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ANALYSIS OF THE ASSOCIATION BETWEEN TYPE 2 DIABETES MELLITUS AND THE DEVELOPMENT OF ALZHEIMER'S AND DEMENTIA: COMPLICATIONS AND PREVENTION STRATEGIES

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ABSTRACT
Introduction: Alzheimer's disease (AD) is the main cause of dementia in the elderly population, accounting for 60% to 70% of cases, as a consequence it leads to cognitive decline. At the same time, the prevalence of type 2 diabetes mellitus (T2DM) has been increasing, with the metabolic disorder increasing the risk of dementia. The relationship between AD and DM2 is complex and involves risk factors associated with lifestyle and eating habits, as well as the brain-gut axis. Inflammation mediated by cytokines, such as IL-6 and TNF-α, results in exacerbation of AD and contributing to insulin resistance, forming a link between the two conditions. Objective: To analyze and associate AD and Dementia as a complication of DM2, as well as its prevention. Methodology: This is an integrative literature review using the prism method, where articles from the last 5 years were analyzed and selected from the electronic databases: Pubmed and VHL (Virtual Health Library). The following descriptors were used: "Diabetes Mellitus", "Alzheimer's", "Dementia" combined with the Boolean operator "AND". A total of 99 articles were obtained, of which only 12 addressed the objective of the study. Results and Discussion: Studies have shown that T2DM increases the risk of neurodegenerative diseases, such as AD, due to insulin resistance and chronic inflammation. Interventions, such as physical exercise and medications (exenatide and metformin) can help preserve the cognitive function of diabetics. Hypoglycemia and obesity also negatively affect brain health, leading to changes in perfusion and neuronal density. The research seeks to better understand these relationships in order to develop prevention and treatment strategies. Conclusion: The research addresses the effects of systemic inflammation and metabolic alterations by offering new perspectives for interventions aimed not only at controlling T2DM, but also at preserving cognitive function in the at-risk population.

Keywords: Diabetes Mellitus. Alzheimer 's. Dementia.

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INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia among the elderly population, accounting for about 60% to 70% of cases (WHO, 2020). The etiology of AD is not yet fully understood, although significant advances have been achieved in the knowledge of genetic and environmental risk factors, as well as in relation to the pathological findings associated with this neurodegenerative disorder. One of the main characteristics of AD is the aggregation and deposition of β-amyloid peptides (Aβ) on the extracellular surface of neuronal cells, leading to the formation of oligomers and Aβ fibrils in the brain. In addition, AD patients have hyperphosphorylation of TAU proteins in the brain, which accumulate in the microtubules of neurons, resulting in neurofibrillary tangles. These events promote cytotoxic effects on neuronal cells, leading to cognitive decline (Yang, 2019).

At the same time, the prevalence of diabetes mellitus (DM) has increased in recent decades. According to the International Diabetes Federation (IDF), 1 in 10 people live with diabetes worldwide and type 2 diabetes mellitus (T2DM) accounts for almost 90% of all diabetes cases (IDF, 2020), which is characterized by insulin resistance. Similar to dementia, the risk of developing T2D increases with age; on the other hand, this metabolic disorder also increases the risk of dementia (Chen; Yu; Gong, 2019).

Alzheimer's disease and its relationship with type 2 diabetes mellitus (DM2) are still poorly understood mechanisms. In this sense, it is always related to risk factors established in eating habits and lifestyle, in which the association between type 2 diabetes and Alzheimer's disease is characterized in the brain-gut axis (Carranza-Naval *et al*., 2021). Inflammation mediated by cytokines such as IL-6, TNF-α or TGF-β act concomitantly in the exacerbation of Alzheimer's disease (Barroeta-Espar *et al*., 2019). As a result, the release of more inflammatory mediators by adipocytes can also increase insulin resistance in individuals who have type 2 diabetes mellitus (Haghani *et al*., 2015). Thus creating the inflammatory process as a link to the two diseases (Carranza-Naval *et al*., 2021).

