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Exploring The Link: A Comprehensive Review Of The Correlation Between Type 2 Diabetes And Alzheimer's Disease

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ABSTRACT:

This review data suggests that type 2 diabetes mellitus (T2DM) can contribute significantly to the onset or progression of Alzheimer's disease (AD) either directly or as a cofactor. Clinical studies have provided evidence that T2DM is a major risk factor in the pathology of AD [1]. Insulin has multiple important functions in the brain. Some basic research, however, suggests that insulin accelerates Alzheimer-related pathology through its effects on the amyloid beta (Aβ) metabolism [2]. In this review, we give a brief introduction to T2D and AD and then describe the risk factors and molecules that are commonly associated with these diseases[4], several potential mechanisms underlying diabetes-induced cognitive impairment which include, abnormal insulin signaling, amyloid-β accumulation, oxidative stress, immuno-inflammation, mitochondrial dysfunction, advanced glycation end products, acetylcholinesterase and butyrylcholinesterase, advanced lipid peroxidation products, and apolipoprotein E. Also discussed diagnosis and treatment approach of Alzheimer's disease by controlling T2DM. All these interconnected mechanisms may act either individually or synergistically which eventually leads to neurodegeneration and AD [3].

Keywords: Alzheimer's disease, amyloid beta(Aβ), insulin resistance, oxidative stress, type 2 diabetes mellitus(T2DM).

INTRODUCTION

Type 2 Diabetes (T2D) and Alzheimer's disease (AD) are the most common diseases associated with aging [4]. T2DM is a peripheral metabolic disease while AD is a neurodegenerative disorder. The two diseases share common pathologies at the molecular and cellular levels. There is an increasing amount of evidence in the scientific community finding an association between T2DM and AD. The correlation between type 2 diabetes and Alzheimer's disease underscores the need for interdisciplinary research and integrated care approaches [1].

Alzheimer's Disease:

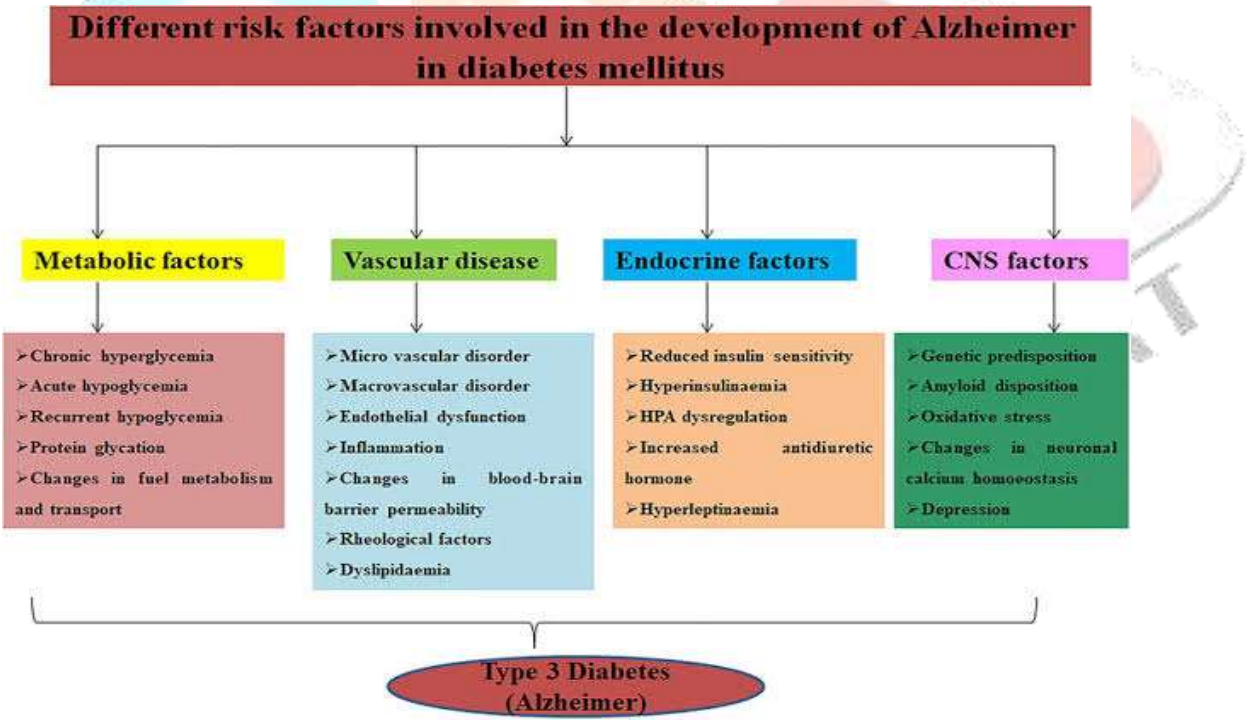
Alzheimer's disease (AD) is the most common form of senile dementia, affecting 10% of individuals older than 65 and nearly 50% of those older than 85. United States is estimated to be approximately 4.5 million and is predicted to increase to up to 13.2 million in the next 50 years. AD is associated with a variety of factors, including the extracellular deposition of b-amyloid (Ab) plaques, accumulation of intracellular neurofibrillary tangles, oxidative neuronal damage, and inflammatory cascades [5]. Hyperinsulinemia also increases the amyloid formation and tau protein hyperphosphorylation, leading to neuronal network

