Humanin: A Possible Linkage Between Alzheimer's Disease and Type 2 Diabetes

Hamidreza Mahboobi[*,1,2], Javad Golmirzaei[3], Siew Hua Gan[4], Mehrdad Jalalian[5] and Mohammad A. Kamal[6]

[1]*Infectious and Tropical Diseases Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran*

[2]*Payame Noor University (PNU), Tehran, Iran*

[3]*Child and adolescent psychiatrist, Pediatric neurology research center, Shahid Beheshti University of Medical Science, Tehran, Iran*

[4]*Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia*

[5]*Electronic Physician, Mashhad, Iran;* [6]*King Fahd Medical Research Centre, King Abdulaziz University, P.O. Box 80216, Jeddah 21589, Saudi Arabia*

Abstract: The prevalence of Alzheimer's disease (AD) is higher among type 2 diabetes mellitus (T2DM) patients. In T2DM patients, the progression of AD is more rapid. Furthermore, several pathophysiological pathways are common to AD and T2DM. Humanin is a recently introduced, mitochondrial-derived peptide with neuroprotective effects. Humanin can alter the mechanisms involved in AD and T2DM pathogenesis. Insulin resistance as well as oxidative stress has been shown to be associated with increased amyloid deposition in brain neurons and islet beta cells. Moreover, advanced glycation end products and lipid metabolism disorders are common pathways of oxidative stress and low-grade systemic inflammation in AD and T2DM. These common pathways may explain AD and T2DM pathogenesis and suggest common treatments for both diseases. Treatments for T2DM and AD attempt to slow cognitive decline, and recent investigations have focused on agents that may alter pathways common to AD and T2DM pathogenesis. Non-steroidal anti-inflammatory drugs, such as interleukin-1 antagonists and statins, are possible drug candidates for both AD and T2DM.

Keywords: Alzheimer's disease, Amyloid beta, Apo-lipoprotein E, diabetes, inflammation, oxidative stress.

INTRODUCTION

Increasing evidence from epidemiological studies has shown an association between Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM). In T2DM patients, AD progression is more rapid, and the disease is more severe. Several mechanisms are purportedly responsible for the linkage between AD and T2DM. Inflammation, oxidative stress, apo-lipoprotein E (ApoE), insulin resistance (IR), advanced glycation end products (AGEs) and humanin (HN) are some of the more important processes and agents that can explain the relationship between AD and T2DM.

AD BACKGROUND

AD is a neurodegenerative disease that has increasing prevalence with increasing age. Currently, AD is becoming a major health problem among the elderly. The most important factors in AD pathogenesis include inflammation, oxidative stress, ApoE, IR and lipid metabolism disorders with mitochondrial dysfunction, axonal and dendritic changes, serum phenylalanine concentrations and glucocorticoid imbalances contributing to a lesser extent.

*Address correspondence to this author at the Hamidreza Mahboobi, Hormozgan University of Medical Sciences (HUMS), Bandar Abbas, Hormozgan, Iran; Tel: +989172121995 Fax: +987613346994;
E-mail: hamidrezamahboobi@yahoo.com

Immune system imbalances in AD patients can result in inflammation. The inflammatory process is an important finding in AD patients and plays a vital role in the disease pathogenesis [1]. Alterations in inflammation and the immune system also contribute to the pathogenesis of several other diseases including cardiovascular diseases (CVD), atherosclerosis, diabetes mellitus (DM), metabolic syndrome, obesity [2] and lipid disorders. Inflammatory mediators are responsible for certain pathophysiological changes in these diseases [3]. ApoE and lipid metabolism disorders have also been reported to be responsible for T2DM and metabolic syndrome [4]. ApoE, inflammation and lipid metabolism disorder are closely related to and are responsible for the main pathophysiological changes in AD patients.

IR, a key pathophysiological factor in metabolic syndrome, T2DM and obesity, has also been reported to be an important contributor to AD. The role of IR in AD may be through increasing oxidative stress (i.e. increase in free radicals and AGEs) and altering lipid metabolism. All of the above conditions are observed in obese patients [3].

