1, BACE2, BCL2L, COL18A1, DYRK1A, IK, KLK6, METTL2B, mTOR, NFE2L2, NFKB1, PRSS1, QTRT1, RCAN1, RUNX1, and SAP18.	Oxidative stress, apoptosis, and processes of inflammation or the immune system may be the basis for the pathogenesis of DS and AD.
15.	"Alzheimer's disease in Down syndrome: an overview of genetic and molecular aspects"	GOMES F. et al., 2021.	To analyze the biomarkers involved in the neuroinflammation and neurodegeneration processes and understand the mechanisms of AD incidence and EOAD in individuals with DS.	Certain genetic factors in DS, mainly the overexpression of APP, contributed to early-onset dementia and directly influenced the neuroinflammatory response. Also, the development of AD in individuals with DS is complex and involves changes in genes within and outside chromosome 21.	Some genes of chromosome 21 associated with neurological disorders in the context of DS and AD were not analyzed. Therefore, future research may help to map the interaction of genes within and outside chromosome 21 in the neuropathology and neuroinflammation of AD in DS.

Fonte: Autores

AD: Alzheimer's disease; DS: Down syndrome; EOAD: early-onset Alzheimer's disease; LOAD: late-onset Alzheimer's disease; APP: amyloid precursor protein; MCI-DS: mild cognitive impairment related to Down syndrome; APOE4: apolipoprotein E4; Aβ: amyloid-β; SOD1: superoxide dismutase type 1; S100B: S100 calcium-binding protein B; CBS: cystathionine beta-synthase; DYRK1A: dual-specificity tyrosine phosphorylation-regulated kinase type 1A; SYNJ1: synaptojanin 1; HDL: high density lipoprotein; ABC: ATP-binding cassette; PSEN: presenilin; ACSM1: acyl-CoA synthetase medium chain family member 1; APBA2: amyloid beta precursor protein binding family A member 2; APLP1: amyloid beta precursor like protein 1; BACE2: beta-site amyloid precursor protein-cleaving enzyme 2; BCL2L: B-cell lymphoma 2-like protein; COL18A1; collagen type XVII alpha 1 chain; KLK6: kallikrein related peptidase 6; METTL2B: methyltransferase-like protein 2B; mTOR: mammalian target of rapamycin; NFE2L2: nuclear factor erythroid 2-like factor 2; NFKB1: nuclear factor kappa B subunit 1; PRSS1: protease serine 1; QTRT1: queuine tRNA-ribosyltransferase catalytic subunit 1; RCAN1: regulator of calcineurin 1; RUNX1: runt-related transcription factor 1; SAP18: Sin3A associated protein 18.

The advances in care of individuals with DS increased their life expectancy, currently ranging between 55 and 60 years old8. Consequently, the prevalence of this condition also increased, affecting 6 million individuals worldwide[10,11]. However, this increase in lifespan has become one of the main risk factors for developing AD12, classifying this pathology as the leading cause of mortality in individuals with DS[5].

About 88% of individuals with DS will develop dementia by the age of 65 years[13], and most individuals will exhibit neuropathology consistent with AD by the age of 40 years[7]. The trisomy 21 from non-disjunction of chromosomes during maternal meiosis (present in 93% to 95% of individuals with DS)[14] is also a risk factor for developing AD. Also, AD markers appear two or three decades earlier in individuals with DS compared with those without this trisomy[15]. Thus, the early onset causes the preclinical phase of AD, with biomarkers undergoing predictable changes for over 20 years[5].

Trisomy 21 induces extra copies of various genes, such as APP, which encodes the protein of the same name[7]. In contrast to the observed in complete trisomy 21, the APP gene may not have an extra copy when chromosome 21 has partial mutation, resulting in no early-onset AD[10]. The APP is found in the plasma membrane and organelles of the neuron, glial cells, and other peripheral tissues[3]. Also, it is cleaved into soluble amyloid precursor protein alpha (sAPPα) fragments in the non-amyloidogenic pathway by α-secretases enzymes after translation, with a neuroprotective effect. In the amyloidogenic pathway, the APP cleavage occurs through β-secretases (primarily β-secretase type 1 [BACE1])[15] and γ-secretases complex, generating sAPPβ fragments and Aβ peptides, respectively[16]. The Aβ peptide can have 40 or 42 amino acids, and the latter is most likely to aggregate[17]. In this sense, 40-year-old individuals with DS have a disturbance in these enzymes, with reduced α-secretases and increased β-secretases, enabling the production of the Aβ peptide[15].

The increased Aβ peptide from the extra APP gene in individuals with DS is diffusely deposited in greater quantities and can be observed in brain tissues during childhood and adolescence12, triggering immune defense mechanisms (e.g., inflammatory processes)[18]. Over the years, increased aggregation develops neuritic plaques, which are responsible for the neurodegeneration related to AD[19] due to the destruction of neuronal connection, synaptic interruption, tissue loss, and reduced brain mass[18]. A study found that all adults with DS aged 35 to 45 years had neuritic plaques and other changes consistent with AD, affirming that Aβ peptide is one of the main pathophysiological markers of this disease[17].

Although the overexpression of the APP gene is considered the primary precursor to Aβ peptide accumulation[12], other genes are involved in AD development in individuals with DS20. Another finding indicated that the encoding gene of the ETS proto-oncogene 2 contributes to the development of this disease[10]. This gene is in the chromosome 21 and activates the promoter of APP, generating its excessive expression due to trisomy 21 and influencing the formation of Aβ peptides, resulting in diffuse deposits and amyloid plaques[10].

