Diabetes and dementia — the two faces of Janus

Athanasia K. Papazafiropoulou¹, Chris Koros², Andreas Melidonis³, Stavros Antonopoulos¹

Abstract

Patients with type 2 diabetes are at high risk for cognitive decline and dementia. Despite the limited data on the possible pathogenetic mechanisms, evidence suggests that cognitive decline, and thus dementia and Alzheimer’s disease, might arise from a complex interplay between type 2 diabetes and the aging brain, including decreased insulin signalling and glucose metabolism, mitochondrial dysfunction, neuroinflammation, and vascular disease. Furthermore, there is increasing interest on the effects of antidiabetic agents on cognitive decline. There are many studies showing that antidiabetic agents might have beneficial effects on the brain, mainly through inhibition of oxidative stress, inflammation, and apoptosis. In addition, experimental studies on patients with diabetes and Alzheimer’s disease have shown beneficial effects on synaptic plasticity, metabolism of amyloid-β, and microtubule-associated protein tau. Therefore, in the present review, we discuss the effects of antidiabetic agents in relation to cognitive decline, and in particular dementia and Alzheimer’s disease, in patients with type 2 diabetes.

Key words: glucagon-like peptide-1 receptor agonists, sodium-glucose co-transporter-2 inhibitors, dementia, Alzheimer’s disease, neurodegenerative diseases, type 2 diabetes.

Introduction

It is well established that the prevalence of type 2 diabetes (T2D) is increasing worldwide, with more than 380 million people currently being diabetic [1]. Diabetic complications, peripheral and autonomic neuropathy, retinopathy, cerebrovascular and cardiovascular disease, and chronic kidney disease act negatively on quality of life and most of all increase the morbidity and mortality of patients with T2D [2, 3]. Cognitive decline has been recognised as another diabetic complication, resulting in mild cognitive impairment (MCI) or dementia [4]. Furthermore, both epidemiological and experimental studies have demonstrated a link between Alzheimer’s disease (AD) and T2D. Most of the studies emphasise the pathogenetic role of insulin resistance (IR) in impairing neuronal function, and some authors refer to AD as “type 3 diabetes” [5]. However, there is evidence that the link between AD and T2D includes decreased brain insulin signalling and glucose metabolism, mitochondrial dysfunction, neuroinflammation, neurotransmitter alteration, and vascular disease.
IR and raising the levels of endogenous insulin secretion are the main mechanisms for the antidiabetic treatment, and many classes of antidiabetic agents have been available for decades targeting the above two pathogenetic mechanisms; these include metformin, sulfonylurea, thiazolidinediones, and insulin. Recently, incretin-based therapies and sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have become available for the treatment of T2D acting in different pathogenetic ways. However, all the above antidiabetic agents are of great interest in relation to prevent cognitive decline, and thus dementia and Alzheimer’s disease because it has been shown to have pleiotropic beneficial effects on the brain, mainly through inhibition of oxidative stress, inflammation, apoptosis, synaptic plasticity, and metabolism of amyloid-β (Aβ) and microtubule-associated protein tau [2–5].

Therefore, in the present review, we will discuss the potential of incretin-based therapies in relation to cognitive decline and dementia, in particular AD, in patients with T2D.

**Dementia and type 2 diabetes**

It is well established that T2D is implicated in cognitive deterioration. In fact, it represents a major risk factor for dementia. The prevalence of dementia related to diabetes has not been assessed in depth yet. Diabetic patients are more prone to develop dementia than non-diabetic individuals [6]. The incidence of dementia in a prospective analysis was higher in diabetic patients (14.9%). The presence of Apolipoprotein E4 (ApoE4) further increased the incidence of cognitive problems. Both diabetes and AD are age-dependent conditions. Given the expectations for future growth of elderly populations, both these disorders are expected to affect millions of patients.

Epidemiological data have shown the association between AD and T2D. A study of the large Danish National Patient Cohort demonstrated that in patients > 50 years old there is a small diabetes-related increase in AD [7]. In a Taiwan registry study diabetes type 2 was linked to a 60% increase in AD risk [8]. A number of smaller studies have also shown an increase in AD risk in diabetic populations.

