

# Diabetes mellitus and Alzheimer's disease: shared pathology and treatment?

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## Keywords

Alzheimer's disease, clinical trial, diabetes,  
insulin physiology

## Received

28 May 2010

## Accepted

22 September 2010

Epidemiological and basic science evidence suggest a possible shared pathophysiology between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). It has even been hypothesized that AD might be 'type 3 diabetes'. The present review summarizes some of the evidence for the possible link, putative biochemical pathways and ongoing clinical trials of antidiabetic drugs in AD patients. The primary and review literature were searched for articles published in peer-reviewed sources that were related to a putative connection between T2DM and AD. In addition, public sources of clinical trials were searched for the relevant information regarding the testing of antidiabetic drugs in AD patients. The evidence for a connection between T2DM and AD is based upon a variety of diverse studies, but definitive biochemical mechanisms remain unknown. Additional study is needed to prove the existence or the extent of a link between T2DM and AD, but sufficient evidence exists to warrant further study. Presently, AD patients might benefit from treatment with pharmacotherapy currently used to treat T2DM and clinical trials of such therapy are currently underway.

## Introduction

Type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are both more prevalent with ageing, but it has generally been assumed that this is coincidental, not a reflection of co-morbidity. However, evidence suggests that patients with T2DM are at an increased risk of getting AD and that hyperinsulinaemia and insulin resistance – hallmarks of T2DM [1–3] – can lead to memory impairment. Animal models of T2DM have reduced insulin transport to the brain, reduced insulin uptake and reduced neuronal insulin [4–6], consistent with reported reduced insulin levels, insulin receptor expression and insulin resistance in brains of AD patients [7–9]. Recently, Takeda *et al.* [10] reported studies in which they crossed two well-established mouse models of T2DM (*viz.* *ob/ob* and NSY mice) into an APP23 transgenic mouse background. They found that in both APP<sup>+</sup>-*ob/ob* and APP<sup>+</sup>-NSY mice, diabetes exacerbated cognitive dysfunction, which supports impairment in insulin signalling as a mechanistic link underlying these seemingly disparate disorders. From a clinical perspective, a link would suggest that currently available 'antidiabetic' drugs might be beneficial in treating AD patients. The present review summarizes the two disorders, the postulated common biochemical links, and the clinical trials of 'antidiabetic' drugs in AD.

## Diabetes

It is estimated that almost 8% (24 million) of the US population has diabetes [11]. Another estimated 57 million or more have prediabetes, defined as an intermediate state of altered glucose metabolism (blood glucose between 110 and 126 mg dl<sup>-1</sup>), placing them at increased risk for diabetes [12]. Type 2 diabetes mellitus is a condition in which a high blood glucose level results from increased hepatic glucose production, impaired insulin production by pancreatic  $\beta$ -cells, impaired insulin release in response to hyperglycaemic stimuli or 'insulin resistance' (inadequate response to insulin by target cells). Type 2 diabetes mellitus accounts for about 90–95% of diagnosed cases of diabetes [13]. Inadequate glucose control leads to medical complications and, possibly through defective leptin signalling, includes effects on the central nervous system (CNS) [14, 15]. Although T2DM affects persons 60 years and older disproportionately, the number of cases in the younger population is on the rise [13]. Type 2 diabetes mellitus is associated with a variety of risk factors (including a family history of diabetes, history of gestational diabetes, impaired glucose metabolism, poor diet, obesity and physical inactivity [16]) and affects men and women about equally [13]. Both genetics and lifestyle play significant roles [17].