Alterations in the immune system and inflammation influence AD pathogenesis [1]. This fact not only leads to the hypothesis of the immunologic therapeutic interventions for AD, but is also a key element for studying the relationship between AD and T2DM. T2DM is associated with lipid disorders and changes in normal immune

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responses as well as the inflammatory processes. Furthermore, immune disorders render individuals susceptible to T2DM.

T2DM BACKGROUND

Hyperglycemia is the most important feature of T2DM, and it is related to IR as well as impaired insulin secretion. The modern lifestyle and the increased obesity in the past decade have resulted in a rapid increase in the T2DM prevalence. It is well known that T2DM is related to obesity, IR, several autoimmune diseases and immune system disorders, lipid abnormalities, metabolic syndrome and cardiovascular abnormalities. Because T2DM pathophysiology is complex, knowledge regarding its pathophysiology is necessary to elucidate its relationship with other diseases. T2DM patients have problems processing pro-insulin to insulin; therefore, IR and impaired insulin secretion play important factors in T2DM pathogenesis. IR is the best predictor of T2DM, and a family history of T2DM is an important risk factor.

The islet amyloid polypeptide (amylin) is increased in T2DM patients [5]. Whether amylin has a causative role in T2DM is still unclear, however, the increased amylin in T2DM patients indicates its role in T2DM pathogenesis. Furthermore, genetic and environmental factors affect T2DM prevalence. Obesity is an important risk factor for T2DM, and obese patients are at increased risk for T2DM development. Moreover, it has been shown that lowering body weight decreases IR and improves blood sugar control [6].

The mechanism behind IR in obese patients is unclear; however, inflammation may play a role. Adipose tissues release tumor necrosis factor alpha (TNF-α), an inflammatory marker and also cause impairment in insulin activities [7]. Increased levels of C-reactive protein (CRP), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), TNF-α and white blood cell counts in T2DM patients indicate the role of inflammation in T2DM pathogenesis. Furthermore, the benefits of thiazolidindions and statins in T2DM may be due to their anti-inflammatory actions.

EPIDEMIOLOGICAL LINKAGE BETWEEN AD AND T2DM

The prevalence of AD and T2DM correlates with age, with increasing prevalence observed with increasing age. Therefore, AD and DM are becoming major health issues among the elderly [8].

Some epidemiological studies have suggested a relationship between the prevalence of T2DM, AD, obesity and cardiovascular diseases. Although some studies have not reported an association between DM and AD [9], other evidence has shown an association between these two diseases [10-12]. The prevalence of DM and impaired fasting glucose (IFG) is higher among AD patients [13]. Furthermore, T2DM increases the risk of AD [14], and diabetic patients are at a greater risk for cognitive decline [15]. This increase in the risk of dementia is not limited to AD, and it has been shown that the prevalence of all causes of dementia is higher among diabetics [16]. For example, diabetic and pre-diabetic women are more susceptible to impairment of cognitive function [17]. Furthermore, it has been shown that dementia occurs two years earlier in patients with DM and is also associated with worse outcomes. This fact is more apparent when DM is diagnosed before middle age and when the duration of DM is more than 15 years [18]. Dementia may occur after three decades in middle-age patients with T2DM [19]. DM influences the functional status of AD patients. It has been shown that AD patients have poorer functional status if they had DM at the assessment. Furthermore, in patients with recent AD, T2DM can deteriorate patient functional status [20].

In T2DM patients, several factors have been shown to increase the risk of dementia including old age, female sex, cigarette smoking, long-standing diabetes and the use of oral hypoglycemic agents and statins [21]. However, some studies have suggested that diabetic patients using oral hypoglycemias are at a lower risk for developing dementia compared with patients who do not use any medications [22]. Furthermore, genetic factors and the *epsilone4 ApoE* allele may be important in the relationship between T2DM and dementia. However, the role of genetic susceptibility is lower in middle-aged T2DM patients, who will develop dementia further [21, 23]. Furthermore, the history of severe hypoglycemic episodes in diabetic patients is associated with a greater risk for dementia [24].