Different studies have demonstrated the existence of a significant association between DM2 and the development of AD. Advances in the field of neuroendocrinology have markedly made the investigation of the underlying molecular mechanisms involved in the link between both disorders. Even though several confounding factors can intervene in this relationship, studies have found that these diseases can share pathophysiological phenomena such as the various abnormalities when it comes to insulin signaling in the

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PI3K and MAPK pathways in brain tissues, as well as the disruption of mitochondrial function, autophagy, defects in glucose transporters (GLUTs 1 and 3) and oxidative stress (Rojas *et al*., 2021).

That said, in Alzheimer's disease, in addition to these factors, the alteration of glucose metabolism and insulin signaling in the brain seems to induce early loss of neurons and impairment of synaptic plasticity in the years prior to the clinical manifestation of the disease. In this sense, due to the large amount of evidence about the existence of insulin resistance in the brain during Alzheimer's disease led to the description of this disease as "type 3 diabetes" (Hamzé *et al*., 2022). The present research aims to analyze and associate Alzheimer's disease and dementia as a complication of type 2 diabetes mellitus, as well as its prevention.

METHODOLOGY

The present study consists of an integrative literature review using the prism method. Thus, the research began with a broad search in the literature, where the electronic databases: PubMed and VHL (Virtual Health Library) were used for the bibliographic search, with the purpose of contemplating the objective of this research. The main terms used were the descriptors "Diabetes Mellitus", "Alzheimer's", "Dementia". The search was restricted to the last five (5) years, from 2019 to October 2024. The website used for the creation and generation of the PRISMA flowchart was CANVA.

Having the following inclusion and exclusion criteria used in the Electronic Database:

INCLUSION CRITERIA

1. Articles in English and Portuguese.
2. Articles classified as Meta-analysis.
3. Scientific articles that have conducted a Clinical Trial.
4. Randomized Controlled Trial articles.
5. Complete and free articles.
6. Articles that carried out the study with humans and both sexes.

EXCLUSION CRITERIA

1. Systematic Review and Literature Articles.

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2. Articles such as Abstract, Letter, Notice, Thesis, Doctorate, Bibliography, studies that have not completed their analysis or have not obtained a concrete analysis of the proposed study.
3. Private articles.
4. Non-original scientific articles.
5. Articles that did not contemplate the purpose of this article.

In the PubMed Electronic Bibliographic platform, the descriptors "Diabetes Mellitus" and "Alzheimer's" were used, combined with the Boolean operator "AND". In addition, the inclusion and exclusion criteria mentioned and detailed above were used, along with the articles available in English and Portuguese from the last 5 (five) years, from 2019 to October 2024, and the filters: "clinical trial", "randomized controlled trial", "meta-analysis", "humans", "both sexes" and "full free text". Thus, a total of 16 (sixteen) scientific articles were obtained, among which 2 (two) articles were selected. In addition, another search was performed containing the same filters and criteria mentioned above, however, the combination of the following descriptors was used: "Diabetes Mellitus", "Alzheimer's", "Dementia" all combined with the Boolean operator "AND", and 6 (six) articles were obtained, of which only 2 (two) articles contemplated the objective of the study. In addition, a 3rd (third) search was performed using the same filters, however, with the following descriptors: "Diabetes Mellitus" and "Dementia" combined with the Boolean operator "AND", and 32 (thirty-two) articles were found, among which only 5 (five) articles were selected for the study.

The following descriptors were used in the VHL (Virtual Health Library) electronic platform: "Diabetes Mellitus", "Alzheimer's", "Dementia", all combined with the Boolean operator "AND". In addition, the inclusion and exclusion criteria mentioned and detailed above were used, along with the articles available in English and Portuguese from the last 5 (five) years, from 2019 to October 2024, and the filters: "Clinical practice guide", "controlled clinical trial" and "prognostic study". In this search, 45 (forty-five) scientific articles were found, of which only 3 (three) met the objective of the present study.

The screening of articles on the platforms mentioned above was demonstrated in Figure 1, and the model for selecting articles is evidenced in a flowchart.

