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Type 2 diabetes and cognitive impairment: linking mechanisms

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Abstract

This manuscript provides a brief review of current concepts in the mechanisms potentially linking type-2-diabetes (T2D) with cognitive impairment. Existing epidemiologic studies, imaging studies, autopsy studies and clinical trials provide insights into the mechanisms linking T2D and cognitive impairment. There seems to be little dispute that T2D can cause cerebrovascular disease and thus cause vascular cognitive impairment (VCI). Whether T2D can cause late onset Alzheimer's disease (LOAD) remains to be elucidated. Many epidemiologic studies show an association between T2D and cognitive impairment, but the association with VCI seems to be stronger compared to LOAD, suggesting that cerebrovascular disease may be the main mechanism linking T2D and cognitive impairment. Imaging studies show an association between T2D and imaging markers of LOAD, but these observations could still be explained by cerebrovascular mechanisms. Autopsy studies are few and conflicting, with some suggesting a predominantly cerebrovascular mechanism, and others providing support for a neurodegenerative mechanism. Thus far, the evidence from clinical trials is mixed in supporting a causal association between T2D and cognitive impairment, and most clinical trials that can answer this question are yet to be reported or finished. Given the epidemic of T2D in the world, it is important to elucidate whether the association between T2D and cognitive impairment, particularly LOAD, is causal, and if so, what are the mechanisms.

Keywords

Type 2 diabetes; mechanisms; dementia; late onset Alzheimer's disease; vascular cognitive impairment

1. Burden, spectrum and markers of cognitive impairment: implication for mechanisms

The spectrum of cognitive impairment ranges from mild deficits that are not detected clinically to the most severe clinical form, dementia. The types of cognitive impairment detected clinically and in research provide mechanistic insights and are thus briefly covered here. Late onset Alzheimer's disease (LOAD) is the most common form of dementia, accounting for between 70% to over 90% of all cases[1], and its prevalence is expected to quadruple by the year 2047 in the United States [2]. As much as 50% of the population aged 85 years and older, the fastest growing segment of the population, may have LOAD [3].

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Vascular dementia (VD) is the second most common form of dementia, although it varies widely depending on the criteria used [4]. Mixed dementia is a term that has been coined to describe the mix of clinical features of LOAD and VD. Other types of dementia such as fronto-temporal dementia and lewy body dementia occur less commonly and will not be covered in this review. The reference to dementia in this review is a reference to LOAD, VD, or mixed dementia. Mild Cognitive impairment (MCI) has been used to describe a transitional state between normal cognitive function and LOAD dementia [5, 6], and has thus been targeted for interventions [7]. Individuals with MCI do not have dementia but have memory complaints without loss of function in their daily activities[6]. While general cognitive performance is well preserved, memory performance on standardized tests falls below expectations for age and education. MCI can be classified in amnestic and non-amnestic MCI. It is believed that amnestic MCI is an early stage of LOAD, while non-amnestic MCI, such as executive MCI, is less specific to LOAD [5] and may be related to vascular cognitive impairment. Persons with amnestic MCI progress to LOAD at the rate of nearly 10% to 15% per year in clinical studies [5] compared to 1 to 2% in elderly persons with normal cognition[6]. The prevalence of amnestic MCI varies between 3% and 20% depending on the criteria applied [8], and increases from about 1% in persons 60 years old to 25% at age 85 [9]. One study in the United States estimated the prevalence of non-dementia forms of cognitive impairment to be over 20% among persons 71 years and older. [10] In terms of milder cognitive deficits, it is traditionally considered that vascular forms of cognitive impairment are characterized by a predominance of impairment in executive-frontal abilities[11] tested with such instruments as the trails and the digit symbol substitution test, while memory deficits, primarily of the consolidation type, are typical of the start of LOAD [12] and are detected primarily in test of verbal memory. However, memory impairment due to retrieval deficits also occurs in cerebrovascular disease, and memory deficits due to strategic infarcts may be difficult to distinguish from those due to LOAD. Risk factors for cognitive impairment are studied in epidemiologic studies through the outcomes of performance in particular cognitive domains, as MCI, or as dementia. Associations with particular cognitive domains and MCI and dementia subtypes suggests potential underlying mechanisms (neurodegenerative vs. vascular), with the caveat that clinical diagnosis and neuropsychological testing has inherent error.