Studies in humans have shown that T2D is associated with dementia. A meta-analysis [9] showed a 60% greater dementia risk in diabetic patients, with women exhibiting a more robust effect. The risk accounts for vascular dementia while it is lower for non-vascular dementia. Concerning MCI there is an 20% rise in diabetic patients. Even for demented individuals, diabetes is linked to lower performance in cognitive functions like episodic memory, verbal fluency, processing speed, and attention [10, 11]. Structural alterations were also evident including higher brain atrophy and lower striatal volume in diabetic patients [12]. Notably, persons with high fasting blood glucose exhibited more pronounced cognitive decline, and the risk for dementia was greater. In a Japanese cohort, higher glycos level correlated with a higher vascular dementia risk [13]. In a large longitudinal cohort, high fasting blood glucose was associated with greater impact on verbal and spatial abilities and on perceptual speed [14].

Cognitive decline is also reflected in macroscopic brain changes like global cerebral and white matter atrophy in T2D [15]. A meta-analysis showed 2% lower brain volumes in diabetic patients [16]. Data on the annual rate of atrophy in diabetic patients are still missing. The duration of diabetes has been linked to grey matter atrophy (1% decrease for every additional 10 years). White matter atrophy and infarct volume was also associated with the disease duration [17, 18].

**Endogenous and environmental factors contributing to dementia in diabetic patients**

The factors that predispose to T2D and dementia tend to overlap. These include endogenous factors such as oxidative damage, inflammation, or mitochondrial dysfunction and environmental factors like diet, physical activity, and exposure to toxins. However, hyperglycaemia is considered to be a keystone in the development of dementia in diabetic patients [19]. Glucotoxicity exerts damage to a number of cell populations mainly via oxidative stress and mitochondrial dysregulation. These conditions lead to brain IR and subsequently to accumulation of Aβ. Notably, glucose transporters (GLUT) 1 and 3 and even 4, which is insulin dependent, play a major role in brain glucose metabolism. Knockout animal models for the latter exhibit abnormal response to hyperglycaemia in brain areas such as the hypothalamic paraventricular nucleus [20].

Chronic rises in blood glucose result in chronic hyperinsulinaemia, which in turn causes chronic brain IR. This condition leads to distorted brain insulin signalling and finally eliminates insulin availability in the brain (by means of insulin transport reduction across the blood-brain barrier). Because insulin receptor is abundant in the hippocampus, insulin resistance and limited brain insulin signaling has an impact on cognitive functions [21]. Additionally, both insulin and leptin regulate synaptic function in different brain areas and may even have a protective role against neurodegeneration. Synaptic dysregulation is considered to be important in the pathogenesis of dementia in diabetes.

The hallmark of the most frequent form of dementia, AD, is the presence of amyloid-rich senile
plagues and neurofibrillary tangles (tau protein). The Aβ is produced by means of cleavage of the original protein (Amyloid precursor protein APP) by beta and gamma secretases. On the other hand, tau protein, especially in phosphorylated form, aggregates and forms neurofibrillary tangles [22]. In animal models of T2D, a high-fat diet can enhance Aβ production and increase tau protein phosphorylation [23]. Animals fed a high sucrose diet exhibit IR, hyperinsulinaemia, and deposition of amyloid in their brains. This histological find is accompanied by cognitive deficits [24].

The molecular mechanism behind these effects is probably the inhibition of APP degradation and subsequent amyloid accumulation due to hyperglycaemia and brain IR. Tau phosphorylation is also increased. In streptozotocin diabetic mice these pathological features are accompanied by hippocampal atrophy, synaptic dysregulation, and poor performance in learning tests. In all of these models diabetic-related neuronal abnormalities lead to structural and functional alterations, which account for profound cognitive deficits [25].

Although the uptake of glucose by neurons does not depend on insulin action, neuronal cells express such receptors along with insulin growth factor type I receptors (IGF-1) [26, 27]. It has been proposed that fluctuations of glucose level, as is the case in diabetes, may facilitate cognitive deterioration. Control of sudden glucose rises (peaks) might eliminate the damaging effect in memory function of diabetic individuals [28]. Medication aiming to decrease glucose fluctuations can have neuroprotective effects. Glucose lowering medication like metformin decrease tau hyperphosphorylation by means of enhancing protein phosphatase 2A. Moreover, thiazolidinediones, like pioglitazone, are agonists of peroxisome proliferator-activated receptor γ (PPAR-γ) and appear to act beneficially on cognitive [29].