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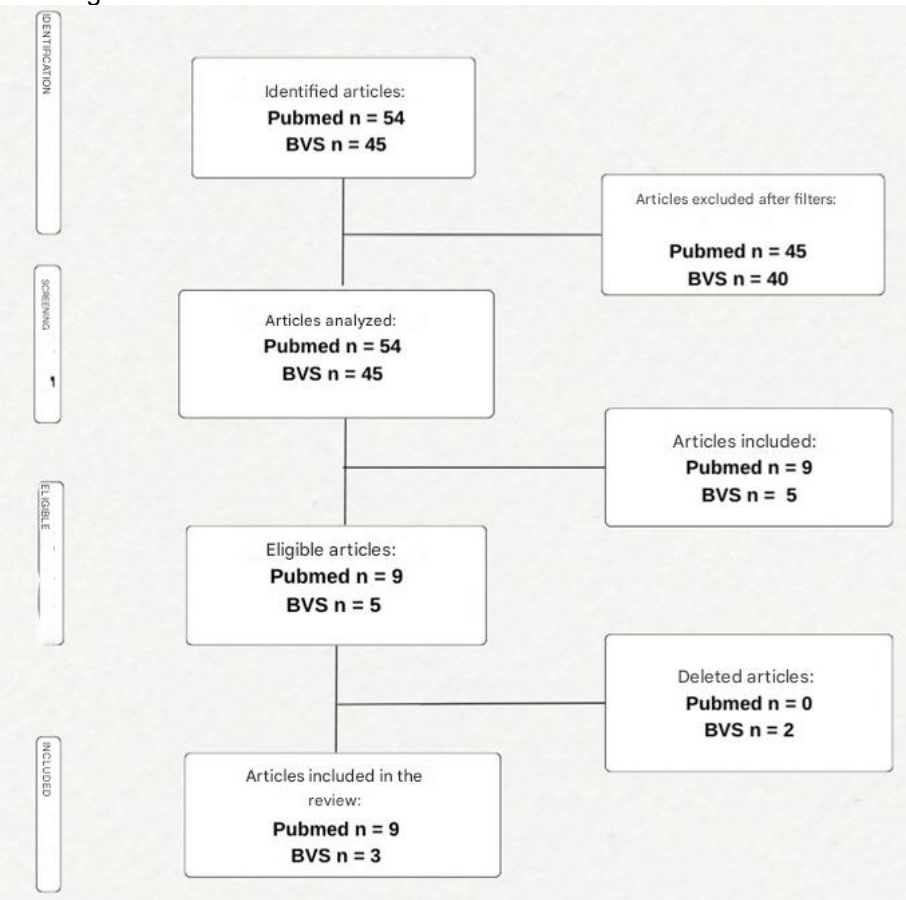
Figure 1 - PRISMA flowchart of the articles included in this review.



Source: Respective works of the authors.

RESULTS

A total of 12 (twelve) articles selected for the present study were obtained, 9 (nine) articles from the PubMed Database and 3 (three) articles from the VHL platform. The description of the articles included in this systematic review, which were separated by the Electronic Database, PubMed and VHL platforms, is shown in Table 1 and Table 2, respectively. The following criteria were considered to compose Tables 1 and 2, such as the title of the study, the authors, the year of publication, objective, as well as the results regarding the association of Diabetes Mellitus with Alzheimer's Disease and/or Dementia. The selected studies presented an adequate methodology for the research evidenced.

Table 1 - Data included from the articles selected from PubMed for this review.