Neurofibrillary tangles are also found due to trisomy [21], tripling their quantity between the fourth and fifth decades of life in individuals with DS[10]. Thus, this is another factor demonstrating the early onset of AD-related dementia in this population[10]. The main genes directly involved in the formation of these markers are those encoding DYRK1A and regulators of calcineurin 1 (RCAN1), found on chromosome 21 and related to hyperphosphorylation of tau protein, which is more abundant in the AD[3].

DYRK1A dysregulates splicing factors, leading to hyperphosphorylation of tau protein by the glycogen synthase kinase 3 (GSK-3) enzyme. The hyperphosphorylation increases tau quantity in the forms with three or four microtubule binding sites (3R-tau and 4R-tau, respectively), contributing to the early onset of neurodegeneration due to neurofibrillary tangles[7]. Also, DYRK1A negatively regulates the quantity of the neuron-restrictive silencer factor protein, which has neuroprotective functions and redu-

ced activity in individuals with DS21.

RCAN 1 stimulates GSK-3 and inhibits the calcineurin enzyme, which dephosphorylates and activates the mitochondrial fission protein, enabling its transport and fission into the mitochondria[3]. Individuals with DS have overexpression of this gene, reducing the efficiency of this mitochondrial process and increasing oxygen consumption, which results in greater oxidative stress[22]. The overexpression of RCAN 1 throughout life triggers harmful cellular effects on synaptic functions, stimulates the formation of neurofibrillary tangles[11], and may inhibit signaling pathways monitored by the nuclear factor of activated T cells, which regulates RCAN 1 expression. Due to these changes in the nuclear factor of activated T cells, the production cascade of Aβ peptides is stimulated primarily by modulation of BACE1 expression, resulting in increased cleavage of the APP[11].

SOD1 is also located on chromosome 21 and involved in oxidative stress. It encodes the superoxide dismutase enzyme, which catalyzes the dismutation of superoxide into molecular oxygen and hydrogen peroxide (a reactive oxygen species). Overexpression of SOD1 in trisomy 21 reduces the activation of catalase and glutathione peroxidase enzymes, which are responsible for converting hydrogen peroxide into water[3]. Consequently, increased levels of hydrogen peroxide induce oxidative stress, inflammatory events, activation of pro-apoptotic factors, and stimulation of cellular senescence, primarily affecting neurons, which become more susceptible to degeneration in individuals with DS[10]. Moreover, this excessive hydrogen peroxide creates a favorable environment for toxicity from Aβ peptides.

The trisomy 21 affects the synaptojanin 1 (SYNJ1) gene, which encodes the lipid phosphatase of the same name, responsible for decreasing levels of phosphatidylinositol-4,5-bisphosphate involved in membrane transduction and their transport during endocytosis in synapses[7]. The mutation causes an increase in the endosome size[23], influencing the pathway of production and accumulation of Aβ peptides in AD in individuals with DS[12]. Corroborating this finding, the reduced expression of SYNJ1 was related to the reduced levels of Aβ peptide, neuronal dysfunction, and cognitive deficits[23].

An additional copy of the cystatin B gene is also observed in trisomy 2110, which encodes the cystatin B enzyme and inhibits the endogenous lysosomal protease that inhibits cathepsins (proteases), causing an imbalance in lysosomal proteolysis. In addition, this change influences the accumulation of Aβ peptides and all their effects in the early-onset AD[3].

Another process contributing to AD in individuals with DS is neuroinflammation, which is mainly related to the triplication of the calcium-binding protein B (S100B) gene on chromosome 21. The S100B gene encodes the S100B cytokine from astrocytes and is involved in the growth and maintenance of neurons. When in excess due to trisomy 21, it is related to prominent growth of dystrophic neuronal processes, especially in amyloid plaques17. In addition, S100B induces mRNA synthesis and translation of APP in neurons[15] and stimulates hyperphosphorylation of tau protein, accumulating the major neuropathological markers of AD10. The S100B also regulates the expression of the interleukin-1 encoding gene (located on chromosome 2), which is involved in the neuropathology of DS and influencing the development of AD[15].

Interleukin-1 is an inflammatory cytokine primarily produced in microglial cells and found in excess due to trisomy 21, leading to the synthesis and evolution of amyloid plaques by inducing the synthesis of the APP in neural cells and other tissues. Also, it stimulates the p38 mitogen-activated protein kinase, an essential enzyme in the hyperphosphorylation of the tau protein and formation of neurofibrillary tangles[15]. Interleukin-1 also reduces synaptophysin and participates in the synthesis and activation of the acetylcholinesterase enzyme that degrades the acetylcholine neurotransmitter, essential for learning and memory abilities, which are early compromised in AD[15]. In addition, the influence of these clinical characteristics induced by interleukin-1 on AD in individuals with DS has been demonstrated and found in more than 70% of

those who exceed the age group of 55 to 60 years[8].

The ubiquitin-specific peptidase 16 (USP16) gene (triplicated in trisomy 21) encodes the specific histone H2 deubiquitinase enzyme related to increased cellular senescence in individuals with DS11. This aging process may also be associated with telomere shortening, in which TTAGGG repeats located at chromosome ends shorten in each cell cycle until the cell is unable to replicate[24]. In this sense, studies have shown a relationship between telomere length in T lymphocytes and development of mild cognitive impairment and dementia in adults with DS[24].

