# Type 2 diabetes mellitus and Alzheimer's disease in the elderly population: A narrative review

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**Larissa Silva Clementino[1], Ana Georgia Amaro Alencar Bezerra Matos[2], Rian Barreto Arrais Rodrigues de Morais[3], Leonardo Torres Camurça[4], Patricia Cibelle Leite de Morais[5], William Cândido of Lorraine[6], Priscila Herbelle Leite de Morais[7], Wendryus William de Lima[8], Lucas Casarotto Versa[9], Douglas Vicente Balensiefer[10], Genilson Pereira Gurgel[11] and Lara Beatriz Cunha da Silva Paixão[12]**

[1] Medical student
Regional University of Cariri - URCA
E-mail: larissa.clementino@urca.br
ORCID: https://orcid.org/0009-0005-9479-2751
[2] Master's Degree in Teacher Education and Interdisciplinary Practices
Regional University of Cariri - URCA
E-mail: anageorgia@leaosampaio.edu.br
ORCID: https://orcid.org/0000-0003-3478-1573
[3] Medical student
Centro Universitário São Lucas - UNISL
E-mail: rianbarretojm10@gmail.com
ORCID: https://orcid.org/0000-0003-1971-1243
[4] Medical student
Faculdade metropolitana (unnesa)
E-mail: leocamurca@gmail.com
ORCID: https://orcid.org/0009-0008-2888-2486
[5] Medical student
FACENE (Nova Esperança College of Nursing)
E-mail: patricia_cibelle@hotmail.com
ORCID: https://orcid.org/0009-0003-9332-4417
[6] Medical student
Faculdade Metropolitana - UNNESA
E-mail: guillermolorena82@gmail.com
ORCID: https://orcid.org/0009-0003-2314-1463
[7] Medical student
Three Borders International University - UNINTER
E-mail: phlm.herbellemorais@gmail.com
ORCID: https://orcid.org/0009-0006-6324-8910
[8] Medical student
Alto do Rio do Peixe University - UNIARP
E-mail: wendryus@yahoo.com.br
ORCID: https://orcid.org/0009-0003-2125-7681
[9] Medical student
University of Southern Santa Catarina - Unisul
E-mail: wertherestavacerto@gmail.com
[10] Training in medicine
Three Borders International University - UNINTER
E-mail: douglas_balensiefer@hotmail.com
[11] MSc in Quality Management in Health Services
Federal University of Rio Grande do Norte
Lagoa Nova, Natal - RN
E-mail: genilsongurgel@hotmail.com
ORCID: https://orcid.org/0000-0003-4331-8484
[12] Medical Student
Faculdades Integradas Aparício Carvalho - FIMCA
Porto Velho- RO
E-mail: larabeatriz1901@gmail.com

**ABSTRACT**
Type 2 diabetes has pathological mechanisms similar to those of Alzheimer's, indicating a correlation between the two conditions. This article aims to present the effects of type 2 diabetes mellitus on the development of Alzheimer's, emphasizing the molecular mechanisms that correlate these two factors. This study is a qualitative narrative review that aims to comprehensively present the topic "type 2 diabetes mellitus and Alzheimer's disease in the elderly population". The search was carried out in the virtual libraries PubMed, VHL and Scielo, using keywords and MeSH terms such as "Type 2 Diabetes", "Alzheimer's Disease" and "Susceptibility to Diseases". The search resulted in 252 articles. After several stages of analysis and selection, 8 relevant articles were chosen to compose the narrative review. The review addresses the relationship between Alzheimer's and type 2 diabetes, exploring risk factors, common molecular mechanisms, and the role of glucose in neural function. The review indicates a link between type 2 diabetes and Alzheimer's in the elderly population, with complex biological mechanisms connecting the two conditions. Future research is encouraged to improve patient care.

**Keywords:** Type 2 Diabetes Mellitus, Alzheimer's disease, Neural Degeneration.

## INTRODUCTION

The world's population has been aging and, according to the United Nations Population Fund, by 2050, there will be an unprecedented number of elderly people than children under 15 years of age (UNFPA, 2012). In this sense, the understanding of diseases such as diabetes mellitus and Alzheimer's, which mainly affect the elderly population, becomes essential for maintaining the health of the old and new generations.

About Alzheimer's disease, it was discovered in 1906 by the German pathologist Alois Alzheimer (ADI, 2023?), and is classified as a neurodegenerative condition of unknown causes that can be genetically expressed (Brasil, 2023).

