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Review Article

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Diabetes and Brain

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Abstract

The term "brain diabetes or type 3 diabetes" has begun to be used by researchers targeting the possible link between AD and T2 diabetes mellitus (DM). The main reason for using this term is to emphasize the common neurodegenerative mechanisms with AD and diabetes and the importance of brain In-Res. Insulin dysregulation and advanced glycation end products (AGEs) can be considered as the main associated factors for the disruption of glucose homeostasis and the pathophysiology of AD. AGE accumulation increases Aβ-42 formation via oxidative stress, NF-κβ activation, upregulation of BACE1, PSEN1 and γ-secretase, and mitochondrial dysfunction. In addition, the presence of insulin receptors and insulin signalling pathways identified in different brain regions indicates the important physiological (neurodevelopment, feeding behaviour, etc.) and cognitive (attention, learning and memory, etc.) effects of insulin on the brain, and in a way, emphasizes that the brain is an insulin-sensitive organ. The simultaneous occurrence of insulin-related CNS and systemic dysregulation in the early stages of AD suggests that these two diseases are inextricably linked. Hypometabolism, which develops as a result of insulin signalling pathway disruption, is among the altered bioenergetic parameters that associate T2DM with AD. In-Res in AD&DM cause hyperinsulinemia, leading to insulin and Aβ build up and insulin-degrading-enzyme saturation. However, when insulin levels rise, as seen in T2DM, insulin competes for insulin-degrading-enzyme, leading to reduced Aβ degradation and its subsequent accumulation in neurons. Dysfunctional insulin pathways and In-Res are characterized by receptor dysfunction, changed expression levels, poor binding, and defective events in the phosphorylation cascade. Overall, poor insulin signalling may result in altered cerebral metabolism, which can contribute to brain dysfunction, providing potential explanations for the relationship between DM&AD.

Keywords: ***Alzheimer's Disease, Diabetes Mellitus, Brain insulin resistance, Brain diabetes.***

Introduction

Diabetes prevalence is expected to approach 600 million by 2030 [1]. Diabetes Mellitus (DM) was previously classified as type 1 (T1DM), which causes insulin deficiency, and type 2 (T2DM), which causes insulin resistance (In-Res) and insulin secretion disorders. T2DM is one of the most prevalent metabolic illnesses worldwide and is responsible for almost 90% of DM cases [2]. Obesity, a lifestyle without physical activity, bad eating habits, and In-Res, which usually occurs years before the onset of the disease, can be counted among the main causes of T2DM [3]. Up to 20% of T2DM is linked to Alzheimer's disease (AD), as both pathologies are considered to be markers for each other. A meta-analysis study highlighted that the risk of dementia in individuals with diabetes is increased by 59% compared to individuals without diabetes [4]. Additionally, individuals who develop T2DM after hypertension have been reported to exhibit increased risks for types of dementia [5]. On the other hand, studies have also taken their place in the literature, reporting that the relationship between diabetes and dementia is subtype-specific, in the sense that it increases the risk of vascular dementia rather than being associated with AD [6]. However, the terms type 3 (T3DM) and type 4 diabetes (T4DM) have recently emerged [7,8]. T3DM is defined as a metabolic syndrome associated with abnormalities in central insulin signalling pathways that can lead to progressive brain In-Res. T4DM has a different mechanism than T2DM; the predominant factor is not In-Res but insufficient insulin secretion. While T4DM is considered a metabolic syndrome that occurs with aging, T3DM is associated with dementia and AD. The most important cause of T3DM is the energy deficit in the brain due to insulin deficiency or insulin inactivity [7,9]. The term "brain diabetes or type 3 diabetes" has begun to be used by researchers targeting the possible link between AD and T2DM [10]. The main reason for using this term by researchers is to emphasize the common neurodegenerative mechanisms with AD and the importance of brain In-Res.

Glucose Homeostasis Disruption and Pathophysiology of AD

Various factors have been reported to accelerate cognitive decline and even cause AD in diabetic patients; insulin dysregulation and advanced glycation end (AGEs) products are considered to be the main factors [10].

