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EVALUATING THE ASSOCIATION BETWEEN TYPE 2 DIABETES AND ALZHEIMER'S DISEASE BY BIOMARKERS, PATHOLOGICAL TRAITS & MANAGEMENT

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ABSTRACT

Introduction: In recent years, extensive research has indicated that, in addition to the traditional process of neurodegenerative disease, neurodegeneration can also be caused by a variety of unconventional pathways. One of these is type 2 diabetes mellitus, a dysmetabolic condition that has been widely investigated. The majority of our knowledge of glucose metabolic dysfunction in neurodegeneration comes from investigations in Alzheimer's disease (AD) models. Type 3 diabetes is a term given to Alzheimer's disease since it is significantly associated with hyperglycemia. The pathophysiology of Alzheimer's disease is first discussed., from the aspects of typical protein aggregation and the newer T2DM-dependent pathways, which are validated by evidence from T2DM patients such as epidemiological, neuroimaging, and pathological evaluations. Second, we analyzed the several routes through which neurodegeneration is exacerbated in diabetic conditions, taking Alzheimer's disease as an instance. Finally, recent scientific advancements in metabolic disorders-driven neurodegeneration are highlighted, as well as some of the major developments in AD management.

Methods: We reviewed the literatures that are found in PubMed and google scholar searches.

Results: Aside from the established causes of Alzheimer's disease, T2DM sheds new light on the disease's pathophysiology in a variety of ways. It's a two-way interplay whose molecular and signaling mechanisms only have recently been explored. This is our attempt to reconcile them all together to derive a comprehensive molecular explanation for T2DM neurodegeneration.

Conclusion: The relation within T2DM and Alzheimer's disease has been observed and investigated thoroughly. It's encouraging to learn that these investigations have resulted in some advancements in the treatment of AD.

KEYWORDS: Alzheimer's disease, neurodegeneration, epidemiological, neuroimaging, type 3 diabetes

INTRODUCTION

Diabetes and Alzheimer's disease (AD) are diseases that afflict millions of people in industrialized countries and are increasing in prevalence in emerging countries. Furthermore, hyperglycemia has long been suspected to be a significant risk factor for the emergence of late-onset AD (1). Many scientists have a hard time understanding the molecular basis of AD pathophysiology due to the

increasing number of cases. Despite the various breakthroughs in the field of neuroscience, the disease is still poorly explained and is expected to worsen its symptoms over the next decades. Although the etiology of the illness is still poorly understood, it has been shown that T2DM is a risk factor for the condition (2). According to a study, being overweight and obese can lead to the development of metabolic disorders, which can result in the onset of AD (3). T2DM can increase the level of proinflammatory cytokines and stimulate the secretion of these chemicals in the body. This can lead to neuroinflammation of the brain (4). Insulin's primary purpose is to regulate body metabolism, but it also plays a role in encouraging synaptic and neural plasticity, both of which are substantially impacted in Alzheimer's disease (5). Chronic inflammation, irregular Amyloid-β metabolism, oxidative stress, hyperinsulinemia, and associated ischemic depression are all metabolic pathways that may link T2DM and AD (6, 7).

Due to low blood flow in the brain of T2DM patients occurs cerebral hypoperfusion, which can lead to cognitive dysfunction and higher insulin resistance level (8). The longer the disease has been present and the worse the blood glucose control in the blood, will be higher the risk of dementia (9). The irregular modes of AD rises are likely related to the way of living and conceivably controlled and may be reversed if correctly targeted. As a result, it's critical to focus on the study of the link between diabetic complications and neuronal changes that result from them, to figure out the molecular mechanisms involved (10). The purposes of this review are to discuss diabetes-associated mechanisms of cognitive impairment and neurodegeneration, with a significance on the pathophysiology and the shreds of evidence offered by clinical trials and antidiabetic treatments in Alzheimer's disease.

1. Alzheimer’s Disease & its pathophysiology

Alzheimer’s disease was observed at the beginning of the 20th century by the German psychiatrist and neuropathologist, Prof. Alois Alzheimer in 1906, Alzheimer’s disease is the most prevailing form of dementia in the ageing populace (11). According to the World Alzheimer Report 2015, there are around 46.8 million of the population worldwide diagnosed with dementia. In AD, irreparable neurodegeneration causes serious damage to the brain tissue and a diminution in the size of the brain, characterized by tangles of hyperphosphorylated tau proteins and β-amyloid plaques, besides cholinergic dysfunction (12-14). There is an erratic form of the disease and about eight years is the average survival (15). The typical AD pathology is serious and progressive impairment of cognitive function (16), which includes dementia and language problems as well as non-cognitive dysfunction (executive) often followed by behavioral disorders such as anxiety, aggressiveness, and dejection (15). Summary of the pathophysiology of AD is shown in (Fig. 1).

1.1. Cholinergic hypothesis

ApoE protein genotype is the most important factor in acetylcholinesterase inhibitors (AChEIs) medications as the treatment of AD. Polymorphism in the Apolipoprotein E (apoE) genotype is an important factor determinant of AD, Apolipoprotein E4 (apoE4) allele of the apoE genotype is associated with the increasing risk factors. Strong shreds of evidence from basic and clinical research indicated that apoE4 increases the risk of AD by driving earlier and has a role in the interaction with Aβ which leads to phosphorylation of tau protein, and mitochondrial dysfunction in the brain (17). This major effect of APOE inspects the concern of the “Cholinergic Hypothesis” of AD (18). It is also

reported that an intense loss of cholinergic neurons in the basal forebrain, particularly the nucleus basalis of Meynert (NBM) of patients with AD (19).