About 60–70% of diabetics also exhibit mild to severe forms of nervous system damage [13]. This manifests as impaired sensation or pain in the feet or hands (diabetic neuropathy), slowed digestion of food in the stomach, carpal tunnel syndrome, erectile dysfunction and other peripheral nerve problems. Central nervous system complications can include stroke and possibly cognitive impairment [15]. Persistent blood glucose elevation contributes to atherosclerosis that impairs blood flow to the brain. Individuals with glycosylated haemoglobin (HbA<sub>1c</sub>) levels (a test that indicates blood glucose levels over the previous 3 months) greater than 7% are nearly three times as likely to have a stroke compared with people who have an HbA<sub>1c</sub> level less than 5% [18]. Other CNS complications may result from changes in blood–brain barrier or transport functions of the cerebral microvasculature [19]. Such damage might be associated with vascular dementia. Studies also suggest that diabetics are at greater risk of depression than nondiabetics [15], but the mechanistic link is not clear.

## Alzheimer's disease

Alzheimer's disease [20] currently accounts for 60–80% of cases of dementia [21]. Onset of symptoms progresses to cognitive decline that impairs social and other functioning and eventually leads to death [22, 23]. The exact pathological defects in AD are unknown, but prevailing theories implicate build-up of soluble  $\beta$ -amyloid oligomers or insoluble plaques or neurofibrillary tangles [22, 24].  $\beta$ -Amyloid [A $\beta$ , a 39–43 amino acid peptide formed from cleavage of amyloid precursor protein (APP)] is a naturally occurring transmembrane glycoprotein of unknown function [25, 26]. Neurofibrillary tangles are hyperphosphorylated 'tau' protein associated with microtubules in axons of neurons [27]. Early-onset AD has been linked to mutations on chromosomes 1, 14 and 21, suggesting that there is a genetic component or predisposition [28]. Consistent with this, Down's syndrome (trisomy 21) patients have a higher risk of developing AD by 50 years of age [29]. Late-onset AD appears linked to a gene on chromosome 19 coding for the cholesterol transporter protein apolipoprotein E (apoE). There are several alleles of the apoE gene, of which *apoE- $\epsilon$ 2*, *apoE- $\epsilon$ 3* and *apoE- $\epsilon$ 4* occur with the highest frequencies [30]. Inheritance of *apoE- $\epsilon$ 4* increases the risk of developing AD in an autosomal-dominant fashion (i.e. inheriting one copy *apoE- $\epsilon$ 4* results in a 50% chance of developing AD). Environmental factors appear to play key roles [31, 32], and there are postulated links to cardiovascular risk factors, such as high cholesterol, hypertension and obesity, as well as T2DM [33].

The single greatest risk factor for AD is increasing age [34]. In 2000, there were approximately 4.5 million AD patients in the USA, of whom 7% were between 65 and 74 years old, 53% between 75 and 84 years old, and 40% were  $\geq$ 85 years old [35]. Currently, there may be as many as 5.3

million [21], and projections are that by 2050 there will be 13.2 million [35]. Age-specific incidence reveals no significant sex difference [36], but possible race differences [37,38].

Average survival after onset of symptoms is 8 years (range about 3–20 years) [39]. At time of diagnosis, life expectancy is approximately half that of those of the same age not afflicted with AD [40]. Alzheimer's disease is currently one of the top 10 leading causes of death in the USA [41]. Alzheimer's disease patients typically die from opportunistic bacterial infections, nutritional deficiencies, choking, aspiration or trauma [42, 43]. No current treatment stops brain deterioration. The drugs available are able to slow worsening of symptoms for 6–12 months, but are effective in only about half the treated population [44].

## Possible links

There have been reports of links between T2DM and AD (sample shown in Table 1). Some of these are highlighted below.

### Insulin processing

Insulin (two peptidic chains joined by two disulfide bonds) is primarily secreted by  $\beta$ -cells of the pancreas and normally is released into the circulation through the portal vein in response to a rise in blood glucose. Insulin-degrading enzyme (IDE) catalyses the catabolism of insulin in the liver, kidneys and muscles [45, 46]. It is generally agreed that insulin located within the brain is mostly of pancreatic origin, having passed through the blood–brain barrier, although there is debate about the amount that is produced *de novo* within the CNS [47]. Insulin has a significant function in the hypothalamus and probably other brain regions. Major known actions of insulin in the brain include control of food intake (via insulin receptors located in the olfactory bulb and thalamus) and effects on cognitive functions, including memory [48, 49].