The presence of at least one allele of apolipoprotein E4 (APOE4) in individuals with DS is another genetic factor (not directly influenced by trisomy 21) that contributes to early-onset AD. The inheritance of the APOE4 allele influences the early and rapid increase of endosomes in the preclinical stages of AD and increases the burden of Aβ peptides[25,26]. This mechanism occurs by impairing the clearance of Aβ peptides in brain tissues due to the increased susceptibility of APOE4 to proteolysis. However, further studies should confirm the direct relationship between trisomy 21 and the presence of one or more APOE4 alleles[10,25].

DS is recognized as a genetically determined form of AD, mainly due to the significant increase in the risk of developing AD[5]. These findings emphasized the importance of further studies on the relationship between DS and AD and multidisciplinary care for this population.

CONCLUSION

The DS caused by trisomy 21 (mainly the complete form) influences the early development of AD. This influence arises from the extra copies of genes on chromosome 21 (e.g., APP, ETS proto-oncogene 2, DYRK1A, RCAN1, SOD1, SYNJ1, cystatin B, S100B, interleukin-1 encoding gene, and USP16). Although not located on chromosome 21, the APOE4 is also a significant marker for AD and associated with higher mortality in individuals with DS. Thus, the neuropathological complexity in the relationship between DS and AD requires further studies, focusing on genes triplicated by trisomy 21 and the inheritance of the APOE4 allele. This research field is particularly important due to the increasing life expectancy of individuals with DS, resulting from advances in multidisciplinary care for this population.

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SGLT2 INHIBITORS FOR TREATING HEART FAILURE WITH REDUCED EJECTION FRACTION

INIBIDORES SGLT2 NO TRATAMENTO DA INSUFICIÊNCIA CARDÍACA COM FRAÇÃO DE EJEÇÃO REDUZIDA

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Abstract

Introduction: Heart failure (HF) is a syndrome characterized by decreased left ventricular ejection fraction. The use of sodium-glucose transporter 2 inhibitors (ISGLT2) showed efficacy in reducing mortality and hospitalization of patients with HF. **Methodology:** A bibliographic survey was conducted in the main databases to analyze the benefits of ISGLT2 in the main high-impact journals. **Discussion:** EMPA-REG showed lower mortality in the use of empagliflozin than the placebo group (3.7% vs. 5.7%). The canagliflozin study (CANVAS) showed a 14% lower risk of cardiovascular death in patients without cardiovascular disease (CVD) and an 18% lower risk in patients with CVD. DECLARE-TIMI 58 showed that patients with type 2 diabetes mellitus (T2DM) have a lower risk of HF and death from cardiovascular events among patients who used dapagliflozin than patients who received a placebo (4.9% vs. 5.8%). In DAPA HF, the number of deaths from cardiovascular causes was 9.7% vs 11.5% of patients who took placebo. EMPEROR-REDUCED tested empagliflozin and the primary outcome occurred in 361 of 1863 patients (19.4%) in the drug group against 462 of 1867 patients (24.7%) in the placebo group. SOLOIST-WHF analyzed sotagliflozin and observed the occurrence of a primary outcome in 245 patients in the drug group and 355 in the placebo group. **Conclusion:** Patients with HF have gained a new drug class for their treatment, which was mentioned in the most recent guidelines worldwide, but its efficacy in HF with preserved ejected fraction still needs to be tested.

Keywords: Cardiovascular diseases; diabetes mellitus; heart Failure; mortality; renal insufficiency, chronic.

Resumo

Introdução: A insuficiência cardíaca (IC) é uma síndrome clínica caracterizada pela diminuição da fração de ejeção do ventrículo esquerdo. O uso do sodium-glucose linked transporter 2 inhibitors (ISGLT2) em portadores de IC evidenciou eficácia na diminuição de mortalidade e internação. **Metodologia:** Para conduzir a presente pesquisa, realizou-se estudo bibliográfico nas principais bases de dados e analisou-se os benefícios do ISGLT2 nas principais revistas de alto impacto. **Discussão:** O EMPA-REG revelou menor mortalidade no uso de empagliflozina comparado ao placebo (3,7% contra 5,7%). A canaglifozina (estudo CANVAS) evidenciou uma redução de 14% no risco de morte por doença cardiovascular (DCV) em pacientes sem a referida condição cardíaca, contudo, a redução foi de 18% em pacientes com DCV conhecida. O DECLARE-TIMI 58 evidenciou que indivíduos com diabetes mellitus tipo 2 possuem menor risco de IC e falecimento por eventos cardiovasculares entre aqueles que utilizaram a dapagliflozina comparados ao placebo (4,9% contra 5,8%). No Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF), o número de mortes por causa cardiovascular foi de 9,7% contra 11,5% dos pacientes que tomaram placebo. No estudo EMPEROR-REDUCED, o desfecho primário ocorreu em 361 dos 1863 pacientes (19,4%) que receberam empagliflozina, em comparação com 462 dos 1867 pacientes (24,7%) no grupo que recebeu placebo. No estudo SOLOIST-WHF, analisando

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o efeito da sotagliflozina, observou-se que o desfecho primário ocorreu em 245 pacientes no grupo que recebeu o medicamento comparado com 355 pacientes no grupo que recebeu placebo. **Conclusão:** Os pacientes com IC ganharam uma nova opção para o seu tratamento, a qual é, inclusive, citada nas diretrizes mais recentes de todo o mundo. No entanto, ainda são necessários novos estudos para avaliar sua eficácia e aplicabilidade na IC com fração de ejeção preservada.