The receptor expressions of AGEs formed as a result of glycation of proteins or lipids exposed to glucose were detected higher in the hippocampus and prefrontal regions in diabetic rats. In addition, high amyloid beta (Aβ) expression was detected in these same regions in diabetic rats [11,12]. In the results of the research using a transgenic AD mouse model, it was thought that the factor leading to Aβ plaque formation and tau hyperphosphorylation was high AGE

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receptor expression in the hippocampus and cortex regions of AD mice [13]. This process contributes to Aβ-42 formation through several mechanisms: Firstly, AGEs increase oxidative stress and trigger various stress-sensitive transcription factors, including mitogen-activated protein kinase (MAPK), nuclear factor kappa Beta (NF-κβ), and signal transducer and activator of transcription (STAT) pathways [14]. NF-κβ activation increases the expression of β-secretase 1 (BACE1), one of the enzymes that initiates Aβ production by cleaving amyloid precursor protein (APP). Second, NF-κβ activation can increase the expression of presenilin-1 (PSEN-1), which facilitates the degradation of APP to Aβ-42. This process results in increased levels of accumulated toxic Aβ-42, which occurs particularly in AD. Third, Aβ-42 impairs mitochondrial function, promoting further production of reactive oxygen species (ROS) and the diversion of APP products to the amyloid pathway. Consequently, AGE accumulation increases Aβ-42 formation via oxidative stress, NF-κβ activation, upregulation of BACE1 and γ-secretase, RAGE signalling, and mitochondrial dysfunction [10,15].

A study conducted in the last quarter of the 20th century determined that insulin levels in the rat brain were approximately 25 times higher than plasma insulin levels. Havrankova even found insulin concentrations in some brain areas 100 times higher than in plasma. The role of insulin in the central nervous system (CNS) was not clear at the time [16]. Subsequent studies suggest that disruptions in brain glucose usage and energy metabolism are early abnormalities that occur before or alongside the onset of cognitive decline. This led to the idea that impaired insulin signalling plays a crucial role in the development of dementia and AD [17-19]. Although insulin's primary role is to control peripheral glucose homeostasis, the effects of insulin on the brain have been addressed more carefully in recent years. The presence of insulin receptors (IRs) and insulin signalling pathways identified in different brain regions indicates the important physiological (neurodevelopment, feeding behaviour, etc.) and cognitive (attention, learning and memory, etc.) effects of insulin on the brain, and in a way, emphasizes that the brain is an insulin-sensitive organ. The simultaneous occurrence of insulin-related CNS and systemic dysregulation in the early stages of AD suggests that these two diseases are inextricably linked. The dysregulation of insulin levels seen in individuals with AD deepens the roots of the link between DM and AD [20].

Studies in the literature report that In-Res may contribute to the pathogenesis of AD in different ways [21]. Recent studies have attributed impairments in the hippocampus insulin signalling pathway, affecting memory and other cognitive functions, reducing insulin signalling, and developing concomitant In-Res [22,23]. These findings indicate the significant link between hyperinsulinemia and In-Res, as well as the consequent diseases such as T2DM and AD. It has been suggested that peripheral In-Res decreases CNS insulin signalling and consequently causes changes in brain metabolism.

Diabetes and AD-Related Pathologies

By evaluating the pathology of AD in rodent diabetic models, the widespread presence of AD features in DM has been revealed [10]. Among the AD pathologies observed in diabetic rats in literature reports, it is possible to count the following: Neurodegeneration, decreased hippocampus volume, and increased Aβ-42 plaque levels (especially in the cortex and hippocampus) [8,10]. It has been reported that Aβ plaques, tau phosphorylation, synaptic loss, and inflammation with neuronal death are exacerbated due to diabetes in a model created by crossing transgenic diabetic mice with transgenic AD mice [24].

Another study conducted in primate brains showed that insulin receptor substrate 1 (IRS-1) phosphorylation decreased and tau phosphorylation increased, especially in the hippocampus, temporal cortex, frontal cortex, and cerebellum of T1DM primate model [25]. It has been observed that senile plaques form more rapidly in the frontal and temporal lobe regions in diabetic monkeys compared to normal monkeys [26].