Brain imaging correlates are also important to consider in exploring mechanisms linking T2D and cognitive impairment. The most common brain imaging modalities used in cognitive research are magnetic resonance imaging (MRI), both structural and functional, and positron emission tomography (PET) scan[13].

In structural MRI, white matter hyperintensities and infarcts are commonly considered proxies of cerebrovascular disease[14], while small Hippocampal volume and atrophy are considered markers of neurodegenerative disease[15]. However, it is increasingly accepted that not all WHI are equal. Frontal WHI may be more strongly related to ischemia, whereas posterior WHI may be related to neurodegenerative disease[16] and cerebral amyloid angiopathy (CAA) [17]. Microbleeds on MRI may be markers of CAA [18].

In functional MRI, decreased cerebral blood volume (CBV) in the entorhinal cortex of the hippocampus has been associated with LOAD, while decreased CBV in other areas may be related to normal aging or cerebrovascular disease[19].

fluorodeoxyglucose (FDG) PET is an accepted tool for the detection of LOAD and decreased uptake in particular areas such as the posterior cingulate are highly predictive of amnestic MCI and LOAD [20, 21].

PET scans with amyloid binders have become available more recently and hold the promise of showing amyloid burden in vivo[22], whereas recently this could be determined only through autopsy studies. In autopsy studies, the hallmarks of LOAD are amyloid plaques and neurofibrillary tangles[23], while the hallmarks of vascular disease are WHI and infarcts.

It is important to point out that pathology studies suggest that dementia, including LOAD, is more heterogeneous than previously recognized[24], and the association between the pathologic hallmarks of LOAD and dementia is attenuated with advancing age. In addition, elderly people with normal cognition have brain pathology usually ascribed to dementia. Thus, some propose that the classification of dementia into LOAD, VD, and mixed dementia should no longer be used. This is particularly important for the topic at hand because T2D and its related disorders are known to cause cerebrovascular disease and it is not surprising that they cause VD. Whether they cause LOAD or Alzheimer's disease (AD) pathology is a matter of controversy.

2. Burden of type 2 diabetes and related conditions

According to 2007 prevalence data from the Centers for Disease Control and Prevention (CDC) in the United States, T2D affects nearly 24 million people in the United States (US) [25]. T2D disproportionately affects the elderly, the group most at risk for cognitive impairment. Almost 25% of the population 60 years and older had T2D in 2007. Another 57 million people have pre-T2D, making the prevalence of T2D and pre-diabetes over 50% in persons 60 years and older. It is important to point out that both cognitive impairment and T2D are disorders that are more common in the elderly. This co-occurrence could mean that the processes that lead to T2D also cause cognitive impairment. However, this co-occurrence could also happen in a scenario in which T2D and cognitive impairment share causal pathways, or even that processes involved in cognitive impairment cause T2D.

When considering the links between T2D and cognitive impairment, it important to consider the natural history that leads to T2D. It is projected that a third of Americans born in 2000 will develop T2D [26]. A rise in adiposity, or body fat, is the cause of the increase in T2D [27]. Abdominal adiposity, the accumulation of body fat around the waist, also named central adiposity, seems to be the most important predictor of T2D[28]. Two-thirds of American adults are overweight or obese[29] and the prevalence of abdominal obesity among U.S. adults has increased continuously during the past 2 decades. Those with other metabolic syndrome components (high blood pressure, low HDL cholesterol, and high triglycerides) are at higher risk of T2D [30, 31]. The common link of these conditions (obesity, pre-T2D, T2D, high blood pressure, low HDL cholesterol, and high triglycerides) is insulin resistance[32]. There are two underlying mechanisms which lead to the onset of clinical T2D, the resistance of target tissues that dispose of glucose, such as muscle, to the actions of insulin (insulin resistance resulting in hyperinsulinemia) and inadequate insulin secretion from pancreatic β-cells[33]. In the natural history of progression to T2D, pancreatic β-cells initially in**c**rease insulin secretion in response to insulin resistance causing hyperinsulinemia and are able to effectively maintain glucose levels below the T2D range. When β-cell function begins to decline, insulin production is inadequate to overcome the insulin resistance, and blood glucose levels rise, resulting in pre-diabetes and T2D. Insulin resistance, once established, remains relatively stable over time. Therefore, progression of T2D is a result of worsening β-cell function with preexisting insulin resistance and hyperinsulinemia.