Palavras-chave: Diabetes mellitus; insuficiência cardíaca; doenças cardiovasculares; doença renal crônica; mortalidade.

Introduction

Heart failure (HF) is a syndrome characterized by dyspnea or limitation to exertion caused by impaired ventricular filling, blood ejection, or both. HF can be classified according to the ejection fraction: preserved (≥ 50%), intermediate (between 41% and 49%), or reduced (≤ 40%)[1,2].

Studies using the oral antidiabetics sodium-glucose linked transporter 2 inhibitors (ISGLT2) showed its efficacy for reducing hospitalization and mortality due to HF3. ISGLT2 drugs were initially designed for treating type 2 diabetes mellitus (T2DM); however, they seem to be useful for other diseases. Recently, its beneficial effects have been discovered in patients at cardiovascular risk, focusing on HF with reduced ejection fraction (HFREF)[4].

The action mechanism of ISGLT2 in T2DM is the reduction of renal glucose reabsorption by inhibiting the sodium-glucose co-transporter-2 in the proximal tubule of the nephron. The action mechanism of ISGLT2 in HF is not yet known; however, the main studies on the topic (EMPA-REG, CANVAS, DECLARE-TIMI 58, dapagliflozin and Prevention of Adverse Outcomes in Heart Failure [DAPA-HF], dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD], EMPEROR-Reduced, and SOLOIST-WHF) showed a decreased number deaths and hospitalizations due to cardiovascular causes[5-11].

METHODOLOGY

For the selection of the studies, we initially included randomized studies that qualified the ISGLT2 to be incorporated into clinical practice and the most updated guidelines worldwide. Then, complementary readings were chosen, including reviews published in high-impact journals, such as the Lancet, the New England Journal of Medicine, and Circulation.

Studies containing other benefits of ISGLT2 (e.g., renovascular protection) were selected to complement the review, and the literature on the treatment of HF was revisited.

Results and discussion

HFREF is the most important type of HF since it has an elucidated therapeutic basis and established treatments, such as symptom-relieving diuretics, disease-modifying drugs, and device therapies[12,13].

Patients with HFREF should be treated with a β-blocker and an angiotensin-neprilysin receptor inhibitor, except in cases of specific contraindications. The therapy may include the angiotensin-converting enzyme or the angiotensin sensor, and mineralocorticoid receptor antagonists may be added when persistent symptoms occur[14,15].

According to recent studies, ISGLT2 is a class of oral antidiabetics that is beneficial for patients with cardiovascular disease (CVD). The drugs empagliflozin, canagliflozin, dapagliflozin, and sotagliflozin are part of this class, and specific studies have been conducted to evaluate their effects in patients with and without diabetes[16].

One of the first high-impact studies was EMPA-REG, published in 2015, which evaluated 7,020 patients with T2DM and some previous CVD and had a mean follow-up of three years. This study was the first analysis to show the efficacy of ISGLT2 in CVD. The patients with T2DM at high risk of cardiac events receiving empagliflozin added to the standard treatment presented a lower rate of primary composite cardiovascular outcome and death from any cause than the placebo group. The primary outcome was death from cardiovascular causes, which occurred in 490 of 4687 patients (10.5%) from the empagliflozin group and in 282 of 2333 patients (12.1%)

from the placebo group. The hazard ratio in the empagliflozin group was 0.86 (p < 0.001, 95% confidence interval [95%CI]: 0.74 - 0.99)[5,17].

The canagliflozin research (CANVAS), published in 2017, included 10,142 patients with diabetes at high cardiovascular risk and with a mean follow-up of 3.5 years; the primary outcomes (death, acute myocardial infarction, stroke or hospitalization for cardiac causes) were less frequent in the group using canagliflozin than the placebo group (26.9 to 31.5 per 1000 patients per year, p < 0.001, 95%CI: 0.75 - 0.97). However, this study also found that the amputation risk increased by about 56% in patients using canagliflozin[6,18,19].

Dapagliflozin, one of the newest drugs in its class, has two impact studies on its efficacy. In addition, DECLARE-TIMI 58 was published in 2019 and followed 17,160 patients (7,000 with some atherosclerotic disease) for a mean period of 4 years. The study found that cardiovascular death or hospitalization due to HF significantly decreased (p = 0.005, 95%CI: 0.73 - 0.95). Although dapagliflozin does not result in a significant decrease in major cardiac events, it may cause adverse renal outcomes (p = 0.17, 95%CI: 0.84 - 1.03)[7,20].

A study published on dapagliflozin (DAPA HF) in September 2019 included 4,744 patients with HFREF and followed for a mean of 1.5 years; the risk of worsening HF or death from cardiovascular causes was lower in the dapagliflozin group than in the placebo group. Regardless of T2DM, patients (p < 0.001) presented 2.0% fewer deaths (9.6% with dapagliflozin vs. 11.5% in the placebo group; 95% CI 0.69 - 0.98) and 3.7% fewer hospitalizations (9.7% with dapagliflozin vs. 13.4% in the placebo group; 95% CI 0.59 - 0.83) in the primary outcome[7,8,21].