In this disorder, which has four stages of progression, poorly metabolized proteins accumulate in the brain, causing the death of neurons and affecting areas related to memory processing, such as the hippocampus and the cerebral cortex. In addition, in addition to affecting the storage of information, Alzheimer's causes the loss of functions related to language, reasoning, and abstract thinking (Brasil, 2023).

Worldwide, 55 million elderly people are affected by dementia (ADI, 2020), with Alzheimer's being the most frequent type, corresponding to about 50-75% of cases (ADI, 2023?). In addition, there are estimates that 78 million elderly people will be affected by Alzheimer's by 2030, indicating that the disease will affect an even larger portion of the population in the next decade (ADI, 2020). In this sense, the high statistics on this pathology highlight the need for greater discoveries about this neurodegenerative condition, as well as the incorporation of new preventive actions for this disorder.

In addition, type 2 diabetes mellitus (T2DM) has pathological mechanisms similar to those of Alzheimer's disease, a fact that indicates a correlation between the two conditions (Lima; Moreira and Sakamoto-Hojo, 2021). From this perspective, to aggravate this finding, the extent reached by T2DM in the world population is 537 million people (IDF, 2021).

Thus, recent evidence correlating type 2 diabetes mellitus and the development of Alzheimer's shows promise both in preventing and clarifying the causality of this disease, contributing to an improvement in the global diagnosis currently observed.

Thus, this article aims to present the effects of diabetes mellitus (Lima; Moreira and Sakamoto-Hojo, 2021) for the development of Alzheimer's disease, emphasizing the molecular mechanisms that correlate these two factors, based on recent findings on the relationship between type 2 diabetes mellitus and the onset of dementia in old age.

In this sense, with the dissemination of the impacts of type 2 diabetes mellitus on neurodegenerative conditions, the social environment will be able to have greater autonomy over their health status, in order to achieve a healthy and productive longevity. (WHO, 1986)

## OBJECTIVES

### GENERAL OBJECTIVE

- To highlight in the literature studies that correlate type 2 diabetes mellitus and Alzheimer's disease.

### SPECIFIC OBJECTIVES

- Dissertation on the pathophysiology of type 2 diabetes mellitus and Alzheimer's;
- Describe the risk factors for type 2 diabetes mellitus and Alzheimer's disease;
- Describe the main molecular mechanisms shared between the two conditions;
- Dissertation on the correlation between glucose and neural function.

## METHOD

The present study is a narrative review, with a qualitative approach, whose objective is to present, in a comprehensive way, a theme (Cordeiro *et al.*, 2007). This type of review, although it does not present methodological rigor or exhaustion of databases, is of great value for theoretical updating on a given topic, highlighting ideas and knowledge that are little evidenced in current discussions (Noronha and Ferreira, 2000 *apud* Vosgerau and Romanowsk, 2014).

In addition, the virtual libraries used to search for the theme "type 2 diabetes mellitus and Alzheimer's disease in the elderly population" were PubMed, VHL and Scielo. In addition, the selected descriptors were configured as keywords or were removed from the list of MeSH (Medical Subject Headings) terms, widely used in the medical literature. The descriptors and keywords used are detailed in the table below.

Finally, the time frame of the last five years was used and the languages English, Spanish and Portuguese were included. In addition, articles with incomplete text, paid articles, and articles whose objectives differed from the theme proposed in this narrative review were excluded.

Table 1 – Descriptors and keywords used to compose the search strategy.