Obesity is also associated with dementia. It has been shown that obesity in the middle-age group increases the risk of dementia in the elderly, independent of comorbid conditions [25]. In a cohort study of 130 human immunodeficiency virus (HIV) patients, the patients with central obesity have an increased risk of neurodegenerative disorders [26]. Physical activity can decrease obesity, and life style changes are effective in decreasing the prevalence of dementia in diabetic and obese patients. However, to date, the role of physical activity and exercise in improving cognitive function or preventing dementia remains unclear [27].

T2DM is an important risk factor for CVD. The patients with multiple risk factors for CVD are at increased risk of dementia [28]. Systolic hypertension increases the risk of dementia in diabetic patients [29]. Based on magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) brain imaging, the patients with AD and T2DM can be divided into four subgroups. The classification is based on the presence (or absence) of CVD on the MRI as well as the pattern of AD according to posterior cerebral hypoperfusion on SPECT. The patients are divided into four subgroups. First group is the patients with CVD and AD. Second group is patients without CVD but with AD, third is patients with CVD and without AD, and fourth is the patients without CVD and without AD. The classification is important because a subgroup of patients with AD and T2DM may show neither a CVD nor AD pattern and may have different clinical characteristics. They have an older age, high hemoglobin A1C (HbA1C) levels, a longer duration of diabetes, a higher frequency of insulin therapy, a lower frequency of ApoE4 carriers, less severe medial temporal lobe atrophy, more impaired attention, less impaired word recall and a slower progression of cognitive impairment compared with the subgroup showing an AD

pattern [30]. Therefore, it can be concluded that one subgroup of AD and T2DM is related to the metabolic abnormalities of DM.

Both AD and T2DM are age-related diseases, and changes in lifestyle and diet decrease the age of T2DM onset. The relationship between T2DM prevalence, cognitive impairment and AD raised a concern regarding the rapid increase in AD prevalence in the community [31]. Older communities are susceptible to higher mortality and morbidities. Furthermore, related conditions comorbid with T2DM such as obesity and CVD further increase the risk of AD. Obesity, hypertension and hyperinsulinemia are factors related to vascular health and neurodegenerative processes in T2DM [32].

Several studies have suggested the possible mechanisms of the relationship between T2DM and AD. However, the relationship cannot be explained by a single mechanism, and other studies are needed. It appears that hypoglycemia, vascular injury, oxidative stress, lipid metabolism disorders and hyperinsulinemia are important mechanisms that can explain the relationships between T2DM and AD [33]. Cerebrovascular pathology appears to be the most important mechanism responsible for the association between T2DM and AD. For example, in patients with T2DM and dementia, the presence of cerebral infarction favors the AD-type of dementia. However, in patients with dementia, both the AD-type and the cerebrovascular type of AD play a role in the disease pathogenesis. Another important point is that in patients with cerebral infarcts, the patients show clinical manifestations of dementia with fewer AD lesions compared with patients who do not have a cerebral infarction [34]. Immunohistochemical studies on human hippocampal vessels indicated that disease progression is more severe in AD patients who also suffer from DM. In the study, semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 was used to determine whether vascular endothelial damage is present in both AD and DM patients [35].

A large study with an average follow up of 18 years of patients with type 1 DM (T1DM) reported no significant decline in cognitive function despite a high frequency of hypoglycemic episodes in these patients [36]. These research findings favored the role of other factors related to T2DM in contributing to AD development in these patients. For example, obesity, oxidative stress, IR, genetic susceptibility and CVD are important factors that may alter the pathogenesis of AD in T2DM patients.

As discussed above, based on epidemiologic findings, T2DM and AD are inter-related. The epidemiologic findings are useful to distinguish possible mechanisms involved in this important relationship but are not enough to explain the association of the two diseases. Therefore, reviewing other papers is helpful to elucidate the possible mechanisms that play a role to explain the relationship between AD and T2DM. AD and T2DM have common enzymes that contribute to their pathogenesis [37]. For example, both AD and T2DM patients have higher levels of beta-galactosidase and beta-hexosaminidase activities which are related to T2DM complications, and can be used to distinguish AD patients from AD and T2DM patients [38].