Possible common or interactive processes in T2DM and AD have been reviewed [50–52]. Within brain, insulin binds to the  $\alpha$ -subunit of the insulin receptor, activates tyrosine kinase phosphorylation of the  $\beta$ -subunit of the receptor, and leads to activation of several second-messenger transduction pathways. The neural Shc/MAP (Src homology collagen mitogen-activated protein) kinase pathway activates gene expression required for neuronal cell and synapse growth, maintenance and repair processes. It also serves as a modulator of hippocampal synaptic plasticity that underlies learning and memory [53]. Another pathway involves binding of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) to phosphatidylinositol 3-kinase (PI3K), which is necessary for synaptic plasticity and memory consolidation [54], retrieval and extinction of contextual memory [55], and A $\beta$ -induced memory loss [56]. It also induces the synthesis of nitric oxide, which in turn plays a

**Table 1**

Sample of studies that suggest a link between type 2 diabetes mellitus and Alzheimer's disease

Reference	Mechanism	Synopsis
Munch <i>et al.</i> , 1998 [135] Janson <i>et al.</i> , 2004 [89]	AGE Amyloid deposition in islet and brain cells	In diabetes, accelerated AGE formation is caused primarily by a higher level of plasma glucose. More islet amyloid in AD patients than control subjects. No greater brain amyloid in diabetic patients compared with control subjects. In cases of T2DM patients with brain amyloid, the extent of amyloid increased with longer duration of diabetes.
Rivera <i>et al.</i> , 2005 [75]	Low insulin and a decrease in ChAT	Low insulin levels and low insulin sensitivity can contribute to a decrease in acetylcholine synthesis, leading to AD.
Razay <i>et al.</i> , 2007 [128]	Metabolic syndrome	AD patients, compared with healthy, normal patients, had a greater waist circumference, higher triglyceride and glucose levels, and lower HDL cholesterol.
Beydoun <i>et al.</i> , 2008 [126]	Weight gain and obesity	Baltimore Longitudinal Study of Aging. Obesity, central obesity and weight loss among women seem to play a role in AD, while underweight and weight gain among men increase the risk.
Vilalta-Franch <i>et al.</i> , 2008 [129]	Metabolic syndrome	Patients with metabolic syndrome are diagnosed with AD at a younger age than AD patients without metabolic syndrome.
Miklossy <i>et al.</i> , 2010 [87]	Amyloid and hyperphosphorylated tau	Islet amyloid polypeptide and hyperphosphorylated tau were found in islet cells of the pancreas in T2DM patients (on autopsy).
Beeler <i>et al.</i> , 2009 [84]	JNK, IB1 and hyperphosphorylated tau with amyloid deposits	Both DM and AD involve co-localization of JNK, IB1 and hyperphosphorylated tau with amyloid deposits.

AGE, advanced glycation end-products; AD, Alzheimer's disease; T2DM, type 2 diabetes mellitus; ChAT, acetylcholine transferase; HDL, high density lipoprotein; JNK, c-Jun N-terminal kinase; IB1, islet brain 1.

role in learning and memory processes [57, 58]. Insulin receptors also modulate neurotransmission by phosphorylation of NMDA glutamate receptors (increasing the opening of the associated Ca<sup>2+</sup> channel), through influence on internalization of the AMPA receptor and by recruiting GABA receptors to the postsynaptic site [59].

Abnormal insulin processing, insulin receptor defects or postreceptor defects can lead to CNS problems [60], including AD, Parkinson's disease [61], Huntington's disease [62], malignancies [63], migraine headaches [64] and schizophrenia [64, 65].

