Review

Connecting the Dots: Neurobiological Interplay Between Type 2 Diabetes and Alzheimer's Disease

Analia Foncea-Bitrán , Cristián Barros-Osorio , Francisca Arriaza , Catalina Ramírez-López , Lina M. Ruiz , Marlen Barreto , Fernando C. Ortiz , Francisca Cornejo * , Gonzalo I. Gómez *

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Connecting the Dots: Neurobiological Interplay Between Type 2 Diabetes and Alzheimer's Disease

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Abstract

Diabetes Mellitus is a chronic metabolic disorder characterized by impaired insulin production and/or action, leading to persistent hyperglycemia and insulin resistance. It has been associated with several comorbidities, including cognitive dysfunction, affecting functions such as attention, memory, and processing speed. Mounting evidence indicates a complex relationship between type 2 Diabetes Mellitus (DM2) and neurodegenerative disorders such as mild cognitive impairment and Alzheimer's disease (AD). Beyond the conventional hallmarks of each pathology, patients with DM2 face an increased risk of neuronal degeneration, while AD is characterized by a marked reduction in insulin receptor density. Although aging, neuroinflammation, and vascular dysfunction have been recognized as key risk factors in AD, the precise molecular mechanisms driving AD pathogenesis remain incompletely understood. Various studies have been conducted to identify reliable biomarkers that elucidate the connection between DM2 and AD, including insulin dysregulation, neuroinflammation, amyloid-β aggregation, and tau hyperphosphorylation. Investigation on these biomarkers is still ongoing and may serve not only as diagnostic tools but also as therapeutic targets. Here, we review the current evidence supporting a convergent biological framework between DM2 and AD. Clarifying these shared pathways may improve early detection and guide the development of targeted therapeutic strategies aimed at reducing neurodegeneration in metabolically vulnerable populations.

Keywords: Alzheimer's disease; amyloid-β; biomarkers; hyperglycemia; neuroinflammation; cognitive dysfunction; type 2 diabetes mellitus

1. Introduction

Diabetes Mellitus (DM) is a metabolic disorder that accounts for 90% - 95% of all diabetes cases and is considered one of the most significant public health concerns (Burillo et al., 2021). The global prevalence of DM in 2019 was 9.3% (463 million people), and it is projected to rise to 10.2% (578 million people) by 2030 and 10.9% (700 million people) by 2045 (Takeishi et al., 2021). DM is characterized by disrupted insulin secretion and/or function, leading to persistent hyperglycemia and insulin resistance (IR) in peripheral tissues (Bakker et al., 2009; Saini, 2010).

In addition to its metabolic complications, DM has been increasingly associated with cognitive dysfunction, including impairments in executive functions, attention, memory, and processing speed (G. J. Biessels & Despa, 2018; Hameed et al., 2015; Sebastian et al., 2023). Recent studies have identified

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DM as a potential risk factor for cognitive decline, including mild cognitive impairment (MCI), vascular dementia, and particularly Alzheimer's disease (AD) (Hameed et al., 2015).

AD is the most prevalent form of dementia worldwide, affecting nearly 50 million people, and is marked by progressive memory loss and cognitive decline (Takeishi et al., 2021). At the molecular level, AD is characterized by extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, and activation of immune glial cells, mainly microglia (Calabrò et al., 2021; Lee et al., 2022).

Emerging evidence suggests that DM and AD share overlapping pathophysiological mechanisms, including insulin signaling dysfunction, Aβ accumulation, tau hyperphosphorylation, oxidative stress, vascular dysfunction, and neuroinflammation (Arvanitakis et al., 2004; Rasool et al., 2021). About 50-52% of patients with DM develop dementia as a late complication, with an increased risk of over 65% for AD (Arvanitakis et al., 2004; Barbagallo, 2014; Rasool et al., 2021). Understanding the intricate relationship between peripheral metabolic disorders and brain pathologies is critical to unraveling the molecular mechanisms that link DM -particularly DM2- and AD (Behl et al., 2022).

The relationship between metabolic dysfunction and cognitive impairment has gradually emerged over the past decades. In 1980, hypoglycemia was first observed to influence brain function (Adolfsson et al., 1980), and by 1994, researchers began to associate altered glucose metabolism with dementia (Razay & Wilcock, 1994). In 1996, further studies reported that DM2 patients and elevated blood glucose levels exhibited learning and memory deficits (Messier & Gagnon, 1996). Similarly, in AD patients, hyperglycemia was associated with neuronal damage due to Aβ accumulation (Messier & Gagnon, 1996). This led to the conceptualization of the term "brain diabetes" in 2005 (Li & Hölscher, 2007), to describe overlapping features between diabetes and AD, and to the identification of shared pathological features between DM2 and AD in subsequent years, such as the presence of fibrillar protein aggregates: amylin in pancreatic islets in DM2, and Aβ plaques and NFTs in AD patients (de la Monte & Wands, 2008; Götz et al., 2009).

Additional contributors to this intersection have been identified, including inflammation, oxidative stress, insulin receptor downregulation, and Aβ accumulation (Park, 2011; Saini, 2010). DM2 can impact brain function through various mechanisms, including glucose-induced toxicity, blood-brain barrier (BBB) disruption, increased production of reactive oxygen species (ROS), and IR in the brain (Behl et al., 2022; Garcia-Serrano & Duarte, 2020). Hyperglycemia and reduced brain glucose uptake also contribute to the formation of advanced glycation end products (AGEs), which are now considered a molecular bridge between DM2 and AD pathologies (Behl et al., 2022; Kong et al., 2020; Uribarri et al., 2020).

Patients with DM2 have a higher risk of neurodegeneration and AD development (Stanciu et al., 2020). In AD, insulin receptor density is reduced by 80%, and dysfunctional insulin signaling is believed to play a pivotal role in the development of AD (Hernández-Contreras et al., 2021). Therefore, DM2 patients not only have a higher predisposition to cognitive impairments but also an elevated risk of developing AD later in life (Pasquier et al., 2006; Verdelho et al., 2007). These cognitive impairments have also been replicated in animal models of diabetes, reinforcing the likelihood of a biological connection (Biju & Paulose, 1998; Winocur & Greenwood, 2005).

Additionally, the brains of AD patients exhibit features like those of insulin-deficient states, including reduced insulin and Insulin Growth Factor (IGF) signaling, as well as increased markers of oxidative and inflammatory stress (Craft, 2005, 2006; Rivera-Meza et al., 2017; Steen et al., 2005). Together, these findings support the notion that DM2 and AD are interrelated conditions, linked by common metabolic and neurobiological pathways.

This review aims to explore the neurobiological mechanisms linking DM2 to AD, identify additional risk factors contributing to this association, and analyze current advancements in shared biomarkers. By assessing these connections, we aim to provide a comprehensive understanding of the relationship between DM2 and AD from a neurobiological perspective and to suggest targeted therapeutic strategies (Figure 1).

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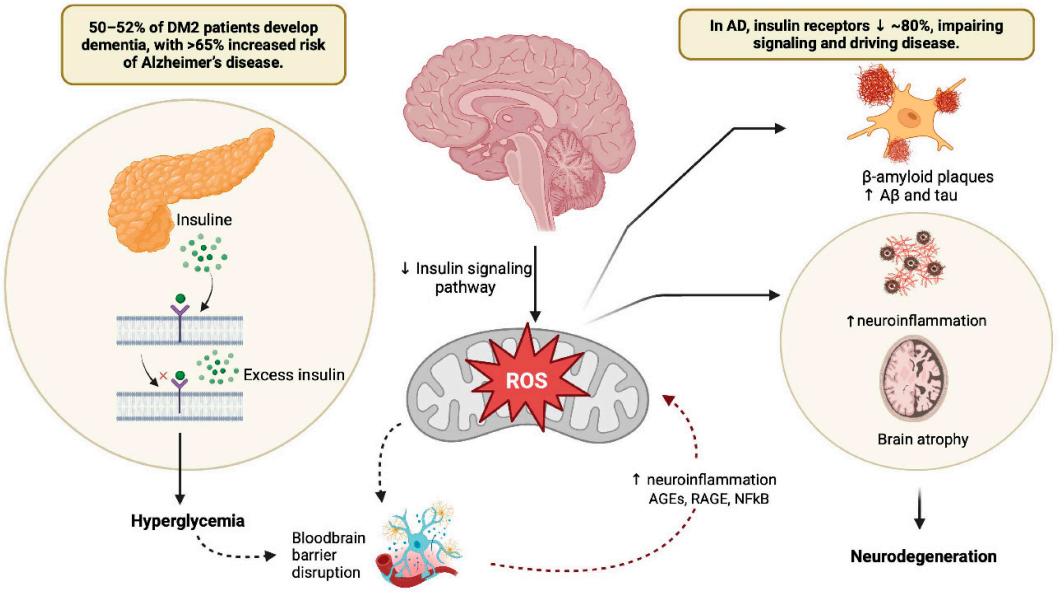

Figure 1. Mechanistic links between type 2 diabetes mellitus (DM2) and Alzheimer's disease. Chronic hyperglycemia and insulin resistance in DM2 result in altered insulin receptor signaling. This altered insulin signaling compromises neuronal energy homeostasis and synaptic plasticity. Concurrently, hyperglycemia increases oxidative stress through the overproduction of ROS, leading to mitochondrial dysfunction and endothelial damage that contribute to the disruption of the blood-brain barrier. Barrier impairment/permeabilization facilitates infiltration of peripheral immune cells and amplifies central neuroinflammatory responses, mediated by the activation of microglia and astrocytes. Chronic inflammation further promotes the accumulation of Aβ and tau hyperphosphorylation, leading to the formation of neurofibrillary tangles. Together, these pathological processes converge to accelerate neuronal loss, cortical and hippocampal atrophy, and cognitive decline. Created in https://BioRender.com.

2. Unraveling the Molecular Nexus Between Type 2 Diabetes Mellitus and Alzheimer's Disease: Insights Into Shared Pathways and Therapeutic Implications.

DM2 and AD represent two seemingly distinct disorders, but they increasingly intersect at multiple molecular levels (Petermann et al., 2018). Despite their clinical differences, accumulating evidence suggests shared features, particularly involving IR, chronic inflammation, oxidative stress, and the presence of common brain proteins such as Aβ (Costache et al., 2023; Formiga et al., 2015; Mestizo Gutiérrez et al., 2014; Zapata-Tragodara et al., 2020).

Insulin plays a fundamental role in brain function, particularly in cognition and memory. Beyond its well-known role in regulating glucose metabolism, insulin crosses the BBB and modulates various critical pathways involved in neuronal survival, including synaptic plasticity, neuroinflammation, and cell viability (Costache et al., 2023). In the context of AD, insulin can influence the dynamics of Aβ; for example, elevated levels of insulin in the brain may increase Aβ production or reduce its clearance, promoting its accumulation (Costache et al., 2023). This is because insulin shares metabolic pathways with Aβ, and dysfunction in insulin signaling can contribute to increased amyloid plaque deposition, a hallmark of the disease. Therefore, insulin levels can also serve as a surrogate marker for the efficiency of Aβ clearance, acting as an indirect indicator of Alzheimer's-related pathological processes (Costache et al., 2023; Sánchez-Zúñiga et al., 2020). In this sense, brain IR or impaired signaling pathways may be key factors linking metabolic dysfunction characteristic of type 2 diabetes with the neurodegenerative changes observed in AD.

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Soluble oligomers of the Aβ peptide (AβOs), widely distributed in the brain, have been implicated in pathologies like AD, inducing hyperphosphorylation of neuronal tau protein, oxidative stress, neurodegeneration, synaptic loss, and inhibition of synaptic plasticity (Chrem Mendez et al., 2019; Haass & Selkoe, 2007; Lamport et al., 2013; Watson et al., 2005). These features are also observed in insulin-involved AD pathogenesis in patients with DM2, suggesting that impaired insulin signaling may underlie a shared pathogenic mechanism (Sims-Robinson et al., 2010) (Figure 2).