HUMANIN

HN is a recently introduced, mitochondrial-derived peptide with neuroprotective effects that appears to act as a signal peptide to inhibit neurotoxicity from various AD-relevant insults [39, 40]. HN suppresses neuronal cell death through the alteration of intracellular toxic mechanisms that have been shown to be important in AD and also through the inhibition of Abeta neurotoxicity [41]. Injection of exogenous HN has been reported to have cytoprotective effects in rats [42]. This effect is mediated by the interaction with endogenous HN and by the inhibition of B-cell lymphoma 2 (Bcl2)-associated X protein (a protein that induces apoptosis and cell death) entry into the mitochondria [42, 43].

HN can protect cells from oxidative stress [44] and can also partially antagonize the inflammatory processes [45, 46]. Immune system imbalances, inflammation and oxidative stress are common pathophysiologic changes in both AD and T2DM. HN plays a major role in the inhibition and modulation of these processes; therefore, HN can be considered a possible novel therapeutic agent for both diseases.

The discovery of HN and its *in vivo* production [47] resulted in new pathophysiological insights for AD. Researchers attempted to access new therapeutic options by determining the mechanisms of HN-induced neuroprotection and cytoprotection [48, 49]. Mamiya *et al.* reported the benefits of HN in improving learning and memory in an animal model of learning and memory deficit induced by scopolamine. The study not only indicated the therapeutic effects of HN but also the possible role of the cholinergic system in its action [50]. Furthermore, HN has been found to improve cognitive deficits in animal models [51]. The therapeutic roles of HN may be mediated *via* the alteration of Abeta fibril formation, which is an important pathological change in AD. This is because HN inhibits the formation of the Abeta1-42 fibril. Moreover, recent studies have shown that HN can disaggregate Abeta1-42 fibrils [52].

The benefits of HN for the prevention of apoptosis and cell death in the central nervous system (CNS) are not limited to AD patients. HN can prevent cell death and apoptosis in traumatic brain injury, intra-cerebellar hemorrhage and ischemia and reperfusion injury in animal models [53-55]. The prevention of cell death by HN is not limited to neurons; its benefits have also been observed in other cell types [56]. HN inhibits Abeta-mediated cell death in human cerebrovascular smooth muscle cells [57]. The association of HN circulatory levels with preserved human coronary endothelial function provides further evidence that HN has protective effects that are not limited to the CNS [58]. Furthermore, other similar peptides such as rattin, a 38-residue peptide, is significantly expressed not only in the CNS but also in cardiac and skeletal muscle [59].

It has been shown that HN delays or prevents the onset of diabetes in non-obese diabetic (NOD) mice. Furthermore, HN has a role in the regulation of glucose intolerance in NOD mice. The protection of islet beta cells offered by HN again makes it a suitable candidate for a novel therapeutic option for T2DM [60]. HN levels tend to decrease with increasing age [61], which further suggests its role in the

pathogenesis of age-related disorders such as T2DM and AD as well as in other neurodegenerative diseases.

The role of HN in the linkage between AD and T2DM is based on the direct protective effects of HN on CNS cells and islet beta cells and on other mechanisms related to inflammation prevention and the modulation of the immune system. In ApoE-deficient mice, HN has been shown to prevent kidney disease [62]. The cytoprotective effects of HN are mediated *via* several different mechanisms. One of the most important mechanisms is the prevention of Abeta fibril formation and the disaggregation of Abeta fibrils [52]. Another important role of HN is cell protection against oxidative stress [46]. Not only can the association of AD and T2DM be explained by the role of oxidative stress in both diseases, but recent findings on the role of HN in glucose regulation is another important avenue that requires investigation.

As previously discussed in this paper, HN is a newly discovered peptide with significant neuro and cytoprotective effects, and several different mechanisms of action have been described. The HN receptors have a close relationship with immunological mechanisms important in AD pathophysiology. Inflammation is an important process in T2DM and AD pathophysiology. Zhao *et al.* reported the role of HN in decreasing IL-1, IL-6 and TNF-α, which are pro-inflammatory cytokines. Their results indicated that HN partly antagonizes inflammatory injuries [45]. Furthermore, the role of the immune system in the apoptosis of islet beta cells in T2DM is clear, and it has been shown that HN protects islet beta cells in NOD mice [60], possibly through the reduction of inflammation and the infiltration of immune system cells.