The DAPA-CKD study evaluated the long-term efficacy and safety of dapagliflozin in patients with chronic kidney disease with or without T2DM. Published in September 2020, the study included 4,304 patients, 2,906 (67.5%) with T2DM, and a mean glomerular filtration rate of 43.1 mL/min per 1.73 m2. The study concluded that patients receiving dapagliflozin had a lower risk of primary outcomes than those who received a placebo. In addition, those who received the drug had a lower risk of death from cardiovascular causes or hospitalization due to HF and longer survival than the placebo group (100 [4.6%] vs. 138 [6.4%], respectively, [p = 0.009, 95%CI: 0.55 - 0.92]). Considering those who presented primary outcomes, 112 under dapagliflozin (5.2%, 95%CI: 0.42 - 0.67) had a drop in the glomerular filtration rate estimated at more than 50%[9,22].

The EMPEROR-Reduced, a double-blind study published in 2020, analyzed 3,730 patients with ejection fraction below 40% and presented consistent results in the presence or absence of T2DM. A total of 1,863 received empagliflozin 10 mg once daily for 16 months, and 1,867 patients received a placebo. The primary outcome occurred in 361 of 1,863 (19.4%) in the empagliflozin group and 462 of 1,867 (24.7%) in the placebo group (p < 0.001, 95%CI: 0.65 - 0.86). Patients from the empagliflozin group had a lower risk of cardiovascular death or hospitalization due to HF, regardless of the presence of diabetes. The decreased glomerular function rate was slower, with a lower risk of severe kidney problems in the group receiving the drug; however, uncomplicated genitourinary infections were more often reported[10,23,24].

In November 2020, the SOLOIST-WHF study, published in the New England Journal of Medicine, was the latest study involving an ISGLT2 drug, which sought to evaluate the safety and benefits of sotagliflozin in patients with T2DM and recent hospitalization for decompensated HF. The study included 1,222 patients (608 from the sotagliflozin group and 614 from the placebo group). A total of 600 primary outcomes occurred: 245 in the drug group and 355 in the placebo group (p < 0.001, 95%CI 0.52 - 0.85). Those who received sotagliflozin had reduced cardiovascular mortality and hospitalization due to HF. Although the study was finished early because of the loss of funds from the sponsor, the benefits of this drug in patients with T2DM and HF were evidenced[11,25,26].

COMPLETION

ISGLT2 is very promising for the future treatment of HF, especially for patients with some other pre-existing comorbidity, such as diabetes and chronic kidney disease. However, more

studies must elucidate its real effectiveness and efficacy; in this context, more robust studies are expected for HF with preserved ejection fraction, considering the benefit demonstrated by these medications in patients with reduced ejection fraction. In future international and Brazilian cardiology guidelines, the use of these new drugs for treating CVD may be updated.

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DEVELOPING RECREATIONAL ACTIVITIES WITH OLDER ADULTS LIVING IN LONG-TERM CARE FACILITIES: AN EXPERIENCE REPORT

DESENVOLVIMENTO DE ATIVIDADES RECREACIONAIS COM IDOSOS INSTITUCIONALIZADOS: RELATO DE EXPERIÊNCIA

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ABSTRACT

The demographic transition has resulted in population aging and a search for care for older adults, increasing the demand for long-term care facilities. This experience report aimed to describe the experience of medical students in one of these institutions using the problematization methodology. The inclusion of recreational activities in the daily lives of older people improved cognitive impairment and self-esteem, providing collective integration and experiences that were different from their routine. The proposed activities promoted the integration of older adults and improved their quality of life and self-esteem.

Keywords: Aging, Long-stay Institution for the Elderly, Elderly, Quality of Life.

RESUMO

A transição demográfica tem como consequências o envelhecimento populacional e a busca por assistência à pessoa idosa, expandindo a procura por instituições de longa permanência de idosos. O objetivo deste estudo foi descrever a experiência vivenciada por estudantes de medicina em uma dessas instituições. Foi um estudo descritivo do tipo relato de experiência, realizado de acordo com a metodologia da problematização. Foi perceptível que a inserção de atividades lúdicas no cotidiano dos idosos contribuiu para a melhora do comprometimento cognitivo e da autoestima, proporcionando-lhes integração coletiva e vivências diferenciadas da rotina habitual. As atividades propostas promoveram a integração dos participantes, a melhora da qualidade de vida e da autoestima dos longevos.

Palavras-chave: Envelhecimento, Instituição de Longa Permanência para Idosos, Idoso, Qualidade de Vida.

INTRODUCTION

Over the last few decades, Brazil has been presenting significant changes in the age pyramid due to increased life expectancy and reduced birth rates. According to the Brazilian Institute of Geography and Statistics, the older population is expected to be larger than the young population in the next decades[1]. These changes promote population aging and the need for adaptation focused on older adults, increasing the demand for long-term care facilities (LTCF)[2].

Although Brazilian public health policies prioritize the family as the provider of care for older adults, the LTCF often becomes an important alternative to ensure care, quality of life, and satisfaction for older adults and their families. However, many institutions need help with human, physical, and financial resources, including a shortage of healthcare professionals and qualified caregivers. Thus, the Brazilian LTCFs face the challenge of complying with public health policies aimed at caring for the health of older adults and their limitations[3].

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Older adults living in LTCF are more likely to be less active, resulting in sedentary lifestyles that reduce physical fitness and increase diseases related to the lack of physical activity and leisure. Therefore, exercise practice for health promotion can minimize these factors in this population[4].

Aging is also associated with reduced functional capacity, considering the biological, psychological, and social changes of this phase. Amnesia, difficulty in concentrating on an activity, and memory loss are common complaints during aging, especially when difficulties appear in remembering names, words, topics, and places where objects have been left[4,5].