T2D has been correlated with an increase in blood cholesterol and triglycerides as a part of metabolic syndrome. Dyslipidaemia has also been implicated in cognitive deficits. The connection of this condition to memory is exemplified by the role of cholesterol in the activity of secretases. By means of this action Aβ protein production and aggregation is enhanced. Dyslipidaemia could thus influence cognitive functions in diabetic patients via the amyloid cleavage pathway [30].

In diabetes, an increased inflammation background might explain in part the triggering effects on brain dysfunction. Advanced glycosylation end products (AGEs) lead to inflammatory responses, which in turn play a role in blood-brain barrier integrity [31]. Subsequently, the disrupted barrier makes the brain parenchyma more vulnerable to toxic circulating products including fibrin, plasmin, thrombin, and other proteins. Normal neuron homeostasis is then severely disturbed. Furthermore, inflammatory mediators like interleukins, tumour necrosis factor α, and C-reactive protein, which are abundant owing to diabetes-driven inflammation, have been implicated in cognitive deficits [32, 33].

Hypertension, which is common in diabetic patients as part of the metabolic syndrome, plays a role in the development of cerebrovascular complications of diabetes. The exact pathway remains obscure, but it has been shown that lowering blood pressure exerts a neuroprotective role in diabetic patients and decreases the possibility of dementia [34].

Vascular problems represent a common outcome of chronic diabetes either in the form of macro- or microvascular disease. The presence of cerebral infarcts that accumulate in the brain white matter have a severe impact on memory and other cognitive functions. This condition often results in mild cognitive impairment or even frank dementia (vascular dementia) [35]. Microvascular abnormalities like those observed in the retina are also associated with cognitive deterioration. The effect of diabetes on the retina effectively reflects the status in cerebral small vessels. The pathology background of this condition includes endothelium alterations and capillary vessel loss [36]. It has been demonstrated that the dysregulation of endothelium stems from toxic agents that are produced in diabetic patients, such as lipids and AGEs. The latter lead to the generation of reactive oxygen species (ROS), which in turn influence endothelial cells [37]. Moreover, ROS have many additional harmful properties including the activation of metalloproteinases and the decrease of vasodilatory substances. Overall, this condition impacts vascular permeability in the brain, and this represents an obstacle to neuronal homeostasis. The combination of macro- and microvascular brain disease trigger cognitive decline in diabetic patients [26, 38].

Other factors could also contribute to the development of diabetes-induced cognitive decline. Calcium metabolism alterations also play a role in neurodegeneration in diabetic patients. The major mechanism is considered to be Ca/calmodulin-dependent protein kinase II modification in diabetics [39]. Amylin represents a hormone secreted by pancreatic beta cells. Increased amylin in diabetes or prediabetes results in oligomerisation and secretion of oligomers in plasma. Circulating oligomers influence brain parenchyma by causing amylin amyloid deposition, microbleeds, and subsequent inflammation and degeneration. These deposits have been traced in the brain parenchyma of patients with AD [40, 41].

Additionally, the formation and accumulation of misfolded proteins in T2D leads to brain dam-
The ability of neurons to cleave misfolded proteins is impaired. Furthermore, cerebrovascular disease further prohibits the clearance of misfolded protein and accelerates neuronal damage [42]. Neurogenesis is an important procedure of neural cell proliferation, but in the adult brain it is restricted mainly to the hippocampus. In diabetes, high blood glycosylated with low trophic factor levels like brain-derived neurotrophic factor and impaired neurogenesis, which may have an indirect effect on cognitive functions in the long run [43].