INSULIN RESISTANCE (IR)

IR is a common pathologic change in both AD and T2DM [63]. IR has been shown to worsen AD in animal models [64]. The role of IR in AD is mediated *via* several mechanisms. Chronic hyperglycemia exacerbates the inflammation process and is associated with increased inflammatory cytokines. The inflammation and inflammatory cytokines are increased in AD patients; this increase is considered an underlying pathology in AD. Furthermore, IR increases oxidative stress, another common feature among AD patients [65]. Therefore, insulin is a neuro-modulator and regulates the release of neurotransmitters from brain neurons.

IR in brain neurons results in amyloid precursor protein (APP) and accumulation of Abeta, thus activating the pathways involved in oxidative stress and neurodegeneration. Metabolic syndrome, T2DM and obesity, all of which are related to IR, are also epidemiologically related to AD and other neuro-degenerative diseases [66-68]. IR in the brain results in resistance to insulin like growth factor-1 (IGF-1), which has been reported to initiate Abeta accumulation, inflammation, oxidative stress, neurodegeneration and cognitive decline [69].

Steen *et al.* have reported a significant reduction in the genes encoding insulin, IGF-1 and IGF-II in AD patients. Furthermore, insulin and IGF-1 receptors are decreased in the CNS. This important finding not only shows the role of IR in AD pathogenesis but also confirms that AD is a neuroendocrine disorder. Therefore, the authors have suggested the new term "type 3 diabetes mellitus" for AD [70], which reflects the importance of IR in AD pathogenesis.

Based on the studies confirming the role of IR in AD pathogenesis, drugs that can alter insulin sensitivity, the inflammatory process and oxidative stress may also be used in the management of AD. The thiazolidinedione rosiglitasone is an option for altering insulin sensitivity and preventing the pathologic pathways involved in AD [71]. Furthermore, the etiological role of butyrylcholinsterase and acetylcholinesterase in AD and DM patients may also be mediated through IR and lipid metabolism [72].

OXIDATIVE STRESS

Oxidative stress is a common pathologic finding in both AD and T2DM. Its role in DM pathogenesis is clearly defined, and evidence is available for the role of oxidative stress in AD. In AD, destruction of the brain neurons favors the role of free radicals in disease pathogenesis. Oxidative stress is one of the most important pathologic findings in AD patients [73, 74]. The findings of iron, cooper and zinc imbalances in the areas with severe damage in AD patient brains confirm the possibility of the role of oxidative stress in AD pathogenesis [75-77].

The mechanisms of this action are purported to be *via* a reduction in DNA damage, lipid peroxidation, protein oxidation and AGEs [78, 79]. The relation of neurofibrillary tangle (NFT) and senile plaques to oxidative stress has been established in several studies [80-82]. Abeta peptide has been shown to be linked to oxidative stress in AD [83, 84], and genetic factors such as *ApoE* alleles have a role in the AD oxidative stress pathogenesis [85].

Oxidative stress leads to inflammation and an increase in inflammatory cytokines and interleukins, which is an underlying process in AD pathogenesis. Furthermore, in T2DM, inflammation is an important pathologic finding that may have a role in susceptibility of T2DM patients to AD and in AD progression in T2DM patients. Linkage of oxidative stress and AD makes antioxidants a potential common therapeutic agents for AD and T2DM [83]. The role of antioxidants in prevention of AD progression has been shown in animal models. In humans, further studies in this field are required.

ApoE

ApoE and lipid metabolism disorders are important factors in T2DM pathophysiology. Furthermore, these factors have been shown to be important in AD pathophysiology. Oxidative stress and inflammation are other mechanisms related to the role of ApoE in the pathogenesis of AD and T2DM. The *epsilon4* allele of ApoE increases the probability of temporal lobe atrophy in patients with oxidative stress [4]. Brain atrophy is an important change in AD patients. The most prominent alteration in AD occurs in the hippocampus, and its atrophy can better distinguish AD patients from healthy subjects [86]. Therefore, the *epsilon4* allele of ApoE has a role in AD

pathogenesis. Cognitive decline is more common in patients with the *epsilon4* allele of ApoE and overt CVD compared with those without the *epsilon4* allele or subclinical CVD [87, 88].

