International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn24307

Insulin resistance and metabolic syndrome as a risk factor for Alzheimer's Disease: systematic literature review

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DOI: https://doi.org/10.54448/ijn24307

Received: 03-14-2024; Revised: 05-23-2024; Accepted: 07-04-2024; Published: 07-09-2024; IJN-id: e24307

Editor: Fernando Alberto Carrasco Naranjo, MD, MSc, MPH.

Abstract

Introduction: It is estimated that worldwide, 65.7 million people will live with the disease in 2030, with Alzheimer's disease being the most prevalent in the world, accounting for 60% of dementia cases. The hypothesis was then raised that through the neuroprotective effect of insulin and insulin resistance in the genesis of Metabolic Syndrome, the hypothetical relationship is made that metabolic syndrome is a risk factor for Alzheimer's disease. **Objective:** The literature that verifies the impact of vitamin D deficiency on the quality of life of individuals undergoing bariatric surgery was reviewed. **Methods:** The search strategy was carried out in the virtual databases PubMed, Scielo, LILACS, Scopus, Web of Science, Embase, and Biblioteca Virtual em Saúde, in addition to gray literature such as Google Scholar, OpenGrey, Ibict/BDTD (Brazilian digital library of theses and dissertations) and ProQuest using the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) descriptors with the Boolean logical operators AND, OR and NOT. The studies considered eligible were those that presented metabolic syndrome as a risk factor for the development of Alzheimer's disease**. Results**: The online search found 216 studies in virtual bibliographic databases and 70 in gray literature. After removing duplicates, 282 articles remained and were read the title and abstract, with 25 articles chosen for full-text reading, leaving 13 that met the inclusion criteria. Most of the studies included corroborated the hypothesis that metabolic syndrome is a risk factor for Alzheimer's disease. Even the two studies that provide some results in which BMI showed a slower decline in cognitive function, stated that the phenotype studied was that of metabolically healthy obese individuals. **Conclusion:** The results of this study confirmed the idea that there is an interaction between metabolic health and brain health. First, chronic inflammation and oxidative stress associated with metabolic syndrome can cause damage to blood vessels, compromising cerebral blood flow and impairing the supply of essential nutrients to the brain. Additionally, insulin resistance, one of the key components of metabolic syndrome, can hurt brain function by interfering with the absorption of glucose, a vital fuel for the brain. Finally, how changes in blood lipid levels can contribute to the accumulation of beta-amyloid protein plaques in the brain, one of the markers of Alzheimer's disease.

Keywords: Insulin Resistance. Metabolic Syndrome. Alzheimer Disease.

Introduction

Metabolic syndrome (MS) is characterized by at least three changes such as abdominal circumference greater than 102 cm in men and greater than 88 cm in women, increased triglycerides, decreased concentration of high-density lipoprotein (HDL), higher blood pressure or equal to 135/85 mmHg or higher and fasting blood glucose greater than or greater than 100 mg/dL. These characteristics, closely related to excess adipose tissue (especially visceral fat), contribute to

metabolic changes, such as insulin resistance (the genesis of MS), and increased cardiovascular risk (such as dyslipidemia and atherosclerosis, resistance to insulin and diabetes mellitus and ischemic events). Insulin is a hormone released in pancreatic β-cells, which acts on the brain and peripheral tissues. It has a neuroprotective effect and regulates synaptic plasticity, making it vital for optimal cognitive functioning. Its receptors are expressed by the number of synaptic terminals of neurons in the hippocampus, amygdala, hypothalamus, cortex, entorhinal cortex, and olfactory bulb **[1,2]**.

Alzheimer's disease (AD) is related to a decrease in cognitive capacity with increasing age, with shrinkage of the brain and progressive loss of neurons, usually the hippocampus and basal part of the forebrain **[3]**. It is estimated that worldwide, 65.7 million people will live with the disease in 2030, with Alzheimer's disease being the most prevalent in the world, accounting for 60% of dementia cases. Anatopathological findings range from diffuse atrophy with flattened cortical grooves and enlarged cerebral ventricles to the development of senile plaques, neurofibrillary tangles, neuronal loss, sympathetic loss, and granulovascular degeneration of neurons. Some of the neurotransmitters associated with this dementia are acetylcholine and norepinephrine, assuming that both are involved in hyperactivity in the individual affected by AD **[4]**. Senile plaques or amyloid plaques are composed of a specific protein β/A and are strong indicators of Alzheimer's syndrome **[3,4]**.