The glymphatic brain system represents the glial component of the outer boundary of the perivascular space, which plays a crucial role in the clearance and turnover of substances between the brain parenchyma and the vessels. This system is severely affected in degenerative disease like AD [44]. The main mechanism of glymphatic system dysfunction in AD is the lack of efficiency in Aβ clearance because toxic amyloid can be transported via low-density lipoprotein-related receptor I [45]. In AD, previous studies have demonstrated a defect in the clearance of amyloid via the glymphatic system. Furthermore, decreased aquaporin receptor expression in AD has been linked to reduce Aβ and tau clearance via the glymphatic system. Accordingly, in T2D, recent reports have shown decreased activity of the glymphatic system. IR and hyperglycaemia possibly play a role in this deficit [46]. Moreover, diabetic patients exhibit problems in the blood brain barrier permeability, a decline in norepinephrine secretion in the brain, and decreased ApoE levels. These conditions influence the function of the glymphatic system, and the resulting brain dysfunction leads to cognitive deterioration [47]. In diabetic patients an increased glymphatic influx of molecules to the cerebrospinal fluid is noted along with a reduction of clearance of parenchymal molecules, including amyloid [48]. Moreover, small-vessel disease is accompanied by glymphatic malfunction in diabetes. The blood-brain barrier when intact is protective against a number of neurotoxins that could affect normal brain activity. On the other hand, sleep has been linked to amelioration of the impaired function of the glymphatic system in diabetic patients and to decrease the impact of diabetes on cognitive functions of affected individuals [44, 49].

A number of environmental factors have been implicated in the pathogenesis of both T2D and AD. Air pollution has been linked to T2D. Large longitudinal studies have demonstrated an increased risk of diabetes in individuals exposed to environmental toxins. Air pollution is also related to the development of AD, with higher exposures doubling the risk for AD. Currently, few studies have assessed the possible interaction of air pollution and T2D on cognition. The results are indicative of the influence of metabolic disturbances triggered by toxic substances on AD risk. A number of other environmental toxic substances like pesticides used in agriculture have also been implicated in the development of both T2D and dementia [1].

### Antidiabetic agents and dementia

#### Metformin

Metformin is a biguanide, and for more than half a century it has remained the first-line therapy for T2D. Its action occurs by the inhibition of gluconeogenesis in the liver and activation of the liver kinase B1 (LKB1)/AMPK pathway through the inhibition of the mitochondrial respiratory-chain complex [50]. The existing literature data show that metformin therapy in T2D patients is associated with a significantly lower risk of dementia and cognitive impairment. Metformin’s neuroprotective effects are explained in part by the activation of AMPK-dependent pathway [51] and its effect on IR [52, 53]. The later was confirmed by Lin et al., showing that metformin can improve cognitive function in patients with non-dementia vascular cognitive impairment and abnormal glucose metabolism by a beneficial result on IR [54].

It is known that AD is characterised by deposition of Aβ plaques, neurofibrillar tangles, and neuronal loss, accompanied by neuroinflammation. A study in APP/PS1 mice showed that metformin attenuated spatial memory deficit and neuron loss, and decreased Aβ plaque load and chronic inflammation in the hippocampus and cortex [55]. In addition, in an experimental model in male Wistar rats, metformin offered a protective effect against scopolamine-induced cognitive impairment, mainly due to a significant reduction of inflammation and to a lesser extent to reduction of oxidative stress [56].

A large retrospective study in 5528 elderly patients with T2D, with a median follow-up of 5.2 years, showed that long-term metformin therapy was associated with lower incidence of neurodegenerative disease [57]. In accordance, a retrospective study of 17,200 new users of metformin and 11,440 new users of sulfonylureas showed that the hazard ratio (HR) for dementia in metformin vs. a sulfonylurea group was 0.67 (95% confidence interval: 0.61–0.73) and 0.78 (95% CI: 0.72–0.83) for those < 75 and ≥ 75 years of age, respectively [58]. Another study, from 2000 to 2015, in 73,761 African American and white patients, showed that metformin was associated with a substantially lower risk of dementia compared to sulfonylurea initiation among African American patients aged 50 to 64 years (HR = 0.6; 95% CI: 0.45–0.81) [59].
The population-based Singapore Longitudinal Aging Study in older patients with T2D showed that metformin use was associated with a low risk of cognitive impairment [60]. The favourable effect of metformin therapy on risk of dementia (HR = 0.76, 95% CI: 0.58–0.98) was also confirmed in a study using data from 800,000 patients in Taiwan’s National Health Insurance database [61]. Even in the presence of mild cognitive impairment or mild dementia due to AD metformin was associated with improvement in learning/memory and attention [62]. However, a cohort study in 4651 patients using Taiwan's National Health Insurance Research Database, with a 12-year follow-up, showed that patients on metformin therapy had a higher risk of Parkinson’s disease (PD) (HR = 2.27, 95% CI: 1.68–3.07), and an increased risk of all-cause dementia (HR = 1.66, 95% CI: 1.35–2.04), AD (HR = 2.13, 95% CI: 1.20–3.79) and vascular dementia (HR = 2.30, 95% CI: 1.25–4.22) compared to the non-metformin group [63].