Although the exact mechanism is not clear, the exact mechanism of the impairments in cholesterol transport reported in both DM and AD remains unclear. In preclinical AD research results, cholesterol was found to be present together with Aβ plaques and tau proteins [27]. Based on this result, it was hypothesized that cholesterol plays a direct role in the development of protein abnormalities in AD. Another study showed that the presence of the ApoE4 allele, which plays an important role in lipid processing, causes a decrease in plaque clearance ability and an increase in Aβ accumulation [28].

T2DM is associated with endoplasmic reticulum and mitochondrial stress, leading to increased ROS production and activation of the inflammatory pathway [29]. Studies in various models have shown that NF-κβ activation plays an important role in the early stages and progression of the disease. In particular, high levels of NF-κβ and other cytokines were observed in the hippocampus in mice treated with streptozotocin (STZ) [30]. Simultaneous activation of NF-κβ and proinflammatory cytokines triggers brain inflammation and neuronal apoptosis, ultimately leading to cognitive decline [30]. The main mechanisms of the common pathogenesis of AD and DM are shown in Figure 1.

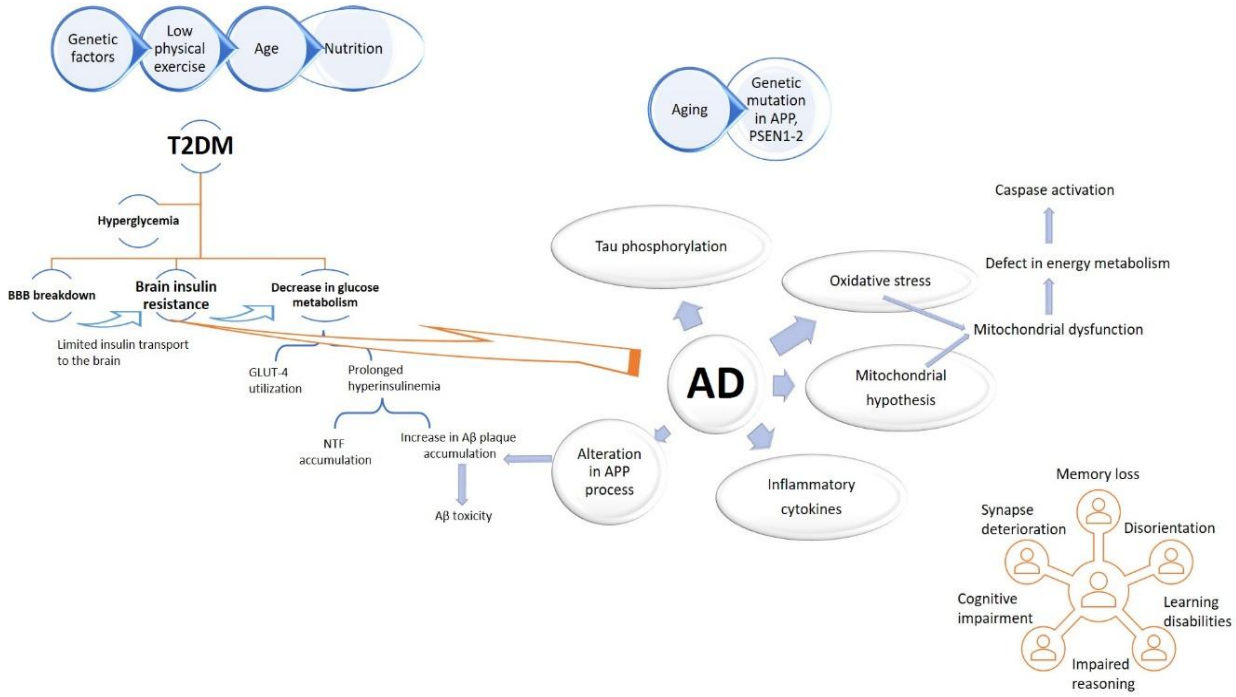

Figure 1: Pathological basis of Alzheimer's disease and type 2 Diabetes Mellitus: Major mechanisms of common pathogenesis of AD and DM. T2DM leads to hyperglycemia over time as cells become less responsive to insulin. Hyperglycemia also reduces glucose metabolism, and BBB breakdown limits insulin transport to the brain, leading to brain insulin resistance. Increased brain insulin resistance decreases GLUT-4 utilization and prolongs hyperinsulinemia. Prolonged hyperinsulinemia leads to the accumulation of Aβ and NFTs. On the other hand, proinflammatory cytokines perpetuate chronic inflammation, while also exacerbating Aβ and tau pathologies in neurons. The inflammatory process is further perpetuated by oxidative stress and mitochondrial dysfunction, which initiate defects in energy metabolism and caspase activation. As a result of all these processes, memory and cognitive functions deteriorate

DM, Diabetes Mellitus; AD, Alzheimer's disease; T2DM, type 2 Diabetes Mellitus; Aβ, amyloid beta; APP, amyloid precursor protein; NFT, neurofibrillary tangles; PSEN1, presenilin-1; PSEN2, presenilin-2; GLUT-4, insulin-sensitive glucose transporter 4.

Glucose Uptake and the Role of Insulin in CNS