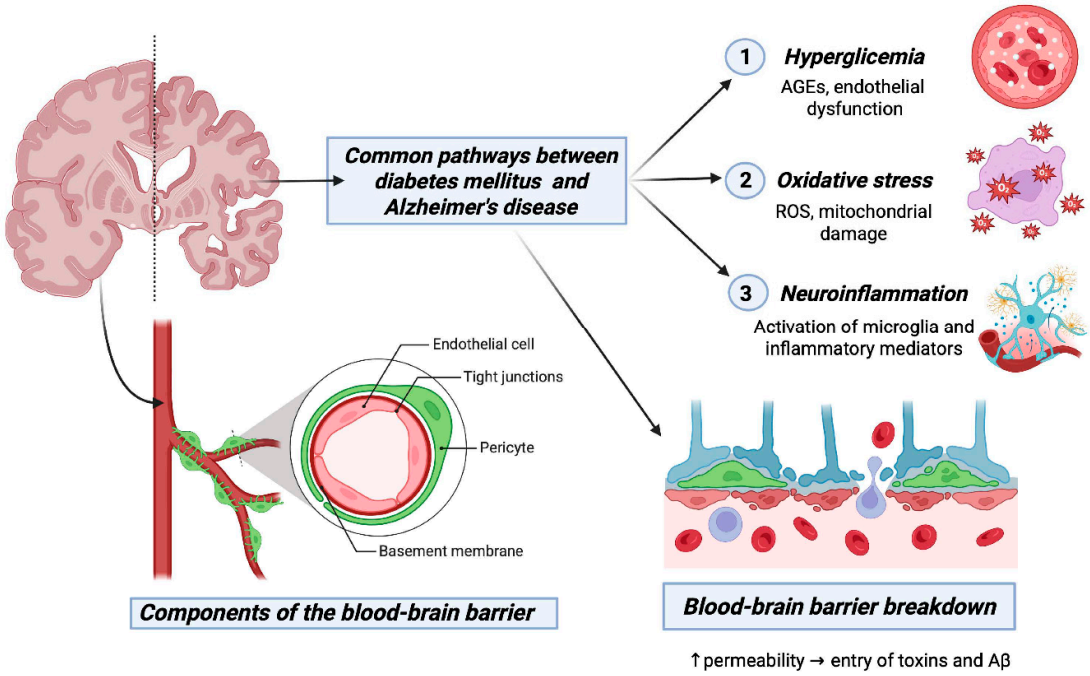

Figure 2. Blood-Brain Barrier Dysfunction in Diabetes Mellitus and Alzheimer's Disease: Mechanisms and Therapeutic Targets. This figure illustrates the intricate relationship between DM2 and AD through the lens of BBB dysfunction. The BBB, composed of endothelial cells, astrocytes, neurons, and pericytes, acts as a critical defense mechanism for the brain against neurotoxic compounds. The figure outlines the breakdown of the BBB in AD, emphasizing the role of impaired tight junctions and adherents' junctions in brain microvascular endothelial cells. Furthermore, the figure delves into the similarities between DM2 and neurodegenerative diseases, such as vascular dementia and AD, showcasing how hyperglycemia, oxidative stress, and chronic inflammation contribute to BBB impairment in DM2. Overall, this comprehensive figure provides insights into the multifaceted mechanisms of BBB dysfunction in the context of DM2 and AD, offering potential avenues for therapeutic interventions. Created in https://BioRender.com.

Recent discoveries in neuroendocrinology have shown that both DM2 and AD share common features, including aberrant insulin signaling in the Phosphoinositide 3-Kinase (PI3K) and Mitogen-Activated Protein Kinase (MAPK) pathways in brain tissues, mitochondrial dysfunction, impaired glucose transport (via GLUT1 and GLUT3), and oxidative stress (Gutiérrez-Rodelo et al., 2017; von Bernhardi, 2004).

In fact, hyperglycemia in DM2 can affect GLUT transporter activity and compromise the integrity of the BBB, promoting the entry of neurotoxic substances into the brain and exacerbating inflammation (Sienes Bailo et al., 2022; Yaffe, 2004). These metabolic and vascular alterations contribute to cognitive dysfunctions, highlighting the importance of glycemic control in AD prevention (Bohórquez Moreno et al., 2020; Lamport et al., 2014).

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Mitochondrial dysfunction also represents a common link between DM2 and AD. A study by Liu et al. (2021) demonstrated that vascular endothelial growth factor (VEGF) mitigated Aβ-induced mitochondrial depolarization and promoted mitochondrial biogenesis, thereby improving cognitive performance (X. Liu et al., 2021). Although VEGF did not significantly affect autophagy or mitophagy, its specific role in preserving mitochondrial function suggests a therapeutic bridge between these two conditions (Demetrius & Simon, 2012; Hansson Petersen et al., 2008; X. Liu et al., 2021; Naia et al., 2023) (Figure 2).

As mentioned, DM2 shares multiple pathological mechanisms with neurodegenerative diseases such as AD and vascular dementia, including alterations in cerebral blood flow, endothelial health, and an exacerbated inflammatory response. Moreover, recent research has demonstrated that dysfunction in brain insulin signaling—characteristic of cerebral insulin resistance or 'type 3 diabetes'—plays a central role in the pathogenesis of these conditions. Disrupted insulin pathways contribute to the accumulation of Aβ and hyperphosphorylation of tau, two key events in neurodegeneration. Therefore, the interplay between metabolic dysfunction and neurodegenerative processes not only supports the hypothesis that brain insulin resistance is a common factor but also highlights potential therapeutic avenues aimed at restoring insulin signaling to slow disease progression (Bedse et al., 2015).

Structural and functional integrity of the BBB is compromised in DM2 due to hyperglycemia, oxidative stress, and chronic inflammation (Bogush et al., 2017; Pooja Naik, 2014). This leads to the accumulation of glycolytic intermediaries, ROS, and activation of inflammatory pathways such as the AGEs-RAGE-NFκB axis (Chelombitko, 2018; Han & Kim, 2023; Jais & Brüning, 2017; Mittal et al., 2014; Tobon-Velasco et al., 2014).

While glycemic control remains the primary target in the management of diabetes, certain therapeutic strategies may inadvertently increase the risk of hypoglycemia, a factor linked to cognitive impairment and memory deficits. Ramirez-Rincón et al. have emphasized the importance of an individualized approach to diabetes treatment, considering patient-specific factors such as cardiovascular risk, comorbidities, and potential adverse events, including hypoglycemia (Ramírez Rincón et al., 2022). They highlight that overly aggressive glucose-lowering regimens, particularly in vulnerable populations, can elevate hypoglycemia risk and potentially accelerate cognitive decline. In contrast, some evidence suggests that maintaining optimal glycemic levels through careful management may help mitigate neurodegenerative processes associated with AD, if hypoglycemia is avoided (Cukierman-Yaffe et al., 2015; Fava, 2014; Vanhandsaeme & Benhalima, 2021). This underscores the need for a balanced approach that not only targets glycemic control but also minimizes hypoglycemia to preserve cognitive function. These observations underscore the intricate interplay between metabolic regulation and neurological outcomes.

IR in the brain has been associated with atrophy and AD phenotype, including tau pathology and Aβ accumulation (Ciudin, 2016). Insulin is vital not only for glucose uptake but also for maintaining axonal integrity through its regulation of cytoskeletal proteins and growth factors (detailed in the next section). The reduction in insulin production, commonly seen in aging and AD, interferes with these processes, thereby promoting synaptic dysfunction and neurodegeneration (Domínguez et al., 2014).

Genetic factors further modulate the link between DM2 and AD. The ε4 allele of apolipoprotein E (APOE), which is the strongest genetic risk factor associated with late-onset AD, is also linked to impaired lipid and glucose metabolism. It is important to note that late-onset AD typically appears after the age of 65, whereas early-onset AD occurs before this age and often involves different genetic and pathological mechanisms. The APOE ε4 allele particularly influences the development and progression of late-onset AD, highlighting its critical role in the neurobiological interplay between metabolic dysregulation and neurodegeneration in the aging population (Jabeen et al., 2022). Individuals carrying the ε4 allele exhibit increased risk of hyperglycemia, IR, and Aβ aggregation (Donoso S & Behrens P, 2005; Jabeen et al., 2022; Roda et al., 2019). By contrast, APOE ε2 confers

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protection for cognitive impairments and IR, while ε3 is considered neutral (Delikkaya et al., 2019; Martínez et al., 2022; Roda et al., 2019; Snyder, 2015).

The overlapping role of APOE in lipid transport, neuronal repair, and glucose metabolism suggests that it is a key integrator of vascular, metabolic, and neurodegenerative processes (Jabeen et al., 2022). Studies have found that APOE ε4 carriers show specific cognitive deficits—particularly in long-term memory—while individuals with diabetes are more prone to working memory impairments (Ravipati et al., 2022). Importantly, the co-occurrence of APOE ε4 and diabetes does not appear to synergistically elevate AD risk, suggesting distinct but converging mechanisms of damage (Ravipati et al., 2022) (Figure 3).

In summary, multiple overlapping mechanisms—vascular dysfunction, insulin signaling defects, neuroinflammation, Aβ deposition, and tau pathology—may contribute to the link between DM2 and AD. Understanding these intersections opens potential avenues for therapeutic intervention aimed at modulating common molecular targets.

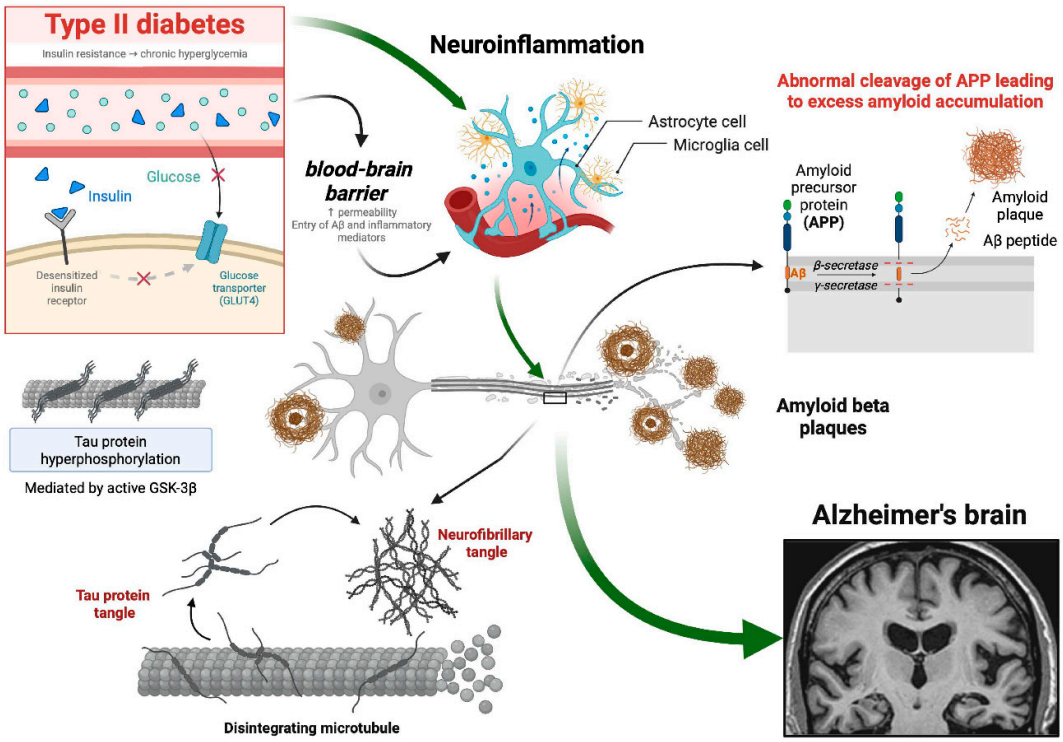

Figure 3. Interconnected Mechanisms Linking Diabetes Mellitus Type 2 and Alzheimer's Disease. The figure illustrates the interconnected mechanisms that establish a link between DM2 and AD. It focuses on shared elements such as insulin resistance, chronic inflammation, and common brain proteins. The impact of insulin on cognitive processes, Aβ peptide levels, and tau protein hyperphosphorylation is highlighted. Additionally, it shows mechanisms like neuroinflammation, Aβ accumulation, and tau phosphorylation, emphasizing blood biomarkers for AD diagnosis. In the amyloidogenic pathway, amyloid precursor protein is first cleaved by β-secretase and subsequently cleaved by γ-secretase to generate Aβ peptides. The accumulation and aggregation of Aβ peptides results in neurotoxic amyloid plaques. This figure provides a visually comprehensive overview of the complex interplay between DM2 and AD, unraveling the interconnected mechanisms that contribute to their shared pathophysiology and mutual promotion of cognitive dysfunction. Created in https://BioRender.com.

3. Bridging the Gap: Exploring the Interplay Between Insulin Signaling, Diabetes, and Alzheimer's Disease.

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Insulin is a hormone secreted by pancreatic β-cells permeable to the BBB and, therefore, able to enter the CNS via systemic circulation (Xourgia et al., 2019). In the brain, insulin acts as a potent neurotrophic factor, regulating metabolism, synaptic plasticity, and cognitive function through the activation of insulin receptors (Galea, 2021; Sima & Zhang, 2014; Sonar & Lal, 2018).