disruption, neurodegeneration, and, finally, death. Along with these pathologies, certain other mechanisms support the link between and AD, which include the release of pro-inflammatory mediators by NF-κ-activation, AGE formation, abnormal lipid peroxidation on neuronal membrane, and alteration in the level of AChE and BChE. These can aggravate A- production, oxidative stress, mitochondrial dysfunction, neurofibrillary tangle formation, and finally, loss of neuronal functions, which subsequently lead to AD during diabetic conditions [3].

Type 2 Diabetes Mellitus:

Type 2 Diabetes Mellitus (T2DM) is one of the most common metabolic disorders worldwide and its development is primarily caused by a combination of two main factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond to insulin [6]. Internationally, the total number of people who have T2DM is likely to increase from 171 million in 2000 to 366 million by 2030. The prevalence of T2DM has increased dramatically in Arabic-speaking countries over the last three decades, an increase that corresponds to increased industrial development. As many as six Arabic-speaking countries have the world's highest T2DM prevalence; this includes Kuwait (21.2%), Qatar (20.1%), Saudi Arabia (20.0%), Bahrain (19.8%), and the United Arab Emirates (19.2%). Furthermore, an estimated 9.1% of the population from the Middle East or North Africa had T2DM (32.8 million) in 2011, and this figure is projected to reach 60 million by 2030[7].

Different risk factors involved in the development of Alzheimer in diabetes mellitus-

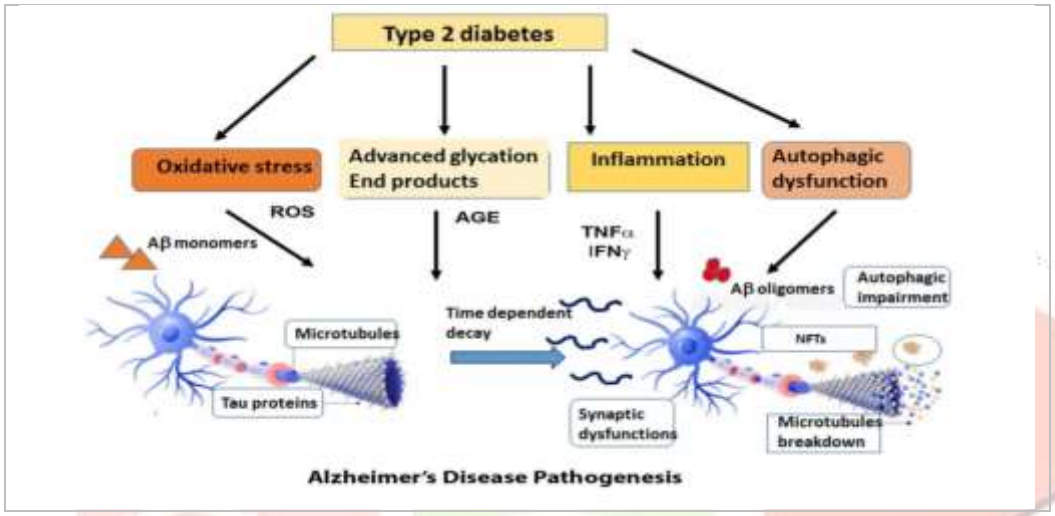


Underlying Mechanism of cognitive dysfunction in T2DM:

The precise mechanism underlying T2DM-related cognitive dysfunction or the development of dementia, especially AD-type dementia, remains to be elucidated; however, several hypothetical mechanisms have been proposed. High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation endoproducts (AGEs), which have potentially toxic effects on neurons. AGEs are formed as the end-products of the Maillard reaction," during which reducing sugars can react with the amino groups of proteins to produce cross-linked complexes and unstable compounds. AGEs have been found in the central nervous system (CNS) of diabetics [8]. High blood sugar in T2D affects every tissue and organ of the body, causing other complications, such as

cardiovascular disease, nephropathy, retinopathy, and neuropathy; however, unlike other complications, the relationship between T2D and AD is not yet fully understood. Studies have indicated that people with T2D have a greater risk of developing AD [38, 39]. The higher risk may be because the high blood sugar levels in T2D damage blood vessels in the brain, which when combined with impaired glucose metabolismleads to mild cognitive impairment (MCI) and cognitive decline (CD), which are hallmarks of AD. In addition, insulin also plays an important role in the biosynthesis of neurotransmitters, which are essential, both for communication between neurons and for memory. However, whether AD can also influence the progression of insulin resistance or T2D is not known. To understand the connection between T2D and AD, it is imperative to find the biochemical factors that are involved in the progression of both T2D and AD. Greater insight into how T2D and AD are connected may eventually lead to new strategies to treat both of these diseases [4]. Important molecular events connecting T2D and AD are listed in the table below, and their implications for disease pathogenesis are discussed.

A Common Characteristic in AD and T2DM-



Brain insulin resistance is a significant yet often overlooked feature of AD. Insulin released from the pancreas is transported to the brain via the blood-brain barrier using a receptor-mediated mechanism. While the crucial role of insulin response in the peripheral tissues is well documented, there are very few reports about the function of insulin in the central nervous system. The insulin levels in human and rodent brain tissue are relatively low compared to circulating levels. There are some reports about reduced insulin levels in the AD brains; however, this finding was not significant compared to the age-matched controls. Recently, several studies have reported reductions of insulin mRNA in AD. However, the results of de novo insulin synthesis have been controversial [9]. Thus, it is hypothesized that the majority of brain insulin comes from the peripheral tissues, and the role of insulin produced in the CNS is still unclear.

Oxidative Stress-

Alzheimer's disease (AD) and Type 2 Diabetes Mellitus (T2DM) share common underlying pathologies, including Oxidative stress: Excessive reactive oxygen species (ROS) damage cells, particularly in the brain and nervous system. Reactive Oxygen Species (ROS) play a crucial role in maintaining cellular homeostasis. At optimal levels, ROS facilitates cell signalling. However, excessive ROS production or decreased scavenging leads to oxidative stress, contributing to various diseases (cancer, atherosclerosis, neurodegeneration, diabetes). ROS also interacts with inflammation, exacerbating tissue damage and endothelial dysfunction. Inflammation triggers ROS production, and conversely, ROS induces inflammatory reactions. Chronic ROS production leads to chronic inflammation, while acute production leads to thrombosis [11]. Maintaining balanced ROS levels is essential for proper physiological functioning and preventing disease progression.