### Insulin receptors

Insulin receptors located in the brain (InsR<sub>b</sub>) differ from insulin receptors found in the periphery (InsR<sub>p</sub>) in size ( $\alpha$ -subunits are smaller in InsR<sub>b</sub>), glycosylation and insulin-binding specifics (absence of negative co-operativity in InsR<sub>b</sub>) [66]. The InsR<sub>b</sub> are widely and irregularly distributed throughout the CNS in distinct patterns, with higher concentrations in olfactory bulb, cerebral cortex, hypothalamus, cerebellum and choroid plexus [67, 68]. The distribution of InsR<sub>b</sub> mRNA is similar [69].

Another receptor from the same protein kinase receptor family is the structurally similar receptor for human insulin-like growth factor (IGF1R) [70–72]. Both consist of two  $\alpha$ - and two  $\beta$ -subunits and are the product of a single gene: *InsR* on chromosome 19 and *IGF1R* on chromosome 15 [66]. Insulin and IGF bind to both receptors with different affinities [73]. Another receptor in the same family, IGF2R, is structurally distinct from InsR and IGF1R [66], binds IGF-I and IGF-II (two different types of IGF), but does not bind insulin [73]. The regional localization of InsR<sub>b</sub>, IGF1R, IGF2R are similar, and the actions of insulin and IGF overlap [66, 74].

### Acetylcholine

Recent research suggests a possible link between blood sugar, insulin resistance and inadequate production of acetylcholine (ACh). Synthesis of ACh involves the enzyme acetylcholine transferase (ChAT). Acetylcholine transferase is expressed in insulin and IGF-I receptor-positive cortical neurons; ChAT expression increases with insulin/IGF-1 stimulation; and ChAT co-localization in insulin or IGF-I receptor-positive neurons is reduced in AD. Therefore, low insulin levels and insulin resistance can contribute to a decrease in ACh levels, which represents a possible biochemical link between diabetes mellitus and AD [2, 75].

### ApoE- $\epsilon$ 4

Diabetes is not only characterized by insulin/glucose abnormalities, but also by dyslipidaemia [76]. As key players in lipid metabolism [77], apolipoproteins are receiving growing attention for their involvement in T2DM [78].

Of particular interest in the area of AD is ApoE, owing to a well-established positive correlation between an increased risk and earlier onset of AD with expression of *apoE- $\epsilon$ 4* isoform [79, 80]. Along with proteoglycans and serum amyloid, ApoE is a nonfibrillar component of cerebral and systemic amyloid deposits [79]. Compared with other ApoE isoforms, *apoE- $\epsilon$ 4* displays an enhanced ability to deposit the neurotoxic A $\beta$  while simultaneously contributing to decreased clearance of plaque. While isomeric differences in the CNS have yet to be entirely elucidated, *apoE- $\epsilon$ 4* exerts less protection against oxidative stress and contributes to cholinergic dysfunction in AD [80]. Furthermore, the lipid-binding capacity of ApoE, influenced by the cholesterol transporter ABCA1, may have implications in AD. Poor lipidation of ApoE, which can result from

transporter ABCA1 deficiency, confers a heavier amyloid burden, while overexpression of ABCA1 in the CNS (i.e. greater ApoE lipidation) results in significant reduction of A $\beta$  plaque formation [81].

Another relationship involving the presence of the *apoE- $\epsilon$ 4* allele is its negative correlation with brain expression of IDE, a highly conserved endopeptidase that degrades cerebral A $\beta$  [82]. However, in non-*apoE- $\epsilon$ 4* carriers, the IDE–A $\beta$  relationship may still be relevant, as hyperinsulinaemia might confer competitive inhibition of the binding (and hence, degradation) of A $\beta$  by IDE. While on average *apoE- $\epsilon$ 4* patients show decreased hippocampal IDE, further investigation is required [83].