Insulin receptors are ubiquitously expressed in the brain, particularly in the hippocampus, cortex, hypothalamus, olfactory bulb, and pituitary, with a higher density in neurons compared to glia (J. Duarte, 2014; Kleinridders et al., 2014). Studies have shown that insulin receptors are densely expressed in the axons of hippocampal pyramidal neurons and are predominantly localized in brain regions essential for learning, memory, and cognitive functions. In addition to their structural presence, functional studies in healthy conditions provide strong evidence that insulin signaling is crucial for optimal cognitive performance (Freychet, 2000; McNay et al., 2010; Pomytkin et al., 2018). Specifically, when insulin receptors are blocked or inhibited within the hippocampus, there is a significant impairment in memory performance, indicating that endogenous insulin signaling is necessary for the maintenance of normal memory processes. This functional disruption emphasizes that insulin action within the hippocampus is not merely supportive but vital for proper cognitive function, with receptor blockade leading directly to deficits in spatial working memory and other hippocampal-dependent tasks (Freychet, 2000; McNay et al., 2010; Pomytkin et al., 2018).

In DM2 patients, a decrease in insulin receptor density and alterations in insulin signaling have been observed, particularly in the hippocampus, cortex, and choroid plexus (A. I. Duarte et al., 2012). Metabolic disturbances associated with diabetes, including hyperglycemia, hyperinsulinemia, and hypercholesterolemia, have been linked to brain atrophy and neuropathological features of AD (C.-C. Huang et al., 2014; Scheltens et al., 2021; Verdile et al., 2015). Furthermore, even in the absence of dementia, insulin resistance has been associated with cognitive impairment in aging (Burns et al., 2012; Gong et al., 2023).

Insulin regulates protein synthesis, post-translational modifications (PTMs), the assembly of cytoskeletal and adhesive proteins, and intracellular support molecules important for axonal integrity (Sima & Zhang, 2014; Yang et al., 2023). Dysregulation of these processes is associated with an increased risk of developing diabetes and can also lead to neuronal dysfunction, synaptic deficits, and increased vulnerability to neurodegeneration (J. M. N. Duarte, 2023; Yang et al., 2023).

Importantly, insulin regulates the metabolism of Aβ and tau, the basic components of amyloid plaques and NFTs, respectively (G. J. Biessels & Kappelle, 2005; Craft et al., 1998; Kim et al., 2013; Steen et al., 2005). Reduced insulin production, as observed in aging and AD, correlates with decreased insulin activity in regions such as the frontal cortex, hippocampus, and hypothalamus (De Felice et al., 2022).

Knopman, in 2014, studied glucose metabolism using positron emission tomography with fluorodeoxyglucose (PET-FDG) in cognitively normal APOE4 carriers, showing reduced uptake in various brain regions, including the temporal lobe (Knopman et al., 2014). Finally, the APOE3 allele is the most common isoform and tends to remain neutral regarding the disease, neither increasing nor decreasing the risk (Langella et al., 2023; Rebeck et al., 2002). Other studies confirm APOE ε4's association with accelerated cognitive decline, especially when combined with different mutations, such as PSEN1 (Langella et al., 2023; Polsinelli et al., 2023) (Figure 4).

Interestingly, some studies suggest that APOE ε4 carriers with diabetes may experience distinct cognitive trajectories compared to non-carriers. While APOE ε4 primarily affects long-term memory, diabetes is more closely linked to deficits in working memory (Ravipati et al., 2022). This suggests that DM2 and APOE ε4 may influence cognition through partially independent but converging mechanisms.

The importance of considering APOE genotype and diabetes as potential risk factors for AD highlights the need for further research to elucidate how these factors contribute to the development and progression of the disease (Ravipati et al., 2022; Shinohara et al., 2021) (Figure 4). Insights gained from such studies could pave the way for targeted interventions and personalized treatment approaches in the field of AD research and management.

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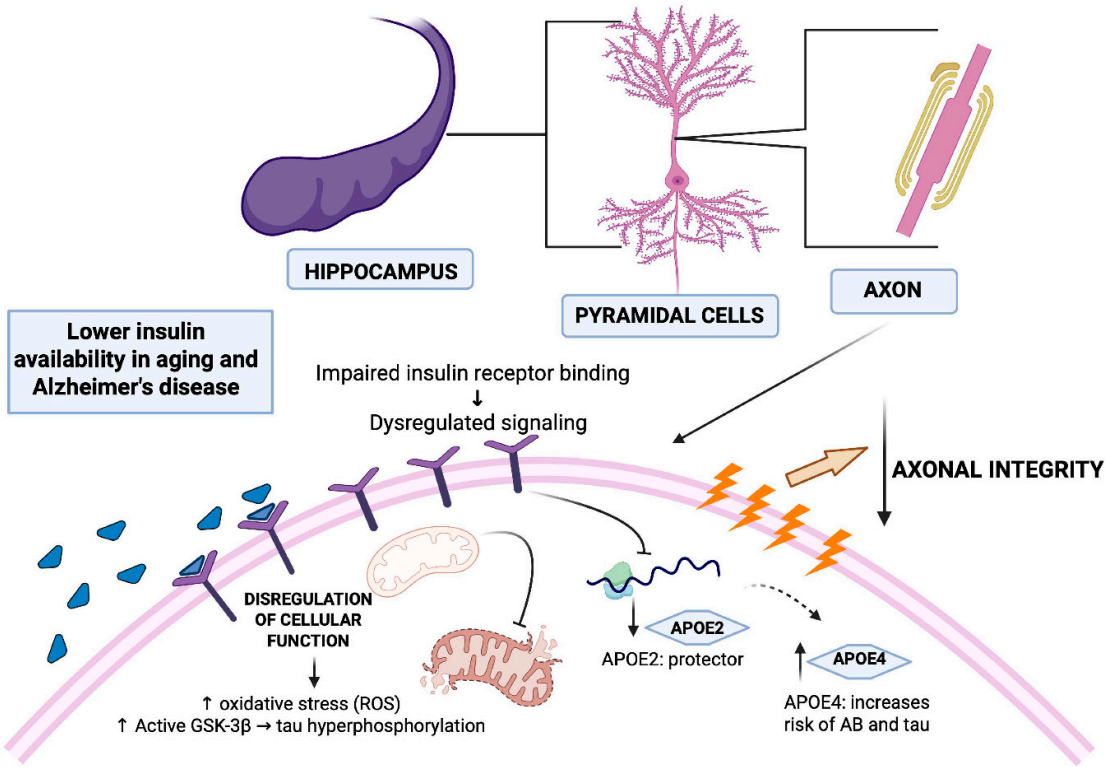

Figure 4. Interplay of Insulin, APOE Genotypes, and Alzheimer's Disease Onset. This figure illustrates the intricate relationships between insulin, APOE genotypes, and AD. Insulin, a crucial trophic factor in the CNS, is transported across the BBB and interacts with insulin receptors, which are widely expressed in the hippocampus. The figure highlights how alterations in insulin levels and signaling contribute to neurodegeneration and cognitive impairment in the context of DM2 and aging. It visualizes how alterations in insulin levels and signaling, particularly in brain regions like the hippocampus, contribute to neurodegeneration in the context of diabetes mellitus and aging. The figure also highlights the impact of APOE genotypes on AD risk, emphasizing the neuroprotective role of APOE2, and the increased risk associated with APOE4. Created in https://BioRender.com.

4. Therapeutic Opportunities and Pharmacological Interventions

Late-onset AD and DM2 share common features, including impaired insulin signaling, chronic inflammation, mitochondrial dysfunction, and glucose dysregulation, suggesting a link between the two conditions (Cholerton et al., 2013; Mancinetti et al., 2023). As mentioned, IR and impaired glucose metabolism may contribute to the development and progression of AD (Mancinetti et al., 2023). These shared mechanisms have raised interest in evaluating anti-diabetic drugs as potential therapies for AD and cognitive decline.

In experimental models, including rodent studies of ischemia and neurodegeneration, pioglitazone has been shown to exert vasculoprotective effects, such as reducing inflammatory responses in adipose tissue, decreasing urinary TGF-β1 excretion, and promoting endothelial progenitor cell mobilization, which enhances angiogenesis (Desouza & Shivaswamy, 2010). These effects are mediated through activation of PPAR gamma and beta/delta pathways, leading to reduced inflammation, improved endothelial function, and potential neuroprotective mechanisms. Clinically, in patients with DM2, pioglitazone's benefits include improved glycemic control, decreased inflammatory mediators like C-reactive protein and VEGF, and possible nephroprotective effects, as evidenced by reduced urinary TGF-β1 excretion. However, risks such as peripheral edema, weight gain, and hypoglycemia when combined with insulin or other hypoglycemic agents are notable considerations (Desouza & Shivaswamy, 2010). By inhibiting the reabsorption of glucose in the

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kidneys and promoting glucose excretion in the urine, SGLT2 inhibitors improve glycemic control while also modulating brain metabolism and neuroinflammatory pathways implicated in AD (Desouza & Shivaswamy, 2010; Dolan et al., 2010; Majid et al., 2025).

Recent population-based studies have compared the effects of SGLT2 inhibitors with other anti-diabetic drugs, such as dipeptidyl peptidase-4 (DPP4) inhibitors, indicating that SGLT2 inhibitors may be more effective in reducing the risk of dementia in DM2 patients (DeFronzo et al., 2013; Mancinetti et al., 2023). The neuroprotective effects of these drugs extend beyond their anti-diabetic properties, suggesting a direct impact on brain health and cognitive function (Cholerton et al., 2013).

Furthermore, SGLT2 inhibitors have been shown to prevent memory impairment in AD animal models, showing beneficial effects on neurogenesis, synaptic plasticity, and neurodegeneration (DeTure & Dickson, 2019). These findings suggest that targeting glucose metabolism through SGLT2 inhibition may offer novel therapeutic strategies for managing cognitive decline associated with AD (DeFronzo et al., 2013).

On the other hand, AD clinical presentations differ between early- and late-onset forms. Early-onset AD is associated with language, visuospatial, or executive function impairments, while late-onset AD patients exhibit the classic amnestic pattern of the disease (Palasí et al., 2015). Comorbidities such as diabetes, cardiovascular dysfunction, and obesity are more commonly observed in late-onset pathology, supporting the metabolic contribution to disease progression (Chen et al., 2017; Gerritsen et al., 2016).

Insulin plays a crucial role in brain health, influencing cerebral bioenergetics, synaptic viability, neurotransmitter turnover, and proteostasis (Kellar & Craft, 2020). Insulin signaling dysregulation in the brain can lead to neurodegeneration by impairing the clearance of Aβ and tau, promoting vascular damage, and increasing inflammation (Busiguina et al., 2000; Clark & Vissel, 2018; El Khoury et al., 2014).

Peripheral IR may result in reduced brain insulin concentrations, impairing insulin signaling within neurons (Könner et al., 2011). Notably, insulin directly interacts with Aβ, reducing its synaptotoxicity and facilitating clearance mechanisms (Craft et al., 2020). This interaction is critical because reduced insulin levels in the brain and cerebrospinal fluid (CSF) have been reported in AD patients (Craft et al., 2020; Kellar & Craft, 2020).

Emerging therapeutic strategies now aim to restore brain insulin function. Intranasal insulin administration has shown promise by enhancing cognitive performance in both preclinical and clinical studies (Craft et al., 2020). This approach increases brain insulin availability without affecting blood glucose, reducing the risk of hypoglycemia.

Other therapeutic targets include insulin-like growth factor-1 (IGF-1) and insulin receptor substrate-1 (IRS-1), which are frequently impaired in AD brains (Arvanitakis et al., 2020; Talbot et al., 2012). Postmortem studies of AD patients have revealed deficient insulin signaling in regions associated with cognition, such as the frontal cortex and hippocampus (Arvanitakis et al., 2020). These abnormalities are associated with both Aβ accumulation and tau hyperphosphorylation, underscoring the relevance of insulin-related pathways in AD pathogenesis (Craft et al., 2020).

In conclusion, therapies originally designed for DM2, such as SGLT2 inhibitors, may have potential in slowing or preventing cognitive decline associated with AD. These strategies target the intersection of metabolism, neuroinflammation, and neurodegeneration, offering a multi-modal approach to treating patients at the crossroads of diabetes and dementia. Further research is warranted to elucidate the specific mechanisms by which SGLT2 inhibitors exert their neuroprotective effects and to optimize their clinical use.

5. Biomarkers Related to Neurodegeneration in Diabetes Mellitus and Alzheimer's Disease

In recent years, the development of highly sensitive immunoassays has significantly advanced the early and less invasive detection of AD biomarkers in plasma and cerebrospinal fluid (Kivisäkk et al., 2024). Given the growing evidence that DM2 may contribute to the pathogenesis of AD,

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neurodegeneration has been considered a possible mechanism establishing a connection between DM2 and AD (Madhusudhanan et al., 2020).