Insulin shows its effect in the periphery by providing glucose uptake through the insulin-sensitive glucose transporter GLUT-4 and by decreasing blood glucose levels. Low levels of glucose decrease insulin secretion through insulin-insensitive GLUT-2. In fat and muscle tissue, insulin stimulates the translocation of GLUT-4 from the intracellular region to the plasma membrane, increasing glucose uptake. Although insulin does not stimulate glucose uptake in the liver, it blocks glycogenolysis and gluconeogenesis, stimulates glycogen synthesis, and thus regulates fasting blood glucose levels [31]. The brain utilizes multiple pathways to use glucose. It first crosses the blood-brain barrier (BBB) through insulin-independent facilitated diffusion before entering brain cells via both insulin-independent and insulin-regulated glucose transporters [31]. Insulin-insensitive glucose transporters GLUT-1, the more abundant glucose transporter (in astrocytes), GLUT-2 (specific neurons in the hypothalamus), GLUT-3 (the major GLUT in the neurons of the cerebellum, striatum, cortex, and hippocampus, and GLUT-5 (in microglia) carry out most of the glucose uptake by the CNS.34 Glucose transport in the CNS is mostly independent of insulin, unlike in peripheral tissue, transport in neurons is provided by insulin-sensitive GLUT-4 and GLUT-8. The cerebellum, hypothalamus and hippocampus contain insulin-sensitive GLUT-4, while GLUT-8 is located intracellularly [32]. Unlike GLUT-1 and GLUT-3, GLUT4 is regulated by insulin and primarily functions to enhance glucose uptake into neurons during periods of high metabolic need [33]. Dysfunction of GLUT4 in the hippocampus leads to decreased metabolism and reduced neuronal plasticity, contributing to the onset of depressive-like behaviour and cognitive impairment. These effects are also observed in AD. Insulin-insensitive GLUT-1 provides glucose transport across the BBB via diffusion. Insulin-insensitive GLUT 3, along with several insulin-regulated GLUT proteins like GLUT 4 and GLUT 8, is co-expressed in various brain regions. These glucose transporters are found in areas such as the basal forebrain, hippocampus, amygdala, sensorimotor cortex, hypothalamus, and pituitary, with lower expression levels in the cerebral cortex and cerebellum [7,34]. Insulin-insensitive GLUT-2, the glucose transporter used by the pancreas, has been observed in some cells in the hypothalamus [35]. It is thought that some of the effects of insulin on cognitive and synaptic development may be mediated by insulin-sensitive glucose transporters [32].