The inclusion of recreational activities in the daily lives of these people is important for improving the cognitive impairment and self-esteem of older adults living in LTCF, bringing various benefits to them. During the development of the tasks, emotions, affectivity, and coexistence can be addressed, reducing the level of anxiety and distress, as well as psychological and cognitive functions[5].

Recreational activities can minimize the impact of common stressors in the routine of older adults because the formation and interaction of work groups benefit the expression of feelings and communication. Thus, efforts to ensure the functional, mental, and cognitive capacity of older adults are crucial, and it is important to invest and adapt public health policies in actions to promote, prevent, and control diseases that occur in this population[6].

In this context, the activities developed by the students were key interventions for active aging and maintaining the autonomy of this population, following the objectives and guidelines of the National Health Policy for Older People[7].

OBJECTIVE OF THE EXPERIENCE

To describe the experience of medical students in an LTCF in the municipality of Abreu e Lima, Pernambuco.

METHODOLOGY

This experience report was described according to the problematization methodology using the five stages represented in Charles Maguerez Arc8. This methodology allowed students to develop activities based on the reality in which the older adults were inserted, making it possible to change that reality.

The activities were proposed through visits to an LTCF located in a municipality in the metropolitan region of Recife (Pernambuco), in the area covered by the Timbó Basic Health Unit. This institution provides comprehensive care for 12 older adults.

After exploring the site, identifying the residents and staff, and being informed about the needs and difficulties, the students planned the activities considering the physical and cognitive conditions of older adults and the infrastructure of the LTCF.

RESULTS

The experience of the students at LTCF began during the practical activities, with a presentation of the infrastructure and knowledge of the trajectory and the difficulties faced there. In this way, the students observed the reality of older adults and gathered information about their characteristics.

The students proposed recreational and interactive activities to stimulate the cognitive and neuropsychomotor development of older adults. Activities were divided into several moments according to the planning and the conditions of each older adult.

To implement the activities, the students provided the materials needed, including interactive games, pencils, brushes, reams of paper, glue, and scissors.

The activities provided collective integration and cognitive stimulation for the older adults, which enabled different experiences from their routine. The students realized that simple, low-cost activities can directly stimulate the cognition and motor coordination of older adults, improving their quality of life.

After the activities, the students observed continuous progress in older adults, improving their quality of life and self-esteem.

Thus, recreational activities were essential to promote active and healthy aging due to the interaction provided interaction between the older adults of the LTCF. Moreover, gains related

to cognitive stimulation and their happiness at enjoying moments of integration and relaxation were noticeable, allowing them to experience a sense of well-being.

CONCLUSIONS

Based on the new social configuration that shows the increase in older adults in Brazil, the proposal of recreational activities in the LTCF has fostered integration among older adults and allowed them to realize that they are not the only ones experiencing problems. Activities also promoted positive changes, such as greater interaction, communication, strengthening bonds, and reduced isolation. Last, older adults must be integrally stimulated to minimize the consequences of aging, concerned not only with biophysical aspects but also with motivational and social aspects.

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BOOK REVIEW

RESENHA DE LIVRO

A REABILITAÇÃO CARDÍACA DE UM PONTO DE VISTA DA INTERVENÇÃO MULTIDISCIPLINAR: ASPECTOS RELEVANTES

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Cardiac rehabilitation from a multidisciplinary intervention point of view: relevant aspects

Developing and Managing Cardiac Rehabilitation Programs is a book written and edited by PhD Linda Hall, director of the Cardiac and Pulmonary Rehabilitation General Hospital in Allegheny, Pittsburg. The book was published by the Human Kinetics Publishers, Champaign, IL (ISBN O-87322-358-6) in 1993 and had 248 pages. Despite the year of publication, it is a classic book about cardiac rehabilitation programs based on the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines, considering technical operationalization, administrative, and marketing aspects. The book presents a new perspective on the multidisciplinary vision for professionals working in this area, making it suitable as a complementary postgraduate text.

The book is divided into 15 chapters and written by ten researchers who aim to explore the pathophysiology of heart disease and promote a discussion between their form of investigation and clinical intervention with the patient. It is a practical and comprehensive guide for cardiac rehabilitation based on the medical practice in a multidisciplinary vision.

In the initial chapters, the reader is led through a systematic reading of the process of taking the patient to a cardiac rehabilitation program; those for patients with diseases other than ischemic heart disease are discussed in a separate chapter. Several tables and lists improve the perception of the reader and familiarize them with dyspnea scales and ratings of perceived exertion, promoting a practical approach to intervention based on clinical and scientific knowledge. Some chapters provide a good overview of the pathology; however, some information is repeated in subsequent chapters, which could have been avoided. Nevertheless, other chapters are crucial and well written, such as the risk stratification of patients with unstable angina and proper investigations, including Holter monitoring and catheterization. Medication management, including the use of antithrombotics, thrombolytics, and antianginal agents, is also appropriately discussed.

Developing and Managing Cardiac Rehabilitation Programs provides a good, readable overview of the topic and should be useful and interesting for any physician involved in the care of patients with cardiac diseases.

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AUTHOR GUIDELINES

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SCOPE

The Journal Annals of Olinda Medical School reflects the thinking and commitment to the production of knowledge based on the social responsibility that we assume as protagonists, and as part of the Institutional Development Project of the Faculdade de Medicina de Olinda (FMO). Aiming to strengthen the inseparability of teaching, research and extension, in addition to consolidating quality education, anchored in scientific bases and ethical values, the journal was created in light of an editorial line committed to a sustainable world and focused on medicine as a profession with a strong social and humanized component.