An implication of the natural history described above is that when an epidemiologic study finds a relation between the components of this continuum and dementia we cannot be

certain if we are looking at a surrogate marker of one of the other components (e.g. T2D is a marker of past adiposity or hyperinsulinemia, obesity is a marker of hyperinsulinemia) or if the important exposure is the one we are examining. From a mechanistic standpoint, it is difficult to discern whether the main mechanism relating T2D to cognitive impairment is related to glycemia, a component of the metabolic syndrome (e.g. hypertension), insulin resistance, or factors specifically related to adipose tissue. The answer could be that there is an aggregate effect of all the components in the lifespan. Biessels has described how individual components of the natural history that lead to T2D may affect cognition in different critical periods of the lifespan[34]. Given these facts, while this review focuses on T2D, it makes reference to components of the natural history that leads to T2D, such as adiposity and hyperinsulinemia. Adiposity, hyperinsulinemia, the metabolic syndrome and its components, are reviewed in more detail in other articles in this issue of the Journal of Alzheimer's Disease.

3. Potential mechanisms relating elevated T2D with cognitive impairment

T2D and its related conditions are known to cause cerebrovascular disease [35–40]. Elevated adiposity[41], hyperinsulinemia, T2D[42], and their clustering with other vascular risk factors[43] are risk factors for stroke. In addition, insulin or diabetes related by-products may affect the Amyloid cascade [44]. Thus, we classify the mechanisms linking this continuum with cognitive impairment as cerebrovascular and non-cerebrovascular.

3.1. Cerebrovascular mechanisms

3.1.1. Brain infarcts—Strokes, ascertained by clinical history[45], or as brain infarcts on MRI[46] are related to a higher risk of dementia including LOAD. The mechanisms for this association are not clear. However, pathology studies have demonstrated that the presence of Amyloid plaques is lower in brains of persons with dementia who also have infarcts [47, 48], suggesting that the presence of infarcts is an insult that lowers the threshold of Amyloid in the brain that is necessary to cause dementia.

3.1.2. White matter disease—White matter disease, ascertained as white matter hyperintensities (WHI) or leukoaraiosis on brain imaging represents microvascular disease in the brain or demyelination. However, the nature of WHI is still a matter of controversy. WHI are thought to be ischemic in origin in the same way that infarcts are[49] and have thus been proposed as surrogate markers of cerebrovascular disease[49]. However, recent evidence shows that WHI are common in LOAD and may be related to cerebral amyloid angiopathy[18, 50–52]. Thus, some WHI may be related to Amyloid burden and LOAD. WHI are common correlates of cognitive impairment in T2D [53], but it is unclear whether this WHI are markers of microvascular injury, or may represent a process related to Amyloid deposition.

3.2. Non cerebrovascular mechanisms

3.2.1. Hyperinsulinemia—Hyperinsulinemia is a plausible risk factor for LOAD independent of cerebrovascular disease because a) insulin can cross the blood brain barrier[54], and peripheral insulin infusion in the elderly may affect Amyloid β42 levels in the CSF [55], a surrogate marker of Amyloid β (Aβ) clearance in the brain and an indirect marker of LOAD risk; b) there are insulin receptors in the brain including the hippocampus and entorhinal cortex[56], structures affected early in LOAD[57]; c) Insulin degrading enzyme (IDE) has been linked to clearance of Aβ in the brain, and insulin and Aβ are both competing substrates for IDE [58]; d) Insulin in the brain can increase the deposition of Aβ and Tau protein phosphorylation, which are central to the pathogenesis of LOAD[54]. The pathways relating insulin in the periphery with Aβ clearance in the brain are multiple and

complex. Craft el al have reviewed how peripheral hyperinsulinemia affects amyloid beta clearance in the brain[59]. One potential pathway is that peripheral hyperinsulinemia down regulates insulin uptake in the blood brain barrier due to saturation over physiologic levels[60]. This may result in reduction of insulin levels in the brain and down regulation of expression of IDE[61] and reduction in IDE mediated Amyloid clearance[58]. This complex observation has been used to support both the seemingly paradoxical use of rosiglitazone, an insulin sensitizer [62, 63], and intranasal insulin [64] in the treatment of LOAD.