It is noteworthy, therefore, that insulin is a hormone released in pancreatic β-cells, which acts on the brain and peripheral tissues, it has a neuroprotective effect and regulates synaptic plasticity, making it vital for optimal cognitive functioning. Its receptors are expressed by the number of synaptic terminals of neurons in the hippocampus, amygdala, hypothalamus, cortex, entorhinal cortex, and olfactory bulb **[5]**.

The hypothesis was then raised that through the neuroprotective effect of insulin and insulin resistance in the genesis of Metabolic Syndrome, the hypothetical relationship is made that metabolic syndrome is a risk factor for Alzheimer's disease. The prevalence of Metabolic Syndrome in the Brazilian population was estimated at 38.4% **[6]**. The prevalence of dementia in Alzheimer's disease is 60% of all dementia conditions, with an estimated 65.7 million individuals worldwide living with the disease in 2030 **[6]**.

Therefore, it was necessary to carry out a literature review to investigate whether there is a relationship between insulin resistance and metabolic syndrome with the development of Alzheimer's disease. The objective of this study was to demonstrate whether there is a relationship between insulin resistance and metabolic syndrome with the development of Alzheimer's disease.

Methods

Protocol

A literature review was carried out with components of a systematic review and, for this purpose, parts of the PRISMA (Preferred Items for Systematic Reviews and Meta-Analyses) protocol were used.

Eligibility Criteria

The PECO structure (population, exposure, comparative, outcome) was used to define the eligibility criteria, with P: general population; E: metabolic syndrome; C: absence of metabolic syndrome; O: Alzheimer's disease. Cross-sectional epidemiological studies, case-control, cohort studies, and clinical trials investigating metabolic syndrome as a risk factor for the development of Alzheimer's disease were included.

Information Sources

The following virtual bibliographic databases were analyzed to search for potentially eligible studies: PubMed, Scielo, LILACS, Scopus, Web of Science, Embase, and VHL. Additionally, gray literature was explored: Google Scholar, OpenGrey, Ibict/BDTD. The descriptors used in the searches were selected from Medical Subject Headings (DeCS / MeSH), as well as the Boolean logical operators (AND, OR, and NOT) based on pre-defined keywords.

Search and Study Selection Strategy

The search strategy included the following DeCS/MeSH terms: *Metabolic Syndrome; Alzheimer's Disease; Risk Factors*. After extracting the studies from the databases, the bibliographic reference manager, Endnote Web, was used to identify and remove duplicate articles. In the first stage, reviewers selected the studies that were included by title and abstract. Those who met the criteria proceeded to the second stage of complete reading of the articles.

Assessment of The Quality of Primary Studies

The assessment of the risk of bias in primary studies was carried out by applying specific tools for each type of epidemiological study.

Data Collection and Extraction Process

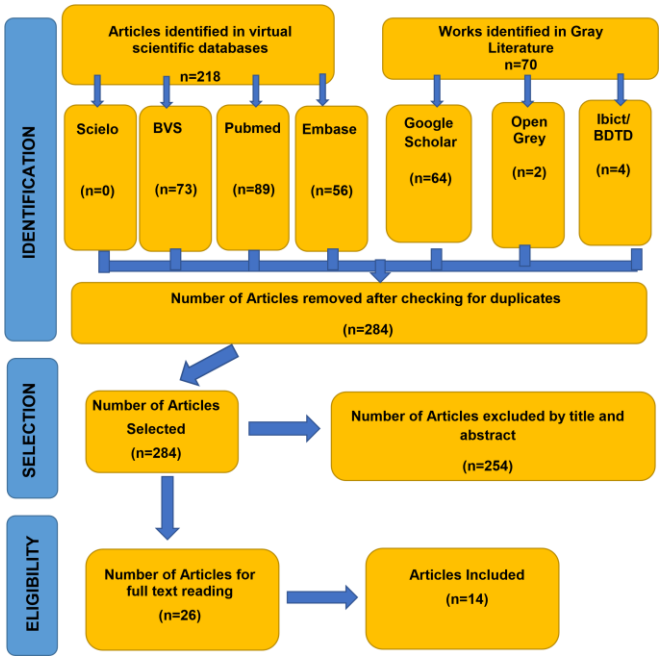
For the narrative synthesis, the following data were extracted from the included studies and tabulated in an Excel 365 spreadsheet: authors, year of publication, type of study, sample size, sex, assessed age, presence of pathologies (diabetes; obesity; hypercholesterolemia;

hypertriglyceridemia; high blood pressure), diagnosis of Alzheimer's disease; statistical analysis, investigated outcomes, general results, conclusions. Studies excluded from the review were registered and justified. Once this process was completed, the data extracted from the included studies was synthesized.