The Journal Annals of Olinda Medical School - Health Social Responsibility, was created in 2018. Since then, it has been the official vehicle of the Olinda School of Medicine to support its principles, especially those related to encouraging research, teaching, and professional medical practices. It is an important instrument for disseminating knowledge, allowing exchange with other areas that favor medicine and the community, and enabling improvement of the standard care provided to the population. Since its inception, Anais FMO has faithfully complied with the requirements for biannual online and printed periodicity for scientific publication, following the recommendations of the International Committee of Medical Journal Editors (www.icmje.org) , which are commonly used in the areas of medicine and related sciences. Currently, Anais FMO is duly registered as a journal in the ISSN system. Articles are published in a continuous flow and all are free and open access, offered through the link https://afmo.emnuvens.com.br. By publishing their article in Anais FMO, authors transfer copyright to the journal and grant it the right of first publication. Manuscripts are submitted online through the platform, available at https://afmo.emnuvens.com.br/afmo/about/submissions.

POLICIES OF THE JOURNAL ANNALS OF OLINDA MEDICAL SCHOOL

Research Ethics Committee Approval

All publications submitted to the Annals of Olinda Medical School must have followed the research ethics recommendations of the Declaration of Helsinki and the standards of Resolution no. 466/2012 (http://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf http://conselho.saude.gov.br/resolucoes/2016/Reso510.pdf) of Brazilian National Health Council. Studies that analyze aggregated data without identifying participants, such as those available in official databases in the public domain are exempt from research ethics committee approval.

Following the guidance of the National Research Ethics Commission, National Health Council, Ministry of Health (CONEP/CNS/MS), no institution is superior to the research ethics committee to analyze the nature of research proposals. The research ethics committee that approves the research must be registered with CONEP.

Research ethics committee must also approve case reports, following the provision no. 166/2018, of the Research Ethics Committee/CONEP/CNS, (http://conselho.saude.gov.br/images/comissoes/conep/documentos/CARTAS/CartaCircular166.pdf).

Case reports involving cadaveric parts must also have a research ethics committee approv-

al. Reports that use parts from cadavers destined for medical schools or similar areas for teaching and research purposes, in addition to ethical approval, must have authorization from the responsible institution to conduct the research.

It is mandatory to send a copy of the research ethics committee approval before submission.

Peer Review

Annals of Olinda Medical Schools recognizes that peer review is important in the publication process.

Therefore, we analyze the submitted manuscripts with ethics and maximum scientific rigor, following the steps below:

Every manuscript received is analyzed for suitability to the scope of the journal, its contribution to knowledge advancement, its originality, the methodological rigor with which the study was conducted, and the adequacy of the conclusions in relation to the results presented. In addition, the formatting is evaluated according to the standards of the journal. If any inaccuracy is identified, the manuscript is returned to the corresponding author, indicating the necessary adjustment. Only manuscripts that meet all the criteria described in the “Author Guidelines” undergo peer review.

Peer review is performed by at least two reviewers with extensive competence to evaluate the manuscript. The entire process is double-blinded; that is, reviewers and authors do not know each other’s identities.

The editorial decision is made based on the comments from the reviewers. It may follow one of the following outcomes: (1) rejection, (2) new submission chance by addressing the comments received, or (3) approval with or without changes.

Manuscripts falling under outcome (1), rejection, will be returned to the authors. In the case of outcomes (2) and (3), more than one round of review may be necessary. Conflicting opinions will have a third opinion requested or will undergo editorial arbitration. Failure by authors to comply with the review deadlines stipulated by the journal may result in the submission being archived. Approved manuscripts may receive layout changes as long as they do not alter the merit of the work.

The final editorial decision is recorded and is the responsibility of the editorial board. The manuscript content is the sole responsibility of the authors.

TYPES OF MANUSCRIPTS ACCEPTED FOR PUBLICATION

Original article: a full paper of a clinical or experimental investigation with unpublished research results (limit of 3,400 words, seven authors, and 30 references).

Integrative, systematic review, and meta-analysis: they should address topics of interest in health. Narrative reviews will not be accepted. Authors must include the study motivation in the Introduction. Summary and abstract must be formatted as a single paragraph in a block format with up to 250 words (limit of 3,400 words, seven authors, and 45 references).

Short Communication: short communication of original research results. In general, short communications are leaner analyses with a brief discussion of the results (summary and abstract must be formatted as a single paragraph in a block format with up to 120 words; the manuscript must be up to 1,000 words with Introduction, Methods, Results, and Discussion sections; up to two tables/figures can be included in up to three pages combined; references are limited to six).

Case reports: description of clinical cases of interest due to their rarity, presentation, innovative diagnosis, or treatment (summary and abstract must be formatted as a single paragraph in a block format with up to 120 words; the manuscript must be up to 2,000 words with Introduction, Case Report, and Discussion sections; up to two tables/ figures can be included in up to three pages combined; references are limited to fifteen; limit of seven authors).

Experience reports: detailed description of a successful or unsucessful experience of an author or a team, which contributes to the discussion, exchange, and proposition of ideas

for improving health care. It must include an introduction with a theoretical framework for the experience, objectives of the experience, methodologies used (including a description of the context and procedures), results, and final considerations. Summary and abstract must be formatted as a single paragraph in a block format with up to 120 words; the manuscript must have up to 2,000 words and up to two tables/figures; limit of 15 references and seven authors).