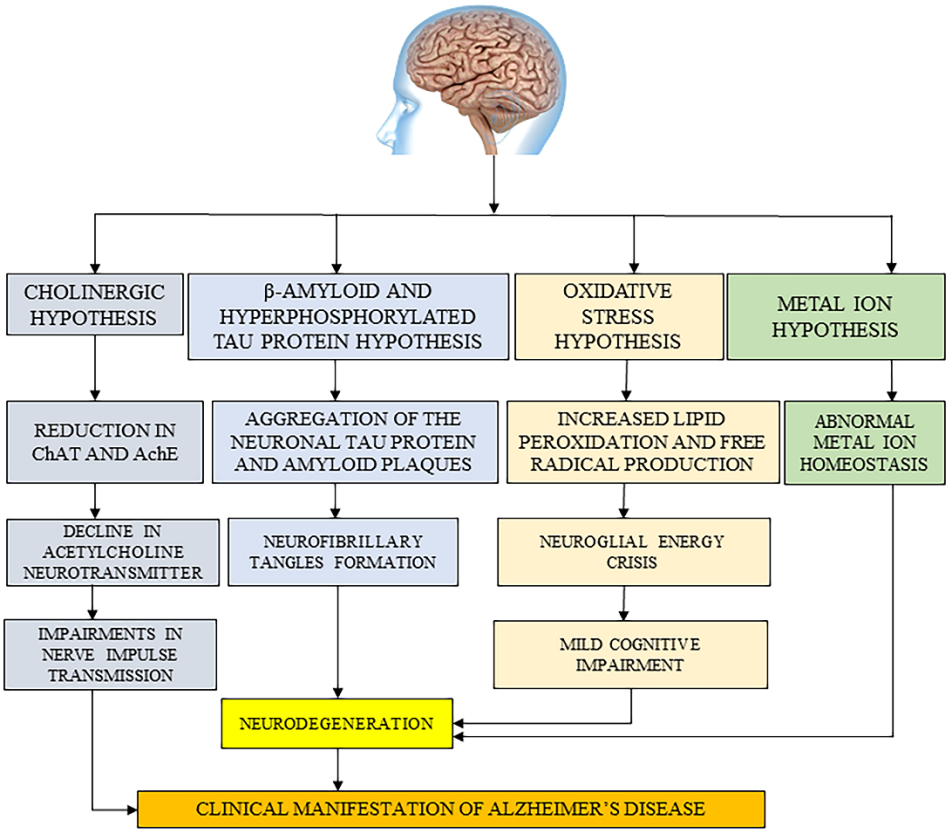

Fig. 1. Hypothesis for the pathophysiology of Alzheimer's disease.

The cholinergic hypothesis of AD is based upon the presynaptic neuronal deficits found in the brains of patients with AD and studies of the role of acetylcholine in human and animal behaviour (15). Among healthy geriatric adults, lower receptor binding may be linked with slower processing speed and could be a sign of neurodegenerative illness. Acetylcholine receptor binding in vivo possibly links to other key changes in the brain associated with aging and senile dementia and may provide a promising molecular-targeted medication (20). In AD, there is an extensive loss of cholinergic neurons located in the basal forebrain and a related decline in acetylcholine neurotransmission, some drugs are used to maintain the acetylcholine transmitter levels, such as donepezil and cholinesterase inhibitors (ChEIs), are serving as the symptomatic medication for AD (21). The pathophysiology of AD is credited to several factors such as amyloid/tau toxicity, and oxidative stress/ mitochondrial dysfunctions.

1.2. β-Amyloid and hyperphosphorylated tau protein hypothesis

One of the major pathological characteristics of AD is the formation of Neuritic plaques (also known as senile plaques), which are caused by β-amyloid (Aβ) deposition. Normally, Aβ is soluble small peptides of 36-43 amino acids, which are produced through the proteolytic processing of a transmembrane protein, known as amyloid precursor protein (APP) by the action of β-secretase and γ-secretase (22). The irregularity between amyloid-beta peptide (Aβ) production and clearance gives

rise to several types of toxic Aβ oligomers, namely protofibrils and fibrils depending on the extent of protein oligomerization. The sequence, concentration, and conditions of stability of Aβ protein are important factors, but the reason behind the formation of Aβ is still obscure (23).

Alois Alzheimer first described the tau neurofibrillary tangles in neurodegenerative disease, but the pathological diagnosis is still required for the main characteristics of neurofibrillary tangles that he described (24). The presence of tau neurofibrillary tangles and senile plaques defines AD, but with the best neuroimaging and neuropathological studies, it may reveal the standard to attribute clinical symptoms and identify comorbidities to their root cause.

1.3. Oxidative stress hypothesis

In the condition of AD, the brain is under prolonged oxidative stress, associated with β-amyloid peptide oligomers. Reactive nitrogen species (RNS) and reactive oxygen species (ROS) are produced throughout the body and play a dual role as both have advantageous functions in cell signaling pathways and disadvantageous processes can give rise to structural cellular injuries (including DNA, lipid, cell membrane, and protein). The neurons are the structural and functional unit of the brain. It can interact with ROS, leading to molecular apoptosis and lipid peroxidation reaction can trigger senile dementia (25). Aggregation of excessively high levels of ROS leads to oxidative stress. Accumulation of ROS can occur either by excessive production or an inadequate elimination of ROS (26). The role of mitochondria is also important as a source and target of ROS/RNS during the switch between cell death and survival. The brain is particularly sensitive to oxidative damage due to its high rate of oxygen consumption, it uses 20% more oxygen compared to other mitochondrial respiratory tissues (27).

1.4. Metal ion hypothesis

Biometal dyshomeostasis is involved in the progression and pathogenesis of cancer, and neurodegenerative diseases including Alzheimer's disease, Huntington’s disease, Parkinson's disease, and other fatal diseases. The effects of neurotoxicity by metal imbalance are mainly linked with the reduction of enzymatic activities, and oxidative stress in the brain, and give rise to protein aggregation which leads to cellular death and neuronal degeneration (28).

Ionophores and metal-based chelating compounds are acclaimed modulators of transition metal ion homeostasis and are making progress in clinical trials for the treatment of neurodegenerative diseases. Furthermore, metal-based chelating agents are not the only effective drugs capable of targeting transition metal ion homeostasis (29). The metals like Aluminum (Al), Zinc (Zn), Copper (Cu), Iron (Fe), and Manganese (Mn) are the crucial trace metals involved to trigger metal neurotoxicity and neuronal degeneration. However, some shreds of evidence indicate that Mn can be a neuroprotective agent and prevent neurodegeneration (30).

Currently, scientists are working on different factors of the disease to illuminate complete molecular mechanisms, design advanced diagnostic tools, identification of drug targets, and plan effective methods for the management of AD. Recently, some clinical studies have demonstrated a detectable correlation linking AD and metabolic diseases such as type 2 diabetes mellitus (10). Hence, AD is now gaining the attention of neurobiologists as a feasible complication of defective glucose metabolism (31).

2. The invariant hallmark of cerebral glucose metabolism in AD

2.1. The aspect of glucose metabolism in the brain

The brain has the highest rate of energy metabolism of any organ in the human body. The adult brain contributes alone to 2% of body weight on average. In the resting awake state, it receives around 15% of cardiac output and consumes around 20% of total body oxygen and 25% of total body glucose (32). The fact that the human brain's respiratory ratio is approximately 1 in its physiological condition shows that carbohydrates are the primary substrate for the brain's oxidative metabolism (33). Under physiological conditions, glucose is now universally accepted as a necessary and primary energy substrate for the adult brain (34). Although various alternative substrates such as ketone bodies, glycogen, and amino acids may well be utilized in some conditions, such as during the baby developing phase and long fasting status in adults, glucose remains the brain's primary energy source in most cases. Furthermore, the small pool size and compartmentation of these alternate substrates limit their flexibility to satisfy cerebral energy demands (35). It has been shown that increasing plasma ketones through dietary supplementation while maintaining a modest and safe level of ketonemia improves the proportionate contribution of ketones to the brain's energy source (36). As a result, ketones may be a viable fuel source for improving impaired cerebral energy metabolism in Alzheimer's disease.