On the basis of the presented results, it seems that metformin exerts beneficial effects regarding dementia and AD. However, the exact pathogenetic mechanism is not yet fully known. Therefore, further well-designed, multicentre, placebo-controlled, randomised clinical studies are necessary in order to explain the beneficial effects of metformin on dementia and AD.

**Sulphonylurea**

The existing literature data regarding the effect of sulphonylurea on dementia are very limited. It has been shown that glimepiride might reduce synapse damage and hence delay the progression of cognitive decline in AD [64]. It seems that the protective effects of glimepiride were multi-faceted: altered synaptic membranes, increased synaptic gangliosides, and altered cell signalling [64]. However, further studies using sulphonylurea are needed in order to explore the potential effect that might have on dementia as well as the effect of hypoglycaemic episodes that are fully related with sulphonylurea therapy on the risk of dementia.

**Glitazones**

PPAR-γ agonists are insulin sensitising drugs indicated mostly for T2D patients with IR. Many mechanisms have been proposed in order to explain the beneficial effects of PPAR-γ agonists on AD [65]. In AD models, PPAR-γ agonists improved learning and reduced amyloid burden and inflammation [66]. An experimental model with diabetes-induced vascular dementia showed that treatment with PPAR-γ agonists, pioglitazone, and rosiglitazone significantly reversed diabetes-induced impairment of learning and memory behaviour, and endothelial function [67].

Several studies have shown that pioglitazone treatment improved cognitive performance, lowered oxidative stress, and improved cerebral glucose utilisation [68–70]. In accordance, a study using aged APP transgenic mice with severe cerebrovascular and memory deficits demonstrated that pioglitazone therapy not only overcame cerebrovascular dysfunction and altered neuropeptidic coupling, but also counteracted cerebral oxidative stress, glial activation, and cholinergic denervation [71]. Furthermore, in another model, combination treatment with leptin and pioglitzone reduced plaque-associated neuritic pathology and synapse loss, as well as neocortical glial response [72].

Another study in a mouse model of AD with accelerated Aβ deposition and tau pathology showed that after 4 months of pioglitazone treatment, animals showed improved learning on the active avoidance task, reduced serum cholesterol, decreased hippocampal Aβ and tau deposits, and enhanced short- and long-term plasticity [73]. It has also been shown that low-dose pioglitazone might increase the expression of low-density lipo-protein receptor-related protein 1 (LRP1), which upregulates the clearance of Aβ, using human brain microvascular endothelial cells [74]. Another study found increased phosphorylation levels of CRMP2 as well as increased p35 protein levels in the cerebellum of APP/PS1 mice. Pioglitazone normalised the p35 protein and CRMP2 phosphorylation levels in the cerebellum. Interestingly, impaired motor coordination ability and long-term depression in APP/PS1 mice were ameliorated by pioglitazone treatment at the pre-Aβ accumulation stage [75]. However, a study failed to show any beneficial effects of pioglitazone therapy and showed that chronic treatment with pioglitazone decreased cerebral glucose utilisation in vivo. This evidence does not support the hypothesis that pioglitazone could act as a metabolic enhancer in AD, but it raises the question of how thiazolidinediones could be beneficial in neurodegenerative diseases [76].

A study using data from 5048 patients with new-onset T2D from the Taiwan National Health Insurance Research Database, during 1999–2006, showed that rosiglitazone treatment had a neutral effect on the risk of dementia (HR = 0.86, 95% CI: 0.70–1.15) [77]. However, another study from 2004 to 2009, using again data from the Taiwan National Health Insurance Research Database, in 6401 patients with T2D, who were treated with pioglitazone and 12,802 age- and sex-matched patients with T2D, who were never treated with pioglitazone and who were free of dementia at
baseline, showed that the risk of dementia decreased by 23% in the pioglitazone-treated cohort compared to the control group after adjustment for age, sex, hypertension, and stroke (HR = 0.77, 95% CI: 0.62–0.96) [78]. The same finding was confirmed when pioglitazone was used in combination with metformin in the same database [79]. It is noteworthy that a lower incidence of dementia was found in users of metformin plus pioglitazone compared with users of metformin plus rosiglitazone [79], showing a possible different action of the two agents on dementia. Another observational study, from 2004–2010, using data from 145,928 subjects aged ≥ 60 years, who were free of dementia at baseline, showed that long-term use of pioglitazone reduced the risk of dementia by 47% [80].