ApoE increases amyloid synthesis [89]. Therefore, ApoE is related to AD and other amyloidoses diseases. An increase in amyloid synthesis in pancreatic islets is important in disease initiation and development. Amyloid synthesis increases with age, which can explain the increase in T2DM prevalence with age. Furthermore, in AD and other neurodegenerative diseases, an increase in disease prevalence is observed with increasing age. Amyloid synthesis has an important role in AD and neurodegenerative diseases. Amyloid synthesis is directly associated with NFT and amyloid plaques, which are hallmarks of AD [90]. Other factors such as hyperglycemia, inflammation and IR are other factors associated with an increase in amyloid production in islet beta cells [91].

Furthermore, it has been shown that under physiological conditions, ApoE binds to amylin and prevents its accumulation in islet beta cells, and ApoE has a protective effect on islet function. However, in T2DM, the enhanced ApoE-amylin binding causes amylin accumulation in islet beta cells and a further decrease in their function [92].

A-BETA PEPTIDE

Abeta and tau are two proteins that play prominent roles in AD pathologies. It has been shown that DM can accelerate the onset of AD and increase its severity. The mechanism of these actions may through the Abeta and tau proteins according to immunohistochemical studies [93]. The Abeta autoantibody levels have been reported to be higher in patients with T2DM [94].

Impaired brain insulin signaling and cerebrovascular changes in T2DM may accelerate the pathologic changes observed in AD. Although recent studies in animal models have suggested a possible role of amyloid pathology in aggravating DM [95], some human studies have reported no significant differences in the extent of Abeta accumulation among diabetics compared to non-diabetics with AD. For example, positron emission tomography using BF-227 was used to investigate amyloid beta accumulation among diabetic and non-diabetic patients with AD. The researchers found no significant difference in the degree or extent of Abeta accumulation in diabetic and non-diabetic patients with AD [96]. However, other studies on the pathology of T2DM and AD have suggested a relationship between the diseases with respect to the pathological level. For example, cortical atrophy in T2DM patients increases the AD risk in these patients [97]. The vascular and immunological changes in T2DM in these patients are responsible for the cortex atrophy that makes these patients more susceptible to AD.

Accumulation of Abeta peptide and hyperphosphorylated tau deposits in the islet cells suggest a common pathologic pathway for T2DM and AD, which can explain the epidemiological link between the two diseases [98]. In brain neurons, Abeta peptide accumulation results in NFT and amyloid plaques, which are characteristic features of AD along with oxidative stress and inflammation. In T2DM, amyloid deposition in islet cells is stimulated by hyperglycemia, inflammation and oxidative stress. Amyloid accumulation in beta cells decreases beta cell function and leads to T2DM progression [99]. Amyloid accumulation in islet beta cells causes their dysfunction and apoptosis [100].

Apoptosis and a decrease in beta cell content lead to T2DM progression and a decrease in insulin secretion. Therefore, new therapeutic methods to prevent beta cell apoptosis have been considered for the treatment of T2DM and the prevention of disease progression [101, 102]. New findings on the role of amyloid deposition in islet beta cells suggest the possibility of preventing apoptosis in these cells by preventing amyloid deposition. These therapies may prevent amyloid deposition in brain neurons and also prevent AD.

Sertilin-related vacuolar carboxypeptidase-sorting receptor 10 (VPS10) domain-containing receptor 1 protein decreases the generation of Abeta, which plays a prominent role in AD pathophysiology [103]. It has been reported that T2DM influences the linkage between sertilin-related VPS10 domain-containing receptor 1 and AD [103].

INFLAMMATION

T2DM and AD are considered low-grade, systemic inflammations [104, 105]. Therefore, as expected, the levels of CRP, IL-6, TNF-α and lipid peroxides are increased in patients with T2DM and AD [106]. Acute and chronic inflammations have been shown to be associated with AD progression. An increase in TNF-α is associated with an increase in cognitive decline in AD patients [107]. In T2DM, there is an underlying chronic inflammation, which makes these patients susceptible to disease progression.