3.2.2. Advanced products of glycosilation (AGE)—AGE are closely linked with glycemia and diabetes, as elevated glucose concentration promotes AGE accrual. In a hyperglycemic environment, diabetic animal and human tissues contain increased AGE and upregulation of its receptor (RAGE).[65–67] AGE are known to be related to the traditional microvascular complications of T2D. [68–73] Increased expression of RAGE is also observed in LOAD [74–76] and expression of RAGE is enhanced in blood vessels near Aβ deposits in LOAD brain [74, 77].

3.2.3. Lipoprotein related proteins (LRP)—LRP is a family of lipoprotein receptors that affect lipid metabolism. LRP-1, found in the liver and other tissues, clears Aβ from plasma, and also mediates transport of Aβ out of the brain.[78, 79] LRP-1 is diminished T2D without affecting lipid levels[78]. Soluble LRP (sLRP) facilitates the clearance of Aβ by LRP-1 and may be a therapeutic candidate for the treatment of LOAD [80, 81]. Thus, LRP-1 is a plausible mechanism linking T2D with Aβ and LOAD.

4. Mechanistic insights from epidemiological studies linking T2D to cognitive impairment

T2D has been related to a two-fold higher risk of developing MCI among postmenopausal women [82]. A multiethnic study in elderly from New York city found that T2D was related to a higher risk of cognitive impairment-no dementia with stroke although the effect on cognitive impairment-no dementia without stroke was not evident after adjusting for demographic variables and the presence of Apo E-ε4 allele [83]. An Italian study showed a non-statistically significant increase of MCI with T2D in an elderly population[84], while a Canadian study found that T2D was related only to vascular cognitive impairment-no dementia [85]. A study in New York City found that T2D was related to a higher risk of both amnestic and non-amnestic MCI, underlining the potential importance of T2D as a risk factor for both neurodegenerative and vascular types of cognitive impairment [86]. A recent study in Olmstead county, Minnesota found that presence of T2D was not related to MCI risk, but longer T2D duration and treatment with insulin, a surrogate marker of T2D duration, were related to higher MCI risk [87]. Numerous studies have examined the relation between T2D and dementia. Table 1 shows the results of some representative prospective studies in different countries and age groups. In general, the association between T2D and dementia seems to be stronger for vascular dementia compared to LOAD, but these observations are inconsistent. Some studies have also reported an interaction between T2D and the APOE-ε4 allele, while others have not found this interaction. Importantly, the same study in Japanese Americans reported no associations between T2D and dementia at midlife[88], but strong associations when T2D was ascertained in old age[89] supporting our previous statement that T2D and cognitive impairment co-occur in the elderly.

The diagnosis of T2D is somewhat arbitrary and many cases go undetected. Few studies have examined the relation between continuous measures of glycemia and cognitive impairment. One study in postmenopausal women found that the risk of MCI and dementia increased with each 1% elevation in glycosilated hemoglobin, a stable measure of glucose

levels, even in women without T2D [90]. Glycosilated hemoglobin in persons without T2D correlates with both glucose intolerance and insulin resistance, and this study underscores the continuous nature of the relation between these constructs and higher dementia risk.

In summary, in epidemiologic studies, T2D and its related conditions are related to both vascular and neurodegenerative forms of cognitive impairment. However, the relation of the T2D with vascular forms for cognitive impairment is stronger and more consistent than the relation with neurodegenerative forms, begging the question of whether T2D could cause cognitive impairment primarily through cerebrovascular mechanisms.