Therefore, there is insufficient evidence to support any beneficial effect of rosiglitazone in AD patients. However, the efficacy of pioglitazone seems to be promising and needs to be further confirmed in well-designed trials with large sample sizes. The cardiovascular risk associated with this class of medications is also a concern and has limited their use to just selected patients with T2D.

Incretins

Dipeptidyl peptidase 4 inhibitors

There is sufficient evidence based on experimental and clinical trials to indicate that dipeptidyl peptidase 4 inhibitors (DPP-4i) have neuroprotective properties, and several mechanisms have been proposed in order to explain the neuroprotective properties of DPP-4i. An animal study showed that sitagliptin treatment improved working and reference memories with reduction in HOMA-IR and incensement of the hypothalamic acetylcholine level, possibly through increased AdipoR1 expression [81]. The impact of sitagliptin on the deposition of Aβ within the brain was demonstrated in an animal model of AD, while in the same study sitagliptin improved deficits in memory-related behavioural paradigms [82]. Another study, using a model of AD mice, showed that sitagliptin reduced the escape latency times in the learning phase and elongated the time spent in the target quadrant. Furthermore, sitagliptin significantly reduced Aβ plaque deposition and elevated the spine density and the protein levels of synaptoneurosome GluA1- and GluA2-containing AMPA receptor in the brain of an APP/PS1 mouse model [83]. Finally, a human study in AD patients showed that sitagliptin therapy was associated with an increase in the Mini-Mental State Examination scores, showing significant improvement of cognitive function in elderly T2D patients [84]. Unexpectedly, one study found that sitagliptin was not effective against pathological tau phosphorylation in the hippocampus of OLETF T2D rats. On the contrary, sitagliptin aggravated tau phosphorylation. This paradoxically increased tau phosphorylation was attributed to activation of the glycogen synthase kinase 3β [85].

A study tested the in vivo actions of glucagon-like peptide-1 (GLP-1) in the diabetic brain by a 10-week treatment of ZDF rats with alogliptin treatment. Alogliptin increased the circulating levels of GLP-1 by 125% and decreased blood glucose in by 59%. Results like the above suggest that incretin therapies might reduce cognitive decline in aging T2D patients and also might have a favourable effect in treating AD [86]. Another DPP-4i, linagliptin, significantly protected against Aβ-induced cytotoxicity, and prevented the activation of glycogen synthase kinase 3β and tau hyperphosphorylation by restoring insulin downstream signalling, suggesting a finding that might have a therapeutic impact in the reduction of Aβ-induced impairment of insulin signalling and neurotoxicity in AD pathogenesis [87]. In another study, linagliptin improved brain incretin levels and attenuated Aβ, tau phosphorylation, and neuroinflammation [88].

A study investigated the role of vildagliptin in diabetes-induced vascular endothelial dysfunction and subsequent vascular dementia in rats. Administration of vildagliptin significantly attenuated impairment of learning, memory, endothelial function, and blood-brain barrier permeability [89]. Results of another two studies showed that vildagliptin had a protective effect against cognitive deficits by reducing tau phosphorylation and increasing the expression of proteins associated with synaptic plasticity in the hippocampus of the tested animal models [90, 91]. Attenuation of Aβ, tau phosphorylation, and inflammatory markers and an improvement in hippocampal GLP-1 and memory retention were also observed following saxagliptin treatment [92].

Summarising, there is supporting evidence that DPP-4i might prevent cognitive decline. However, more clinical trials are needed in patients at high risk of cognitive decline, including those with and without diabetes, in order to establish a protective association.