Several converging mechanisms, such as vascular endothelial dysfunction, insulin dysregulation, dysglycemia, neuroinflammation, Aβ accumulation, and abnormal tau phosphorylation, have been identified as shared contributors in the pathogenesis of cognitive impairment associated with both DM2 subtypes and AD (Burillo et al., 2021; Sible et al., 2022; Trimm & Red-Horse, 2023; Tumminia et al., 2018; Willette et al., 2015) (Table 1).

Table 1: Summary of Biomarkers Related to Neurodegeneration in Diabetes Mellitus and Alzheimer's Disease.

Biomarker	Association with DM2 and AD	Detection Method	Implications	Levels in DM2	Levels in AD	Reference
Endothelin	Vascular damage, inflammation	Immunoassays	Indicator of endothelial dysfunction in DM2 and AD	↑	↑	(Trimm and Red-Horse, 2023)
Insulin	Alterations in signaling	Immunohistochemistry	Decrease in availability related to AD	↓	↓	(Mullins et al., 2017; Willette et al., 2015)
Proinsulin	Cellular stress, beta dysfunction	ELISA	Possible indicator of cellular stress and beta-cell health	↑	↑	(Saraya et al., 2023)
C-peptide	Influence on diabetes	Immunoassays	Linked to diabetes and suggestive of neuroprotection	Varies in DM2	Varies in AD	(Wang et al., 2012)
Aβ42:Aβ40	Plaque accumulation, relation to t-tau	CSF Measurement	Associated with Aβ plaques and t-tau in AD	Altered ratio in DM2	Altered ratio in AD	(Andersson et al., 2023; Zhang et al., 2021)
t-tau, p-tau	Neurofibrils and tangles in AD	CSF Measurement	Indicators of pathology in AD	↑	↑	(Barthélemy et al., 2023, 2020)
Neuroinflammation	Inflammatory response	Inflammatory markers	Related to inflammation in DM2 and AD	↑	↑	(Ehtewish et al., 2022)
GLP1-RA	GLP-1 receptor agonist	Clinical trials	Potential therapeutic intervention in DM2 and AD	Varied response in DM2	Varied response in AD	(García-Casares et al., 2023; Klausen et al., 2022)
Hyperphosphorylated Tau	Hyperphosphorylated Tau in AD	Western blot	Linked to tau pathology in AD	↑	↑	(Olesen and Quintanilla, 2023)

This table provides an overview of key biomarkers associated with the complex interplay between DM2 and AD. The biomarkers include endothelin, insulin, proinsulin, C-peptide, Aβ42, Aβ40, t-tau, p-tau, neuroinflammation, hyperphosphorylated tau, and GLP1-RA. Each biomarker is associated with specific references that highlight its relevance in the context of neurodegeneration, insulin signaling, and AD pathogenesis.

AD is pathologically defined by extracellular Aβ plaques and intracellular NFTs composed of hyperphosphorylated tau (Zhang et al., 2021). In CSF, lower levels of Aβ42 and lower Aβ42:Aβ40 ratios have been related to AD (Andersson et al., 2023). This is due to the sequestration of Aβ42 into amyloid plaques, which induces elevated levels of total tau (t-tau) and tau phosphorylated at Thr 181 (p-tau181) in CSF (Lim et al., 2023). Additionally, increases in t-tau and p-tau181 in CSF tend to correlate with Aβ burden rather than with NFT load (Horie et al., 2023), suggesting that they may reflect early pathophysiological changes rather than late-stage neuronal loss (Barthélemy et al., 2023).

Recent advances in plasma biomarkers have demonstrated that phosphorylated tau species, particularly at Thr181 (p-tau181), Thr217 (p-tau217), and Thr231 (p-tau231), can predict AD

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pathology with high accuracy (Milà-Alomà et al., 2022). For example, p-tau231 in CSF is considered an early marker of Aβ pathology, and p-tau217 may offer better discrimination between AD patients and control groups, with better accuracy than proton emission tomography (Groot et al., 2022; Kimura et al., 2023; Milà-Alomà et al., 2022).

Tau hyperphosphorylation remains a central pathological mechanism in AD and may be exacerbated by chronic hyperglycemia, as seen in diabetes (R. Huang et al., 2020). Tau protein is essential for microtubule stability in neurons, but high glucose levels promote tau hyperphosphorylation in hippocampal neurons, leading to its detachment from microtubules, misfolding, and aggregation into NFTs, inducing cognitive dysfunction in diabetes (Barbier et al., 2019; Cheng et al., 2022; Ke et al., 2009; Tabeshmehr & Eftekharpour, 2023).

This pathological process disrupts axonal transport and cytoskeletal integrity, resulting in neuronal dysfunction, synaptic damage, and cell death (Cheng et al., 2022). Tau is also subject to proteolytic cleavage by endogenous enzymes, such as caspases and calpains, which enhances its aggregation propensity (Barthélemy et al., 2020; Mietelska-Porowska et al., 2014). These cleaved forms of tau further promote NFT formation and correlate with cognitive decline (Olesen & Quintanilla, 2023; Pérez et al., 2018).

Patients with DM2 often exhibit cognitive impairment, including deficits in verbal and visual memory, processing speed, and executive function (Y. Liu et al., 2024). Insulin has been implicated in the clearance of Aβ and the regulation of tau phosphorylation in the CNS (Mullins et al., 2017), with evidence supporting a protective role against Aβ synaptotoxicity by regulating Aβ elimination through the modulation of lipid metabolism, proteases, and insulin-degrading enzymes (Saraya et al., 2023).

C-peptide, traditionally considered a byproduct of insulin synthesis, has gained recognition as a bioactive molecule that may modulate insulin signaling, influencing diabetes (Wang et al., 2012). Emerging evidence suggests that treatment with a C-peptide receptor agonist, such as Glucagon-like peptide-1 receptor agonists (GLP1-RA), may offer therapeutic benefits by improving insulin signaling and reducing the incidence of dementia in type 2 diabetes (DM2) patients (García-Casares et al., 2023; Klausen et al., 2022).

On the other hand, a negative correlation has been observed between insulin signaling and tau phosphorylation (Gonçalves et al., 2019). Upon its binding, the insulin receptor activates different IRS, such as phosphorylated IRS-1, leading to PI3K activation, the phosphorylation of MAPK and protein kinase B (AKT) downstream, and inhibiting GSK-3β, a prominent tau kinase, white its inactivation by AKT signaling inhibits GSK-3β-mediated tau phosphorylation (Boucher et al., 2014; Gabbouj et al., 2019; Ye et al., 2017). When insulin signaling is impaired, GSK-3β remains active, resulting in tau hyperphosphorylation and NFT formation (Hobday & Parmar, 2021; Woodfield et al., 2022).

Hyperglycemia also exacerbates cognitive impairment through osmotic stress, oxidative damage, and inflammatory responses, particularly through the formation of advanced glycation end products (AGE), which subsequently leads to the production of ROS and the release of inflammatory cytokines such as IL-1β and IL-6 (C. Liu et al., 2015), causing systemic inflammation, microvascular dysfunction, and long-term neuronal injury (Ehtewish et al., 2022).

6. Conclusions and Perspectives

This comprehensive review highlights the intricate connections between insulin, neurodegeneration, and AD, shedding light on the multifaceted roles of insulin in maintaining cognitive function. Insulin receptors are ubiquitously expressed in brain regions critical for memory and learning, including hippocampus, cortex, hypothalamus, olfactory bulb, and pituitary (Mullins et al., 2017). Notably, the high density of insulin receptors in hippocampal neurons highlights insulin's crucial role in synaptic plasticity and memory consolidation (G.-J. Biessels et al., 1998; Malenka, 1994).

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Both DM2 and AD exhibit reduced insulin levels and altered signaling, particularly in the hippocampus, cortex, and choroid plexus. These changes are associated with brain atrophy and cognitive decline, indicating a potential connection between metabolic disturbances and neurodegeneration.

Insulin plays a multifaceted role in several cellular processes relevant for neuronal survival, including cytoskeletal assembly, synaptic plasticity, energy metabolism, and the clearance of Aβ and phosphorylated tau (Mullins et al., 2017; Saraya et al., 2023). As insulin production declines with aging and disease progression, the loss of its neurotrophic and protective effects may directly contribute to AD pathology.

Genetic factors significantly contribute to the risk of AD. Variants of the APOE gene, particularly the ε4 allele, are strongly associated with increased AD risk and earlier onset. APOE4 influences lipid metabolism, neuroinflammation, and amyloid β (Aβ) aggregation. In contrast, the ε2 allele appears protective, while ε3 remains neutral (Raulin et al., 2022). Understanding these genetic influences not only clarifies the clinical variability seen in AD but also has the potential to guide the development of personalized interventions.

Biomarkers offer another promising avenue. Advances in immunoassays have enabled the measurement of p-tau isoforms in plasma and CSF, enhancing early and precise AD diagnosis. Key biomarkers, including insulin dysregulation, endothelial dysfunction, neuroinflammation, Aβ accumulation, and abnormal tau phosphorylation, serve as indicators of disease progression and therapeutic targets (Milà-Alomà et al., 2020).

Therapeutic interventions aimed at restoring insulin signaling and related molecules are under scrutiny. GLP1 receptor agonists and SGLT2 inhibitors show promise not only in controlling glycemia but also in reducing the incidence and progression of dementia in DM2 patients (Gonçalves et al., 2019). These agents may exert neuroprotective effects through multiple mechanisms, including reducing oxidative stress, enhancing neurogenesis, and improving mitochondrial function.

Hyperglycemia leads to neuronal damage through mechanisms such as osmotic imbalance, oxidative injury, and chronic inflammation. The accumulation of AGEs and release of cytokines like IL-1β and IL-6 further exacerbate microvascular damage and contribute to cognitive decline (Ehtewish et al., 2022; García-Casares et al., 2023; C. Liu et al., 2015; Luna et al., 2021). Insulin protective role in Aβ clearance and tau phosphorylation regulation highlights the potential of targeting insulin signaling pathways in both the prevention and treatment of AD.

Future research should focus on clarifying the molecular links between insulin resistance, genetic risk, and neurodegeneration, with the goal of identifying predictive biomarkers and tailoring individualized therapies. Moreover, non-invasive methods to improve brain insulin signaling, such as the use of intranasal insulin, should be further explored in clinical studies.

In conclusion, the overlap between DM2 and AD reflects a complex interplay between metabolism and neurodegeneration. A deeper understanding of insulin central role in these conditions opens new opportunities for early diagnosis, the development of biomarkers, and the design of targeted treatments aimed at delaying or preventing cognitive decline.

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Abbreviations

Aβ	Amyloid-beta
AD	Alzheimer's Disease
AGEs	Advanced Glycation End Products
AKT	Protein Kinase B
APOE	Aprolipoprotein E
APP	Amyloid Precursor Protein
BBB	Blood-Brain Barrier
BMECs	Brain Microvascular Endothelial Cells
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DM2	Type 2 Diabetes Mellitus
GLP1-RA	Glucagon-Like Peptide-1 Receptor Agonist
GLUT1 and GLUT3	Glucose Transporters
GSK-3β	Glycogen Synthase Kinase 3 beta
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
IR	Insulin resistance
MAPK	Mitogen-Activated Protein Kinase
NFT	Neurofibrillary Tangles
PET-FDG	Positron Emission Tomography with Fluorodeoxyglucose
PI3K	Phosphoinositide 3-Kinase
PS1/PS2	Presenilin-1/Presenilin-2
p-tau	Phosphorylated Tau Protein
PTM	Posttranslational Modifications
RAGEs	Receptor for AGEs
ROS	Reactive Oxygen Species
t-tau	Total Tau Protein
VEGF	Vascular Endothelial Growth Factor

References

Adolfsson, R., Bucht, G., Lithner, F., Winblad, B., 1980. Hypoglycemia in Alzheimer's disease. Acta Med Scand 208, 387–8. https://doi.org/10.1111/j.0954-6820.1980.tb01217.x

Andersson, E., Schultz, N., Saito, T., Saido, T.C., Blennow, K., Gouras, G.K., Zetterberg, H., Hansson, O., 2023. Cerebral Aβ deposition precedes reduced cerebrospinal fluid and serum Aβ42/Aβ40 ratios in the AppNL−F/NL−F knock-in mouse model of Alzheimer's disease. Alzheimers Res Ther 15, 64. https://doi.org/10.1186/s13195-023-01196-8

Arvanitakis, Z., Wang, H., Capuano, A.W., Khan, A., Taïb, B., Anokye-Danso, F., Schneider, J.A., Bennett, D.A., Ahima, R.S., Arnold, S.E., 2020. Brain Insulin Signaling, Alzheimer Disease Pathology, and Cognitive Function. Ann Neurol 88, 513–525. https://doi.org/10.1002/ana.25826