### Amyloid and tau

Deposition of amyloid in brain and pancreatic islet cells represents a pathogenic similarity between AD and T2DM [84]. Pancreatic amyloid is produced in  $\beta$ -cells and is coreleased with insulin [85]. A study of transgenic mice found that excess accumulation of pancreatic amyloid leads to  $\beta$ -cell dysfunction, disruption in glucose homeostasis and T2DM [86]. In humans, on autopsy islet amyloid polypeptide and hyperphosphorylated tau were found in pancreatic islet cells of patients with T2DM [87]. An increased amount of neurofibrillary tangles and amyloid plaques in the hippocampus have been found on autopsy in patients with diabetes [88].

A community-based study investigated whether there is greater prevalence of pancreatic amyloid in patients with AD and greater prevalence of cerebral amyloid in patients with T2DM. Islet amyloid was more frequent and extensive in AD patients than in non-AD control subjects, but there was no increased frequency of brain amyloid in T2DM patients compared with non-diabetic control subjects. However, when cerebral amyloid was present, the extent of accumulation correlated with the duration of T2DM [89].

It is well established that A $\beta$  results from cleavage of APP precursor by secretases ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) [90]. Senile plaques develop from the release and accumulation of A $\beta$  peptide [91]. The A $\beta$  interacts with signalling pathways that regulate the phosphorylation of the tau protein, leading to hyperphosphorylation of tau and aggregation of neurofibrillary tangles in neurons [92]. Tau phosphorylation in both AD and T2DM involves activation of glycogen synthase kinase-3 (GSK-3), which phosphorylates glycogen synthase in the rate-limiting step of glycogen biosynthesis [93–95]. Glycogen synthase kinase-3 is a crucial step in formation of neurofibrillary tangles, and therefore, GSK-3 inhibition could be a common target treatment of both AD and T2DM [96, 97]. Glycogen synthase kinase-3 is regulated by the PI3K pathway discussed in the section **Insulin processing** above.

Another potential link involves a c-Jun NH<sub>2</sub>-terminal kinase (JNK) pathway [98]. JNK activity is induced in conditions of chronic hyperglycaemia and insulin resistance,

leading to oxidative stress and programmed cell death (apoptosis) of pancreatic  $\beta$ -cells [99]. Induction of the JNK pathway also leads to phosphorylation of c-Jun and tau found in brains of AD patients [100–102]. The protein JIP-1 [JNK-interacting protein 1; also known as 'islet brain 1' (IB1) protein because it is primarily expressed in brain and islet cells] is a key regulator of the JNK pathway [84]. Co-localization of JNK, IB1/JIP-1, hyperphosphorylated tau and amyloid deposits in neurofibrillary tangles in the brain and pancreatic islets suggests another possible link between the pathogenesis of AD and T2DM [84].

### Inflammation

Insulin resistance, a key aspect of T2DM, is associated with inflammation [45], specifically with elevated levels of the inflammatory mediators interleukin-6 (IL-6), C-reactive protein and  $\alpha$ -1-antichymotrypsin [103–105]. It is postulated that elevated levels of acute-phase inflammatory products are linked with immunological dysfunction, which leads to insulin resistance [106].

Likewise, there is evidence that AD is associated with inflammatory processes [107–109]. Inflammatory products accumulate at different rates in Alzheimer's patients compared with healthy control subjects [110], the inflammatory cytokine IL-6 is present in senile plaques of AD patients [111], and elevated immunoreactivity to IL-6 is found in lumbar and ventricular cerebrospinal fluid in patients with AD [112]. At least two studies link C-reactive protein with an increased risk of AD [113, 114]. There are also reports of reduced incidence of AD in people who take non-steroidal anti-inflammatory drugs for chronic pain [115, 116].

Interestingly, peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) agonists, a class of antidiabetic drugs that reduce insulin resistance, appear to have anti-inflammatory effects [117]. Such drugs should reduce the levels of IL-6 and other inflammatory mediators [45] and might be beneficial in treating or preventing AD.