Glucagon-like peptide-1 receptor agonists

The main described role in the brain for GLP-1 is in the regulation of food intake, because it is primarily distributed on hypothalamic nuclei [93]. GLP-1 receptor expression has also been demonstrated in the thalamus, brainstem, lateral septum, subfornical organ, and the area postrema, suggesting roles in memory, attention, and behaviour, all of which are affected in neurodegen-
Exendin-4 (Ex-4), a GLP-1 receptor agonist, has been shown to protect neurons from diabetes-associated glucose metabolic dysregulation in vitro and might have therapeutic value in the treatment of T2D-related AD [96]. A study using exenatide therapy showed that it had beneficial effects on impaired cognitive performance and hippocampal neuronal viability in AD by suppressing the inflammation response and increasing cholinergic activity [97]. One possible mechanism for the neuroprotection of Ex-4 appears to be the prevention of the hyperphosphorylation of AD-associated tau protein due to increased insulin signalling pathway in the brain [98, 99]. Furthermore, the existing data suggest that GLP-1 receptor agonists can protect neurons against metabolic memory via Forkhead box class O (FoxO) pathways, silent information regulator 2 homolog 1-dependent deacetylation, and protein kinase B-dependent phosphorylation of FoxO1 [100].

Liraglutide can increase progenitor cell proliferation, and induce neuroblast differentiation and subsequent differentiation into neurons in an AD mouse model [101]. Also, the neuroprotective effects of liraglutide on diabetes-induced cognitive impairments are associated with the improvements of hippocampal synapses and inhibition of neuronal apoptosis [102]. Moreover, liraglutide enhances and reverses the impairments of synaptic plasticity induced by Aβ fragments, showing a significant effect on neurotransmission in the brain in AD [103]. Liraglutide treatment significantly decreases IR aberrations in conjunction with a concomitant decrease in amyloid plaque load. Liraglutide also induces a highly significant reduction in astrogliosis and microglial number associated with both plaques and IR pathology [104]. Subcutaneous administration of liraglutide prevented memory impairments and alleviated the ultra-structural changes of pyramidal neurons and chemical synapses in the hippocampal region. Furthermore, liraglutide reduced Aβ1–42-induced tau phosphorylation via the protein kinase B and glycogen synthase kinase-3β pathways [105]. Liraglutide restores both peripheral and brain insulin sensitivity and ameliorates tau hyperphosphorylation in rats with T2D, supporting the potential use of liraglutide for the prevention and treatment of AD in individuals with T2D [106]. Another study using hippocampal neuronal cultures determined one of the possible mechanisms of neuroprotection by liraglutide, which involves activation of the protein kinase A signalling pathway [107].

Furthermore, liraglutide showed restorative effects in late-stage AD in mice. Overall plaque load was reduced by 33%, and inflammation was reduced by 30%, while the neuronal progenitor cell count in the dentate gyrus was increased by 50% [108]. Liraglutide can also delay or partially halt the progressive decline in memory function associated with hippocampal neuronal loss in a mouse model of pathological aging with characteristics of neurobehavioural and neuropathological impairments observed in early-stage sporadic AD [109]. However, an experimental study showed that long-term liraglutide treatment exhibited no effect on cerebral plaque load in two transgenic mouse models of low- and high-grade amyloidosis, which suggests differential sensitivity to long-term liraglutide treatment in various transgenic mouse models mimicking distinct pathological hallmarks of AD [110]. Another recent study reported neural effects of liraglutide in a middle-aged population with subjective cognitive complaints [111].

Another GLP-1 receptor agonist, lixisenatide, has been shown to reduce amyloid plaques, neurofibrillary tangles, and neuroinflammation in an experimental model showing promising results [112]. Lixisenatide, by affecting the PI3K-Akt-GSK3β pathway, can prevent Aβ-related impairments in synaptic plasticity and spatial memory of rats, suggesting that lixisenatide may be a novel and effective treatment for AD [113].