Elevated plasma inflammatory markers indicate that both AD and T2DM are related to low-grade systemic inflammation. IL-6, CRP and TNF-α are inflammatory markers known to exist at higher levels in patients with AD and T2DM, and disorders in the lipid metabolism and oxidative stresses lead to inflammation. Elevated butyrylcholinesterase and acetylcholinesterase concentrations are related to decreased levels of acetylcholine, which is a trigger for low-grade systemic inflammation. It has been shown that the levels of both enzymes are increased in the plasma of AD and T2DM patients [108]. Anakinra is an IL-1 antagonist and has been shown to be effective for lowering the plasma levels of inflammatory markers. Anakinra improves glycemic control and beta cell secretory function in T2DM patients [109]. Anakinra and similar agents that can decrease systemic inflammation may be effective in the prevention and treatment of AD. More evidence for the role of inflammation in AD is the effect of non-steroidal anti-inflammatory drugs (NSAIDs) in these patients. It has been shown that patients who consume NSAIDs are at a lower risk of AD development [110].

AGEs (ADVANCED GLYCATION END-PRODUCTS)

AGEs that play a role in chronic complications of DM also contribute to AD pathogenesis. These agents promote the generation of a vicious cycle of oxidative stress, which is responsible for the severe progression of AD in DM patients

[111]. N epsilon-carboxymethyllysine is one of AGE products. The high levels of carboxymethyllysine present in T2DM and AD patients indicate that DM can lead to AD and accelerate AD progression [112].

SIMILARITIES IN THE MANAGEMENT APPROACH OF TREATMENT FOR T2DM AND AD

In T2DM, the treatment goals focus on lowering blood sugar, decreasing inflammation, lowering lipid levels and ameliorating lipid metabolism disorders. Lowering blood sugar levels is possible by increasing insulin secretion and decreasing IR, the latter of which is more important in T2DM patients. Enough evidence is available to suggest that AD and DM have shared pathologies, leading to the hypothesis that treatment for DM may influence disease progression in AD patients [113]. Currently, researchers are focusing on the drugs that alter the pathways common to both diseases [114-116]. Antidiabetic agents can be considered potential treatments and preventive agents for AD [117]. For example, a study by Hanyu *et al.* reported increased cognition in AD patients after piglitazone use [118].

Current available treatment options for AD are symptomatic treatments such as cholinesterase inhibitors, memantine (an N-methyl-D-aspartate receptor noncompetitive antagonist) and also certain disease-modifying drugs. Long-term use of cholinesterase inhibitors and memantine has been reported to be useful in AD patients [119]. Disease modifying drugs are agents that stop the AD pathogenic process such as Abeta plaques, NFTs, oxidative stress and alterations in lipid metabolism and immune system function [120, 121].

Triethylenetetramine is a recently introduced anti-diabetic agent. Noting the similarities in the pathogenesis and relationships in epidemiological and genetic data available in AD and DM, this agent can be considered a potential therapeutic agent for AD. However, more studies are required to demonstrate this point [122].

Amylin aggregation appears to play a role in the pathogenesis of both AD and DM. Therefore, treatments based on myloidogenic properties may be useful in patients with T2DM and AD [123]. To date, studies on the treatment of AD and T2DM patients and the effect of T2DM treatment on the prevention of AD and alteration of the progress of AD in T2DM patients are still lacking.

Recently, a transducible HN with an extended caspase-3 cleavage sequence (tHN-C3) was introduced by Park *et al.* for the treatment of AD [124]. Several mechanisms have been described for tHN-C3 to explain its therapeutic role in AD. A possible mechanism is the prevention of inflammatory cell infiltration into the brain. Common pathophysiological pathways in AD and T2DM including inflammation suggest a possible role for tHN-C3 in T2DM.

PREVENTION

The role of IR in AD has been well established. T2DM, obesity and metabolic syndrome are diseases resulting from IR and are associated with an increased risk of AD incidence and severity. Thus, lifestyle changes, which are key components of the treatment for T2DM, obesity and metabolic syndrome and are also known to be effective in lowering IR, can be considered for AD prevention [125]. Moreover, changes in lifestyle may lower the rate of disease progression in AD by decreasing IR, hyperglycemia, lipid metabolism disorder, oxidative stress and inflammation.