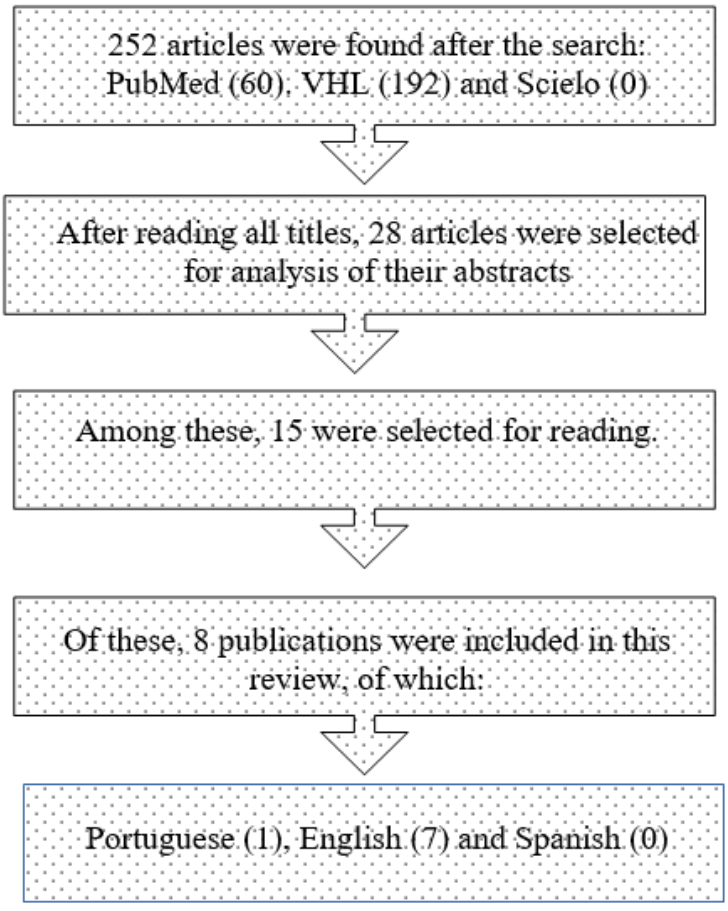
| | English subjects and synonyms | Subjects and synonyms in **Portuguese** | Spanish Subjects and Synonyms |
|---|---|---|---|
| Subject 1 | “Diabetes Mellitus, Type 2”<br>“Type 2 Diabetes” | “Diabetes Mellitus Tipo 2”<br>"Type 2 Diabetes" | “Diabetes Mellitus Tipo 2”<br>"Type 2 Diabetes" |
| Subject 2 | “Alzheimer Disease”<br>“Alzheimer Dementia” | "Alzheimer's disease"<br>"Alzheimer's disease" | "Alzheimer's Disease"<br>"Alzheimer's Disease" |
| Subject 3 | Aged<br>Elderly | Old<br>"Elderly Population" | Ancient*<br>Person* Age |
| Subject 4 | “Disease Susceptibility”<br>Diathes | "Susceptibility to disease"<br>Diathesis | "Susceptibility to disease"<br>Diathesis |

Source: Federal University of Santa Catarina, 2023.

## RESULTS

The searches resulted in 252 articles. After reading all the titles, 28 articles were selected for the reading of their respective abstracts. At the end of this analysis, 15 publications were selected and read in full, of which 8 were included for the purpose of elaborating this narrative review. These articles were selected for their relevance to the topic and for their methodological qualities, including 7 studies in English and 1 in Portuguese, as described in the flowchart below.

Figure 1 – Flowchart of the stages of selection of articles




Source: Authored by the authors.

Table 2 – Data on the selected articles, including author(s), title, objectives, type of study, and results.

| Author(s) | Article Title | Objectives | Type of study | Results |
|---|---|---|---|---|
| Scheltens, P. *et al.* | Alzheimer's Disease | Dissertation on the major advances in the field of Alzheimer's disease | Narrative Review | Promising pharmacological treatments for Alzheimer's disease have been identified. |
| Michailidis, M. et al. | Alzheimer's Disease as Type 3 Diabetes: Common Pathophysiological Mechanisms Between Alzheimer's Disease and Type 2 Diabetes | Discuss the shared correlations between Alzheimer's disease and type 2 diabetes mellitus. | Systematic Review | It has been identified that Alzheimer's disease is a metabolic disease with strong indications of being type 3 diabetes. |
| Hamzé, P. *et al.* | Type 2 Diabetes Mellitus and Alzheimer's Disease: Shared Molecular Mechanisms and Potential Common Therapeutic Targets | To describe the main molecular pathways that correlate type 2 diabetes mellitus and Alzheimer's disease, with emphasis on insulin and IGF-1 signaling and some Alzheimer's markers. | Narrative Review | Experimental evidence was identified for the correlation between type 2 diabetes mellitus and Alzheimer's disease. |
| Barone, E. *et al.* | The interaction between oxidative stress, brain insulin resistance, and AMPK dysfunction contribute to neurodegeneration in type 2 diabetes and Alzheimer's disease | Provide an overview on the detrimental effects of oxidative stress on insulin signaling and how these changes relate to AMPK dysregulation. | Narrative Review | It has been identified that the described processes are closely linked with the molecular mechanisms of Alzheimer's disease. |
| Yonamin, C. I. *et al.* | Glucose transport and utilization in the hippocampus: from neurophysiology to the development of diabetes-related dementia. | To discuss the interaction between diabetes and cognitive dysfunctions, to elucidate the underlying molecular and physiological mechanisms, and to identify possible avenues for therapeutic intervention and future research. | Narrative Review | It identified the complex correlation between diabetes and dementia and the importance of exploring therapeutic interventions to mitigate the effects of diabetes on neurodegeneration. |
| Shen, Z. *et al.,* 2022 | Metabolic Perspective of Astrocyte Dysfunction in Alzheimer's Disease and Brains With Type 2 Diabetes | To investigate the role of astrocyte dysfunction in Alzheimer's disease and type 2 diabetes mellitus and offer new insights into the comorbid mechanisms of these two diseases. | Narrative Review | It identified that astrocyte dysfunction is involved in the pathophysiological processes of AD and T2DM and discussed the impact of astrocyte dysfunction on various aspects of brain function in these diseases. |
| Oliveira, K. S. *et al.* | Assessment of the risk of Alzheimer's disease in the elderly with Diabetes Mellitus | Evaluate<br>The objective of this study was to evaluate the risk of Alzheimer's disease in elderly patients with type 2 diabetes mellitus in Mossoró, Rio Grande do Norte State, Brazil. | Retrospective cohort study | It identified that older adults at higher risk of dementia are users of Glibenclamide, smokers, have a family history of mental disorders and have lower family incomes. |