Insulin, which has a regulatory effect on brain glucose metabolism and plays important roles in neuronal development and neuronal survival, functions as both a neuromodulator and neuroendocrine molecule [36]. Insulin also plays a role as a growth hormone in neurodevelopment and synaptogenesis in the CNS [37]. Insulin modulates the expression and localization of ion channels [GABA, NMDA, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, etc.]. Insulin controls the activation of specific GLUT transporters. In addition to all this, insulin contributes to long-term potentiation and long-term depression via NMDA receptor signalling, and AKT pathways; promotes neurite outgrowth, excitatory synapse development, dendritic spine formation, and neuronal survival; and plays an important role in the proliferation, survival, differentiation, and myelination of oligodendrocytes [38].

AD as Type 3 Diabetes: The role of Insulin Resistance

Previous studies have emphasized that the incidence of AD is higher in T2DM and obese individuals than in normal individuals and that this situation stems from common underlying mechanisms [38,39]. The most commonly identified parameter linking these three diseases is In-Res. If we consider In-Res at the cellular level, we can consider it as a disruption in neuroplasticity or a disorder in neurotransmitter release within neurons [10]. Neuronal glucose uptake may not be completely insulin-dependent, but In-Res is closely associated with defective insulin signalling pathways, as the brain is an insulin-sensitive organ [10,40]. Hypometabolism, which develops as a result of insulin signalling pathway disruption, is among the altered bioenergetic parameters that associate T2DM with AD. Excessive insulin increase and In-Res may cause neuronal functionality and cognitive abilities to deteriorate as a result of a relative decrease in peripheral insulin activity [41]. As a result of many studies in the literature, AD has been linked to metabolic syndrome by reducing insulin delivery to the brain and increasing levels of Aβ, tau protein phosphorylation, oxidative stress, proinflammatory cytokines, AGEs, dyslipidemia, mitochondrial dysfunction, and apoptosis [42]. All these findings lead to the emergence of the concept of T3DM, which suggests that AD may be a metabolic disorder caused by insulin and insulin growth factor-1 (IGF-1) resistance in the brain [9,41].

An incomplete insulin response can cause impaired cerebral insulin signalling in AD and T2DM, downregulated IRs, reduced binding to IRs, or improper activation of the insulin signalling cascade. The primary outcome of this changed cascade is decreased neuronal glucose absorption, which manifests as poor neuroplasticity, neurotransmitter deficits, bioenergetic system collapse, and the commencement of an unavoidable inflammatory cascade. Overall, poor insulin signalling may result in altered cerebral metabolism, which can contribute to brain dysfunction, providing potential explanations for the relationship between DM and AD.

In-Res in AD and DM cause hyperinsulinemia, leading to insulin and Aβ build-up and insulin-degrading enzyme (IDE) saturation [43]. Under normal conditions, both insulin and Aβ are broken down by IDE. However, when insulin levels rise, as seen in T2DM, insulin competes for IDE, leading to reduced Aβ degradation and its subsequent accumulation in neurons [44].

Some experts say insulin insufficiency is a major contributor to AD cognitive deficits [45]. An incomplete insulin response can cause impaired cerebral insulin signalling in AD and T2DM, downregulated IRs, reduced binding to IRs, or improper activation of the insulin signalling cascade. Dysfunctional insulin pathways and In-Res are characterized by receptor dysfunction, changed expression levels, poor binding, and defective events in the phosphorylation cascade. The primary outcome of this changed cascade is decreased neuronal glucose absorption, which manifests as poor neuroplasticity, neurotransmitter deficits, bioenergetic system collapse, and the commencement of an unavoidable inflammatory cascade. As a result of a clinical study, it was suggested that AD patients may experience glucose intolerance and therefore there is a biface connection/relationship between these two metabolic diseases [46]. Overall, poor insulin signalling may result in altered cerebral metabolism, which can contribute to brain dysfunction, providing potential explanations for the relationship between DM and AD. Recent studies indicate that, under physiological conditions, this pathway functions as a flip-flop switch for specific cell types, and insulin response may be a threshold phenomenon [21,47]. Many factors, including free fatty acids, might impair the pathway's sensitivity to insulin, leading in In-Res [48,49].