Results

Based on the criteria established for the search, 284 publications were found. Of these 284 works, 26 were chosen after reading the title and abstract, to read the full text (Figure 1). After reading, 12 articles were excluded, resulting in a final number of 14 articles that make up this review (Table 1).

Figure 1. Flowchart of the article selection process.



Source: Own Authorship.

Table 1. Justification for excluding articles.

Author	*Title*	*Year*	*Justification for Exclusion*
Chornenkyy Y et al [7]	Alzheimer's disease and type 2 diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction upstream of observed cognitive decline	2019	Non-original study (review)
Zhuang Q et al [8]	Associations Between Obesity and Alzheimer's Disease: Multiple Bioinformatic Analyses	2021	Other factors associated with AD
Bradley D et al [9]	Clusterin as a Potential Biomarker of ObesityRelated Alzheimer's Disease Risk	2020	Non-original study (review)
Bouges S et al [10]	Effect of Metabolic Syndrome Risk Factors on Processing Speed and Executive Function in Three Racialized Groups	2023	Other factors associated with AD
Ahn S et al [11]	Factors Predicting the Onset of Amnestic Mild Cognitive Impairment or Alzheimer's Dementia in Persons With Subjective Cognitive Decline	2020	Other factors associated with AD
Vinuesa A et al [12]	Inflammation and Insulin Resistance as Risk Factors and Potential Therapeutic Targets for Alzheimer's Disease	2021	Non-original study (review)
Mole JP et al [13]	Insulin resistance in Alzheimer's disease: The Genetics and Metabolomics links	2020	Non-original study (review)
Atti AR et al [14]	Metabolic Syndrome, Mild Cognitive Impairment, and Dementia: A Meta-Analysis of Longitudinal Studies	2019	Non-original study (review)
Ma L et al [15]	Metabolically healthy obesity reduces the risk of Alzheimer's disease in elders: a longitudinal study	2019	Other factors associated with AD
Omura JD et al [16]	Modifiable Risk Factors for Alzheimer's Disease and Related Dementias Among Adults Aged ≥45 Years - United States, 2019	2022	Other factors associated with AD
Nianogo R A. et al [17]	Risk Factors Associated With Alzheimer's Disease and Related Dementias by Sex and Race and Ethnicity in the US	2022	Association of race/ethnicity with AD
Carty CL et al [18]	Risk Factors for Alzheimer's Disease and Related Dementia Diagnoses in American Indians	2020	Association of race/ethnicity with AD

Source: Own Authorship.

Table 2 shows the articles selected for the study, with details of the type of study, participants, ages, and results achieved.

Table 2. Articles selected for review.

Author and Country	*Kind of study/ Participants/Age*	*Results*
Kim JK. et al Gwangjum/South Korea 2019 [19]	Retrospective study of 110 healthy middle-aged and elderly individuals	Increased muscle tissue was associated with a lower likelihood of AD in older adults, but visceral adipose tissue was not associated with a lower likelihood of AD in middle-aged or older adults.
Moody J. et al USA 2021[20]	Cohort study. 104 older adults aged 55 to 84 years who were diagnosed with mild cognitive impairment at baseline, with 52 individuals who converted to AD within 24 months and 52 matched individuals who did not convert to AD within 24 months	The results showed an interaction between BMI and genetic risk, such that individuals with lower BMI and higher polygenic risk were more likely to convert to AD relative to individuals with higher BMI.
Kang SY et al Seul/South Korea 2021 [21]	Longitudinal Study. 45,076 male and female participants over the age of 60	Loss of BMI over 2 and 4 years was associated with an increased risk of AD, and the risk increased in women with greater BMI variability. Adequate control of body weight is recommended to prevent AD.
Cho Y. et al Seul/South Korea 2021[22]	Longitudinal study. 1,492,776 men and women over the age of 45	More cumulative exposure to metabolic disorders has been associated with a higher risk of dementia.
Haiwon Y et al Chungju/South Korea 2022 [24]	Longitudinal study of 3,619,388 men and women aged 50 to 69 years	A study showed that Metabolic Syndrome was related to an increased incidence of Alzheimer's dementia and vascular dementia.