Title	Author/ Year	Goal	Findings
Computerized Cognitive Training for Older Adults at Higher Risk of Dementia Due to Diabetes: Findings from	Bahar-Fuchs *et al.*, 2020	To evaluate the effects of adaptive and personalized computerized cognitive training on cognition and disease self-management	Moderate improvements in performance in a global cognitive composite at post-treatment assessments were observed in both

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a Randomized Controlled Trial		in older adults with diabetes.	cognitive training conditions, with additional small improvements observed at the 6-month follow-up.
Dietary supplementation with curcumin reduces circulating levels of glycogen synthase kinase-3β and islet amyloid polypeptide in adults at high risk of type 2 diabetes and Alzheimer's disease	Thota *et al.,* 2020	To determine whether dietary supplementation with curcumin reduces plasma levels of peptides, GSK-3β, and IAPP that are implicated in insulin resistance in people at high risk of developing T2D.	Curcumin supplementation significantly reduced circulating levels of GSK-3β (−2.4 ± 0.4 ng/mL vs. −0.3 ± 0.6, p = 0.0068) and IAPP (−2.0 ± 0.7 ng/mL vs. 0.4 ± 0.6, p = 0.0163) and insulin resistance (−0.3 ± 0.1 vs. 0.01 ± 0.05, p = 0.0142) compared with the placebo group.
Acute hyperglycemia leads to altered frontal lobe brain activity and reduced working memory in type 2 diabetes	Backestrom *et al*., 2021	To study the association between acute hyperglycemia and working, semantic, and episodic memory in participants with type 2 diabetes compared to a sex- and age-matched control group.	Participants with T2D had reduced working memory during the 1- and 2-back tests. fMRI during placebo clamp revealed increased BOLD signal in the left lateral frontal cortex and anterior cingulate cortex as a function of working memory load in both groups (3>2>1).
Circulating semaglutide levels determine reductions in HbA1c and body weight in people with type 2 diabetes	Overgaard *et al*., 2021	Analyze oral versus parenteral routes of administration, revealing that circulating levels of semaglutide predict outcomes in people with type 2 diabetes.	At typical exposure levels for oral semaglutide, the estimated response is 1.58% (oral) versus -1.62% (subcutaneous) for HbA 1c and 3.77% (oral) versus 3.48% (subcutaneous) reduction in body weight from baseline after 6 months.
Glucagon-like peptide-1 receptor activation improves cognitive decline in type 2 diabetes mellitus through a metabolism-independent pathway	Li *et al*., 2021	To evaluate whether liraglutide administration can improve cognitive decline in T2DM patients through fNIRS neuroimaging combined with in-person cognitive testing and to investigate whether its neuroprotective effect is associated with metabolic improvement.	Liraglutide significantly increased the activation of the brain regions of the dorsolateral prefrontal cortex and the orbitofrontal cortex (P=0.0038).
Effect of hypoglycemia on cognitive performance in elderly patients with diabetes: a meta-analysis	Mu *et al*., 2024	To use meta-analysis to compile information from multiple studies to investigate the existence and severity of cognitive impairment in older patients with diabetes	Elderly patients with type 2 diabetes with episodes of hypoglycemia had significantly worse memory performance (standardized mean

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		who have episodes of hypoglycemia.	difference, 0.19; 95% CI, 0.29–0.09).
Metformin-induced changes in the gut microbiome and plasma metabolome are associated with cognition in men	Rosell-Díaz *et al*., 2024	To investigate the associations of metformin use with cognition by exploring potential mechanisms through analysis of the gut microbiome and plasma metabolome using shotgun metagenomics and HPLC-ESI-MS/M, respectively.	After stratification by sex, the proportion A. *muciniphila/R.ilealis* was significantly and positively associated with higher memory scores and improved memory in men. Metformin was associated with an enrichment of microbial pathways involved in the TCA cycle and the metabolism of butanoate, arginine and proline in both cohorts.
Alzheimer's Disease-Associated Inflammatory Proteins Reduced by a GLP1 Receptor Agonist: A Post Hoc Analysis of the Randomized Placebo-Controlled Clinical Trial EXSCEL	Koychev *et al*., 2024	To provide further evidence for the potential efficacy and mechanism of action with respect to AD of once-weekly exenatide (EQW), an RA GLP-1, while also considering the effect of non-modifiable (age) and modifiable (previous cardiovascular events) risk factors.	EQW affected FCN2 (Cohen's d -0.019), PAI-1 (Cohen's d -0.033), sVCAM-1 (Cohen's d 0.035), and a cytokine-cytokine cluster (Cohen's d 0.037) significantly compared to placebo. These effects were sustained in individuals over 65 years of age, but not in those under 65 years of age.
Feasibility and Preliminary Efficacy of Different Intensities of Functional Training in Elderly Patients With Type 2 Diabetes With Cognitive Impairment: A Pilot Randomized Controlled Trial	Ghahfarrokhi *et al*., 2024	To investigate the feasibility and preliminary efficacy of six weeks of different intensities of functional exercise in elderly patients with T2D and cognitive impairment.	HIFT had a higher rate of adherence (91% vs. 87.5%), safety, and acceptability compared to LIFT. Changes in Stroop scores were significant only in the HIFT group compared to the control group (P = 0.013).