### Mitochondria and oxidative stress

Mitochondrial dysfunction and oxidative stress play key roles in the pathogenesis of both AD and T2DM, and represent a possible link [118]. There is increased oxidative stress in T2DM, with reduced antioxidant capacity [119], which has been suggested can lead to neuronal injury with mitochondria as specific targets [120]. In a rat model of T2DM, brain mitochondria display age-related impairment of the respiratory chain and an uncoupling of oxidative phosphorylation [121], which is vital for ATP production. Since mitochondria provide about 90% of the ATP required for normal functioning of neurons, mitochondrial dysfunction results in neural degeneration and loss of metabolic control. As the CNS is heavily dependent upon ATP production, it is more susceptible than other systems [122, 123]. According to the 'mitochondrial cascade hypothesis', the rate of accumulation of mitochondrial damage is deter-

mined by the basal rate of production of reactive oxygen species by the electron transport chain, which in turn is determined by genetics. Oxidative changes in nucleic acids, lipids and mitochondrial proteins amplify production of reactive oxygen species and trigger cells to generate A $\beta$ , tau phosphorylation and formation of neurofibrillary tangles [124].

### *Obesity and metabolic syndrome*

Obesity, especially central body obesity, is an independent risk factor for metabolic syndrome, a disorder of dyslipidaemia, insulin resistance and hypertension. Obesity and the metabolic syndrome are important risk factors for the development of T2DM [125]. The following evidence suggests that there may also be a link with AD: the Baltimore Longitudinal Study of Aging found that men with weight gain between the ages of 30 and 45 years and women with a body mass index >30 at ages 30, 40 and 45 years had an increased incidence of AD [2, 126]; a Swedish study found that AD risk increased by 36% for every 1.0 increase in body mass index at age 70 years [127]; men and women with a midlife body mass index >30 kg m<sup>-2</sup> have a greater risk for AD [33]; and patients with AD have a significantly larger mean waist circumference, higher mean plasma concentration of triglycerides and glucose, and lower mean plasma concentration of high-density lipoprotein cholesterol [128]. The significant role of leptin in regulating brain function might also be involved. As recently suggested by Han & Li [129], the proposed link between T2DM and AD would be advanced by studying defective leptin signalling in the absence of perturbed insulin signalling [129].

### *Advanced glycation end-products*

Advanced glycation end-products (AGEs) are created when reducing sugars react nonenzymatically with the amino groups of proteins and then undergo further reactions, such as rearrangement, dehydration and condensation, to become irreversibly cross-linked, heterogeneous derivatives [130]. Advanced glycation end-products were originally identified in 1912 as end-products of the Maillard reaction [131]. Advanced glycation end-products accumulate in various cells due to normal ageing, but the rate of accumulation is significantly elevated in DM [132, 133]. Increased formation of AGEs is also found in AD. However, extracellular accumulation of AGEs in AD is more likely to be caused by the accelerated oxidation of glycosylated proteins, e.g. by redox-active iron bound to proteins in amyloid plaques [134, 135]. Intracellular accumulation of AGEs in both AD and DM is caused by the presence of phosphates and reactive sugars, such as fructose. The metabolic consequences include oxidative stress, glucose hypometabolism and impaired cell function [135]. Advanced glycation end-products have been found in the CNS of diabetic patients, which could provide a mechanistic link [136].

## **Clinical trials of antidiabetic drugs in Alzheimer's patients**

If there is, in fact, some biochemical link between T2DM and AD, then could it be possible that a drug currently approved for T2DM could also be useful for treating AD? We summarize some ongoing trials below.

### *PPAR $\gamma$ agonists*

Peroxisome proliferator-activated receptor- $\gamma$  is a key neuromodulator found in increased amounts in the brain of AD patients [137]. Peroxisome proliferator-activated receptor- $\gamma$  plays a role in multiple processes thought to be involved in the pathogenesis of both diabetes and AD, including inflammatory and metabolic processes, cell growth and differentiation [138]. Initially, the role of PPAR $\gamma$  was explored through the class of drugs known as thiazolidinediones (in particular, rosiglitazone and pioglitazone). Their mechanism involves the stimulation of PPAR $\gamma$  action in response to changes in insulin, thereby triggering a drop in serum glucose [139]. These drugs improve insulin resistance [45], promote cholesterol homeostasis [140] and neuronal Ca<sup>2+</sup> homeostasis in hippocampus [141], and reduce cerebral inflammation through inhibition of IL-6 and tumour necrosis factor [117]. Such actions are hypothesized to control the proliferation of  $\beta$ -amyloid peptide and improve cognitive function in AD patients [45].