Advanced Glycation End Product-

AGE products are a heterogeneous group of molecules formed by non-enzymatic glycation between A and tau proteins [20]. AGE products are the end products of the Maillard reaction and are also formed by ROS-mediated glycoxidation. Chronic hyperglycaemia and oxidative stress synergistically increase protein glycation and enhance the formation of AGEs [2]. Receptors for AGE (RAGE) are found in neuron-derived exosomes that act as binding sites of AGE [42]. RAGE, a member of the immunoglobulin superfamily, is expressed in multiple cell types, including endothelial cells, mononuclear phagocytes, vascular smooth muscle cells, neurons, and microglia [17]. The formation of AGE may contribute to the development of neurodegenerative diseases by increased free radical activity, decreased ligand binding, modified protein half-life, and altered immunogenicity. The study performed by Chou et al. (2019) demonstrated the involvement of AGE products in the pathogenesis of AD/T2DM axis [43]. AGE product modification accelerates the aggregation of soluble A and induces tau hyperphosphorylation, which leads to the facilitated development of neurofibrillary tangles and amyloid plaques [2], which further leads to the modification of functionally important proteins like tubulin and Na/K+ ATPase pump and hence affects neuronal function [44]. Examples of AGE products include majorly methylglyoxal which forms an adduct with DNA nucleic acid and base. Pentosidine and N-carboxymethyl-lysine are common in both diabetes and AD pathologies and could function as important biomarkers for disease progression [3]. diabetes and AD pathologies and could function as an important biomarker for disease progression [3].

Inflammation-

Type 2 Diabetes (T2DM) is associated with excessive immune system activation, leading to increased proinflammatory cytokines, oxidative stress, and inflammation in the brain. Elevated levels of TNFα, IL-1β, IL-2, and IL-6 have been observed in diabetic animals. This inflammation triggers insulin resistance, impairing insulin signalling and contributing to amyloid-β (Aβ) and tau pathological cascades. NF-κβ activation plays a key role in T2DM pathogenesis, inducing cytotoxicity, inflammation, and apoptosis. Studies suggest that targeting inflammatory pathways, such as JNK and IKKβ, can improve insulin action and reduce neurodegeneration. Pharmacological interventions, like salicylates and thiazolidinediones, show promise in reducing inflammation and enhancing insulin sensitivity [9]. The interplay between T2DM, inflammation, and oxidative stress may contribute to the development of Alzheimer's disease (AD), highlighting the need for further research into the relationship between these conditions. T2DM is associated with excessive immune activation and inflammation. Proinflammatory cytokines impair insulin signalling and contribute to Aβ and tau pathologies. NF-κβ activation plays a key role in T2DM pathogenesis. Targeting inflammatory pathways improves insulin action and reduces neurodegeneration. Pharmacological interventions show promise in reducing inflammation and enhancing insulin sensitivity.

Autophagic dysfunction-

Autophagy, a process of clearing misfolded protein aggregates and damaged organelles, is crucial for neuronal homeostasis. Dysregulated autophagy is a shared pathophysiology in Alzheimer's disease (AD) and Type 2 Diabetes (T2DM). In AD, autophagic dysfunction leads to the accumulation of toxic protein aggregates, while in T2DM, insulin resistance generates oxidative stress, and enhanced autophagy acts as a protective factor. Studies suggest that insulin resistance inhibits downstream mTOR signalling, impacting autophagy [9].

Autophagy malfunction in AD is characterized by:

1. Immature autophagic vacuoles formation

2. Accumulation of autophagosomes in neurons

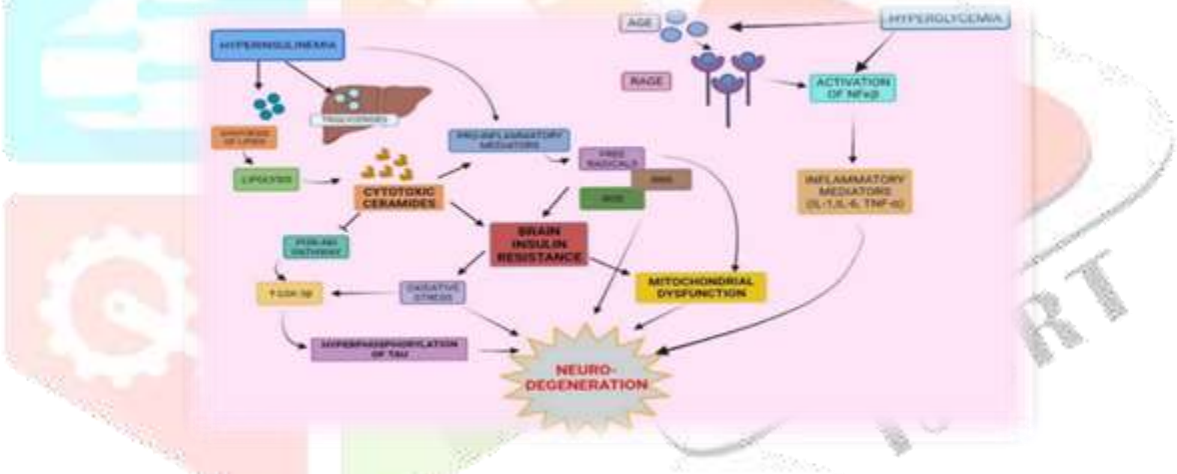
3. Inefficient degradation of amyloid-β (Aβ)

Acetylcholinesterase and butyrylcholinesterase-

AChE and BChE enzymes are a part of the esterasefamily. In AD, AChE levels tend to decrease in thebrain and to compensate for this decrease, BChElevels may increase which hydrolyzes abundantacetylcholine in the brain. Hence, alteration in the ratio of AChE and BChE causes cholinergic deficit. Indiabetes mellitus, AChE levels increase which leadsto aacetylcholine deficit in brain [45]. Therefore, in diabetes mellitus increase in AChE levels with associated acetylcholine deficiency would increase A-peptide levels, which ultimately enhances plaque for-mation in the brain causing AD [3]. In addition to amyloid deposition, a decrease in acetylcholine levels also resulted into elevated levels of inflammatorymediators like IL-1-and TNF[3].

Advanced lipid peroxidation products-

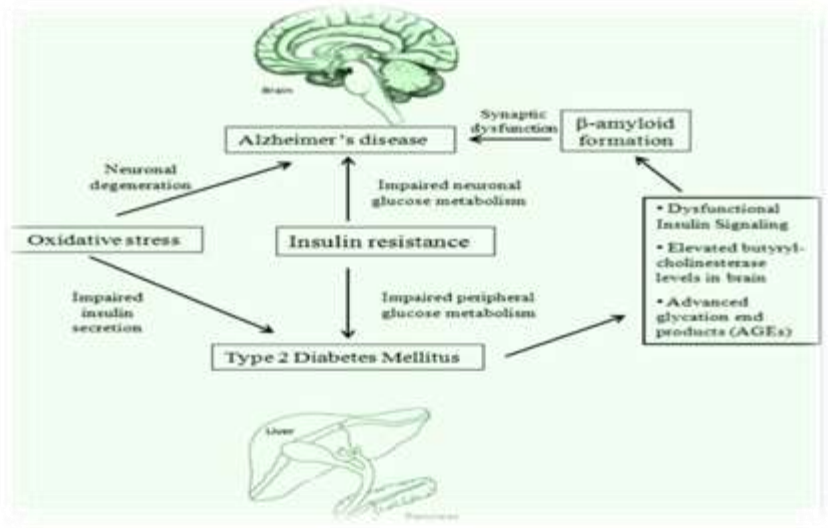
AChE and BChE enzymes are a part of the esterase family. In AD, AChE levels tend to decrease in the brain, and to compensate for this decrease, BChE levels may increase, which hydrolyzes abundant acetylcholine in the brain. Hence, alteration in the ratio of AChE and BChE causes cholinergic deficit. In diabetes mellitus, AChE levels increase, which leads to an acetylcholine deficit in the brain [45]. Therefore, in diabetes mellitus, an increase in AChE levels with associated acetylcholine deficiency would increase A-peptide levels, which ultimately enhances plaque formation in the brain, causing AD [3]. In addition to amyloid deposition, a decrease in acetylcholine levels also resulted in elevated levels of inflammatory mediators like IL-1 and TNF [3].