Source: Respective works of the authors.

Table 2 - Data included in the articles selected from the VHL for review

Title	Author/ Year	Goal	Findings
Identification of Latent Comorbidity Patterns in Adults With Perceived Cognitive Impairment: Network Findings from the Behavioral Risk Factor Surveillance System	Ramos-Vera *et al*., 2022	To explore the network structure of chronic comorbidity in a U.S. national sample spanning all 50 U.S. states, with more than 170,000 participants reporting perceived cognitive impairment.	The results of the EGA show associations between the comorbid conditions assessed. Three patterns of comorbidities were identified: (1) arthritis, asthma, respiratory diseases, and depression; (2) obesity, T2DM, high blood pressure, and high blood cholesterol; and (3) heart attack, coronary heart disease, stroke, and kidney disease.

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Change in the number of neuronal and non-neuronal cells in murine models of obesity	Andrade *et al*., 2023	To determine the absolute composition of neuronal and non-neuronal cells in different brain regions of the genetic models of obesity mice *Lep* $^{ob/ob}$ and *LepR* $^{Null/Null}$.	LepR *Null/Null* ^{mice} have increased density of non-neuronal cells, primarily glial cells, in the hippocampus, frontal cortex, and hypothalamus compared to wild-type mice or *Lep* $^{ob/ob}$, indicating increased inflammatory responses in different brain regions of the *LepR* $^{Null/Null\ model}$.
Neuroprotection against protein misfolding in cerebral hypoperfusion concomitant with metabolic syndrome. A translational perspective.	Bordet *et al*., 2023	Present a summarized updated review of preclinical findings, discussing clinical implications and proposing new experimental approaches from a translational perspective.	Gastrodin (GAS), a bioactive component of the herb TianMa, improved learning and memory impairment in a mouse model of vascular dementia.

Source: Respective works of the authors.

DISCUSSION

Type 2 diabetes mellitus (T2DM) has been identified as an important risk factor for the development of neurodegenerative diseases, such as Alzheimer's and dementia, due to the insulin resistance and chronic inflammatory state associated with the condition (Koychev *et al.,* 2024). The systemic inflammation and oxidative stress present in patients with T2DM contribute to the worsening of neurodegenerative conditions, increasing the risk of cognitive impairment and dementia (Overgaard *et al.,* 2021). The association between T2DM and Alzheimer's can be explained by atherosclerosis of the small cerebral vessels, which generates damage to the white matter, leading to cognitive dysfunction and mental impairment (Ramos-Vera *et al.,* 2022).

Regular physical interventions have been shown to be an effective preventive measure to minimize the risk of neurodegeneration in older adults with T2DM. Ghahfarrokhi *et al.* (2024) showed that exercise training, whether high or low intensity, can improve physical fitness and reduce mild cognitive impairment in the elderly. In addition, the continuous practice of physical activities helps maintain physical and mental health, contributing to the prevention of cognitive decline and diseases such as Alzheimer's, especially in older populations with T2DM (Ghahfarrokhi *et al.,* 2024).