One of the common pathogenic factors between AD and T2DM is the accumulation of Aβ. Elevated amyloid levels disrupt glucose homeostasis. Post-mortem studies in diabetic individuals have reported increased neurofibrillary tangles and amyloid beta plaques. This abnormal amyloid beta activates glycogen synthase kinase-3 beta (GSK-3β), which plays a role in both pathologies, leading to the formation of neurofibrillary tangles following hyperphosphorylation of tau protein (**Figure 2**). STZ-induced diabetes in transgenic mice overexpressing APP has been linked to impaired cognitive performance, reduced IRs phosphorylation, and increased GSK-3β [50]. STZ-induced diabetes in a transgenic mouse model has been shown to increase Aβ accumulation in the brain in 1.5-month-old animals, indicating an early stage of disease [51]. In both rats and humans, appropriate insulin dosages have been found to improve memory by increasing basal glucose availability [52]. Intranasal insulin administration to rodents has been demonstrated to increase cognitive skills without changing blood glucose levels, and it has also been proven to improve memory in people without influencing peripheral insulin and glucose levels [53-55].

Acetylcholine (ACh) synthesis is provided by the enzyme choline acetyl transferase, and choline acetyl transferase expression increases with insulin/IGF-1 stimulation. Choline acetyl transferase co-localization decreases in cortical neurons in AD. Studies suggest that there may be a link between blood sugar, insulin resistance, and inadequate ACh level. This link is also predicted as follows: Low insulin levels and insulin resistance may cause a decrease in ACh levels (**Figure 2**) [56].

Post-mortem brain tissue studies of diabetic patients revealed that microvascular lesions and Aβ plaques characteristic of AD's accompanied dementia in the brain tissue [57]. In the study examining the relationship between diabetes/insulin resistance and hippocampal and amygdala atrophy using magnetic resonance imaging; It has been observed that the degree of hippocampal and amygdala atrophy is higher in diabetic individuals than in the control group and correlates with the severity of insulin resistance [58] (**Figure 2**). The most common cognitive impairments observed in patients with T1DM; are decreases in information processing speed, psychomotor competence, attention and mental functions are observed more in T1DM patients, while memory problems are reported to increase in T2DM patients, and decreases in psychomotor speed and frontal lobe functions are at the forefront. In parallel with this situation, it is observed that cognitive dysfunctions regress in patient groups whose diabetes is under control due to the reduction of diabetic complications [59].