Glucose metabolism in the brain is divided into two processes: glucose transport and intracellular oxidative catabolism. The activity of astrocytes involved in the composition of the blood-brain barrier (BBB) and numerous glucose transporters scattered throughout the brain are crucial for normal physiological glucose transportation (37, 38). Astrocytes are essential to maintaining brain energy homeostasis and regulating glucose transit. It also contains high concentrations of glycogen granules, with more granules accumulating in the more dense synapses (39). In both normal glucose supply and hypoglycemic situations, astrocytes play a key function. Glucose transporters (GLUTs) of various sorts are also involved in the transport of glucose from the bloodstream into neurons (38). GLUT-1 and -3 are thought to be important in the control of brain glucose transporter as well as the etiology of Alzheimer's disease (40).

Complicated pathways comprising glycolysis and pentose phosphate pathway (PPP) in cytoplasms, Krebs cycle, and oxidative phosphorylation in mitochondria are included in intracellular oxidative catabolism (41). PPP is primarily involved in the prevention of oxidative stress and the synthesis of genetic substrates for the brain (42). In fact, both glucose transportation problems caused by insulin resistance and intracellular metabolic changes caused by mitochondrial dysfunction have already been widely reported in AD patients.

2.2. Glucose metabolic disruption raises the risk of cognitive decline

The current understanding of the pathophysiological regulation of glucose homeostasis is influencing how we think about chronic metabolic abnormalities of the brain, such as Alzheimer's disease. The brain is sensitive to poor energy metabolism due to its high energy use, which is primarily derived from glucose metabolism. In addition, both hyperglycemia and hypoglycemia homeostasis abnormalities have a significant impact on human brain health, particularly cognitive abilities (43). Significant evidence has been revealed that insufficient cerebral glucose supply causes performance losses in aging individuals during training on a variety of cognitive activities. Raising glucose supply in specific brain locations can improve individuals' cognitive function, particularly in elderly animals. The specific locations of the brain i.e, striatum, hippocampus, amygdala, and medial septum can all benefit from microinjections of glucose (44, 45). Some findings suggest that an aging adult is more vulnerable to glucose depletion, particularly during long-term cognitive performance tasks or exercise. Currently, a few studies are being conducted to assess the brain's vulnerability to varying

degrees of low glucose in elderly, T2DM, and AD patients, to identify if older brain tissue will suffer permanent damage at shorter intervals than young cerebral tissue (46). Understanding the pathophysiology and glucose metabolic mechanisms in the CNS may assist in the development of long-term preventive interventions, which might be implemented to develop metabolic balancing in CNS-related illnesses such as diabetes and Alzheimer's disease (47).

3. Diabetes: A new link to AD pathology

Diabetes mellitus is a lifestyle disease prevailing among humankind from all over the world. It is a condition in which a high level of glucose is present in the blood, because of dysregulation of glucose metabolism in the body. According to a recent report, the number of patients with diabetes in the world has increased from 108 million in 1980 to 463 million in 2019, rising to 578 million by 2030 and 700 million by 2045 (48). Type 2 diabetes is the most frequent form of diabetes. Type 2 diabetes mellitus (T2DM) may be a result of insufficient insulin production by the pancreatic β cells, or because of insulin resistance within the human body. Insulin resistance is the inability of a cell to react adequately to insulin signaling, leading to decreased glucose uptake from the cell (49).

Resultantly, insulin-resistant cells perish resulting in many serious complications and inefficient functioning of numerous organs. Cardiovascular disease, diabetic stroke, hypertension, kidney failure, liver damage, and neurodegenerative disorders are some of them (50). Some disease-specific, and common features among T2DM and AD are illustrated in (Fig. 2). Substantially, there are various studies on the association between Alzheimer's disease and Type 2 diabetes mellitus (51). Diabetes triggers neurodegeneration by various mechanisms and promotes AD pathology (52). In some severe patients of T2DM, oxidative stress triggered by amplified free radical formation causes glucose toxicity in the brain and free radical scavenging mechanisms continued to decline (53). High glucose levels in the neurogenic niche can lead to protein carbonylation, oxidative degradation of lipids, and irreparable DNA damage in neurons in the brain (54). Excessive free radicals in the brain are associated with inflammation. Inflammatory pathway activation may result in the breakdown of the blood-brain barrier (BBB) integrity and induce brain edema (55). Excessive glucose in the brain leads to the accumulation of lactic acid, which causes intracellular acidosis and mitochondrial dysfunction (56).

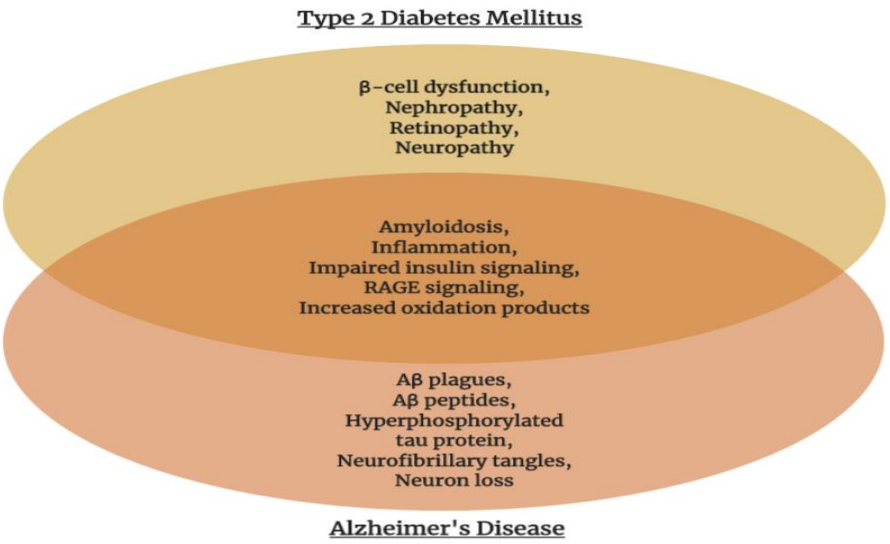

Fig. 2. Common and specific features among Type 2 Diabetes Mellitus and Alzheimer's Disease.

There are several studies using AD animal models that have shown that AD pathology can be developed by diet-induced insulin resistance/chemically induced insulin signaling impairment (57, 58). This insinuates that diabetic patients with insulin resistance may develop problems linked to memory and cognition. Some evidence is also there to hold up the idea that diabetic patients are more prone to develop AD (59). Researchers have hypothesized that diabetes ought to be a novel mechanism of neuronal degeneration whereby the classical pathophysiology of AD can be elucidated from the aspect of impaired insulin/insulin-like growth factor (IGF) signaling and irregular glucose metabolism in the brain. In a diabetic brain, glucose cannot be transferred into the cells because of the lack of expression of glucose transport proteins (mainly GLUT4) on the neuronal membrane (60). This can lead to mitochondrial oxidative stress, and give rise to neurodegeneration by activation of apoptotic pathway (61). Also, Tau hyperphosphorylation is implied by impaired insulin/IGF signaling in the brain. Phosphoinositide 3-kinases(PI3K)/Protein kinase B(AKT)/Mitogen-activated protein kinase (MAPK) are the major protein kinase mediators that work a crucial role in insulin signaling pathways (62). Dysregulation of any of these kinases can lead to tau hyperphosphorylation and accumulation in the diabetic brain which further develops AD (63).