Arvanitakis, Z., Wilson, R.S., Bienias, J.L., Evans, D.A., Bennett, D.A., 2004. Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function. Arch Neurol 61, 661. https://doi.org/10.1001/archneur.61.5.661

Bakker, W., Eringa, E.C., Sipkema, P., van Hinsbergh, V.W.M., 2009. Endothelial dysfunction and diabetes: roles of hyperglycemia, impaired insulin signaling and obesity. Cell Tissue Res 335, 165–189. https://doi.org/10.1007/s00441-008-0685-6

Barbagallo, M., 2014. Type 2 diabetes mellitus and Alzheimer's disease. World J Diabetes 5, 889. https://doi.org/10.4239/wjd.v5.i6.889

 doi:10.20944/preprints202602.1880.v1

Barbier, P., Zejneli, O., Martinho, M., Lasorsa, A., Belle, V., Smet-Nocca, C., Tsvetkov, P.O., Devred, F., Landrieu, I., 2019. Role of Tau as a Microtubule-Associated Protein: Structural and Functional Aspects. Front Aging Neurosci 11. https://doi.org/10.3389/fnagi.2019.00204

Barthélemy, N.R., Li, Y., Joseph-Mathurin, N., Gordon, B.A., Hassenstab, J., Benzinger, Tammie.L.S., Buckles, V., Fagan, A.M., Perrin, R.J., Goate, A.M., Morris, J.C., Karch, C.M., Xiong, C., Allegri, R., Mendez, P.C., Berman, S.B., Ikeuchi, T., Mori, H., Shimada, H., Shoji, M., Suzuki, K., Noble, J., Farlow, M., Chhatwal, J., Graff-Radford, N.R., Salloway, S., Schofield, P.R., Masters, C.L., Martins, R.N., O'Connor, A., Fox, N.C., Levin, J., Jucker, M., Gabelle, A., Lehmann, S., Sato, C., Bateman, R.J., McDade, E., 2020. A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 26, 398–407. https://doi.org/10.1038/s41591-020-0781-z

Barthélemy, N.R., Saef, B., Li, Y., Gordon, B.A., He, Y., Horie, K., Stomrud, E., Salvadó, G., Janelidze, S., Sato, C., Ovod, V., Henson, R.L., Fagan, A.M., Benzinger, T.L.S., Xiong, C., Morris, J.C., Hansson, O., Bateman, R.J., Schindler, S.E., 2023. CSF tau phosphorylation occupancies at T217 and T205 represent improved biomarkers of amyloid and tau pathology in Alzheimer's disease. Nat Aging 3, 391–401. https://doi.org/10.1038/s43587-023-00380-7

Bedse, G., Di Domenico, F., Serviddio, G., Cassano, T., 2015. Aberrant insulin signaling in Alzheimer's disease: current knowledge. Front Neurosci 9. https://doi.org/10.3389/fnins.2015.00204

Behl, T., Arora, A., Sehgal, A., Singh, S., Sharma, N., Bhatia, S., Al-Harrasi, A., Bungau, S., Mostafavi, E., 2022. Molecular and Biochemical Pathways Encompassing Diabetes Mellitus and Dementia. CNS Neurol Disord Drug Targets 21, 542–556. https://doi.org/10.2174/1871527320666211110115257

Biessels, G.J., Despa, F., 2018. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol 14, 591–604. https://doi.org/10.1038/s41574-018-0048-7

Biessels, G.-J., Kamal, A., Urban, I.J.A., Spruijt, B.M., Erkelens, D.W., Gispen, W.H., 1998. Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: effects of insulin treatment. Brain Res 800, 125–135. https://doi.org/10.1016/S0006-8993(98)00510-1

Biessels, G.J., Kappelle, L.J., 2005. Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? Biochem Soc Trans 33, 1041–1044. https://doi.org/10.1042/BST0331041

Biju, M.P., Paulose, C.S., 1998. Brain glutamate dehydrogenase changes in streptozotocin diabetic rats as a function of age. Biochem Mol Biol Int 44, 1–7. https://doi.org/10.1080/15216549800201002

Bogush, M., Heldt, N.A., Persidsky, Y., 2017. Blood Brain Barrier Injury in Diabetes: Unrecognized Effects on Brain and Cognition. Journal of Neuroimmune Pharmacology 12, 593–601. https://doi.org/10.1007/s11481-017-9752-7

Bohórquez Moreno, C.E., Barreto Vásquez, M., Muvdi Muvdi, Y.P., Rodríguez Sanjuán, A., Badillo Viloria, M.A., Martínez de la Rosa, W.Á., Mendoza Sánchez, X., 2020. FACTORES MODIFICABLES Y RIESGO DE DIABETES MELLITUS TIPO 2 EN ADULTOS JÓVENES: UN ESTUDIO TRANSVERSAL. Ciencia y Enfermería 26. https://doi.org/10.29393/CE26-7FMCB70007

Boucher, J., Kleinridders, A., Kahn, C.R., 2014. Insulin Receptor Signaling in Normal and Insulin-Resistant States. Cold Spring Harb Perspect Biol 6, a009191–a009191. https://doi.org/10.1101/cshperspect.a009191

Burillo, J., Marqués, P., Jiménez, B., González-Blanco, C., Benito, M., Guillén, C., 2021. Insulin Resistance and Diabetes Mellitus in Alzheimer's Disease. Cells 10, 1236. https://doi.org/10.3390/cells10051236

Burns, J.M., Honea, R.A., Vidoni, E.D., Hutfles, L.J., Brooks, W.M., Swerdlow, R.H., 2012. Insulin is differentially related to cognitive decline and atrophy in Alzheimer's disease and aging. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1822, 333–339. https://doi.org/10.1016/j.bbadis.2011.06.011

Busiguina, S., Fernandez, A.M., Barrios, V., Clark, R., Tolbert, D.L., Berciano, J., Torres-Aleman, I., 2000. Neurodegeneration Is Associated to Changes in Serum Insulin-like Growth Factors. Neurobiol Dis 7, 657–665. https://doi.org/10.1006/nbdi.2000.0311

Calabrò, M., Rinaldi, C., Santoro, G., Crisafulli, C., 2021. The biological pathways of Alzheimer disease: a review. AIMS Neurosci 8, 86–132. https://doi.org/10.3934/Neuroscience.2021005

Chelombitko, M.A., 2018. Role of Reactive Oxygen Species in Inflammation: A Minireview. Moscow Univ Biol Sci Bull 73, 199–202. https://doi.org/10.3103/S009639251804003X

 doi:10.20944/preprints202602.1880.v1

Chen, Y., Sillaire, A.R., Dallongeville, J., Skrobala, E., Wallon, D., Dubois, B., Hannequin, D., Pasquier, F., 2017. Low Prevalence and Clinical Effect of Vascular Risk Factors in Early-Onset Alzheimer's Disease. Journal of Alzheimer's Disease 60, 1045–1054. https://doi.org/10.3233/JAD-170367

Cheng, Y., Ren, J.-R., Jian, J.-M., He, C.-Y., Xu, M.-Y., Zeng, G.-H., Tan, C.-R., Shen, Y.-Y., Jin, W.-S., Chen, D.-W., Li, H.-Y., Yi, X., Zhang, Y., Bu, X.-L., Wang, Y.-J., 2022. Associations of plasma angiostatin and amyloid-β and tau levels in Alzheimer's disease. Transl Psychiatry 12, 194. https://doi.org/10.1038/s41398-022-01962-6

Cholerton, B., Baker, L.D., Craft, S., 2013. Insulin, cognition, and dementia. Eur J Pharmacol 719, 170–179. https://doi.org/10.1016/j.ejphar.2013.08.008

Chrem Mendez, P., Surace, E., Bérgamo, Y., Calandri, I., Vázquez, S., Sevlever, G., Allegri, R.F., 2019. Biomarkers for Alzheimer's disease. Where we stand and where we are headed. Medicina (B Aires) 79, 546–551.

Ciudin, A., 2016. Diabetes mellitus tipo 2 y enfermedad de Alzheimer: una relación para no olvidar. Endocrinología y Nutrición 63, 191–193. https://doi.org/10.1016/j.endonu.2015.12.004

Clark, I.A., Vissel, B., 2018. Therapeutic implications of how TNF links apolipoprotein E, phosphorylated tau, α-synuclein, amyloid-β and insulin resistance in neurodegenerative diseases. Br J Pharmacol 175, 3859–3875. https://doi.org/10.1111/bph.14471

Costache, A.D., Ignat, B.E., Grosu, C., Mastaleru, A., Abdulan, I., Oancea, A., Roca, M., Leon, M.M., Badescu, M.C., Luca, S., Jigoranu, A.R., Chetran, A., Mitu, O., Costache, I.I., Mitu, F., 2023. Inflammatory Pathways in Overweight and Obese Persons as a Potential Mechanism for Cognitive Impairment and Earlier Onset Alzeihmer's Dementia in the General Population: A Narrative Review. Biomedicines 11, 3233. https://doi.org/10.3390/biomedicines11123233

Craft, S., 2006. Insulin resistance syndrome and Alzheimer disease: pathophysiologic mechanisms and therapeutic implications. Alzheimer Dis Assoc Disord 20, 298–301. https://doi.org/10.1097/01.wad.0000213866.86934.7e

Craft, S., 2005. Insulin resistance and cognitive impairment: a view through the prism of epidemiology. Arch Neurol 62, 1043–4. https://doi.org/10.1001/archneur.62.7.1043-a

Craft, S., Peskind, E., Schwartz, M.W., Schellenberg, G.D., Raskind, M., Porte, D., 1998. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease. Neurology 50, 164–168. https://doi.org/10.1212/WNL.50.1.164

Craft, S., Raman, R., Chow, T.W., Rafii, M.S., Sun, C.-K., Rissman, R.A., Donohue, M.C., Brewer, J.B., Jenkins, C., Harless, K., Gessert, D., Aisen, P.S., 2020. Safety, Efficacy, and Feasibility of Intranasal Insulin for the Treatment of Mild Cognitive Impairment and Alzheimer Disease Dementia. JAMA Neurol 77, 1099. https://doi.org/10.1001/jamaneurol.2020.1840

Cukierman-Yaffe, T., Kasher-Meron, M., Fruchter, E., Gerstein, H.C., Afek, A., Derazne, E., Tzur, D., Karasik, A., Twig, G., 2015. Cognitive Performance at Late Adolescence and the Risk for Impaired Fasting Glucose Among Young Adults. J Clin Endocrinol Metab 100, 4409–4416. https://doi.org/10.1210/jc.2015-2012

De Felice, F.G., Gonçalves, R.A., Ferreira, S.T., 2022. Impaired insulin signalling and allostatic load in Alzheimer disease. Nat Rev Neurosci 23, 215–230. https://doi.org/10.1038/s41583-022-00558-9

de la Monte, S.M., Wands, J.R., 2008. Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diabetes Sci Technol 2, 1101–13. https://doi.org/10.1177/193229680800200619

DeFronzo, R.A., Hompesch, M., Kasichayanula, S., Liu, X., Hong, Y., Pfister, M., Morrow, L.A., Leslie, B.R., Boulton, D.W., Ching, A., LaCreta, F.P., Griffen, S.C., 2013. Characterization of Renal Glucose Reabsorption in Response to Dapagliflozin in Healthy Subjects and Subjects With Type 2 Diabetes. Diabetes Care 36, 3169–3176. https://doi.org/10.2337/dc13-0387

Delikkaya, B., Moriel, N., Tong, M., Gallucci, G., de la Monte, S.M., 2019. Altered expression of insulin-degrading enzyme and regulator of calcineurin in the rat intracerebral streptozotocin model and human apolipoprotein E-ε4–associated Alzheimer's disease. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 11, 392–404. https://doi.org/10.1016/j.dadm.2019.03.004

Demetrius, L.A., Simon, D.K., 2012. An inverse-Warburg effect and the origin of Alzheimer's disease. Biogerontology 13, 583–594. https://doi.org/10.1007/s10522-012-9403-6

Desouza, C. V., Shivaswamy, V., 2010. Pioglitazone in the Treatment of Type 2 Diabetes: Safety and Efficacy Review. Clin Med Insights Endocrinol Diabetes 3, CMED.S5372. https://doi.org/10.4137/CMED.S5372

 doi:10.20944/preprints202602.1880.v1

DeTure, M.A., Dickson, D.W., 2019. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener 14, 32. https://doi.org/10.1186/s13024-019-0333-5

Dolan, H., Crain, B., Troncoso, J., Resnick, S.M., Zonderman, A.B., Obrien, R.J., 2010. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore Longitudinal Study of aging cohort. Ann Neurol 68, 231–240. https://doi.org/10.1002/ana.22055