Pharmacological therapies also play a relevant role in the prevention of neurodegenerative complications related to DM2. Exenatide, a drug used in the treatment of T2D, has been shown to reduce inflammatory markers such as CRP, IL-6, and TNF-α,

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suggesting an anti-inflammatory and neuroprotective effect, which may decrease the risk of Alzheimer's (Koychev *et al.,* 2024). Semaglutide, in addition to aiding glycemic control, also has benefits in weight management in patients with T2DM, suggesting preventive effects against neurodegenerative complications (Overgaard *et al.,* 2021).

Dietary supplementation for 12 weeks with curcumin, a bioactive curcuminoid with anti-inflammatory and antioxidant capabilities, was able to reduce peptides directly linked to insulin resistance (IR) at a dose of 180 mg. The accumulation of beta-amyloid and tau protein in the brain by signaling defect tangentiates DM2, Alzheimer's Disease (AD) and Dementia to GCK-3, inactivated by the action of insulin. When hyperactivated in the condition of insulin resistance, it contributes to the hyperphosphorylation of tau protein and conjunction of beta-amyloid plaques. In addition to reducing inflammatory mediators such as cyclooxygenase-2, cytokines, and transcription factors, curcumin was able to inhibit the activity of GCK-3, an enzyme that participates in glycogen synthesis and therefore glycemic regulation. The study highlights hyperinsulinemia and insulin resistance linked to the pathogenesis of T2DM, and how curcumin acts on both serum GCK-3 levels and IAPP, an amyloid polypeptide from pancreatic islets directly linked to insulin resistance and increased GCK-3 activity. Therefore, the action of this potential drug, through IR, reduces the risk factors associated with conditions subsequent to T2DM and AD related to cognitive impairment (Thota *et al.,* 2020).

When analyzing the metagenomic and metabolomic action of Metformin, it was found that there is a close relationship between the gut microbiota and memory in the study by Rosell-Díaz *et al.* (2024). It is worth noting that people with DM2 are 60% more likely to develop dementia diseases, so treatment with Metformin, a widely used oral hypoglycemic agent, and its relationship with better cognitive and memory performance have been studied. Metformin has intestinal action, with a close relationship in the hosts of the phylum Firmicutes, Bacteriodetes and Proteobacteria, increasing beneficial bacteria. For this, exams applied in clinical practice and neurocognitive tests were applied in the Aging Imageomics Study and Metformin and Intestinal Microflora Study, obtaining as results species associated with metformin, especially the increase of Escherichia coli (Proteobacteria). This bacterium is involved in the metabolism of glutamate-GABA, whose neurotransmitter role is essential for brain development and functioning, improving memory and learning. Lipopolysaccharides act on intestinal inflammation and reduced lipid absorption as a direct effect of the drug, an advantage of E. coli over other species.

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Therefore, the use of this important oral hypoglycemic agent has been shown to be effective in improving memory, executive and semantic function in T2DM patients (Rosell-Díaz *et al.,* 2024).

A meta-analysis comprising 7 (seven) studies evaluated how hypoglycemia in people over 45 years of age favors cognitive impairment and dementia states in the period from 1989 to 2022. Applying tests that assess memory, intelligence, executive function, processing speed and psychomotor efficiency in patients with type 1 and 2 diabetes, great heterogeneity was obtained, in part due to the scales used. With a standardized mean difference of -0.49; 95% CI, -0.85 to -0.13, there was worse cognitive performance among T2DM patients with hypoglycemic episodes. Hypoglycemia is the dysglycemia that most affects neuronal function, since 70% of glucose metabolism is destined to brain signaling, and when it occurs in elderly diabetics, it profoundly affects cognition and psychomotor function. With a variation of 3.0-3.5 mmol/L of glucose in the blood, cognitive changes can occur by directly affecting the neuronal mitochondria, which in the long term leads to oxidative stress and neuronal death due to the hypoglycemic state, which according to the neuropathological studies carried out, affect more the cerebral cortex and the hippocampus, structures involved in memory. Therefore, cognitive impairment in the fields of intelligence, memory, and psychomotor function due to the hypoglycemic state in diabetic patients over 45 years of age is evident, and prevention and diagnostic measures are necessary for effective intervention (Mu *et al.,* 2024).