Mole J. et al Cardiff, UK 2020 [25]	Randomized study 165 asymptomatic adults aged between 38 and 71 years	Genetic risk modifies the impact of obesity on myelin and white matter microstructure consistent with neuroglial models of aging and late-onset Alzheimer's disease
Sun Z. et al Shanghai, China 2020 [26]	Longitudinal study. Of 1,212 participants included in the study, 439 individuals were in the normal weight range; 518 were overweight; and 250 were obese	Individuals with higher BMI experienced a slower decline in cognitive function. Furthermore, Kaplan-Meier survival analysis revealed that higher BMI in old age had a reduced risk of progression to AD over time (p = 0.009). Higher BMI in old age decreases the risk of AD, and this process may be driven by AD-related biomarkers.
Palta, P. et al New York, USA 2021 [27]	Cross-sectional analysis of 350 middle-aged Hispanics	Metabolic syndrome as an arbitrary measure of aggregate metabolic and vascular risk does not capture the risk of AD neuropathology in late middle age and other approaches to measuring aggregate risk should be examined.
Gregorio, E. et al Guarapuava-PR/Brazil 2019 [28]	Cohort study. 30 elderly people in the study phase (2011) and 16 elderly people in phase 2 (2014)	Patients are likely to be overweight or obese before the development of AD and this may be associated with an increased risk of dementia.
Ly M. et al. St Louis, USA 2021 [29]	Longitudinal study. 104 Elderly people over 60 years old who are cognitively normal	Statistically significant relationships between neuroinflammation, elevated BMI, and hippocampal volume, raise implications for neuroinflammatory mechanisms of obesity-related brain dysfunction in cognitively normal elderly people.
Lee JY et al Seuol/South Korea 2019 [30]	Retrospective cohort study. 12,296,863 adults aged 50+ who had health screenings from 2009 to 2012 without a baseline history of dementia.	A metabolically healthy obese individual at the end of life demonstrated a lower risk of general dementia and AD, but not vascular disease. Additional studies in other populations are needed to elucidate current results and may predict individuals at increased risk of developing dementia.
Corlier F. et al Pittsburgh/USA 2018 [31]	Longitudinal study. 335 adult humans with a mean age of 77.3 (± 3.4 years)	Found interactions between genetic and environmental factors and the structural health of the brain. The findings support the role of metabolic risk and peripheral inflammation in age-related brain decline.
Cho YK. et al Seoul/South Korea 2021 [32]	136,847 elderly participants aged 60 and over	The metabolically healthy obese phenotype conferred a decreased risk of AD. Maintaining or restoring metabolic health may mitigate the risk of AD among obese individuals.

Source: Own Authorship.

Total Sample

A total of 17,593,360 people were studied, considering the selected articles, with the smallest sample in Guarapuava/Brazil **[28]** (n=16) and the largest sample in Seoul/South Korea **[30]** (n= 12,296,863).

Countries

The studies were carried out in the following locations: 6 studies in South Korea (Kim et al., 2019**[20]**; Kang et al., 2021**[22]**; Cho et al., 2021**[23]**; Haiwon et al., 2022 **[24]**; Lee et al., 2019 **[30]**; Cho et al., 2021 **[32]**), 4 studies in the USA (Moody et al., 2021 **[21]**; Palta et al., 2021 **[27]**; Ly et al.; 2021 **[29]**; Collier et al., 2018 **[31]**), 1 study in the United Kingdom (Mole et al., 2020 **[25]**), 1 study in China (Sun et al., 2020 **[26]**) and 1 study in Brazil (Gregório et al., 2019 **[28]**).

Qualitative Synthesis of Evidence from Included Studies

Of the 14 studies studied, 100% corroborated the hypothesis that metabolic syndrome is a risk factor for Alzheimer's disease. Even the two studies that provide some results in which high BMI experienced a slower decline in cognitive function **[26,32]** stated that the phenotype studied was that of metabolically healthy obese individuals.