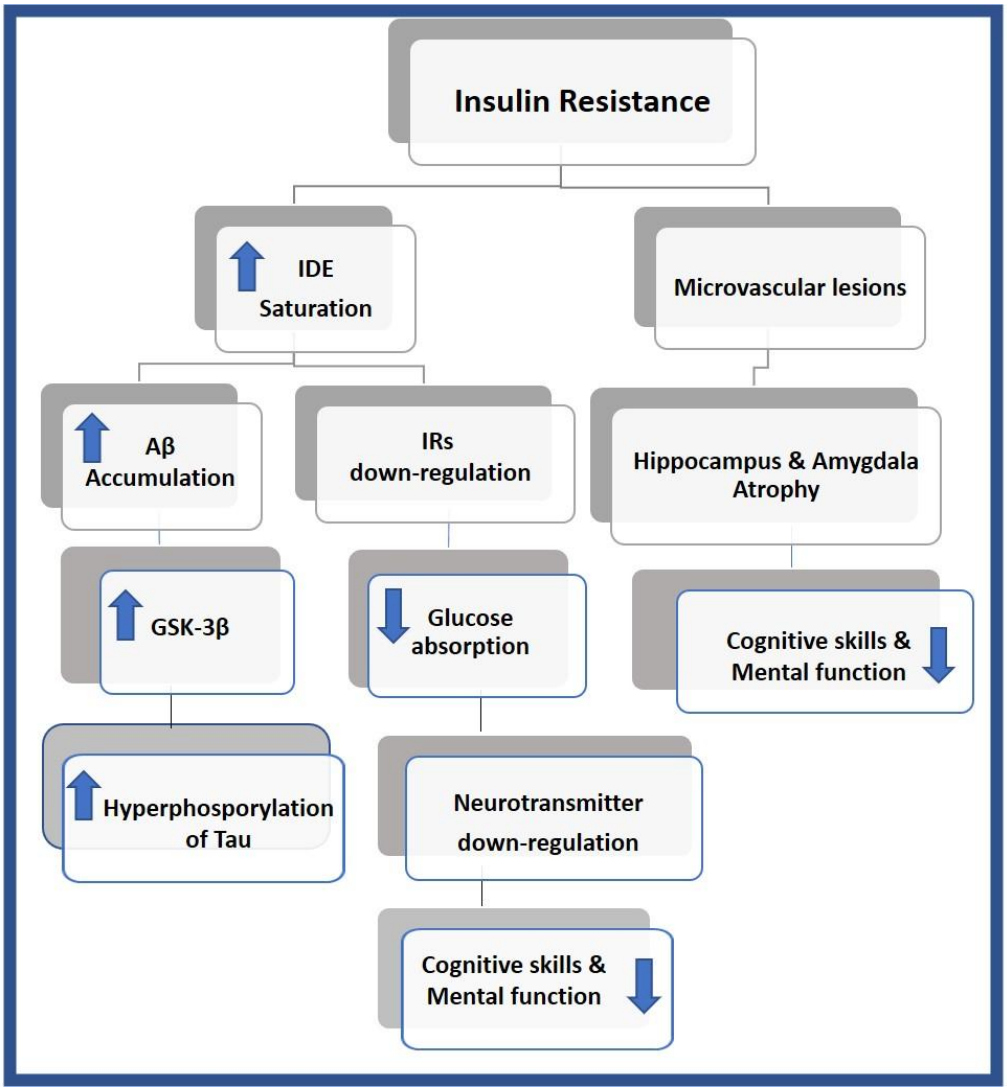

Figure 2: Possible roles of insulin resistance in the pathophysiology of Alzheimer's disease.

IRs, insulin receptors; GSK-3β, glycogen synthase kinase-3 beta

Drug Approaches in The Treatment of AD

Alongside the growth in our understanding of brain metabolism and cognitive functions, there has also been a rise in studies assessing new therapies for metabolic diseases like DM and AD. Currently, treatments developed for the underlying pathologies of AD have not been successful, and the use of neuroprotective, antioxidant or anti-inflammatory agents in individuals with AD has not yielded effective results.

Promising Phase 3 clinical trials are ongoing for the treatment of AD. Prominent among these are the monoclonal antibodies Lecanemab (Leqembi), Aducanumab (Aduhelm), which target beta-amyloid plaques, and Donanemab (Kisunla), which target both Aβ plaques and tau protein [60-62]. Studies on lecanemab and donanemab report that starting treatment in the early stages of AD may be more effective in slowing down the progression of the disease.

Due to the frequent Thiamine deficiency in individuals with AD, the clinical results of drugs targeting this metabolism do not clearly show the desired effect [63]. The increase in knowledge about AD and T2DM has contributed to the development of cocktail therapies that affect the cascades that progress due to dysfunction in glucose metabolism, primarily based on reducing brain In-Res [64]. In the current treatment, agents that increase insulin sensitivity (metformin and peroxisome proliferator activator gamma (PPARγ) agonists) and insulin secretion [incretin insulin mimetic molecules, glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide (GIP)] are used. Metformin, which is perhaps the most commonly used agent in the treatment of T2DM, is an agent that increases insulin's control over liver glucose production and improves insulin levels. It is reported in the literature that metformin treatment reduces the incidence of dementia in diabetic patients [65]. It is reported that metformin provides an effect on insulin resistance and dementia by increasing insulin sensitivity due to its ability to cross the BBB [66]. It has been shown that metformin treatment caused a significant decrease in the level of phosphorylated tau protein in the hippocampus of transgenic mice, resulting in significant improvements in spatial memory and reversing long-term synaptic strengthening deficits [67]. The results of this study suggest that metformin may show its therapeutic effect by targeting both tau and synaptic dysfunction in AD. As a result of the reporting that metformin treatment significantly increased AMPK levels in APP/PS1 transgenic mice, it is stated that the potential therapeutic benefit of metformin in AD shows neuroprotective effect by targeting mitochondrial dysfunction [68].