T2DM and its complications appear to be associated with impairments in working memory. Participants with T2DM had an average BMI of 27.9 kg/m², compared to the control group, which had an average BMI of 26.2 kg/m², representing a significant difference, since the value was 0.03. In addition, the waist circumference of participants with T2DM (101 cm) was significantly larger than that of the control group (91 cm), with a p-value of < 0.001, evidencing the greater presence of obesity in this group. These measures are often associated with insulin resistance, a central feature of T2D, which in turn can impact cognitive function. The mean fasting blood glucose of participants with T2DM was 7.49 mmol/l, significantly higher than that of controls, who had a mean of 5.00 mmol/l ($p < 0.001$). HbA1c, which reflects glycemic control over time, was also higher in the type 2 diabetes group (52 mmol/mol or 6.0%) compared to the control group (37 mmol/mol or 4.6%), with a p-value < 0.001. These results indicate a clear dysregulation of glycemic control in diabetic participants, which may correlate with the cognitive impairments

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observed. Furthermore, with regard to performance in working memory, the median scores in the 2-back task indicated that the DM2 group (31.89) had a lower performance compared to the control group (33.47), with a p-value of 0.028. This suggests that hyperglycemia, in particular, may have a negative impact on working memory function in individuals with T2D. In addition, the relationship between hyperglycemia and deviation in brain activity during working memory tasks was evidenced in the use of fMRI (Backstrom *et al.,* 2021).

In addition, regarding the activation of the glucagon-like peptide 1 receptor, studies describe cognitive improvement in T2DM through a pathway independent of metabolism, with the use of Liraglutide for 12 (twelve) weeks in which it resulted in significant improvements in intellectual function, when compared to conventional hypoglycemic treatment. The evaluations indicate that the drug activated not only specific brain regions, such as the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC), but also that this activation was associated with improvements in independent cognitive performance, such as metabolic parameters (blood pressure, blood glucose and body weight). This evidence suggests that liraglutide's beneficial effects on cognition may be attributed to a direct neuroprotective mechanism, rather than just improvements in metabolic health. However, the study had limitations, such as the lack of randomization and the questioning of the generalization of the results to other GLP-1 analogues. In addition, the possibility of bias in the repetition of cognitive tests should be considered. Despite these limitations, the results suggest a new direction for future research, especially with regard to the use of GLP-1 ARs as a treatment for cognitive impairment in patients with T2DM (Li *et al.,* 2021).

The impacts of multi-domain CCT (Computerized Cognitive Training) on both cognitive and non-cognitive outcomes in older adults at higher risk of dementia due to T2DM. The investigation conducted and the effects of a secondary emotional support (ECS) intervention in relation to adherence and disease self-management outcomes. At the six-month post-intervention assessment, participants reported a significant reduction in mood-related symptoms, especially anxiety, compared to the study's baseline. This may explain the continuous cognitive improvements observed after the intervention ends. A notable aspect of the study was the analysis of the effects of CCT on self-management of the disease, which was evaluated subjectively. However, this finding is limited to participants' self-reports and was not corroborated by informants' analyses. Although the information reported by informants may have greater validity in areas such as mood and behaviors, the

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assessment of T2D self-management may be less reliable, especially since the information collected did not reside with participants or did not interact frequently enough to accurately assess self-management behaviors. The correlation observed between the self-management behaviors reported by the participants and the informants (r = 0.68) suggests a good overall agreement between the observations made. However, there is no evidence to indicate that improvements in T2D self-management were more associated with those who showed a "clinically meaningful" improvement in global cognition, defined as a change of at least 0.5 standard deviations. Given the modest improvements in self-management, the question of how cognitive changes could moderate CCT-induced improvements in T2DM self-management still requires investigation in a study with a larger sample (Bahar-Fuchs *et al.,* 2019).