We found 12 studies (three pilot studies and nine clinical trials) that were designed to explore the potential benefits of PPAR $\gamma$  agonists. Of the 12, three were terminated early and one is currently ongoing. The remaining eight studies were all placebo controlled (three open label, five double blind). Seven evaluated placebo vs. rosiglitazone 2, 4 and/or 8 mg (monotherapy or concomitant with an acetylcholinesterase inhibitor, frequently donepezil); one assessed cognitive efficacy of donepezil compared with rosiglitazone and placebo; and two evaluated pioglitazone 15–30 mg vs. placebo. The mean age range of patients across the eight studies was 50–90 years. Subjects with T2DM were only included in the three pilot studies. Enrolled patients had either amnesic mild cognitive impairment (MCI, a prodromal stage of AD [142]) and/or mild to moderate AD (NINCDS/ADRDA classification [143]) with a MMSE (Mini Mental State Examination) level of cognitive impairment score of 10–26 (of a possible 30). Cognitive measures included the Assessment Scale-Cognitive (ADAS-Cog) test, Clinician's Interview-Based Impression of Change plus Caregiver Input (CBIC+) and MMSE, among others. Sato *et al.* [144] also measured regional cerebral blood flow via single photon emission computed tomography studies. The mean duration of the studies was 24–48 weeks.

The results of Watson *et al.* [145] demonstrate a positive correlation between insulin levels and cognitive improvement (increase in recall and lower error rate) at month 6 with rosiglitazone compared with placebo. Plasma A $\beta$  levels remained stable throughout rosiglitazone

treatment. Although Risner *et al.* [146] did not initially observe statistically significant differences between treatment groups, subgroup analysis revealed that improvement in cognitive function was related to ApoE genotype, in particular, to the *apoE-ε4* negative allele. Subsequent larger studies were unable to confirm such a connection, except for one study that reported a small potential benefit with rosiglitazone 2 mg and donepezil across all ApoE genotypes. However, two recent pilot studies [144, 147] agreed with the results of Watson *et al.* [145]. Sato *et al.* [144] reported that the pioglitazone cohort had an increase in regional cerebral blood flow in the right and left parietal lobe and some degree in the frontal lobe at month 6. The adverse effects most commonly noted in these studies were peripheral oedema with rosiglitazone and pioglitazone.

In summary, based on the eight studies reviewed, the use of thiazolidinediones might confer some therapeutic benefit as an adjunctive agent in select patients in the pre-initial to initial stages of AD, especially if AD is a consequence of insulin dysregulation and/or the patient has a prior medical condition of T2DM.

### Intranasal insulin

Another therapeutic strategy is intranasal administration of insulin [148]. Insulin is able to enter the brain within a short time via transport across olfactory and trigeminal perivascular channels and axonal pathways [149]. Two randomized, placebo-controlled studies that explored the effects of intranasal insulin on memory in individuals with MCI or mild AD have been reported [150, 151]. Baseline characteristics were similar for the insulin group and placebo group with respect to age (mean range 60–80 years) and fasting glucose/insulin levels. Participants were either diagnosed with AD (NINCDS-ARDA criteria) or had amnesic MCI. In the study of Reger *et al.* [151], participants were further subdivided based on ApoE genotype (*apoE-ε4*  $-/+$  allele), and cognitive function was measured 45 min postadministration of treatment agent. The participants treated with intranasal insulin (20 IU twice daily) displayed greater improvement in memory and attention on day 21. Participants with *apoE-ε4* negative allele displayed significant improvement in story recall at both 20 and 40 IU doses compared with the saline group and *apoE-ε4* positive group. In the assessment for word list recall, patients in the *apoE-ε4* negative group taking 40 IU of insulin performed better than patients in other groups, while no significant difference was observed between insulin groups and between insulin and placebo in the parameters of attention and working memory. In the *apoE-ε4* positive group, cognitive function (working and verbal memory) was reduced with treatment. Plasma insulin levels were unchanged. Given what is known about AD and diabetes, it is not surprising that intranasal insulin could have different effects depending on the *apoE-ε4* genotype. Adverse effects were minor and included head-