5. Mechanistic insights from imaging studies

T2D is known to be related to a higher risk of cerebrovascular disease, including high WHI volume [53], and infarcts. What is controversial is whether T2D is related to traditional imaging markers of LOAD. A recent report showed that insulin resistance in persons with normal cognition and pre-T2D and early T2D without treatment is associated with reductions in cerebral glucose metabolic rate (CMRglu) measured with FDG-PET in frontal, temporoparietal, and cingulate regions, similar to those observed to predict the development of clinical AD. In addition, persons with pre-T2D and T2D demonstrated a different pattern of brain activation during a memory encoding task in the same study. The fact that insulin resistance was related to decreases in CMRg uptake in regions known to be predictive of MCI and AD in this supports a direct mechanism linking insulin resistance and T2D with LOAD. However, it is possible that CMRg decreases in those regions could be due to non AD mechanisms. Similar CMRg decreases are observed in non-amnestic MCI, thought to be in the spectrum of vascular cognitive impairment, as in amnestic MCI[91], thought to be a precursor of LOAD. Thus, it is possible that these CMRg differences are due to a vascular form of cognitive impairment, and not due to AD. Another important consideration is that the association observed by Baker et al could be caused by the aggregate of various mechanisms, including cerebrovascular and neurodegenerative, that result in a phenotype similar to AD from an imaging and neuropsychological standpoint. The adverse risk factor profile that accompanies insulin resistance and diabetes (hypertension, dyslipidemia) may lead to subclinical brain damage that makes persons with these conditions more susceptible to brain insults such as AD pathology[34]. One study examining the differential effects of insulin, glucose and cerebrovascular disease on the hippocampus, one of the early structures affected in AD, showed that these factors are related to global hippocampal dysfunction [19]. However, cerebrovascular disease by itself was associated with dysfunction in the CA1 subfield, a region more susceptible to ischemia; while, in contrast, dysfunction in the entorhinal cortex, a hippocampal subregion more specifically linked to AD, was found in association with elevation of insulin together with cerebral vascular disease. The results of these complimentary effects is global hippocampal damage resulting is a clinical syndrome that could be indistinguishable from amnestic syndromes similar to amnestic MCI and LOAD.

6. Mechanistic insights from pathology studies

There are few pathology studies exploring the association of T2D with brain pathology. The Religious Orders Study, a study of religious orders across the United States based at Rush University in Chicago, found that T2D was related to infarcts on autopsy but not AD pathology in persons with dementia [92]. This observation was interpreted as suggesting that the main mechanism linking T2D to dementia is the presence of infarcts, which lowers the burden of Amyloid necessary to cause memory decline and dementia. However, the Honolulu-Asia Aging Study[89], a study of Japanese-Americans, found that T2D was related to AD pathology, particularly in persons with the APOE-ε4 allele. The Adult

Changes in Thought Study, based at the University of Washington, reported that persons without T2D and with dementia had a greater amyloid-β peptide load and in the cerebral cortex, while those with both T2D and dementia patients had more microvascular infarcts. The number of microvascular infarcts was greater in persons with dementia and treated T2D, whereas amyloid plaque load tended to be greater for persons with dementia with untreated T2D[93]. A study from Japan with information on metabolic markers measured one decade before death, showed associations between one type of AD pathology, neuritic plaques, and T2D as well as with insulin resistance. In addition, the investigators found that this relationship was stronger in persons with the APOE-ε4 allele, also found in other epidemiologic [94] and pathology studies[89]. However, there were no associations between neurofibrillary tangle pathology and any measure of glycemic control. There are several caveats that must be taken into account in autopsy studies. Sample sizes tend to be relatively small, and selected from a much larger pool of participants. This lends itself to selection bias and the possibility of chance findings. Another potential explanation is reverse causality. Although the measurement of metabolic parameters preceded death by a decade or more in one study, β-amyloid pathology and metabolic changes may precede dementia diagnosis by decades [22] and insulin resistance and T2D could be a metabolic consequence or correlate of AD rather than a cause. Lastly, there is a growing notion that the dementias are more heterogeneous than originally thought. This heterogeneity may explain conflicting findings across studies.