In the study by Bordet *et al.* (2023) that used murine animal models with leptin and leptin receptor deficiency, which simulated hyperphagia, massive obesity and increased BMI, therefore simulating the clinical Metabolic Syndrome and development of DM2, it was possible to conclude that it is still necessary to understand the metabolic alterations that evolve to cognitive decline. It is understood that DM2 increases cerebral hypoperfusion in mouse models, as the hyperglycemic state is capable of causing microvascular changes and directly affecting cerebral perfusion, being a significant precursor of neurodegenerative pathologies, such as AD. In addition, DM2 is one of the consequences of obesity, both constituting risk factors for neurodegenerative diseases. In the etiology of these pathologies is pathological protein unfolding and aggregation, which generate the cytotoxicity responsible for neuronal death. Thus, chronic cerebral hypoperfusion and neurodegeneration have at their core the metabolic changes resulting from T2DM and cardiocerebrovascular risk factors (Bordet *et al.,* 2023).

Analysis of the impact of obesity on brain cell composition of mouse models has provided important information for understanding the brain changes associated with obesity. The study conducted by Andrade *et al*. (2023) used the immunofluorescence (IF) technique to identify absolute changes in cell composition and brain density in two models of obesity: Lep ob/ob and LepR Null/Null mice. The data suggest that obesity is linked to a reduction in brain size and changes in the number and density of cells in various regions of the brain of these mice. There was a reduction in the number of neurons in the hippocampus, a region essential for cognitive functions such as learning and memory, in the Lep ob/ob and LepR Null/Null mice. In contrast, the density of non-neuronal cells, predominantly glial cells,

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increased in the frontal cortex, hippocampus, and hypothalamus of LepR Null/Null mice, suggesting an exacerbated neuroinflammatory response in these regions. The IF technique is an advantageous tool for quantitative analyses compared to sterology, especially in studies on brain cell composition, as it offers greater precision, cost-benefit and reproducibility. In addition, the IF method allows for more efficient staining with specific antibodies, such as NeuN, which is essential for neuron labeling, as well as minimizing tissue shrinkage problems often associated with sterology, which ensures more reliable results. The models used replicate aspects of human obesity, allowing us to investigate the association between obesity and neurodegeneration. in addition to highlighting the growing relevance of this relationship in view of the prevalence of metabolic disorders. Future studies should explore inflammatory and metabolic components that affect brain cell composition and consider alternative models to better understand the direct effects of obesity on neurogenesis and neurodegenerative diseases (Andrade *et al.,* 2023).

CONCLUSION

The present study presents an analysis of type 2 diabetes mellitus (DM2) and its relationship with neurodegenerative diseases, such as Alzheimer's disease (AD) and dementia, and reveals the complexity of the mechanisms involved in cognitive deterioration. Studies indicate that insulin resistance and chronic inflammation associated with T2D contribute to oxidative stress and atherosclerosis of the brain's small vessels, resulting in cognitive impairment. Regular physical interventions, such as high- or low-intensity physical training, have been shown to be effective in reducing the risk of neurodegeneration in older adults with T2DM, underscoring the importance of physical activity in maintaining mental and physical health. In addition, medications such as exenatide and semaglutide not only control glycemic levels, but also have anti-inflammatory and neuroprotective effects, suggesting that they may reduce the risk of AD. Curcumin, with its anti-inflammatory and antioxidant properties, has been shown to be effective in reducing markers of insulin resistance, standing out as a potential adjuvant therapy in the management of T2DM and its cognitive complications.

From this perspective, metformin, widely used in the treatment of T2DM, has demonstrated cognitive benefits associated with the modulation of the gut microbiota. Studies indicate that metformin may improve memory and executive function in diabetic patients, possibly due to the increase in beneficial bacteria that influence brain metabolism.

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The relationship between hyperglycemia and cognitive impairment is evident, with evidence showing that episodes of hypoglycemia negatively affect neuronal function, especially in individuals over 45 years of age.

Therefore, continued research on the effects of systemic inflammation and metabolic changes on the brain may offer new perspectives for interventions that aim not only to control T2DM but also to preserve cognitive function in at-risk populations. However, there is a need for additional studies that explore the relationships between pharmacological interventions, changes in the gut microbiota, and cognitive performance.

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