A wealth of evidence draws a connection between T2DM and neurodegenerative diseases such as that observed in AD. However, the explicit mechanism remains unveiled (64). Elucidation of the molecular mechanism that associates these two diseases will be significantly beneficial for designing novel drug targets for AD and also for further studies in the future.

4. Possible pathological traits linking Alzheimer's Disease and Type 2 Diabetes Mellitus

4.1. Role of Amylin in neuronal degeneration

Amylin or islet amyloid polypeptide (IAPP) is a hormone that is secreted by the pancreatic islet beta cells along with insulin in the postprandial state (65). IAPP regulates the blood sugar level through various mechanisms such as inducing satiation, delaying gastric emptying, and inhibition of glucagon secretion (66). It accumulates within the brain of AD patients and the pancreas of diabetic patients respectively, and share many pathological, physiological, and other biological properties (67).

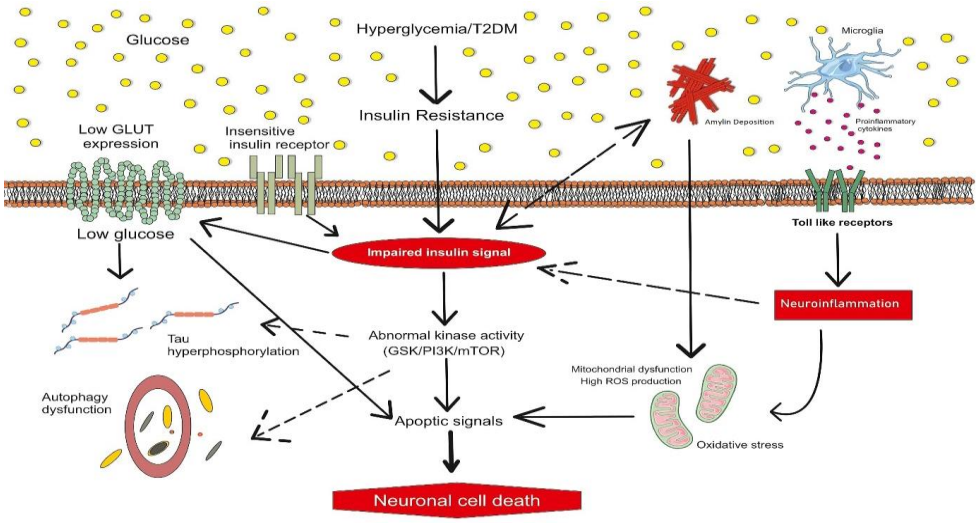

Fig. 3. The several pathways involved in glucose-mediated neuronal cell death are depicted in this diagram. T2DM patients have impaired insulin signaling, which leads to a variety of AD symptoms and, eventually, neurodegeneration.

More importantly, the accumulation of amylin has been observed in the islets of Langerhans in the region of the pancreas of diabetic patients (68). It gives rise to apoptosis of β cells and thus reduces insulin secretion. It also promotes insulin resistance and cellular oxidative stress responses are also been observed. As Amylin is co-secreted with insulin, its blood levels are higher in patients with Type 2 diabetes and insulin resistance. Interestingly, IAPP can cross the BBB quite readily and thereby get deposited in the brain parenchyma and blood vessels of individuals with Alzheimer's disease (69).

4.2. Impaired insulin (Diabetic) signaling in tau hyperphosphorylation and β-amyloid plaque formation

Tau is a natively soluble, unfolded protein that was first isolated from the porcine brain (70) and was identified as part of paired helical filaments (PHF). Impaired insulin signaling in the brain of T2D patients has been shown to cause hyperphosphorylation of the Tau proteins with the help of an enzyme called Glycogen synthase kinase-3 (GSK-3). These hyperphosphorylated Tau proteins eventually lead to the formation of neurofibrillary tangles that in turn cause neurodegeneration in AD (10).

Insulin is involved in the regulation of APP metabolism in neurons. Therefore, altered insulin signaling influences the metabolism and processing of APP which causes Aβ to accumulate that eventually leads to neurodegeneration (71).

4.3. Cognitive impairment in T2DM

The CNS is one of the major targets for insulin to act because of the presence of insulin receptors in different parts of the brain as in the hippocampus. Several transgenic and genetic T2DM models have shown a reduction in long-term potentiation (LTP), synaptic damage, decreased neuronal growth, impaired BBB integrity, and neuroinflammation which are directly or indirectly associated with cognitive impairment and memory deficiency (72). Insulin acts as an important mediator in the expression and recruitment of receptors such as AMPA, GABA, and NMDA. It also regulates the release of neurotransmitters such as Acetylcholine and norepinephrine which directly help in generating the LTP that the hippocampus requires for the formation of long-term memory. Insulin has an established neuroprotective role and is capable of activating PI3-K/Akt and S6K/mTOR kinase pathways. These pathways mediate functions such as neuronal growth, synaptic plasticity, and regulation of glucose metabolism (72, 73).

4.4. Neuroinflammation and defective insulin signaling in T2DM and AD

In T2DM, elevated mitochondrial activity within the cell leads to enhanced ROS production which causes the activation of neuroinflammatory pathways (74). The induction of these pathways results in inflammation in the CNS thus contributing to neurodegeneration and promoting the pathogenesis of AD (75). Increased levels of neuroinflammatory mediators such as TNF-α, interleukin-6 (IL-6), C-reactive protein, and a-1-antichymotrypsin (76-78) leads to insulin resistance in T2DM. Likewise, these mediators are present in elevated levels in AD and are found in amyloid plaques and the associated glial cells in patients suffering from AD (79). Increased production of vascular pro-inflammatory cytokines also affects the brain insulin signaling (80). These cytokines can cross the BBB because of the damaged cerebral vascular tissue in an AD-affected brain and can cause phosphorylation of IRS-1. The receptor for advanced glycation end-products (RAGE) is also one of

the mediators of vascular inflammation and its levels are increased in both AD and T2DM (81). A class of anti-diabetic drugs called the Peroxisome proliferator-activated receptor-g (PPARg) agonists reduce insulin resistance and possess anti-inflammatory effects (82). Hence, these drugs should be able to decrease the levels of inflammatory mediators such as IL-6 (83) and thereby help in the treatment of AD.