Domínguez, R.O., Pagano, M.A., Marschoff, E.R., González, S.E., Repetto, M.G., Serra, J.A., 2014. Enfermedad de Alzheimer y deterioro cognitivo asociado a la diabetes mellitus de tipo 2: relaciones e hipótesis. Neurología 29, 567–572. https://doi.org/10.1016/j.nrl.2013.05.006

Donoso S, A., Behrens P, M.I., 2005. Variabilidad y variantesde la enfermedad de Alzheimer. Rev Med Chil 133. https://doi.org/10.4067/S0034-98872005000400013

Duarte, A.I., Moreira, P.I., Oliveira, C.R., 2012. Insulin in Central Nervous System: More than Just a Peripheral Hormone. J Aging Res 2012, 1–21. https://doi.org/10.1155/2012/384017

Duarte, J., 2014. Metabolic Alterations Associated to Brain Dysfunction in Diabetes. Aging Dis. https://doi.org/10.14336/ad.2014.1104

Duarte, J.M.N., 2023. Loss of brain energy metabolism control as a driver for memory impairment upon insulin resistance. Biochem Soc Trans 51, 287–301. https://doi.org/10.1042/BST20220789

Ehtewish, H., Arredouani, A., El-Agnaf, O., 2022. Diagnostic, Prognostic, and Mechanistic Biomarkers of Diabetes Mellitus-Associated Cognitive Decline. Int J Mol Sci 23, 6144. https://doi.org/10.3390/ijms23116144

El Khoury, N.B., Gratuze, M., Papon, M.-A., Bretteville, A., Planel, E., 2014. Insulin dysfunction and Tau pathology. Front Cell Neurosci 8. https://doi.org/10.3389/fncel.2014.00022

Fava, S., 2014. Glycaemic Control: A Balancing Act or A Different Approach? Curr Diabetes Rev 10, 124–130. https://doi.org/10.2174/1573399810666140421124051

Formiga, F., Reñe, R., Pérez-Maraver, M., 2015. Demencia y diabetes: ¿relación casual o causal? Med Clin (Barc) 144, 176–180. https://doi.org/10.1016/j.medcli.2014.01.026

Freychet, P., 2000. Insulin receptors and insulin actions in the nervous system. Diabetes Metab Res Rev 16, 390–392. https://doi.org/10.1002/1520-7560(200011/12)16:6<390::AID-DMRR161>3.0.CO;2-T

Gabbouj, S., Ryhänen, S., Marttinen, M., Wittrahm, R., Takalo, M., Kemppainen, S., Martiskainen, H., Tanila, H., Haapasalo, A., Hiltunen, M., Natunen, T., 2019. Altered Insulin Signaling in Alzheimer's Disease Brain – Special Emphasis on PI3K-Akt Pathway. Front Neurosci 13. https://doi.org/10.3389/fnins.2019.00629

Galea, I., 2021. The blood–brain barrier in systemic infection and inflammation. Cell Mol Immunol 18, 2489–2501. https://doi.org/10.1038/s41423-021-00757-x

García-Casares, N., González-González, G., de la Cruz-Cosme, C., Garzón-Maldonado, F.J., de Rojas-Leal, C., Ariza, M.J., Narváez, M., Barbancho, M.Á., García-Arnés, J.A., Tinahones, F.J., 2023. Effects of GLP-1 receptor agonists on neurological complications of diabetes. Rev Endocr Metab Disord 24, 655–672. https://doi.org/10.1007/s11154-023-09807-3

Garcia-Serrano, A.M., Duarte, J.M.N., 2020. Brain Metabolism Alterations in Type 2 Diabetes: What Did We Learn From Diet-Induced Diabetes Models? Front Neurosci 14, 229. https://doi.org/10.3389/fnins.2020.00229

Gerritsen, A.A.J., Bakker, C., Verhey, F.R.J., de Vugt, M.E., Melis, R.J.F., Koopmans, R.T.C.M., Oosterveld, S.M., Kessels, R.P., Olde Rikkert, M.G., Hamel, R., Ramakers, I.H., Aalten, P., Sistermans, N., Smits, L.L., Pijnenburg, Y.A., van der Flier, W.M., 2016. Prevalence of Comorbidity in Patients With Young-Onset Alzheimer Disease Compared With Late-Onset: A Comparative Cohort Study. J Am Med Dir Assoc 17, 318–323. https://doi.org/10.1016/j.jamda.2015.11.011

Gonçalves, R.A., Wijesekara, N., Fraser, P.E., De Felice, F.G., 2019. The Link Between Tau and Insulin Signaling: Implications for Alzheimer's Disease and Other Tauopathies. Front Cell Neurosci 13. https://doi.org/10.3389/fncel.2019.00017

Gong, Y., Luo, H., Li, Z., Feng, Y., Liu, Z., Chang, J., 2023. Metabolic Profile of Alzheimer's Disease: Is 10-Hydroxy-2-decenoic Acid a Pertinent Metabolic Adjuster? Metabolites 13, 954. https://doi.org/10.3390/metabo13080954

Götz, J., Ittner, L.M., Lim, Y.-A., 2009. Common features between diabetes mellitus and Alzheimer's disease. Cell Mol Life Sci 66, 1321–5. https://doi.org/10.1007/s00018-009-9070-1

 doi:10.20944/preprints202602.1880.v1

Groot, C., Cicognola, C., Bali, D., Triana-Baltzer, G., Dage, J.L., Pontecorvo, M.J., Kolb, H.C., Ossenkoppele, R., Janelidze, S., Hansson, O., 2022. Diagnostic and prognostic performance to detect Alzheimer's disease and clinical progression of a novel assay for plasma p-tau217. Alzheimers Res Ther 14, 67. https://doi.org/10.1186/s13195-022-01005-8

Gutiérrez-Rodelo, C., Roura-Guiberna, A., Olivares-Reyes, J.A., 2017. [Molecular Mechanisms of Insulin Resistance: An Update]. Gac Med Mex 153, 214–228.

Haass, C., Selkoe, D.J., 2007. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol 8, 101–112. https://doi.org/10.1038/nrm2101

Hameed, I., Masoodi, S.R., Mir, S.A., Nabi, M., Ghazanfar, K., Ganai, B.A., 2015. Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. World J Diabetes 6, 598. https://doi.org/10.4239/wjd.v6.i4.598

Han, Y., Kim, S.Y., 2023. Endothelial senescence in vascular diseases: current understanding and future opportunities in senotherapeutics. Exp Mol Med 55, 1–12. https://doi.org/10.1038/s12276-022-00906-w

Hansson Petersen, C.A., Alikhani, N., Behbahani, H., Wiehager, B., Pavlov, P.F., Alafuzoff, I., Leinonen, V., Ito, A., Winblad, B., Glaser, E., Ankarcrona, M., 2008. The amyloid β-peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae. Proceedings of the National Academy of Sciences 105, 13145–13150. https://doi.org/10.1073/pnas.0806192105

Hernández-Contreras, K.A., Martínez-Díaz, J.A., Hernández-Aguilar, M.E., Herrera-Covarrubias, D., Rojas-Durán, F., Aranda Abreu, G.E., 2021. Mecanismos de asociación entre Enfermedad de Alzheimer y Diabetes Mellitus: La paradoja de la insulina. Archivos de Neurociencias 25. https://doi.org/10.31157/an.v25i4.212

Hobday, A.L., Parmar, M.S., 2021. The Link Between Diabetes Mellitus and Tau Hyperphosphorylation: Implications for Risk of Alzheimer's Disease. Cureus. https://doi.org/10.7759/cureus.18362

Horie, K., Salvadó, G., Barthélemy, N.R., Janelidze, S., Li, Y., He, Y., Saef, B., Chen, C.D., Jiang, H., Strandberg, O., Pichet Binette, A., Palmqvist, S., Sato, C., Sachdev, P., Koyama, A., Gordon, B.A., Benzinger, T.L.S., Holtzman, D.M., Morris, J.C., Mattsson-Carlgren, N., Stomrud, E., Ossenkoppele, R., Schindler, S.E., Hansson, O., Bateman, R.J., 2023. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. Nat Med 29, 1954–1963. https://doi.org/10.1038/s41591-023-02443-z

Huang, C.-C., Chung, C.-M., Leu, H.-B., Lin, L.-Y., Chiu, C.-C., Hsu, C.-Y., Chiang, C.-H., Huang, P.-H., Chen, T.-J., Lin, S.-J., Chen, J.-W., Chan, W.-L., 2014. Diabetes Mellitus and the Risk of Alzheimer's Disease: A Nationwide Population-Based Study. PLoS One 9, e87095. https://doi.org/10.1371/journal.pone.0087095

Huang, R., Tian, S., Zhang, H., Zhu, W., Wang, S., 2020. Chronic hyperglycemia induces tau hyperphosphorylation by downregulating OGT-involved O-GlcNAcylation in vivo and in vitro. Brain Res Bull 156, 76–85. https://doi.org/10.1016/j.brainresbull.2020.01.006

Jabeen, K., Rehman, K., Akash, M.S.H., 2022. Genetic mutations of APOEε4 carriers in cardiovascular patients lead to the development of insulin resistance and risk of Alzheimer's disease. J Biochem Mol Toxicol 36. https://doi.org/10.1002/jbt.22953

Jais, A., Brüning, J.C., 2017. Hypothalamic inflammation in obesity and metabolic disease. Journal of Clinical Investigation 127, 24–32. https://doi.org/10.1172/JCI88878

Ke, Y.D., Delerue, F., Gladbach, A., Götz, J., Ittner, L.M., 2009. Experimental Diabetes Mellitus Exacerbates Tau Pathology in a Transgenic Mouse Model of Alzheimer's Disease. PLoS One 4, e7917. https://doi.org/10.1371/journal.pone.0007917

Kellar, D., Craft, S., 2020. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol 19, 758–766. https://doi.org/10.1016/S1474-4422(20)30231-3

Kim, B., Backus, C., Oh, S., Feldman, E.L., 2013. Hyperglycemia-Induced Tau Cleavage in vitro and in vivo: A Possible Link Between Diabetes and Alzheimer's Disease. Journal of Alzheimer's Disease 34, 727–739. https://doi.org/10.3233/JAD-121669

Kimura, N., Aota, T., Aso, Y., Yabuuchi, K., Sasaki, K., Masuda, T., Eguchi, A., Maeda, Y., Aoshima, K., Matsubara, E., 2023. Predicting positron emission tomography brain amyloid positivity using interpretable machine learning models with wearable sensor data and lifestyle factors. Alzheimers Res Ther 15, 212. https://doi.org/10.1186/s13195-023-01363-x

 doi:10.20944/preprints202602.1880.v1

Kivisäkk, P., Fatima, H.A., Cahoon, D.S., Otieno, B., Chacko, L., Minooei, F., Demos, C., Stengelin, M., Sigal, G., Wohlstadter, J., Arnold, S.E., 2024. Clinical evaluation of a novel plasma pTau217 electrochemiluminescence immunoassay in Alzheimer's disease. Sci Rep 14, 629. https://doi.org/10.1038/s41598-024-51334-x

Klausen, M.K., Thomsen, M., Wortwein, G., Fink-Jensen, A., 2022. The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. Br J Pharmacol 179, 625–641. https://doi.org/10.1111/bph.15677

Kleinridders, A., Ferris, H.A., Cai, W., Kahn, C.R., 2014. Insulin Action in Brain Regulates Systemic Metabolism and Brain Function. Diabetes 63, 2232–2243. https://doi.org/10.2337/db14-0568

Knopman, D.S., Jack, C.R., Wiste, H.J., Lundt, E.S., Weigand, S.D., Vemuri, P., Lowe, V.J., Kantarci, K., Gunter, J.L., Senjem, M.L., Mielke, M.M., Roberts, R.O., Boeve, B.F., Petersen, R.C., 2014. 18F-fluorodeoxyglucose positron emission tomography, aging, and apolipoprotein E genotype in cognitively normal persons. Neurobiol Aging 35, 2096–2106. https://doi.org/10.1016/j.neurobiolaging.2014.03.006

Kong, Y., Wang, F., Wang, J., Liu, C., Zhou, Y., Xu, Z., Zhang, C., Sun, B., Guan, Y., 2020. Pathological Mechanisms Linking Diabetes Mellitus and Alzheimer's Disease: the Receptor for Advanced Glycation End Products (RAGE). Front Aging Neurosci 12. https://doi.org/10.3389/fnagi.2020.00217

Könner, A.C., Hess, S., Tovar, S., Mesaros, A., Sánchez-Lasheras, C., Evers, N., Verhagen, L.A.W., Brönneke, H.S., Kleinridders, A., Hampel, B., Kloppenburg, P., Brüning, J.C., 2011. Role for Insulin Signaling in Catecholaminergic Neurons in Control of Energy Homeostasis. Cell Metab 13, 720–728. https://doi.org/10.1016/j.cmet.2011.03.021