7. The elephant in the room: possibility of reverse or joint causality

This point is highly speculative. There is no doubt that T2D, its related conditions, and the components of the metabolic syndrome cause cerebrovascular disease. Thus, there seems to be little doubt that T2D can cause vascular cognitive impairment. In addition, T2D is related to increased inflammation, AGE, and hyperinsulinemia. Thus, one is tempted to state that with all the possible mechanisms linking T2D and cognitive impairment (which could act in aggregate), the association between T2D and cognitive impairment must be causal. However, the association between T2D and LOAD has not been determined to be causal. Several lines of evidence provide some support to speculate that LOAD could cause T2D or that both could share causal pathways. First, from an ecological perspective, it is important to remember that both T2D and LOAD are diseases of the elderly that are likely preceded by long pre-clinical phases. Thus, it is difficult to establish causality in epidemiologic, imaging, or autopsy studies. Second, some have suggested that LOAD is characterized by insulin signaling deficits in the central nervous system [95, 96] that may be independent of “peripheral” insulin resistance and diabetes. It is important to understand whether primary insulin signaling deficits in the central nervous system can affect systemic metabolism and cause T2D- again, it is important to point out that this statement *is highly speculative*. Recent evidence shows one example in which T2D could share a common causal pathway without having a causal relationship. The sortilin pathway may be involved in the cause of LOAD [97], and this pathway may also be separately involved in T2D [97]. It is possible that observations made in epidemiologic studies are the balance of the possibilities described above: T2D causes cognitive impairment, LOAD causes or is accompanied by T2D, and T2D and LOAD share common causal pathways. The discrepancies among studies could be caused by the differential prevalence of these phenomena in a particular sample or population. The ideal way to demonstrate that the association between T2D and cognitive impairment is at least partially causal and gain further insight into mechanisms is through clinical trials. Lastly, both T2D and LOAD are prevalent conditions of aging, and it is possible that their association is coincidental. More information on the potentially complex relationship between diabetes and cognitive impairment can be found in published reviews[98, 99].

8. Mechanistic insights from clinical trials

There are several types of interventions that have been demonstrated to prevent T2D in persons at risk though the increase of insulin sensitivity and the reduction of insulin levels that have been or are being tested for cognitive impairment: Lifestyle intervention (diet, exercise), metformin, and rosiglitazone[100]. There are 2 studies of lifestyle intervention that now include measures of cognitive impairment. These are the Finnish Diabetes Prevention Study (FDPS) and the Diabetes Prevention Program (DPP) Outcomes Study (DPPOS). The FDPS was a trial of lifestyle intervention vs. no intervention in 522 middle aged persons with overweight or obesity and glucose intolerance [101]. The risk of T2D was decreased by approximately 58% in the intervention group after approximately 3 years of follow-up. This improvement was achieved mostly through improved insulin sensitivity [102]. More importantly, lifestyle improvements and the risk of T2D remained lower in the intervention group several years after stopping the counseling [103]. The DPP was a trial of lifestyle vs. Metformin vs. placebo in over 3,000 participants with glucose intolerance[104]. The lifestyle intervention, which consisted of a program to achieve weight loss and increased physical activity, was the most effective with a 58% reduction in the incidence of T2D compared to placebo after 3 years, a reduction similar to that achieved in the FDPS. After 3 years the DPP became an observational study called the DPPOS, but participants remained in their randomization groups and persons in the placebo group received a lifestyle intervention. The DPPOS recently reported that benefits in the prevention of T2D continue after 10 years of follow-up [105]. The FDPS and DPPOS may report results of their cognitive assessments in 2012. If the intervention arms of the FDPS and The DPPOS showed decreased cognitive impairment compared to the control arm, it would provide solid support to the notion that the relationship of T2D with cognitive impairment is causal. If no association was found, multiple explanations should be considered including that the timing of the intervention and the measurement of cognitive impairment; however, in this scenario of negative findings in both studies, consideration should be given to the possibility that the association between T2D and cognitive impairment is not causal.