Nitrosamine-related agents increase IR-related diseases, especially T2DM and AD. Therefore, minimizing human exposure to nitrosamine-related agents may decrease the prevalence of both AD and T2DM [63]. Nitrosamines cause DNA damage, oxidative stress, lipid peroxidation and inflammation. Exposure to these agents renders individuals susceptible to AD and T2DM. Decreasing exposure to these agents through decreasing nitrate use in food and fertilizers may help prevent AD and T2DM [126].

Table 1. Summary of the Evidence of T2DM and AD Linkage

Linkages	
Epidemiological studies	• Both disease prevalence rates increase with age • T2DM and IFG prevalence rates are higher among AD patients • T2DM increases the risk of AD • T2DM deteriorates the functional status of AD patients
HN	• HN has protective effects on both CNS and islet beta cells
IR	• AD is associated with a reduced expression of genes encoding insulin, IGF-I and IGF-II • AD is known as T3DM
Oxidative stress	• Oxidative stress causes inflammation, an underlying process in the pathogenesis of AD and T2DM
ApoE	• ApoE increases the synthesis of amyloid, which is important in AD pathogenesis and is related to lipid metabolism disorders, which are important in T2DM pathogenesis
A-beta peptide	• Abeta peptide accumulation and hyperphosphorylated tau deposits in islet cells suggest a common pathologic pathway for T2DM and AD
Inflammation	• T2DM and AD involve low-grade, systemic inflammation, and CRP, IL-6, TNF-α and lipid peroxides are increased in patients with T2DM and AD
AGEs	• AGEs promote the generation of the oxidative stress vicious cycle that is responsible for the severe progression of AD in DM patients

CONCLUSIONS

Increasing evidence indicates a relationship between AD and T2DM [127-130]. A summary of the evidence of the linkage between T2DM and AD is shown in Table **1**. Studies on molecular mechanisms that could affect both AD and DM have shown that IR, vascular injuries, inflammation, receptors for AGEs and HN are shared mechanisms that can affect both AD and DM [131]. Role of HN in linkage between T2DM and AD is through inhibiting neurotoxicity, and protecting cell against oxidative stress. Considering these molecular mechanisms leads to the hypothesis that treating DM may influence AD progression [132, 133]. HN can be considered for future researches on finding new treatments which can affect both the patophysiology of AD and T2DM.

LIST OF ABBREVIATIONS

AD = Alzheimer's disease

T2DM = Type 2 diabetes mellitus

HN = Humanin

IR = Insulin resistance

AGEs = Advanced glycation end products

NSAIDs = Non-steroid anti-inflammatory drugs

IL-1 = Interleukin-1

ApoE = Apo-lipoprotein E

DM = Diabetes mellitus

CRP = C-reactive protein

IL-6 = Interleukin-6

PAI-1 = Plasminogen activator inhibitor-1

TNF-α = Tumor necrosis factor alpha

IFG = Impaired fasting glucose

HIV = Human immunodeficiency virus

MRI = Magnetic resonance imaging

SPECT = Single-photon emission computed tomography

CVD = Cardiovascular diseases

HbA1C = Hemoglobin A1C

T1DM = Type 1 diabetes mellitus

CNS = Central nervous system

NOD mice = Non-obese diabetic mice

IGF-1 = Insulin like growth factor-1

NFT = Neurofibrillary tangle

T2DM = Type 2 diabetes mellitus

IFG = Impaired fasting glucose

AD = Alzheimer's disease

HN = Humanin

CNS = Central nervous system

IGF-I = Insulin like growth factor-I

IGF-II = Insulin like growth factor-II

T3DM = Type 3 diabetes mellitus

ApoE = Apo-lipoprotein E

CRP = C-reactive protein

IL-6 = Interleukin-6

TNF-α = Tumor necrosis factor alpha

AGEs = Advanced glycation end products

CONFLICTS OF INTEREST

The authors confirm that this article has no conflicts of interest.

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