ache, nosebleed and nose soreness. Although the results reveal statistically and clinically significant differences between intranasal insulin vs. placebo, the studies were preliminary. They provide a direction for larger studies.

### Metformin

Metformin (*N,N*-dimethylimidodicarbonimidic diamide) is an orally active biguanide that lowers blood glucose levels by suppression of hepatic gluconeogenesis. It also increases insulin sensitivity and peripheral uptake, increases fatty acid oxidation, and decreases gastrointestinal absorption of glucose. One phase II clinical trial is currently investigating the effect of metformin in patients with MCI [152]. The results have not been reported at the time of writing.

## Type 1 diabetes mellitus and AD

Although the majority of recent attention has focused on the association of T2DM with AD and is the subject of the present review, it should be noted that cognitive deficits (such as impaired learning, memory, problem solving and mental flexibility) have been found to be more common in patients with type 1 diabetes mellitus than in the general population [153, 154], and type 1 diabetes mellitus negatively affects brain pathology and cognitive performance in a mouse model of AD [155].

### Caveats

The link between T2DM and AD must still be considered a postulate at this time. Critical evaluation of some aspects of the cited studies reveals potential areas for further verification or elaboration. For example, because several of the changes in markers of insulin homeostasis occur increasingly in old age, AD as type 3 DM should be balanced within the ageing spectrum; Takeda *et al.* [10] suggest that the cognitive dysfunction noted in the T2DM  $\times$  APP cross mice was probably caused by cerebrovascular changes (this has implications for treatment where brain vascular lesions have to be considered); overall, studies have found little or no influence of T2DM on the progression of AD lesions, but as the recent work of Sonnen *et al.* [156] shows, increased risk of dementia or even AD (where there might be mixed pathology) is associated with microvascular pathology or small vessel disease rather than AD increased pathology (this would be relevant to future therapeutic approaches). Furthermore, while the epidemiological studies are quite convincing, the observations regarding decreases in insulin, insulin receptors and insulin/IGF-1 signalling in the AD brain are open to interpretation. For example, it is possible that the decrease is in fact protective and is reflective of what is occurring in the nerve cells that survive, consistent with recent results showing that

decreases in insulin or IGF1 signalling in AD mice prolong lifespan, reduce A $\beta$  deposition and enhance cognitive function [157–159]. Likewise, several studies have noted a connection between diabetes and AD only in *apoE- $\epsilon$ 4* negative individuals (e.g. [160]) and that intranasal insulin transiently enhances cognitive function in normal individuals as well as AD patients [148], suggesting that the effect is unrelated to the AD phenotype. Finally, safety concerns have arisen about the use of the PPAR $\gamma$  agonist rosiglitazone for treating patients with diabetes (e.g. [161]). In relation to this topic, rosiglitazone increases weight gain, and obesity is a risk factor for cognitive dysfunction and AD.

## Summary

Diabetes and Alzheimer's disease have traditionally been thought to be independent disorders. However, the results of recent epidemiological and basic science investigation have suggested possible associations and some common pathophysiological mechanisms. If true, common pharmacotherapy should be effective. There are currently clinical trials testing the effectiveness of 'antidiabetic' drugs in AD patients. The results will not only be important for potential new pharmacotherapy for AD patients, but will also shed light on a connection between these otherwise seemingly disparate serious disorders.

## Competing interests

There are no competing interests to declare.

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