| | | | | |
|---|---|---|---|---|
| Adachi, Y. et al. | Lower insulin secretion is associated with atrophy of the hippocampal and parahippocampal gyrus in elderly patients with type 2 diabetes mellitus | To evaluate the association between type 2 diabetes and atrophy of the hippocampal and parahippocampal gyrus (HPGA), determining its risk factors. | Cohort study | It identified that abnormalities in insulin secretion have strong correlations with the pathophysiology of Alzheimer's disease. |

Source: Authored by the authors.

## DISCUSSION

Alzheimer's disease, the leading cause of dementia in older people, is a neurodegenerative disease whose progress is associated with the loss of neurons, affecting the hippocampus and neocortical areas. This pathology is also characterized by the extracellular aggregation of insoluble fibrils and β-amyloid peptides (Aβ) and by the phosphorylation and destabilization of the tau protein, which is associated with microtubules and whose aggregation forms neurofibrillary tangles within neurons. Both lesions (Aβ and tau proteins) accumulate in synaptic and neuronal malfunction, and can generate, in the long term, neurodegeneration through atrophy of specific areas of the brain, especially the cortex and hippocampus. (Hamze *et al.*, 2022)

In addition, evidence indicates that pathophysiological changes in Alzheimer's disease can occur up to 20 to 30 years before the onset of clinical symptoms. Due to the limited information on the early stages of the neurodegenerative process and the fact that the diagnosis of Alzheimer's usually occurs in advanced stages, there is an urgent need to identify the molecular aspects of the disease that begin in the pre-symptomatic phases so that the condition can be detected early. (Barone, E. *et al.,* 2021)

In addition, there are two variants of the disease: the familial form, which manifests itself early, around the age of 50, due to dominant genetic mutations that affect the production of β-amyloid peptide; and the sporadic form, which occurs in more than 95% of cases, usually developing after the age of 65. (Hamze *et al.*, 2022)

In this sense, the sporadic form of Alzheimer's disease is influenced by genetic and environmental risk factors. The most significant are aging and the presence of the ApoE4 allele, which acts on the elimination of amyloid beta peptide (Hamzé *et al.*, 2022). In addition, female gender (Scheltens *et al*., 2021) and cardiovascular risk factors such as strokes, poorly controlled hypertension, high cholesterol, obesity, and diabetes are considered potential predisposing factors. (Hamze *et al.*, 2022)

On the other hand, diabetes mellitus, the most prevalent metabolic disease, is a condition characterized by chronic hyperglycemia, promoted by insufficient insulin secretion or ineffective

action (Hamzé *et al.*, 2022). In addition, it can lead to increased immune system activity and brain neuroinflammation, a typical feature of Alzheimer's disease, with which it shares several dysfunctions, including faulty insulin signaling, insulin resistance, reduced hippocampal volume, and accelerated cognitive decline. (Oliveira, K. S. *et al., 2021*)

In addition, diabetes can lead to serious long-term complications, many of which result from diseases that affect small (such as retinopathy and nephropathy) or large blood vessels (such as peripheral arterial disease, cardiac events, and strokes), as well as several other conditions, such as cognitive impairment, depression, and neurodegenerative diseases, most notably, again, Alzheimer's disease. (Hamze *et al.*, 2022)