4.5. Oxidative stress process

The presence of abnormally high levels of reactive oxygen species (ROS) or reactive nitrogen species (RNS) or an imbalance between their production and levels of antioxidant protection can lead to oxidative stress, which plays a major role in the pathogenesis of AD and T2DM and appears to be a possible link (84). High lipid and fatty acids content, high oxygen requirement, and weakened antioxidant defense mechanisms in AD make the brain very prone to oxidative stress. Oxidized lipids, proteins, and DNA act as markers of oxidative stress and are present in elevated levels in AD affected brain which indicates that excessive generation of ROS is one of the key features of AD (85). Oxidation of enzymes such as alpha-enolase (ENO1), malate dehydrogenase (MDH), fructose bisphosphate enolase (MDH), fructose bisphosphate aldolase (FBA/AC), ATP synthase and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in an AD brain tissue as studied with the help of Redox proteomics has been demonstrated to correlate with decreased glucose metabolism in AD affected brain which can further lead to the loss of synaptic function, impaired neuronal glucose homeostasis and neuronal dysfunction (86).

4.6. Involvement of cell adhesion molecules in AD glucose transport

Prion protein (PrPc) is a neuronal membrane protein that plays a major role in cell-to-cell adhesion and intercellular communication. The interaction of these proteins with beta-amyloid causes neurotoxicity which has been shown to decrease with the use of Prion antagonists in AD models (87). PrPc was also observed to have a modulatory effect on intracellular iron levels in the neuronal cells and other cells as well. If the iron homeostasis is gets disrupted then it may cause beta-cell failure and insulin resistance (88). Intracellular iron overload promotes hypoxia that leads to the down-regulation of GLUT1 and GLUT2 by hypoxia-inducible factors (HIF), ROS generation which can cause oxidative stress, and glucose-mediated degeneration of neurons. Prion has also been reported to have an indirect effect on glucose metabolism (89).

4.7. Autophagic dysfunction in diabetes triggers AD

Autophagy is a self-degradative process that removes misfolded or aggregated proteins, damaged cell organelles as well as intracellular pathogens (72). The down-regulation of autophagy in the neuronal cells may cause Aβ accumulation and formation of intracellular tau neurofibrillary tangles which are two main pathologic changes in the brain in AD (90). Autophagy also has a major role in the maintenance of structural and functional integrity of the pancreatic beta cells and improvement of insulin resistance (72). Insulin resistance and impaired insulin signaling lead to the disruption of the PI3K/mTOR pathway which plays a significant role in the regulation of autophagy (91). Hence, alteration in autophagy is also associated with T2DM that further indicating that autophagic dysfunction could play an important role in the disruption of homeostasis in the neuronal cells thereby causing other neurodegenerative diseases (92).

5. Preliminary biomarkers for diabetes-related cognitive deterioration

The occurrence of cognitive deterioration is significantly related to the progression of diabetes. However, the cognitive damage associated with diabetes is frequently underestimated and untreated, resulting in thousands of diabetics experiencing cognitive impairment. Thus, managing diabetes-related brain dysfunction and identifying useful biomarkers for memory decline at an initial stage are essential areas that need improvement immediately (93). Multiple molecules or comorbidities have been linked to cognitive deterioration in diabetic individuals, according to studies. Based on the foregoing, we set out to find effective biomarkers for early cognitive deterioration in diabetic patients.

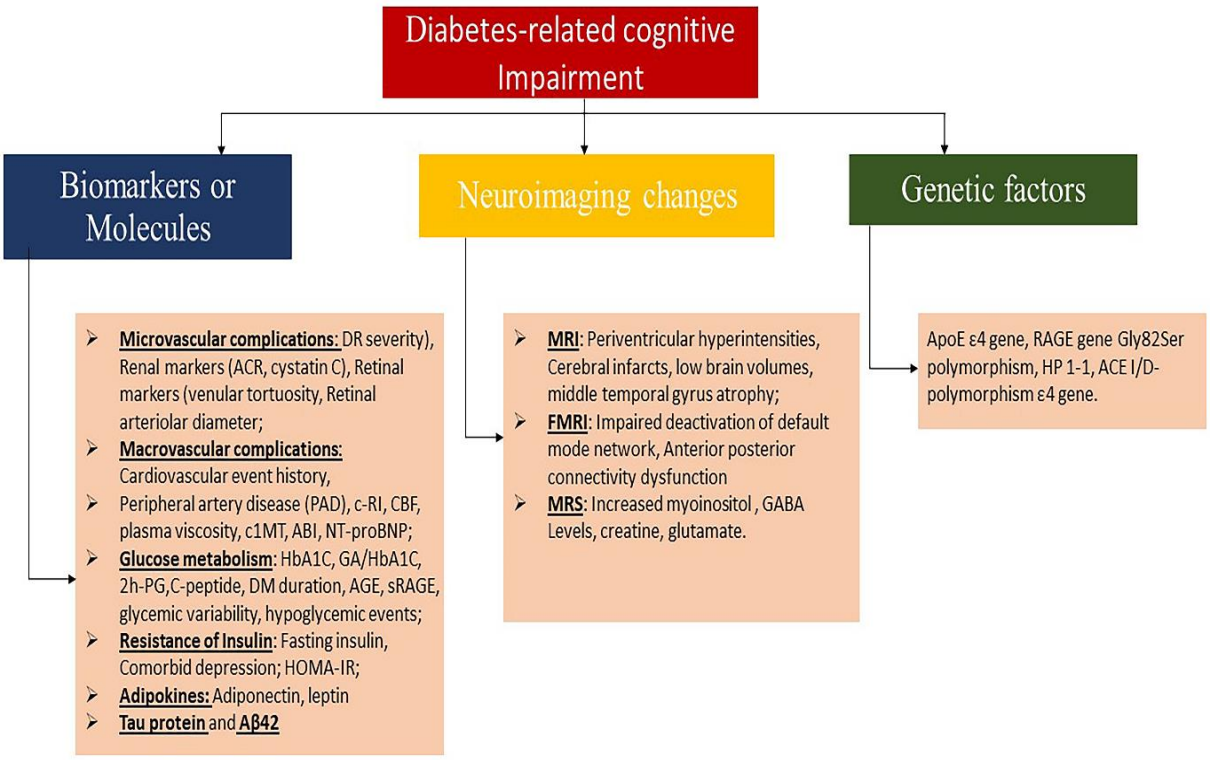

Fig. 4. The diagram depicts relevant biomarkers from the perspective of diabetes-related cognitive impairment.

This could be beneficial in the treatment and management of cognitive deficits in diabetic individuals. After thorough analysis, biomarkers or risk factors for cognitive deterioration in diabetic individuals might be divided into three categories: serum components or associated comorbidities, metabolic alterations identified using neuroimaging methods, and genetic variants. (Illustrated in Fig. 4.)

"The use of biomarkers in AD diagnosis and treatment establishes optimism for a more effective evaluation of the stage and disease progression, the implementation of effective therapy, which can also be a measure of therapeutic efficacy," according to reports issued by the US Food & Drug Administration and the European Medicines Agency (94, 95). The search for and study of body fluid AD biomarkers can help researchers better understand the disease's origin and etiopathogenesis, as well as enhance prognosis and diagnosis preciseness.