Interrelationship between type-2 diabetes mellitus and Alzheimer's disease via oxidative stress, mitochondrial dysfunction, andinflammation: Peripheral insulin levels regulate synthesis and breakdown of lipids. Inflammatory mediators are formed by various pathways-activation of NF-κvia binding of AGE to its receptors, cytotoxic ceramides formed as a result of lipolysis and peripheral insulin levels.Formations of inflammatory mediators elicit a series ofresponses that leads to brain insulin resistance and oxidative stress and mitochondrialdysfunction and results into neurodegeneration. AGE, Advanced glycated end products; RAGE, Receptors of AGE; NF-κβ, Nuclear factor kappa β.

Amyloid -β (Aβ) Accumulation-

Amyloid-β (Aβ) protein, derived from amyloid precursor protein (APP), plays a crucial role in Alzheimer's disease (AD). APP's normal function, along with amyloid precursor-like protein 2 (APLP-2), is to maintain learning and memory. However, elevated APP levels in AD brains lead to increased Aβ deposition and neuronal damage. In diabetes, islet amyloid polypeptide (IAPP or amylin) produced by pancreatic β-cells regulates glucose levels. IAPP's amyloidogenic properties cause β-cell death and cognitive impairment. Moreover, IAPP interacts with Aβ peptides, hyperphosphorylating tau protein and contributing to neurofibrillary tangle formation in AD.



Mitochondrial Dysfunction-

Mitochondrial dysfunction is a key factor in aging and diabetes-related oxidative stress, increasing vulnerability to neurodegenerative diseases like Alzheimer's. Given the brain's high energy demands, its reliance on mitochondrial function makes it particularly susceptible to oxidative damage, more so than other parts of the body. Mitochondrial dysfunction, exacerbated by the brain's high energy needs, contributes to oxidative stress and increased risk of neurodegenerative diseases, including Alzheimer's, in aging and diabetes. Mitochondrial dysfunction, a hallmark of aging and diabetes, renders the brain vulnerable to oxidative damage due to its high energy requirements, thereby increasing the risk of neurodegenerative diseases like Alzheimer's disease [13]. The brain's cognitive functions rely heavily on synaptic communication between neurons, which requires immense energy. Consequently, synapses contain high concentrations of mitochondria. However, mitochondria are also vulnerable to oxidative damage due to reactive oxygen species (ROS) production. Research suggests mitochondrial dysfunction plays a crucial role in diabetes-related brain damage, contributing to neurodegeneration. In insulin-resistant brains, mitochondrial damage leads to Impaired electron transport chain activity and reduced mitochondrial respiration [12].

Abnormal insulin signalling-

Unlike peripheral tissues, neuronal glucose uptake is partially insulin-independent. Therefore, brain insulin resistance primarily affects insulin signalling pathways rather than glucose uptake [10]. Disrupted insulin signalling and subsequent hypometabolism are key factors linking Alzheimer's disease (AD) and Type 2 Diabetes (T2D) through altered bioenergetics. Or, in an even more concise version, Brain insulin resistance in AD and T2D is characterized by impaired insulin signalling, not glucose uptake. This disruption leads to hypometabolism, connecting the two diseases through altered bioenergetics. Brain insulin resistance in AD and T2D is characterized by impaired insulin signalling, not glucose uptake. This disruption leads to hypometabolism, connecting the two diseases through altered bioenergetics [10]

DIAGONOSIS:

Diagnosis for Alzheimer's Disease-

Accurate diagnosis is crucial for treating Alzheimer's Disease (AD), but distinguishing it from other memory and behavioural disorders is challenging, particularly in the early stages [25]. To improve early detection, researchers are exploring biomarkers using Non-invasive imaging (MRI, PET), Cerebrospinal fluid analysis (amyloid beta, tau proteins), and Plasma IDE levels (potential new biomarker). Alzheimer's disease diagnosis is challenging, especially in the early stages. Researchers seek early biomarkers using MRI, PET, CSF

analysis, and plasma IDE levels to differentiate AD from other memory disorders and enable timely treatment [15].