Methodological paper and theoretical/technical essays: manuscripts that deal with techniques or theories used in epidemiological studies or that portray an original clinical observation or description of technical innovations. Manuscript should be concise, limited to 1,500 words, five references, two illustrations, four authors, summary and abstract in must be formatted as a single paragraph in a block format with up to 120 words.

Critical review: restricted to a book or film in the medical field and related sciences. Argumentative manuscript in which the author describes and analyzes a social production aiming to influence his readers by recommending the work for its qualities or rejecting it for its flaws. It must be presented as follows: (1) presentation - summary of the work analyzed with both technical information and information about the book or film content; (2) analysis – interpretation and analysis of the work highlighting its main points, whether positive or negative, and the critical analysis from the author; (3) conclusion - opinion on the work, resuming the main points analyzed (up to 1000 words and two authors);

Letters to the Editor: comments from readers on works published in the Annals of Olinda Medical School (500 to 700 words).

Editorial: It is the initial article of a volume and is generally requested by the Chief and Deputy Editors to guests with recognized technical and scientific skills.

The word count includes Introduction, Methods, Results, and Discussion (title page, summary, abstract, references, tables, and figures are not included in the word count).

Manuscripts submitted must be intended exclusively for the Annals of Olinda Medical School, and simultaneous submission to another journal is prohibited. The information and concepts presented in the manuscript, as well as the veracity of the research content, are the sole responsibilities of the author(s).

Formatting

Manuscripts are accepted in Portuguese or English and must have an abstract in the original language of the manuscript and English. Manuscripts in English must have an abstract in English and Portuguese.

Manuscripts must be sent in Word, double-spaced, and Arial font size 12. Do not use line breaks. Do not use force manual hyphenations. The full term must follow abbreviations cited for the first time in the document. Title and abstract must not contain abbreviations.

Title page

Title of the manuscript in Portuguese and English (up to 25 words for each title);

Author information (full name, email, ORCID, affiliation, city, state, and country — do not include title and position);

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Conflicts of interest, in accordance with the Resolution of the Federal Council of Medicine (CFM) no. 1595/2000, which prohibits the publication of works for advertisement purposes of medical products and equipment, available at https://sistemas.cfm.org.br/normas/visualizar/resolucoes/BR/2000/1595. Conflicts of interest must be presented as follows: “The author(s) (name them) received financial support from the private company (mention its name) to conduct this study”. If there are no conflicts of interest, the authors must declare: “The authors have no conflicts of interest to declare”.

Source of financing, stating whether public or private; if there is none, mention that the study was not funded;

Number of the Certificate of Presentation for Ethical Assessment (CAAE) or number of Research Ethics Committee approval;

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On the following pages, always starting on a new page, the following sections must be presented:

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Summaries must comply with the recommendations for each category of manuscript. In general, it must contain up to 250 words and be in structured format, covering the sections Objective, Methods, Results, and Conclusion. The same rule applies to the abstract.

Authors must include a minimum of four and a maximum of six keywords in both English and Portuguese regardless of the language in which the manuscript was submitted.The keywords must be standardized according to the Health Sciences Descriptors (DeCS), available at http://decs.bvs.br/.

References

References must be numbered consecutively according to the first mention in the manuscript and using superscript Arabic numerals in accordance with Vancouver style (www.icmje.org). The reference list must follow the numerical order of the manuscript, ignoring the alphabetical order of authors. Journal titles must follow the Index Medicus/Medline. The name of the first six authors must appear, followed by the expression et al. when this number is exceeded. Whenever available, the Digital Object Identifier (DOI) must be provided (see examples below). Personal communications, unpublished or ongoing work, citations from books, thesis, and dissertations should be avoided. The accuracy of references is the responsibility of the authors.

EXAMPLES

Reference to a journal publication:

Ng OT, Marimuthu K, Koh V, Pang J, Linn KZ, Sun J, et al. SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study. Lancet Infect Dis. 2021 Mar; 21(3):333-343. doi: 10.1016/S1473-3099(20)30833-1

Jardim BC, Migowski A, Corrêa FM, Azevedo e Silva G. Covid-19 no Brasil em 2020: impacto nas mortes por câncer e doenças cardiovasculares. Rev Saude Publica. 2022; 56:22. https://doi.org/10.11606/s1518-8787.2022056004040.

Reference to a World Health Organization Report

World Health Organization. Clinical Care for Severe Acute Respiratory Infection—Toolkit—Update 2022. Genebra: World Health Organization; 2022.

Reference to electronic documents

Brasil. Casos de aids notificados no SINAN, declarados no SIM e registrados no SISCEL/SICLOM, segundo capital de residência por ano de diagnóstico. Brasil, 1980-2021 [Internet]. 2021 [acessado em 12 abr. 2022]. Available at: http://www2.aids.gov.br/cgi/deftohtm.exe?tabnet/br.def

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Figures and tables must be inserted at the end of the manuscript, followed by their respective captions. Submission in separate files is not permitted. There must be page breaks between each one, respecting the maximum number of three pages for tables and figures combined. Do not format tables using the TAB key.

Figures must be up to 15 cm wide in Portrait orientation and 24 cm wide in landscape orientation and be presented within the requested margin (Normal Word setting). Colored figures are accepted. Figures must be provided in high resolution, plots in editable format, and tables, equations, charts, and flowcharts must be sent in an editable file (Word or Excel), never as an image.

Contact Methods

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