More specifically, vascular illnesses, inflammation, concomitant depression, glucose metabolism, and as well as adipokines, have all exhibited substantial changes in the early stages of diabetes-related cognitive deterioration (96, 97). Advanced brain imaging techniques, such as functional magnetic resonance imaging (fMRI), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS) provides an appropriate interface for detecting minor modifications in cerebral metabolism and brain morphology (43). All of these forewarning signs that appear during the process of cognitive deterioration in diabetes individuals should be taken seriously (93). These molecules or alterations also give insights into the etiology of diabetes-related brain damage and the possibility of therapeutic monitoring in further studies.

6. T2DM-Related Biomarkers in Alzheimer's Disease

Early biomarkers that have the best chance of predicting and/or detecting neurocognitive consequences like AD in diabetes are tau protein, β-amyloid, glycogen synthase kinase 3β(GSK-3β), C-reactive protein (CRP), paraoxonase 1 (PON-1), phosphoinositide 3-kinases (PI3K), amylin, dopamine, gamma-glutamyl transferase (GGT), and homocysteine. Table 1 summarises the biomarkers and pathophysiological pathways that are being studied. Here, We have provided possible T2DM-related biomarkers for their early diagnosis of AD.

TABLE 1. Associations between biomarkers discussed in this review and diabetes-related AD complications.

Biomarkers	Role/Effect in Human physiology	Link with T2DM patients	Link with AD Complications	References
Amylin (hIAPP)	- Decrease of secretion of gastric acid, - control the balance of insulin and glucagon to maintain blood glucose (glucose homeostasis).	Aggregation of amylin → cytotoxicity of amylin oligomers to pancreatic islet β-cells	Aggregation of amylin → senile plaque formation by amylin, β-amyloid	(66, 98, 99)
Paraoxonase-1 (PON-1)	- Antioxidant, antiatherogenic, and anti-inflammatory properties - inhibits lipid oxidation, breakdown of lipid peroxides	Rises glucose level → Hyperglycaemia → glycosylation and oxidative stress	oxidative stress → abnormality in acetylcholine metabolism and enzymatic detoxification of organophosphates	(100-102)
Homocysteine (HCY)	- role in brain damage, cognitive and memory decline, - activation of oxidative stress mechanisms, - damage the lining of the arteries	Rises glucose level → Hyperglycaemia → oxidative stress → production of mitochondrial reactive oxygen species (ROS)	insufficiency of cofactors linked to homocysteine metabolism → neurotoxic effect by HCY → production of ROS → plaque accumulation by β-amyloid in the brain → neuronal apoptosis	(103-107)
Phosphoinositide 3-kinase (PI3K)	- antiatherogenic and vasodilatory effects, - e-NOS activation and NO production - glucose homeostasis	impaired insulin/PI3K/Akt signaling → molecular alteration of mTOR signaling	Molecular alteration of mTOR signaling → hyperphosphorylation of tau protein, accumulation of amyloid β-peptide → neurotoxicity, and dementia	(62, 108, 109)
Gamma-glutamyl Transferase (GGT)	- cellular antioxidant	increases glucose level → Hyperglycaemia → oxidative stress	oxidative stress → neuropathological alterations and cognitive decline, progression of Aβ aggregation	(110-113)
C-reactive protein (CRP)	- Acute-phase protein, - produced in response to inflammation and interleukin IL-6	Increases glucose concentration → inflammation → microvascular changes	microvascular changes → chronic cerebral hypoperfusion → neuronal degeneration	(114, 115)
Amyloid-β peptide, GSK-3β, tau protein	- intracellular transport, morphogenesis, and cell division	Impairment of insulin signaling → enhances GSK-3β activity →Increased Advanced glycation end products (AGEs) formation	enhances AGE formation → tau hyperphosphorylation, plaque accumulation by β-amyloid on nerve cells → synaptic loss	(10, 116, 117)

7. Evidence from Neuroimaging studies

Various neuroimaging techniques have been applied to investigate the anatomical and functional alterations in the brain of patients affected by AD and T2DM. This approach also defines the structural correlates of neurocognitive dysfunction in the diabetic brain. The shreds of evidence from the neuroimaging studies acknowledge a significant link between the affected regions of the brain in both patient groups. However, Neuroimaging studies of AD are not that clear and may not be precise to DM, as there are conflicts among the studies, because some studies have established that cognitive impairment is not dependent on microvascular complications burden, (118) whereas others have mentioned small or moderate links with the cognitive decline (119).

7.1. Neuroimaging studies of morphological changes

Studies have shown that T2DM is linked with cerebral atrophy. Structural MRI studies have shown that T2DM is also associated with structural alterations that are also seen in AD patients. In a cohort study of an older population, Schmitz et al., demonstrated that based upon magnetic resonance imaging (MRI) on people with cognitive impairment and AD proclaimed that the earliest indications of AD pathology develop in the cholinergic neurons of the nucleus basalis of Meynert (NBM) and leads to Basal forebrain degeneration (120). Although cerebral atrophy and/or cerebrovascular lesions are believed to relate to the link between cognitive dysfunction and T2DM, A cross-sectional study of individuals conducted by Moran et al., in 2013 reported that T2DM can be associated with cognition disabilities, cerebral atrophy that can be linked to cognitive impairment at earlier stages of the disease (121). Longitudinal case studies have reported that the development rate of cerebral atrophy in T2DM is faster than in normal cognitive aging (122). A cohort study conducted by Moran et al., found that T2DM associated with the risk of corticobasal degeneration (CBD), can lead to cerebral infarction, decrease the volumes of gray matter, white matter, and volume loss in hippocampal layers faster than the non-diabetic individuals. Their finding also proposed that in people with T2DM, the loss of gray matter was most prominent in the medial frontal lobes and medial temporal lobes and reduced thickness in the AD-vulnerable regions (122). However, some recent reports have suggested that brain atrophy is detected in particular regions that directly reflect the total brain injuries (43). Roberts et al., conducted a study on 1,437 elderly individuals without dementia and examined the connection of T2DM with imaging cognitive abilities and biomarkers. They found that the age of 40 to 59 years of T2DM patients was associated with the reduction of the whole brain volumes and hippocampal region which strongly reflects the mild cognitive impairment (MCI) at the later stage (123).

Functional MRI (fMRI) is an effective way to investigate changes in brain function in patients with cognitive impairment. Functional changes in the brain may occur before the development of structural changes, according to research (124). As a result, fMRI may be a useful method for detecting early signs of diabetes-related cognitive loss. The default mode network (DMN) is a part of the brain that regulates cognitive processes. Marder et al. discovered that patients with diabetes had impaired deactivation of DMN areas during recognition tasks, which was associated with regional blood glucose levels (125).

As a neuroimaging approach, magnetic resonance spectroscopy (MRS) can identify changes in neurochemicals associated with metabolic and energetics in vivo (126). Wang et al. investigated 188 Patients with type 2 diabetes and found that brain metabolites were affected in the hippocampus instead of the frontal lobe. Impaired cognitive test scores were associated with an increase in myoinositol and creatine levels in the hippocampus (127). Lyoo et al. reported from a clinical study of 123 T1DM patients when compared to healthy controls, had substantially higher glutamate, glutamate, and GABA levels in the prefrontal area. These metabolites were discovered to have an inverse relationship with cognitive ability (128).