A study **[20]** increase in muscle tissue is associated with a lower probability of AD in the elderly, that is, maintaining an ideal weight, with a lower percentage of fat, is ideal, confirming the findings of two other studies **[22,28]**. Genetic risk was cited by 3 studies **[21,25,31]** as an interaction between high BMI and risk of developing AD. Neuroinflammation was also a cause cited in research **[29]** as one of the causes of the development of AD in elderly people with metabolic syndrome.

Discussion

Kim and collaborators **[19]** state that it is important to increase skeletal muscle mass to reduce the risk of AD in the elderly, a finding confirmed by Gregorio et al. **[27]**, and Kang et al. **[21]**, who recommend that adequate control of body weight is highly recommended to prevent AD.

Ly et al. **[28]** mention that there was an identification of statistically significant correlations between neuroinflammation, BMI, and hippocampal volume, with implications for the mechanisms of neuroinflammation in brain dysfunction. Individuals with a Body Mass Index (BMI) equal to or greater than 25 demonstrated an association between increased edema in the white matter of the corpus callosum, internal capsule, cingulate gyrus, and superior frontal-occipital fasciculus, and reduced hippocampal volume. This

finding corroborates the research of De Falco and collaborators **[32]**, who mention that as AD is a multifactorial condition, there is evidence of biochemical markers that include neuroinflammation, calcium dysregulation, abnormalities in the distribution and function of mitochondria, as well as oligomerization of alpha and beta peptides.

Regarding the hypothesis that AD is related to insulin resistance and diabetes, Cho et al. **[22]**, Haiwon et al **[23]** and Lee et al. **[29]** validate this hypothesis. The risk of dementia increases with longer cumulative exposure to metabolic syndrome (MetS) or its components, including diabetes. It is important to highlight that even minimal exposure to MS factors has a significant impact on the risk of dementia **[22]**. Therefore, it is essential to emphasize stricter management of metabolic risk factors as a preventive measure against dementia.

Oliveira et al. **[6]** had also already discussed this hypothesis, citing that the increased risk can be attributed to insulin resistance and hyperinsulinemia, which are associated with neuronal death and the formation of extracellular beta-amyloid. Peptide oligomers of beta-amyloid precursor protein are known to be neurotoxic and to affect synaptic plasticity **[5]**. These findings are also in line with the observation that AD patients often show a decrease in glucose metabolism in brain areas related to memory and learning **[29]**.

Moody et al. **[20]**, Mole et al. **[24]**, and Corlier et al. **[30]** describe the genetic risk in which MetS increases the risk of AD. Mole et al. **[24]** describe that genetic risk influences how obesity affects the microstructure of myelin in white matter, in line with models of aging and late-onset Alzheimer's disease in the context of neuroglia. Furthermore, these results may help clinicians identify individuals at higher risk of developing AD who should be monitored more closely for pathological decline and may benefit most from interventions that attempt to delay or prevent progression to AD. These studies underscore the importance of examining the synergistic effects of genetic and health risk factors to better characterize late-onset AD, which can be used to inform prevention methods.

Two studies suggested that high BMI is not related to AD **[25,26]**. Palta **[26]** came to the conclusion that Metabolic Syndrome (MetS), used solely as an arbitrary measure of metabolic risk, does not adequately cover the risk of neuropathology associated with Alzheimer's disease in middle age. This suggests the need to explore other approaches to assessing this aggregate risk. Sun **[25]** assessed the impact of Body Mass Index (BMI) on the risk of Alzheimer's Disease (AD) using the Kaplan-Meier test and found an inverse association between BMI and the risk of AD. Surprisingly, older people with obesity demonstrated a lower risk of progressing to AD over the subsequent six years compared to those with overweight and normal weight. The Kaplan-Meier survival analysis showed that a higher BMI in advanced ages is associated with a lower incidence of conversion to AD. However, the researcher also suggests the need to investigate alternatives to assess this combined risk.

Two studies concluded that loss of BMI could increase the risk of AD. Kang **[21]** reported that a decrease in BMI over periods of 2 and 4 years resulted in an increased risk of AD, and this relationship was also strengthened in individuals with greater variability in BMI. These associations were particularly notable in women. Moody **[20]** concluded that her study showed that the polygenic risk for AD had a greater impact on the risk in those with a lower BMI on the probability of conversion to AD in 24 months, but in this study, specifically among men. No association was observed between polygenic risk and AD in individuals with higher BMI. These results suggest that genetic risk for AD in the context of lower BMI may serve as a predictor of future progression to AD.