In this sense, there are two main variants for diabetes mellitus: type 1 diabetes, which accounts for 10% of cases and is caused by the autoimmune destruction of pancreatic β cells, resulting in progressive loss of insulin secretion; and type 2 diabetes, responsible for 90% of cases, which occurs due to insulin resistance in tissues such as the liver.  muscle and adipose tissue. In the latter case, β cells attempt to compensate for insulin resistance by increasing in number and secretion, but eventually become depleted and undergo apoptosis, leading to partial insulin deficiency and subsequent hyperglycemia. (Hamze *et al.*, 2022)

In addition, type 2 diabetes mellitus develops from a combination of genetic predispositions and various environmental risk factors. Among them are a sedentary lifestyle, poor diet, stress and exposure to pollutants such as bisphenols, pesticides and air pollution. (Hamze *et al.*, 2022)

In short, type 2 diabetes mellitus is a metabolic disease marked by insulin resistance, resulting in impaired glycemic control. Although certain genetic polymorphisms are associated with the development of type 2 diabetes mellitus, risk factors such as obesity and physical inactivity are considered more relevant to the development of the condition, promoting inflammation and cellular stress, which can lead to systemic insulin resistance (Barone, E. *et al.,* 2021).

With regard to this hormone, insulin has several effects on the body: cognition, modulation of acetylcholine and noradrenaline, expression of genes related to long-term memory, regulation of synapses, formation of dendrites; formation of the postsynaptic junction, proliferation of glial cells; maintenance and functioning of oligodenthrocytes, in the regulation of inhibitory synapses through the recruitment of the neurotransmitter GABA (gamma-aminobutyric acid),  among other various features. (Hamze *et al.*, 2022)

It was believed that the origin of insulin in the brain was peripheral, however, studies demonstrate the presence of insulin-expressing mRNAs in the organ itself, indicating the production of insulin, independently, by the brain (Michailidis *et al.,* 2022 and Hamzé *et al.*, 2022).

Thus, when the target tissues of this hormone become insensitive to it, a condition called systemic insulin resistance arises, which can affect adipose tissue, liver and muscles. Similarly, this

process is believed to occur in the brain, due to the activation of glial cells, especially astrocytes and microglia, which promote, in the long term, a deleterious inflammation capable of generating progressive neuronal damage. This damage is caused in part by the brain's sensitivity to insulin, which is necessary for glucose transport and metabolism, as well as for the regulation of memory and learning activities in areas such as the hippocampus and cortex. (Michailidis *et al.,* 2022)

From this perspective, the phenotypic mechanism for the development of insulin resistance consists of (1) *up-regulation* (compensatory production) of insulin in order to supply the lower cellular uptake of glucose, a state known as prediabetic, and (2) the maintenance of insulin resistance by increasing glucose production and decreasing endogenous insulin production. (Hamze *et al.*, 2022)

In addition, peripheral insulin resistance can promote neuroinflammation by generating cytotoxic lipids capable of crossing the blood-brain barrier. In this process, microglial cells induced by beta-amyloid are activated, promoting the release of several inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-6, which is also involved in the progression of Alzheimer's. (Michailidis *et al.,* 2022)

In this sense, in Alzheimer's disease, astrocytes, which are fundamental for the regulation of neuronal excitatory-inhibitory balance, synaptic function, learning and memory, can contribute to neuroinflammation and the formation of amyloid plaques. Despite this, astrocytes also have a neuroprotective role by maintaining glutamate homeostasis and promoting neurovascular coupling. (Shen, Z. *et al.,* 2022)

Under a new analysis, cerebrovascular disease can affect cognition in patients with type 2 diabetes mellitus, considering that oxidative stress and chronic hyperglycemia can damage the vascular endothelium, causing atherosclerosis and vascular complications, such as an increased risk of ischemic stroke and cerebral infarctions. In addition, chronic hyperglycemia, described above, can also cause changes in cerebral microvascularization, leading to thickening of the cerebral capillary basement membrane, changes in the integrity of vascular smooth muscle cells, and increased microvascular resistance. These changes can impact circulation and brain function, as well as the rate of elimination of metabolites from the brain. Otherwise, type 2 diabetes mellitus can affect vessel-mediated Aβ clearance, leading to accumulation of Aβ in the brain and thus making cerebrovascular disease a common link between T2DM and Alzheimer's disease. (Michailidis *et al.,* 2022)