Diagnosis of Type 2 Diabetes Mellitus-

Diagnostic tests:Haemoglobin A1c (HbA1c), Fasting plasma glucose, Random plasma glucose, Oral glucose tolerance test (OGGT) [19].

BLOOD GLUCOSE		STATUS	HbA1c	
mmol/L	mg/dL		%	mmol/mol
5.4	97	Normal	5	31
7.0	126		6	42
8.6	155	Pre-Diabetes	7	53
10.2	184	Diabetes	8	64
11.8	212	Diabetes	9	75
13.4	241		10	86
14.9	268	Diabetes	11	97
16.5	297		12	108

TREATMENT FOR AD AND T2DM:

Currently, AD patients appear to benefit from pharmacotherapy targeted for treating T2DM, and clinical trials for the effectiveness of such treatments are still in progress. There is no existing treatment available to stop or decrease the decline of brain function. Currently, available drugs are only able to slow the deterioration of symptoms for up to 6-12 months, and even then, they have been effective in only 50% of the patients [44]. Tau phosphorylation in both AD and T2DM plays a role in the stimulation of glycogen synthase kinase-3 (GSK-3) which in turn phosphorylates glycogen synthase in the rate-limiting step of glycogen biosynthesis [103-105]. GSK-3 plays an important role in the development of NFTs, and therefore, GSK-3 suppression could be a mutual target for the treatment of both AD and T2DM [27]. Neurotoxicity induced by amyloid β can be averted by pre-treatment with insulin-like growth factors (IGFs), and the neuroprotective nature of IGFs is regulated by activation of phosphatidylinositol 13-kinase/Akt pathway and inhibition of GSK-3 [26]. Many AD patients have distorted insulin signalling, which is also apparent in brain-specific diabetes [15]. Therefore, a probable prospective approach to AD could be pharmacological management of the insulin-signalling pathway. Moreover, as far as treatment is concerned, Bacopa Monnier has been suggested as a potential neuroprotectant as well as a cognitive enhancer against the AD model [33].

Medication	Benefits of use	Risks of use
Metformin	Low risk hypoglycaemia, well tolerated	Risk in renal impairment (dehydration), gastrointestinal side effects, comorbidities can limit use
Sulfonylureas	Quick glucose stabilisation, relatively well tolerated	Increased risk of hypoglycaemia, especially if comorbidities, risk of heart failure
Thiazolidinediones	Useful but limited glycaemic control	Long-term effects (cardiovascular/bladder/ fracture risk)
Meglitinides	Rapid insulin promoting action, useful in erratic eaters, possible lower risk hypoglycaemia	Limited availability, cost
DPP-4 inhibitors	Benefit especially in renal impairment, low risk hypoglycaemia	Moderate glycaemic improvement
GLP-1 agonists	Low risk hypolycaemia, good glycaemic improvement	Weight loss may not be ideal, satiety effects not ideal, gastrointestinal side effects, cost benefit, may not be effective at late stage
SGLT-2 inhibitors	Good glycaemic improvement but avoid	Risk of dehydration, UTIs/thrush and confusion, comorbidities limit use

CONCLUSION-

T2DM poses a significant threat to brain health and its detrimental effects on cognitive deterioration and neurodegeneration are well documented. Numerous epidemiological and experimental studies have established a strong correlation between diabetes, namely T2D, and AD. Although both disorders possess several overlapping features, mitochondrial abnormalities, oxidative stress, and insulin signalling impairment are relevant events [16]. Amylin and Aβ aggregates collectively form the amylin–Aβ plaques, promoting the progression of AD [25]. Therefore, it is well understood how important it is to prevent and treat diabetes through changes in lifestyle (physical activity, low-fat diet, etc.) as well as achieving good and stable glycaemic control, avoiding both hyperglycaemia and hypoglycaemia and the administration of antioxidant agents and antidiabetic drugs to prevent cognitive decline and then AD [17]. This fresh perspective takes us toward an entirely different approach, which involves targeting insulin signalling, and glucose metabolism as a novel therapeutic strategy for AD.

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