Lamport, D.J., Dye, L., Mansfield, M.W., Lawton, C.L., 2013. Acute glycaemic load breakfast manipulations do not attenuate cognitive impairments in adults with type 2 diabetes. Clinical Nutrition 32, 265–272. https://doi.org/10.1016/j.clnu.2012.07.008

Lamport, D.J., Lawton, C.L., Mansfield, M.W., Moulin, C.A.J., Dye, L., 2014. Type 2 diabetes and impaired glucose tolerance are associated with word memory source monitoring recollection deficits but not simple recognition familiarity deficits following water, low glycaemic load, and high glycaemic load breakfasts. Physiol Behav 124, 54–60. https://doi.org/10.1016/j.physbeh.2013.10.033

Langella, S., Barksdale, N.G., Vasquez, D., Aguillon, D., Chen, Y., Su, Y., Acosta-Baena, N., Acosta-Uribe, J., Baena, A.Y., Garcia-Ospina, G., Giraldo-Chica, M., Tirado, V., Muñoz, C., Ríos-Romenets, S., Guzman-Martínez, C., Oliveira, G., Yang, H.-S., Vila-Castelar, C., Pruzin, J.J., Ghisays, V., Arboleda-Velasquez, J.F., Kosik, K.S., Reiman, E.M., Lopera, F., Quiroz, Y.T., 2023. Effect of apolipoprotein genotype and educational attainment on cognitive function in autosomal dominant Alzheimer's disease. Nat Commun 14, 5120. https://doi.org/10.1038/s41467-023-40775-z

Lee, B.C., Choe, Y.M., Suh, G.-H., Choi, I.-G., Lee, J.H., Kim, H.S., Hwang, J., Yi, D., Kim, J.W., 2022. A combination of midlife diabetes mellitus and the apolipoprotein E ε4 allele increase risk for cognitive decline. Front Aging Neurosci 14. https://doi.org/10.3389/fnagi.2022.1065117

Li, L., Hölscher, C., 2007. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev 56, 384–402. https://doi.org/10.1016/j.brainresrev.2007.09.001

Lim, Y.Y., Yassi, N., Bransby, L., Ayton, S., Buckley, R.F., Eratne, D., Velakoulis, D., Li, Q.-X., Fowler, C., Masters, C.L., Maruff, P., 2023. CSF Aβ42 and tau biomarkers in cognitively unimpaired Aβ- middle-aged and older APOE ε4 carriers. Neurobiol Aging 129, 209–218. https://doi.org/10.1016/j.neurobiolaging.2023.05.009

Liu, C., Wang, Z., Song, Y., Wu, D., Zheng, X., Li, P., Jin, J., Xu, N., Li, L., 2015. Effects of Berberine on Amelioration of Hyperglycemia and Oxidative Stress in High Glucose and High Fat Diet-Induced Diabetic Hamsters In Vivo. Biomed Res Int 2015, 1–9. https://doi.org/10.1155/2015/313808

Liu, X., Chu, B., Jin, S., Li, M., Xu, Y., Yang, H., Feng, Z., Bi, J., Wang, P., 2021. Vascular endothelial growth factor alleviates mitochondrial dysfunction and suppression of mitochondrial biogenesis in models of Alzheimer's disease. International Journal of Neuroscience 131, 154–162. https://doi.org/10.1080/00207454.2020.1733564

Liu, Y., Jiang, Y., Du, W., Gao, B., Gao, J., Hu, S., Song, Q., Wang, W., Miao, Y., 2024. White matter microstructure alterations in type 2 diabetes mellitus and its correlation with cerebral small vessel disease and cognitive performance. Sci Rep 14, 270. https://doi.org/10.1038/s41598-023-50768-z

Luna, R., Talanki Manjunatha, R., Bollu, B., Jhaveri, S., Avanthika, C., Reddy, N., Saha, T., Gandhi, F., 2021. A Comprehensive Review of Neuronal Changes in Diabetics. Cureus. https://doi.org/10.7759/cureus.19142

 doi:10.20944/preprints202602.1880.v1

Madhusudhanan, J., Suresh, G., Devanathan, V., 2020. Neurodegeneration in type 2 diabetes: Alzheimer's as a case study. Brain Behav 10. https://doi.org/10.1002/brb3.1577

Majid, H., Islam, S.U., Kohli, S., Nidhi, 2025. Neuroinflammation and metabolic dysregulation as predictors of cognitive impairment, depression, and quality of life in type 2 diabetes mellitus patients on SGLT2 inhibitors and sulfonylureas. Inflammopharmacology. https://doi.org/10.1007/s10787-025-01824-9

Malenka, R.C., 1994. Synaptic plasticity in the hippocampus: LTP and LTD. Cell 78, 535–538. https://doi.org/10.1016/0092-8674(94)90517-7

Mancinetti, F., Xenos, D., De Fano, M., Mazzieri, A., Porcellati, F., Boccardi, V., Mecocci, P., 2023. Diabetes-Alzheimer's connection in older age: SGLT2 inhibitors as promising modulators of disease pathways. Ageing Res Rev 90, 102018. https://doi.org/10.1016/j.arr.2023.102018

Martínez, S., Ochoa, B., Pérez, M.R., Torrico, F., García, I., Garcia, C.C., 2022. Polimorfismos del gen de la apolipoproteína E en adultos mayores de 60 años con disminución de la memoria cognitiva y enfermedad de Alzheimer en diferentes poblaciones venezolanas. Biomédica 42, 116–129. https://doi.org/10.7705/biomedica.5889

McNay, E.C., Ong, C.T., McCrimmon, R.J., Cresswell, J., Bogan, J.S., Sherwin, R.S., 2010. Hippocampal memory processes are modulated by insulin and high-fat-induced insulin resistance. Neurobiol Learn Mem 93, 546–553. https://doi.org/10.1016/j.nlm.2010.02.002

Messier, C., Gagnon, M., 1996. Glucose regulation and cognitive functions: relation to Alzheimer's disease and diabetes. Behavioural Brain Research 75, 1–11. https://doi.org/10.1016/0166-4328(95)00153-0

Mestizo Gutiérrez, S.L., Herrera Rivero, M., Cruz Ramírez, N., Hernández, E., Aranda-Abreu, G.E., 2014. Decision trees for the analysis of genes involved in Alzheimer's disease pathology. J Theor Biol 357, 21–25. https://doi.org/10.1016/j.jtbi.2014.05.002

Mietelska-Porowska, A., Wasik, U., Goras, M., Filipek, A., Niewiadomska, G., 2014. Tau Protein Modifications and Interactions: Their Role in Function and Dysfunction. Int J Mol Sci 15, 4671–4713. https://doi.org/10.3390/ijms15034671

Milà-Alomà, M., Ashton, N.J., Shekari, M., Salvadó, G., Ortiz-Romero, P., Montoliu-Gaya, L., Benedet, A.L., Karikari, T.K., Lantero-Rodriguez, J., Vanmechelen, E., Day, T.A., González-Escalante, A., Sánchez-Benavides, G., Minguillon, C., Fauria, K., Molinuevo, J.L., Dage, J.L., Zetterberg, H., Gispert, J.D., Suárez-Calvet, M., Blennow, K., 2022. Plasma p-tau231 and p-tau217 as state markers of amyloid-β pathology in preclinical Alzheimer's disease. Nat Med. https://doi.org/10.1038/s41591-022-01925-w

Milà-Alomà, M., Salvadó, G., Gispert, J.D., Vilor-Tejedor, N., Grau-Rivera, O., Sala-Vila, A., Sánchez-Benavides, G., Arenaza-Urquijo, E.M., Crous-Bou, M., González-de-Echávarri, J.M., Minguillon, C., Fauria, K., Simon, M., Kollmorgen, G., Zetterberg, H., Blennow, K., Suárez-Calvet, M., Molinuevo, J.L., 2020. Amyloid beta, tau, synaptic, neurodegeneration, and glial biomarkers in the preclinical stage of the Alzheimer's *continuum*. Alzheimer's & Dementia 16, 1358–1371. https://doi.org/10.1002/alz.12131

Mittal, M., Siddiqui, M.R., Tran, K., Reddy, S.P., Malik, A.B., 2014. Reactive Oxygen Species in Inflammation and Tissue Injury. Antioxid Redox Signal 20, 1126–1167. https://doi.org/10.1089/ars.2012.5149

Mullins, R.J., Diehl, T.C., Chia, C.W., Kapogiannis, D., 2017. Insulin Resistance as a Link between Amyloid-Beta and Tau Pathologies in Alzheimer's Disease. Front Aging Neurosci 9. https://doi.org/10.3389/fnagi.2017.00118

Naia, L., Shimozawa, M., Bereczki, E., Li, X., Liu, J., Jiang, R., Giraud, R., Leal, N.S., Pinho, C.M., Berger, E., Falk, V.L., Dentoni, G., Ankarcrona, M., Nilsson, P., 2023. Mitochondrial hypermetabolism precedes impaired autophagy and synaptic disorganization in App knock-in Alzheimer mouse models. Mol Psychiatry 28, 3966–3981. https://doi.org/10.1038/s41380-023-02289-4

Olesen, M.A., Quintanilla, R.A., 2023. Pathological Impact of Tau Proteolytical Process on Neuronal and Mitochondrial Function: a Crucial Role in Alzheimer's Disease. Mol Neurobiol 60, 5691–5707. https://doi.org/10.1007/s12035-023-03434-4

Palasí, A., Gutiérrez-Iglesias, B., Alegret, M., Pujadas, F., Olabarrieta, M., Liébana, D., Quintana, M., Álvarez-Sabín, J., Boada, M., 2015. Differentiated clinical presentation of early and late-onset Alzheimer's disease: is 65 years of age providing a reliable threshold? J Neurol 262, 1238–1246. https://doi.org/10.1007/s00415-015-7698-3

 doi:10.20944/preprints202602.1880.v1

Park, S.A., 2011. A common pathogenic mechanism linking type-2 diabetes and Alzheimer's disease: evidence from animal models. J Clin Neurol 7, 10–8. https://doi.org/10.3988/jcn.2011.7.1.10

Pasquier, F., Boulogne, A., Leys, D., Fontaine, P., 2006. Diabetes mellitus and dementia. Diabetes Metab 32, 403–14. https://doi.org/10.1016/s1262-3636(07)70298-7

Pérez, M.J., Jara, C., Quintanilla, R.A., 2018. Contribution of Tau Pathology to Mitochondrial Impairment in Neurodegeneration. Front Neurosci 12. https://doi.org/10.3389/fnins.2018.00441

Petermann, F., Troncoso-Pantoja, C., Martínez, M.A., Leiva, A.M., Ramírez-Campillo, R., Poblete-Valderrama, F., Garrido-Méndez, A., Díaz-Martínez, X., Ulloa, N., Concha, Y., Celis-Morales, C., 2018. Asociación entre diabetes mellitus tipo 2, historia familiar de diabetes y deterioro cognitivo en adultos mayores chilenos. Rev Med Chil 146, 872–881. https://doi.org/10.4067/s0034-98872018000800872

Polsinelli, A.J., Logan, P.E., Lane, K.A., Manchella, M.K., Nemes, S., Sanjay, A.B., Gao, S., Apostolova, L.G., 2023. *APOE* ε4 carrier status and sex differentiate rates of cognitive decline in early- and late-onset Alzheimer's disease. Alzheimer's & Dementia 19, 1983–1993. https://doi.org/10.1002/alz.12831

Pomytkin, I., Costa-Nunes, J.P., Kasatkin, V., Veniaminova, E., Demchenko, A., Lyundup, A., Lesch, K., Ponomarev, E.D., Strekalova, T., 2018. Insulin receptor in the brain: Mechanisms of activation and the role in the <scp>CNS</scp> pathology and treatment. CNS Neurosci Ther 24, 763–774. https://doi.org/10.1111/cns.12866

Pooja Naik, L.C., 2014. Diabetes Mellitus and Blood-Brain Barrier Dysfunction: An Overview. J Pharmacovigil 02. https://doi.org/10.4172/2329-6887.1000125

Ramírez Rincón, A., Saldarriaga Betancur, S., García Ramos, A.F., González Arango, J., Estupiñán Vargas, V., 2022. Tratamiento farmacológico del paciente que vive con diabetes mellitus tipo 2. CES Medicina 36, 81–105. https://doi.org/10.21615/cesmedicina.6672

Rasool, M., Malik, A., Waquar, S., Zaheer, A., Asif, M., Iqbal, Z., Gauthaman, K., Kamal, M.A., Pushparaj, P.N., 2021. Cellular and Molecular Mechanisms of Dementia: Decoding the Causal link of Diabetes Mellitus in Alzheimer's Disease. CNS Neurol Disord Drug Targets 20, 602–612. https://doi.org/10.2174/1871527320666210212114116