From another perspective, islet amyloid polypeptide (IAPP), or amylin, is a hormone that is secreted with insulin by pancreatic islet β cells. This hormone has several functions, including inducing satiety, regulating blood sugar, inhibiting glucagon secretion, and slowing gastric emptying. Like insulin, amylin levels are elevated in patients with insulin resistance. (Michailidis *et al.,* 2022)

In this sense, in Alzheimer's patients, the presence of amylin receptors in the brain is observed, as well as the deposition of amylin. In addition, amyloid plaques contain stores of amylin and mixed plaques containing amylin and β-amyloids. Thus, there is an indication that amylin has a relevant function for the formation of more amyloids in the central nervous system, especially in conditions of hyperamylinemia. Thus, amylin binds to neurons, having the same toxicity observed in the pancreas of individuals with type 2 diabetes mellitus, causing intracellular oxidative stress and inflammatory responses. (Michailidis *et al.,* 2022)

This oxidative stress can also be promoted by insulin resistance in T2DM, leading to neurodegeneration in Alzheimer's disease. Thus, oxidative damage occurs when there is an imbalance in favor of very reactive forms of oxygen and nitrogen, resulting in the oxidation of proteins, lipids, and DNA, causing functional damage to mitochondria and inducing genetic mutations in DNA and RNA. In addition, reactive forms of oxygen promote programmed cell death and the production of pro-inflammatory cytokines. In addition, mitochondrial dysfunction and the overproduction of reactive oxygen species play a crucial role in the development of DM2 pathology, considering that, in situations of insulin resistance, there is an increase in the products of oxidative reactions in the blood, adipose tissue, brain, muscles and liver. In addition, the human brain is very sensitive to damage from oxidative stress because, although it constitutes a small fraction of the total body weight, it consumes more than 20% of the body's total oxygen. Thus, low levels of antioxidants, high levels of oxidizing ionic metals, and the presence of polyunsaturated fatty acids in brain cell membranes, which are susceptible to hyperoxidation. They make the brain even more vulnerable to oxidative stress-induced damage. Although it is argued that the presence of β-amyloids precedes oxidative stress, much research indicates that oxidative stress may be a precursor of β-amyloid protein and tau proteins. Finally, oxidative stress and insulin resistance can independently lead to the accumulation of β-amyloid and tau proteins. (Michailidis *et al.,* 2022)

With regard to glucose, according to Yonamini (*et al.*, 2023), their transport across the blood-brain barrier is mediated by specialized glucose transporters.

Also according to Yonamini (*et al.,* 2023), this process involves the blood-brain barrier, a highly selective semipermeable boundary that regulates the passage of substances from the blood to the brain; glucose transporters, particularly the GLUT family of transporters; facilitated diffusion, in which glucose is transported from an area of higher concentration (blood) to an area of lower concentration (brain cells), without requiring energy expenditure; GLUT1, which allows glucose to be transported to the brain, ensuring that an adequate amount of glucose is available for the performance of neuronal functions; and intracellular transport, which occurs when glucose is taken up by neurons and other brain cells through the action of various GLUT transporters, including GLUT3 and GLUT4.

In addition, reduced expression and translocation of the insulin-sensitive glucose transporter GLUT4 in hippocampal neurons lead to neurociglycopenia and eventually cognitive dysfunction, highlighting the impact of altered glucose metabolism on the brain. (Yonamini *et al.*, 2023)

In addition, according to Adachi (*et al.,* 2021), patients with lower insulin secretion capacity tend to have atrophy of the inner portion of the temporal lobe, including the hippocampus, amygdala, and ventral portion of the parahippocampal gyrus. The low concentration of insulin in the blood plasma promotes a low concentration in the cerebrospinal fluid, resulting in abnormalities in insulin signaling and generating excessive synthesis of beta-amyloid and hyperphosphorylated tau proteins, both of which are characteristic of Alzheimer's disease.

## FINAL THOUGHTS

Through this narrative review, it was possible to observe a significant relationship between type 2 diabetes mellitus and Alzheimer's disease in the elderly population. The prevalence of both conditions increases with age, and the presence of type 2 diabetes appears to increase the risk of developing Alzheimer's disease.

The biological mechanisms linking these two conditions are complex and involve multiple pathways, including insulin resistance, neuroinflammation, oxidative stress, and amyloid plaque formation. However, there is still much to be discovered about these processes and how they interact with each other.

In summary, this review highlights the importance of an integrated approach in the care of elderly patients with type 2 diabetes. Thus, future research should continue to explore the relationship between these two conditions, with the aim of improving quality of life and health outcomes for the growing elderly population.

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