7.2. Neuroimaging studies of cerebral glucose metabolism and cerebral amyloid load

According to Thientunyakit et al., Imaging studies of the level of glucose metabolism in the brain [PET/MRI fusion images of (18F) FDG] and cerebral amyloid deposition [PET/MRI fusion images of (18F) AV45] have unveiled that hippocampal or neocortical amyloid accumulation and impaired neuronal glucose metabolism are earliest pathological changes of the AD (129). Although, some authors have reported that in T2DM there is a correlation between insulin resistance and cerebral amyloid deposition (130). Neuroimaging studies by Roberts et al., suggested that neuronal damage in T2DM is not dependent on amyloid deposition in the brain. However, the neuronal injury may indicate a better determinant of developing cognitive dysfunction in the brain of T2DM patients (123). A longitudinal study of Ageing by Thambisetty et al., proposed that no link was perceived between neocortical amyloid accumulation and glucose regulation or peripheral insulin resistance, their finding also suggested that irregular glucose metabolism and peripheral insulin resistance are not associated with cerebral amyloid β accumulation (131).

The latest ADNI cohort study by Li et al., reported that T2DM may lead to cognitive decline in patients with MCI rather than patients with senile dementia or healthy older volunteers, by affecting the total brain volume and cerebral glucose metabolism. Furthermore, the effects of T2DM were only detected when considering the total brain volume, particularly in patients with MCI, and no change was observed in any sub-region of the brain (132).

8. Diabetes-related genetic markers linked with cognitive decline

Researchers are very interested in studies related to genetic variables in cognitive decline. Hemoglobin binding protein, which is generated by the haptoglobin (Hp) gene, helps protect cells from oxidative stress. When compared to controls, studies have demonstrated that the Hp gene is significantly downregulated in Patients with MCI (133). Hp 1-1 carriers had a greater link between HbA1c and poor cognitive function ($P < 0.01$), according to Pereira et al. Hp 1-1 carriers have a higher risk of cognitive deterioration, according to these findings (134). The RAGE gene is one of the most important genes in diabetic complications, and the Gly82Ser polymorphism of the RAGE gene (135) has been linked to Alzheimer's disease (136). In MCI patients, Wang et al. discovered RAGE Gly82Ser carriers had lower RAGE levels than non-carriers ($P = 0.003$) (137). However, no statistically significant link was found between cognitive test results and the 82Gly/Ser genotype ($P > 0.05$). One of the major genes in the RAS system is the angiotensin-converting enzyme (ACE) (138). As per evidence, Ang II has been linked to Alzheimer's disease in older people. In T2DM patients ($n = 210$), Tian et al. investigated various I/D single-nucleotide polymorphisms in the ACE gene. Patients with MCI had greater levels of ACE and ACE activity. In these patients, however, there was

no change in the genotype of the ACE I/D allele polymorphism (139). The APOE gene is linked to lipid metabolism in the brain parenchyma, which is linked to cognitive performance (117). Biomarkers for the identification of MCI in diabetic individuals (n = 694) were investigated by Xu et al (140). In older patients, the ApoE ε4 allele, a higher olfactory score, and a higher rGSK-3β were all identified as possible biomarkers for MCI in diabetic individuals in their study. When compared to diabetic individuals without MCI, diabetic individuals with MCI had a higher vulnerability to the ApoE ε4 gene. On the other hand, Jacobson et al., reported different outcomes (141). They found no link between the ACE gene, ApoE 4 gene and increased risk of cognitive impairment in T1DM patients. Although the existing data are limited, consistent findings have been found in many research regarding genetic variables impacting the prevalence of cognitive impairment in diabetic patients. Future research should confirm the aforementioned study results in a wider population, and accurate observations of each factors or biomarkers are strongly advised.

9. The link between T2DM and AD – A study on Epidemiological Evidence

Epidemiological studies demonstrate that T2DM is associated with increased risks for cognitive dysfunction and dementia by at least 2-fold (142). In a cohort study, Leibson et al., demonstrated that adult-onset diabetes mellitus (AODM) is associated strongly with the risk of dementia and AD after adjustment of age and sex. It was further observed that the possibility of dementia was increased significantly for both men and women with AODM if compared with the non-diabetic population (143). In another study cohort, recruited from Taiwan from 2000 to 2008 Wang et al., reported that older female diabetic patients were inclined to have the highest threat of developing cognitive dysfunction and dementia. Their finding also proposed that cerebrovascular dysfunction and neuroinflammation were all significantly associated with an increased hazard of AD (144). According to a Longitudinal study by Solfrizzi et al., reported that Vascular risk factors like Hypertension can increase a 44% higher risk of mild cognitive impairment (MCI) related to diabetes and the rate of progression to dementia (145).

A recent study published by Li et al., reported that in China geriatric population with T2DM and mild cognitive impairment (MCI) has a huge impact on the progression to AD, while no difference in age-matched controls is observed (146). A longitudinal study in Japanese-Americans found no links between diabetes in middle age and dementia; (147) Howbeit, there are some shreds of evidence that reported that hyperglycemic conditions in middle age raised the risk of AD in the elderly when the large sample size is considered for prospective studies (148, 149). Several other studies have reported that T2DM with the APOE-ε4 allele was associated with a raised risk of late-onset AD (LOAD) in individuals.(150) Whereas, population-based cohort studies carried out by Marseglia et al., reported that a link between T2DM and the risk of dementia can raise only with ApoE4 non-carriers (151). A recent hypothesis by Yaffe et al., demonstrated that the risk of dementia and mild cognitive impairment increased with each 1% elevation in glycosylated hemoglobin in postmenopausal osteoporotic women, even women without T2DM (152). From a Cohort study of 12,047 men aged 65-84 years from Australia, Power et al., reported that high adiposity is not connected with incident dementia over 10 years of follow-up (153). A recent study published by Monte et al., reported that Type 3 Diabetes Mellitus (T3DM) which is also known as Brain Diabetes precisely indicates the link with AD, and has molecular and biochemical evidence that overlap with both T1DM and T2DM (154).

10. Advances In Research and AD Management Strategies by Antidiabetic Drugs

Because of the same pathways described above, both AD and T2DM are referred to be amyloidoses. There are currently only a few FDA-approved medications for the treatment of Alzheimer's disease, and they are only partially effective in preventing disease progression. Table 2 contains a list of anti-diabetic drugs that have been studied for their potential advantages in Alzheimer's disease.

As a result, the primary objectives of AD researchers at the moment are to discover alternative medications to develop better pharmacological interventions and to examine novel therapeutic targets to manage AD pathogenesis. Insulin resistance in the brain and impaired glucose uptake by neuronal cells as a result of poor insulin signaling are two common pathophysiological mechanisms seen in many neurodegenerative diseases. however, any novel studies in this field will be encouraged (155).