PPARγ plays important roles in many processes thought to be related to the pathogenesis of both diabetes and AD. PPARγ agonists, which increase insulin sensitivity, enhance the function of adipose tissue, removing fatty acids and triglycerides from the liver and muscles [69]. Studies designed to investigate the potential

benefits of PPARγ agonists generally compare them with placebo or with monotherapy (rosiglitazone and pioglitazone from the thiazolidinedione group of drugs) or donepezil simultaneously. Experimental results have shown that Aβ levels remain stable throughout treatment [70]. In addition, it was reported that regional cerebral blood flow increased in the right and left parietal lobes of AD patients receiving treatment [71]. Experimental reports using PPARγ agonists suggest that these agonists reduce neuroinflammation and Aβ accumulation, resulting in improvements in cognitive impairment [72-75]. The results suggest that these agonists may provide some therapeutic benefits in the initial phase of AD caused by insulin dysregulation and/or as an additional agent in the treatment of the patient's pre-existing T2DM.

GLP-1, which increases insulin secretion in a glucose-dependent manner and can cross the BBB, is extremely useful in treating DM. GLP-1 mimics include gliptins or exenatide and liraglutide, which delay the degradation of GLP-1. In preclinical study results, these agents show neuroprotective effects by increasing insulin sensitivity, reducing neuroinflammation, and supporting neuronal survival. These agents have been reported to have suppressive effects on neurodegeneration and AD progression by reducing oligomeric Aβ and neuritic plaque burden by activating GLP-1 receptors (GLP-1Rs) widely expressed in regions associated with cognitive function, such as the hippocampus and cortex [76,77]. Preclinical reports have shown that GLP-1R antagonists reduce Aβ plaques and phosphorylated tau levels and have a corrective effect on cognitive impairments by improving synaptic function. Among the available treatments, the literature highlights the beneficial effects of intranasal insulin (sometimes peripheral insulin administration causes hypoglycemia) and GLP-1 administration in patients with mild cognitive impairment or T2DM [78,79]. A large clinical trial investigating the effects of Semaglutide (EVOKE and EVOKE+) on AD biomarkers and neuroinflammation in participants with early-stage symptomatic AD, was initiated in 2023. Previous small-scale clinical studies have shown that GLP-1 agonists may have beneficial effects on memory and cognitive function, but definitive evidence is not yet available. Reporting on whether EVOKE and EVOKE+ are promising candidates for AD is expected in 2026 [80].

Conclusion

Following the first diabetic patient with cognitive dysfunction in 1922, numerous studies have been designed to understand the importance of cognitive dysfunction in diabetes. According to the results of research conducted over the last century, cognitive dysfunction and dementia are currently shown among the complications of DM. It is stated that obesity and/or changes in insulin homeostasis are associated with an increase in risk factors not only for vascular dementia but also for AD. It is increasingly accepted that damage to insulin signalling is partly responsible for cognitive dysfunctions in AD [80]. In recent years, AD has been defined as a brain-specific form of DM (Type 3 DM), as it involves changes in tau and Aβ metabolism that occur due to the development of In-Res in the CNS, resulting from the deterioration of insulin receptor sensitivity in the CNS. Primary evidence suggesting a link between diabetes, a metabolic disorder, and AD, a neurodegenerative disorder, focuses on critical metabolic mechanisms that contribute to neurodegeneration, such as changes in insulin signalling pathways, oxidative stress, mitochondrial dysfunction, and inflammation. By placing AD in this metabolic environment, we can better understand how it begins and the origin of the disease. When these two diseases are examined combined, preventive approaches may influence the creation of early detection, treatment plans, and new therapeutic strategies aimed at glucose homeostasis.

Declarations

Ethics of Study

None

Conflicts of Interest

None

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None

Author's Contributions

Conception and design: AA, DÖ; Drafting of the article: AA, DÖ; Critical revision of the article for important; AA, DÖ; ıntellectual content: AA, DÖ; Final approval of the article: AA, DÖ.

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