Raulin, A.-C., Doss, S. V., Trottier, Z.A., Ikezu, T.C., Bu, G., Liu, C.-C., 2022. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol Neurodegener 17, 72. https://doi.org/10.1186/s13024-022-00574-4

Ravipati, K., Chen, Y., Manns, J.R., 2022. Reassessing Diabetes and APOE Genotype as Potential Interacting Risk Factors for Alzheimer's Disease. Am J Alzheimers Dis Other Demen 37, 153331752110709. https://doi.org/10.1177/15333175211070912

Razay, G., Wilcock, G.K., 1994. Hyperinsulinaemia and Alzheimer's disease. Age Ageing 23, 396–9. https://doi.org/10.1093/ageing/23.5.396

Rebeck, G.W., Kindy, M., LaDu, M.J., 2002. Apolipoprotein E and Alzheimer's disease: The protective effects of ApoE2 and E3. Journal of Alzheimer's Disease 4, 145–154. https://doi.org/10.3233/JAD-2002-4304

Rivera-Meza, M., Muñoz, D., Jerez, E., Quintanilla, M.E., Salinas-Luypaert, C., Fernandez, K., Karahanian, E., 2017. Fenofibrate Administration Reduces Alcohol and Saccharin Intake in Rats: Possible Effects at Peripheral and Central Levels. Front Behav Neurosci 11. https://doi.org/10.3389/fnbeh.2017.00133

Roda, A.R., Montoliu-Gaya, L., Villegas, S., 2019. The Role of Apolipoprotein E Isoforms in Alzheimer's Disease. Journal of Alzheimer's Disease 68, 459–471. https://doi.org/10.3233/JAD-180740

Saini, V., 2010. Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. World J Diabetes 1, 68–75. https://doi.org/10.4239/wjd.v1.i3.68

Sánchez-Zúñiga, M. de J., Carrillo-Esper, R., Sánchez-Pérez, H., González-Chávez, A., Elizondo-Argueta, S., 2020. Circuito insulinérgico cerebral. De las bases a su impacto en la clínica. Cir Cir 88. https://doi.org/10.24875/CIRU.18000572

Saraya, A.W., Tunvirachaisakul, C., Sonpee, C., Katasrila, P., Sathaporn, T., Tepmongkol, S., Tangwongchai, S., 2023. Serum proinsulin levels as peripheral blood biomarkers in patients with cognitive impairment. Sci Rep 13, 22436. https://doi.org/10.1038/s41598-023-49479-2

Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C.E., Cummings, J., van der Flier, W.M., 2021. Alzheimer's disease. The Lancet 397, 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4

 doi:10.20944/preprints202602.1880.v1

Sebastian, M.J., Khan, S.K., Pappachan, J.M., Jeeyavudeen, M.S., 2023. Diabetes and cognitive function: An evidence-based current perspective. World J Diabetes 14, 92–109. https://doi.org/10.4239/wjd.v14.i2.92

Shinohara, M., Suzuki, K., Bu, G., Sato, N., 2021. Interaction Between APOE Genotype and Diabetes in Longevity. Journal of Alzheimer's Disease 82, 719–726. https://doi.org/10.3233/JAD-210125

Sible, I.J., Yew, B., Jang, J.Y., Alitin, J.P.M., Li, Y., Gaubert, A., Nguyen, A., Dutt, S., Blanken, A.E., Ho, J.K., Marshall, A.J., Kapoor, A., Shenasa, F., Rodgers, K.E., Sturm, V.E., Head, E., Martini, A., Nation, D.A., 2022. Blood pressure variability and plasma Alzheimer's disease biomarkers in older adults. Sci Rep 12, 17197. https://doi.org/10.1038/s41598-022-20627-4

Sienes Bailo, P., Llorente Martín, E., Calmarza, P., Montolio Breva, S., Bravo Gómez, A., Pozo Giráldez, A., Sánchez-Pascuala Callau, J.J., Vaquer Santamaría, J.M., Dayaldasani Khialani, A., Cerdá Micó, C., Camps Andreu, J., Sáez Tormo, G., Fort Gallifa, I., 2022. Implicación del estrés oxidativo en las enfermedades neurodegenerativas y posibles terapias antioxidantes. Advances in Laboratory Medicine / Avances en Medicina de Laboratorio 3, 351–360. https://doi.org/10.1515/almed-2022-0022

Sima, A.A.F., Zhang, W., 2014. Mechanisms of diabetic neuropathy. pp. 429–442. https://doi.org/10.1016/B978-0-444-53480-4.00031-X

Sims-Robinson, C., Kim, B., Rosko, A., Feldman, E.L., 2010. How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol 6, 551–559. https://doi.org/10.1038/nrneurol.2010.130

Snyder, P.J., 2015. Introducing Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, an open access journal of the Alzheimer's Association. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 1, 1–4. https://doi.org/10.1016/j.dadm.2015.01.001

Sonar, S.A., Lal, G., 2018. Blood–brain barrier and its function during inflammation and autoimmunity. J Leukoc Biol 103, 839–853. https://doi.org/10.1002/JLB.1RU1117-428R

Stanciu, G.D., Bild, V., Ababei, D.C., Rusu, R.N., Cobzaru, A., Paduraru, L., Bulea, D., 2020. Link between Diabetes and Alzheimer's Disease Due to the Shared Amyloid Aggregation and Deposition Involving Both Neurodegenerative Changes and Neurovascular Damages. J Clin Med 9, 1713. https://doi.org/10.3390/jcm9061713

Steen, E., Terry, B.M., J. Rivera, E., Cannon, J.L., Neely, T.R., Tavares, R., Xu, X.J., Wands, J.R., de la Monte, S.M., 2005. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? Journal of Alzheimer's Disease 7, 63–80. https://doi.org/10.3233/JAD-2005-7107

Tabeshmehr, P., Eftekharpour, E., 2023. Tau; One Protein, So Many Diseases. Biology (Basel) 12, 244. https://doi.org/10.3390/biology12020244

Takeishi, J., Tatewaki, Y., Nakase, T., Takano, Y., Tomita, N., Yamamoto, S., Mutoh, T., Taki, Y., 2021. Alzheimer's Disease and Type 2 Diabetes Mellitus: The Use of MCT Oil and a Ketogenic Diet. Int J Mol Sci 22, 12310. https://doi.org/10.3390/ijms222212310

Talbot, K., Wang, H.-Y., Kazi, H., Han, L.-Y., Bakshi, K.P., Stucky, A., Fuino, R.L., Kawaguchi, K.R., Samoyedny, A.J., Wilson, R.S., Arvanitakis, Z., Schneider, J.A., Wolf, B.A., Bennett, D.A., Trojanowski, J.Q., Arnold, S.E., 2012. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. Journal of Clinical Investigation 122, 1316–1338. https://doi.org/10.1172/JCI59903

Tobon-Velasco, J., Cuevas, E., Torres-Ramos, M., 2014. Receptor for AGEs (RAGE) as Mediator of NF-kB Pathway Activation in Neuroinflammation and Oxidative Stress. CNS Neurol Disord Drug Targets 13, 1615–1626. https://doi.org/10.2174/1871527313666140806144831

Trimm, E., Red-Horse, K., 2023. Vascular endothelial cell development and diversity. Nat Rev Cardiol 20, 197–210. https://doi.org/10.1038/s41569-022-00770-1

Tumminia, A., Vinciguerra, F., Parisi, M., Frittitta, L., 2018. Type 2 Diabetes Mellitus and Alzheimer's Disease: Role of Insulin Signalling and Therapeutic Implications. Int J Mol Sci 19, 3306. https://doi.org/10.3390/ijms19113306

Uribarri, J., Buchman, A.S., Cai, W., Haroutunian, V., Beeri, M.S., 2020. Human brain and serum advanced glycation end products are highly correlated: Preliminary results of their role in Alzheimer's disease and type 2 diabetes. Alzheimer's & Dementia 16. https://doi.org/10.1002/alz.045280

 doi:10.20944/preprints202602.1880.v1

Vanhandsaeme, G., Benhalima, K., 2021. The long-term metabolic and neurocognitive risks in offspring of women with type 1 diabetes mellitus. Acta Diabetol 58, 845–858. https://doi.org/10.1007/s00592-021-01692-z

Verdelho, A., Madureira, S., Ferro, J.M., Basile, A.-M., Chabriat, H., Erkinjuntti, T., Fazekas, F., Hennerici, M., O'Brien, J., Pantoni, L., Salvadori, E., Scheltens, P., Visser, M.C., Wahlund, L.-O., Waldemar, G., Wallin, A., Inzitari, D., LADIS Study, 2007. Differential impact of cerebral white matter changes, diabetes, hypertension and stroke on cognitive performance among non-disabled elderly. The LADIS study. J Neurol Neurosurg Psychiatry 78, 1325–30. https://doi.org/10.1136/jnnp.2006.110361

Verdile, G., Fuller, S.J., Martins, R.N., 2015. The role of type 2 diabetes in neurodegeneration. Neurobiol Dis 84, 22–38. https://doi.org/10.1016/j.nbd.2015.04.008

von Bernhardi, R., 2004. La Barrera Hemato-Encefálica en la patología del Sistema Nervioso Central: su importancia en la Respuesta Inflamatoria. Rev Chil Neuropsiquiatr 42. https://doi.org/10.4067/S0717-92272004000200005

Wang, S., Wei, W., Zheng, Y., Hou, J., Dou, Y., Zhang, S., Luo, X., Cai, X., 2012. The Role of Insulin C-Peptide in the Coevolution Analyses of the Insulin Signaling Pathway: A Hint for Its Functions. PLoS One 7, e52847. https://doi.org/10.1371/journal.pone.0052847

Watson, D., Castaño, E., Kokjohn, T.A., Kuo, Y.-M., Lyubchenko, Y., Pinsky, D., Connolly, E.S., Esh, C., Luehrs, D.C., Stine, W.B., Rowse, L.M., Emmerling, M.R., Roher, A.E., 2005. Physicochemical characteristics of soluble oligomeric A β and their pathologic role in Alzheimer's disease. Neurol Res 27, 869–881. https://doi.org/10.1179/016164105X49436

Willette, A.A., Modanlo, N., Kapogiannis, D., Alzheimer's Disease Neuroimaging Initiative, 2015. Insulin resistance predicts medial temporal hypermetabolism in mild cognitive impairment conversion to Alzheimer disease. Diabetes 64, 1933–40. https://doi.org/10.2337/db14-1507

Winocur, G., Greenwood, C.E., 2005. Studies of the effects of high fat diets on cognitive function in a rat model. Neurobiol Aging 26 Suppl 1, 46–9. https://doi.org/10.1016/j.neurobiolaging.2005.09.003

Woodfield, A., Gonzales, T., Helmerhorst, E., Laws, S., Newsholme, P., Porter, T., Verdile, G., 2022. Current Insights on the Use of Insulin and the Potential Use of Insulin Mimetics in Targeting Insulin Signalling in Alzheimer's Disease. Int J Mol Sci 23, 15811. https://doi.org/10.3390/ijms232415811

Xourgia, E., Papazafiropoulou, A., Melidonis, A., 2019. Antidiabetic treatment on memory and spatial learning: From the pancreas to the neuron. World J Diabetes 10, 169–180. https://doi.org/10.4239/wjd.v10.i3.169

Yaffe, K., 2004. The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline. JAMA 292, 2237. https://doi.org/10.1001/jama.292.18.2237

Yang, C., Wei, M., Zhao, Y., Yang, Z., Song, M., Mi, J., Yang, X., Tian, G., 2023. Regulation of insulin secretion by the post-translational modifications. Front Cell Dev Biol 11. https://doi.org/10.3389/fcell.2023.1217189

Ye, L., Maji, S., Sanghera, N., Gopalasingam, P., Gorbunov, E., Tarasov, S., Epstein, O., Klein-Seetharaman, J., 2017. Structure and dynamics of the insulin receptor: implications for receptor activation and drug discovery. Drug Discov Today 22, 1092–1102. https://doi.org/10.1016/j.drudis.2017.04.011

Zapata-Tragodara, D., Roque, H., Parodi, J.F., 2020. Relación entre trastornos neurocognitivos,Diabetes Mellitus Tipo 2 y otros factores en adultos mayores del Centro Médico Naval del Perú, entre los años 2010 a 2015. Rev Neuropsiquiatr 83, 87–96. https://doi.org/10.20453/rnp.v83i2.3751

Zhang, H., Wei, W., Zhao, M., Ma, L., Jiang, X., Pei, H., Cao, Y., Li, H., 2021. Interaction between Aβ and Tau in the Pathogenesis of Alzheimer's Disease. Int J Biol Sci 17, 2181–2192. https://doi.org/10.7150/ijbs.57078