CONCLUDING REMARKS

T2DM and Alzheimer's disease, have been linked in epidemiological, pathophysiological, clinical, and animal research. The specific and essential mechanisms that underpin these linkages are still unknown, although they are likely to involve early-stage neurodegenerative processes such as altered insulin signaling, inflammatory, and oxidative stress pathways. Treatments for diabetes results showed efficacy in lowering AD-related neurodegeneration in preclinical animal experimentation, and are now being tested in human trials as potential therapies to prevent or reduce the progression of AD. Treatments to control hyperglycemia and hyperinsulinemia, as well as treatments to improve peripheral insulin sensitivity, are frequently used in the treatment of diabetes mellitus. Because the processes of AD and T2DM overlap, AD must be classified as "type 3 diabetes." Diabetes-related neurodegeneration is a complex issue that requires more investigation. Because of the alarming rise in the number of diabetic patients worldwide, these remarkable connections are a matter of solicitude not only for researchers but also for the general populace. Thus, we hope that researchers will create more effective and innovative therapies in the near future in terms of exploring new knowledge about the etiology of diabetes-associated neurodegenerative diseases.

CONFLICT OF INTEREST

The authors state that the publishing of this paper does not include any conflicts of interest.

DRUG CLASS	NAMES	MODE OF ACTION IN DIABETES	EFFECTS IN AD FOR *IN-VITRO* AND *IN-VIVO* MODELS	CLINICAL TRIAL EFFICACY DATA	REFERENCES
Biguanides	Metformin	• Insulin sensitization in peripheral tissues, • AMP-activated kinase activation, • Suppression of hepatic gluconeogenesis	• Decreased tau phosphorylation • Increased Aβ levels • Reduction of oxidative stress • Increased acetylcholinesterase activity	• In diabetics, use is linked to a decline in cognitive ability. • Patients with MCI are currently undergoing clinical trials	(156-158)
Sulfonylureas	Glibenclamide, Gliclazide	• stimulates insulin secretion by interacting with pancreatic ATP-sensitive potassium channels also present in neurons	• Decreased tau phosphorylation • Reduction in oxidative stress • Increased antioxidant defense • may reduce the risk of AD in combination with metformin • Improved verbal memory in T2DM	• Sulfonylurea use does not raise the risk of Dementia, but it may lessen the risk when combined with metformin. • Verbal memory enhancement in patients with type 2 diabetes who have been treated.	(159-161)
Thiazolidinediones	Rosiglitazone, Pioglitazone	• Insulin sensitization by activating PPARγ • increased expression of GLUT-4	• Decreased Aβ levels • Reduction in oxidative stress • Inhibited expression of inflammatory response genes	• Pilot trials in moderate AD and aMCI indicated that cognition improved. There was no evidence of this in phase 3 trials. • The treatment was stopped because it was linked to an increase in cardiovascular events.	(162-165)
GLP-1 analog	Exendin-4, Liraglutide, Dulaglutide	• mimetic of GLP-1 • stimulating insulin release.	• Decreased Aβ load • Reduction of tau phosphorylation • Elevated neurogenesis • Potentiation of insulin signaling in neurons • Protection against oxidative stress	• The scientists concluded that a 6-month treatment with the GLP-1 receptor stimulant agent liraglutide reduced intracerebral amyloid deposition in the central nervous system (CNS) in Alzheimer's disease (AD) patients, and hence reduced clinical symptoms.	(166-171)
GLP-1 receptor agonist	Lixisenatide, Liraglutide, Adlyxin	• GLP-1 receptor activation • increased glucose-stimulated insulin secretion	• Reduced amyloid plaques • Decreased neurofibrillary tangles • GLP-1RAs have been shown to have therapeutic effects on brain ischemia in rats, such as reducing the size of the infarct and improving neurological deficits, mostly through inhibiting oxidative stress, inflammation, and apoptosis.	• Phase IIb trial of liraglutide in participants with mild Alzheimer's dementia will be done by ELAD study in the ongoing investigation. • Because current treatments are only symptomatic, finding disease-modifying medicines is a top objective. If the ELAD study is successful, liraglutide and GLP-1 analogs will become novel features of medications to be studied further in Alzheimer's disease clinical trials.	(166, 172-174)
DDP-4 inhibitors	Vildagliptin, Saxagliptin	• Prevention of GLP-1 breakdown, which leads to improved stability	• Reduce Aβ42, total tau, and p-tau levels in the hippocampus • Reduce neuroinflammation • Increase cognitive performance	• It has not yet been evaluated.	(175-177)
Angiotensin II receptor blockers	Telmisartan, Losartan	• Improved insulin sensitivity	• Neuroprotection • Reduced inflammation • Reduced apoptosis	• This ongoing study is using a simplified verified measure of brain atrophy as a surrogate marker in a repurposing initiative that might reinterpret	(178-182)

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			• Renoprotective Effect • Prevention of accumulation of amyloid plaques • Decreased oxidative stress	antihypertensive drugs as a cognitive enhancer/neuroprotective agent, and presumably as the drug of choice for Alzheimer's patients and those at risk of developing the condition. If such concept design results are positive, bigger research with potentially practice-changing implications would be necessary.	
Insulin	Insulin	• It works by signaling the liver, muscle cells, and fat cells to help manage blood glucose levels.	• Enhanced neuronal activity • Prevents Aβ mediated neurotoxicity • Reduced apoptosis • Decreased tau phosphorylation	• A single-site, randomized, double-blind experiment will compare the acute effects of INI (20 International Units) or placebo administered with a nebulizer-like device on CSF insulin levels, AD biomarkers, and cognition in the active investigation. • Participants will be randomly assigned to receive either an acute dose of insulin or a placebo at the start of the study and then the other medication at a later visit. Participants will be enrolled if they are cognitively normal or if they have aMCI (n=20).	(183-186)
Amylin analog	Pramlintide	• Soluble amylin analogue • Increased endogenous amylin levels decrease the rate of gastric emptying which facilitates glucose absorption	• Reduced amyloid levels • Improved cognition • Decreased oxidative stress, • Reduced inflammation • Augmented synaptogenesis	• The researchers hope to develop a simple blood-based test for early diagnosis of Alzheimer's disease in this current multi-center study (AD). The test is based on a single injectable of Pramlintide, an amylin analog that is presently used to treat diabetes and is FDA-approved. • If successful in its application as an early AD biomarker (i.e., at the Mild Cognitive Impairment [MCI] stage), this could be a game-changing medical device for both early AD diagnostics and clinical trials focused on identifying and evaluating the efficacy of the drug useful for treating Alzheimer's disease in its early levels. • If Pramlintide is successful in releasing mobile pools of Aß from the brain into the bloodstream, it may have therapeutic promise in lowering brain amyloid load.	(187-189)

TABLE 2. Drugs that target type 2 diabetes have shown to be effective in clinical studies for Alzheimer's disease.

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