However, the researchers cite some major limitations in their studies. Kang **[21]** mentions that a large number of participants were excluded due to a lack of data, which could result in selection bias. Moody **[20]** has already observed that it was not possible to investigate the relationship between BMI throughout life, genetic risk, and the development of late-onset AD. Furthermore, she highlighted the importance of analyzing the association between BMI in old age and the progression of AD over a substantial period. Therefore, she emphasized the need for additional research to explore the connection between BMI at different stages of life, and genetic risk for AD, including the onset of the disease as some of the neurobiological changes associated with AD begin to manifest. Likewise, she suggested that future studies should investigate the interaction between BMI and polygenic genetic risk in the transition from a cognitively normal state to mild cognitive impairment.

Conclusion

Metabolic syndrome has increasingly been linked to an increased risk of developing Alzheimer's disease, one of the most common forms of dementia. The findings of this study supported the hypothesis that there is an interaction between metabolic health and brain health. First, chronic inflammation and oxidative stress associated with metabolic syndrome can damage blood vessels and impair cerebral blood flow, compromising

the supply of essential nutrients to the brain. Furthermore, insulin resistance, one of the cornerstones of metabolic syndrome, can negatively affect brain function, interfering with the uptake of glucose, an important fuel for the brain. Finally, changes in blood lipids can promote the accumulation of beta-amyloid protein plaques in the brain, one of the markers of Alzheimer's disease. This evidence highlights the importance of adopting a healthy lifestyle and preventive measures to reduce the risk of metabolic syndrome and, consequently, the risk of developing Alzheimer's disease. Maintaining a healthy body weight, practicing regular physical exercise, eating a balanced diet, and controlling blood pressure and glucose levels are fundamental measures to prevent metabolic syndrome and, by extension, reduce the likelihood of developing this devastating form of dementia. Additionally, more research is needed to fully understand the links between metabolic syndrome and Alzheimer's disease to develop more effective prevention and treatment strategies to protect brain health as we age.

Additional research also needs to be conducted to clarify the relationship between BMI loss and AD risk, and also consider other potentially influential factors such as age, gender, and genetic history. Obtaining more solid data and conducting long-term longitudinal studies are crucial to provide a more complete and accurate view of this complex issue and thus assist in making more informed decisions and clinical interventions in the context of AD.

CRediT

Author contributions: **Conceptualization -** Gabriela Fernanda, Leonardo Garcia Baldim, Priscila Witt Said, Rafaela Cristina Camarinho, Jonas Bernardes de Lima Filho, Renan Canale Peres Montanher; **Data curation -** Gabriela Fernanda, Leonardo Garcia Baldim, Priscila Witt Said, Rafaela Cristina Camarinho, Jonas Bernardes de Lima Filho; **Formal Analysis -** Gabriela Fernanda, Leonardo Garcia Baldim, Priscila Witt Said, Rafaela Cristina Camarinho, Jonas Bernardes de Lima Filho, Renan Canale Peres Montanher; **Investigation -** Gabriela Fernanda, Leonardo Garcia Baldim, Priscila Witt Said, Rafaela Cristina Camarinho, Jonas Bernardes de Lima Filho; **Methodology -** Gabriela Fernanda, Leonardo Garcia Baldim, Priscila Witt Said, Rafaela Cristina Camarinho, Jonas Bernardes de Lima Filho; **Project administration -** Gabriela Fernanda, Leonardo Garcia Baldim, Renan Canale Peres Montanher; **Supervision -** Renan Canale Peres Montanher; **Writing - original draft -** Gabriela Fernanda, Leonardo Garcia Baldim, Priscila Witt Said, Rafaela Cristina Camarinho, Jonas Bernardes de Lima Filho, Renan Canale Peres Montanher; **Writing-review & editing -** Gabriela Fernanda, Leonardo Garcia Baldim, Priscila Witt Said, Rafaela Cristina Camarinho, Jonas Bernardes de Lima Filho, Renan Canale Peres Montanher.

Acknowledgment

Not applicable.

Ethical Approval

Not applicable.

Informed Consent

Not applicable.

Funding

Not applicable.

Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate@.

Peer Review Process

It was performed.

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