Finally, novel dual GLP-1/gastric inhibitory peptide (GIP) receptor agonists have been developed to treat T2D, and they also show good neuroprotective effects that are superior to single GLP-1 analogues. Several newer dual analogues have been tested that have been engineered to cross the blood-brain barrier. They show clear neuroprotective effects by reducing inflammation and oxidative stress and apoptotic signalling and protecting memory formation, synaptic numbers and synaptic activity, motor activity, dopaminergic neurons, cortical activity, and energy utilisation in the brain [114]. A study using a novel dual GLP-1/GIP receptor agonist (DA-JC4) once-daily for 14 days showed significant prevention of spatial learning and decreased phosphorylated tau levels in the rat cerebral cortex and hippocampus. DA-JC4 also alleviated the chronic inflammation response in the brain, as well as apoptosis [115]. Furthermore, a novel unimolecular GLP-1/GIP/Gcg triagonist has been shown to be efficacious in ameliorating cognitive deficits and pathological damage of 3xTg-AD mice, suggesting that the triagonist might be beneficial in the treatment of AD [116]. In another study, treatment with the novel triagonist reduced the total amount of Aβ, and reduced neuroinflammation (activated microglia and astrocytes) and oxidative stress in the cortex and hippocampus in rats. These findings show that novel triagonists are a promising lead for the design of future treatment strategies in AD [117].
The above findings support the potential use of GLP-1 receptor agonists for the prevention and treatment of AD in individuals with T2D. Therefore, larger and longer duration studies are warranted to determine whether GLP-1 receptor agonists have neuroprotective benefits in individuals at risk for AD.

Sodium glucose Co-transporter 2 inhibitors

There are very limited data regarding the potential effect of the newest antidiabetic treatment category, SGLT2i. A recent study showed that canagliflozin, a SGLT2i, might act as a potent inhibitor of acetylcholinesterase which is a primary target for AD therapy [118]. The same finding was observed using another SGLT2i, dapagliflozin. Thus, the above results might form the basis of future therapy against diabetes-associated neurological disorders [119]. However, large, well-designed trials are needed in order to find the impact of SGLT2i therapy on dementia and AD.

Insulin

Insulin modulates neurotransmitter release and synaptic plasticity, the basis for cognition, learning, and memory [119–121]. Animal models and human studies have extensively documented impaired insulin signalling and degradation in AD and T2D. It is known that insulin promotes tau hypophosphorylation, which stabilises microtubules and promotes tubulin polymerisation. Therefore, excess exogenous insulin might play a role in overcoming the decreased utilisation and transport of glucose in patients with AD. In addition, it has been demonstrated that intranasal insulin therapy may have beneficial effects on cognition and function in patients with AD [122]. Insulin is a multipotent hormone regulating not only glucose levels, but also cell survival and synaptic plasticity mechanisms of neurons. Insulin has been shown to facilitate reduction of intracellular amyloid plaque and downregulation of Aβ-derived diffusible ligand-binding sites [123]. On the other hand, insulin-induced hypoglycaemia causes adaptive changes in the brain, including an improved ability to use alternative fuels [74].

A study compared the effects of insulin glargine U100, detemir, and degludec on neural functions in an animal model. The results of the study showed that insulin glargine U100 enhanced memory functions and suppressed depression-like behaviour. These effects were more potent than those of detemir [124]. Another study aimed to determine whether treatment with intranasal insulin detemir or regular insulin improves cognition and daily functioning in adults with MCI or AD, and it showed that the regular insulin-treated group had better memory compared with placebo.

Furthermore, regular insulin treatment was associated with reduction in the tau-P181/Aβ42 ratio, while no significant effects were observed for the detemir-assigned group compared with the placebo group [125]. Another trial examined whether intranasal insulin detemir improves cognition or daily functioning in adults with MCI or AD. The results revealed a treatment effect for verbal and visuospatial working memory for subjects who received the high dose of intranasal insulin detemir. However, no significant differences were found for daily or executive functioning [126].

Conclusions

A lot of the existing literature data confirm a relation between T2D and dementia and AD with possible pathogenetic links to decreased brain insulin signalling, mitochondrial dysfunction, neuroinflammation, alteration of neurotransmitters, and vascular disease. On the other hand, many studies have shown that antidiabetic agents, especially metformin, glitazones, and GLP-1 receptor agonists, have a potential therapeutic role in the prevention or treatment of dementia and AD. However, the underlying mechanisms between antidiabetic agents and neurodegenerative diseases are not fully understood, and further studies are needed in order to improve knowledge on the possible pathophysiological links between them and, most of all, on their therapeutic implications.

Conflict of interest

The authors declare no conflict of interest.

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Arch Med Sci Atheroscler Dis 2020 e193
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