There is a rich literature of relatively small short term studies of exercise and its effects on cognition[106] which demonstrate a clear benefit of exercise particularly on executive functions. The assessment of cognition in the FDPS and DPPOS will allow the specific examination of the effects of long term improvements of insulin sensitivity and T2D risk on memory, and non-memory cognitive abilities

Thiazolideniodones are PPAR-gamma agonists and potent insulin sensitizers[107]. Based on the powerful insulin sensitizing actions they are being studied as a potential treatment of AD based on the hypothesis that treating hyperinsulinemia lowers amyloid beta deposition and AD progression. One pilot 6 month trial of rosiglitazone in 30 subjects with mild AD or AMCI showed that persons receiving 4 mg daily had better delayed recall at months 4 and 6 and better selective attention at month 6, and plasma Amyoid beta decreased in persons on placebo while there was no change in persons on treatment[62]. There was a decrease in insulin levels at 6 months demonstrating the metabolic effects of rosiglitazone, and better cognitive performance was related to lower insulin levels. A randomized placebo controlled trial lasting 24 weeks of rosiglitazone 2,4, or 8 mg in 511 persons with mild to moderate LOAD found no effect in their primary outcomes (ADAS-COG) in the ITT analysis[63]. There was a significant interaction between APOE-ε4 and ADAS-COG, and persons on 8 mg rosiglitazone without any APOE-ε4 allele showed an improvement in ADAS-COG (and improvements in insulin levels), while person with APOE-ε4 showed no benefit. However a phase III trial of rosiglitazone (NCT00428090) in mild to moderate LOAD failed to show a benefit. [108]. This result does not support the hypothesis that T2D and LOAD are related. However, it is important to consider that treating persons with established dementia may be

too late to see a response. In addition, rosiglitazone may have adverse cardiovascular effects [109] that could eclipse other beneficial effects. It is possible that the use of thiazolidinediones at earlier stages, such as in persons with MCI, could improve the risk of dementia. The Rosiglitazone Effects on Cognition for Adults in Later Life (RECALL; NCT00242593) study is examining the effects of rosiglitazone on cognition in persons with MCI. The Pioglitazone or Exercise to Treat Mild Cognitive Impairment (POEM; NCT00736996) is exploring the effects of pioglitazone compared to exercise or placebo in persons with MCI.

Metformin is a medication belonging to the biguanide class[110, 111] that has been shown to be effective in the prevention of T2D in the DPPOS. While the mechanisms for the action of metformin are not completely understood, it clearly reduces insulin levels[112], inflammation and thrombosis[113], and the risk of the metabolic syndrome[114] and T2D[115] in persons without T2D. One recent study in cellular models showed that Metformin increases the production of amyloid beta through up-regulation of beta-secretase[116] and the authors raised the concern that Metformin could increase the risk of LOAD. However, this study needs to be replicated, and the relevance of its findings to humans demonstrated. The effect of Metformin on cognition will be assessed in the Metformin arm of the DPPOS. Additionally, there is an ongoing phase II trial of Metformin (NCT00620191) testing whether Metformin can decrease cognitive decline and dementia in persons with MCI. The results of this trial will be reported in 2012.

The causal relation of T2D with cognitive impairment could also be tested examining the effect of T2D control on cognitive impairment. There are 2 aspects to this question. One is whether diabetes control parameters (glycemia, blood pressure, lipids) affects cognition. The other aspect is whether the type of medication that is used for diabetes affects cognition. This is important because some medications increase insulin levels (e.g. insulin, sulfonylureas), and some medications decrease insulin levels (metformin, thiazolidinediones), and insulin could have an important role in Alzheimer's disease [44]. Recently, the "Action to Control Cardiovascular Risk in Diabetes--Memory in Diabetes" (ACCORD-MIND; NCT00182910) reported that that tight glycemic control arm(aiming at HbA1c < 6%) was not related to better cognitive outcomes, although the intensive control arm was related to slower loss of brain volume[117]. These findings do not support intensive glycemic control in persons with diabetes for the prevention of cognitive decline. [118]. However, data from the Informatics in Diabetes Education and Telemedicine Study (IDEATel) a randomized trial of telemedicine vs. usual care in 2169 elderly persons with T2D, showed that persons in the intervention group, which showed better T2D control parameters compared to usual care, had less global cognitive decline during a maximum of 6 years of follow-up[119]. Importantly, the glycemic control goals of IDEATel followed glycemic guidelines (HbA1c < 7%) that were less stringent than the goals in ACCORD, which showed increased mortality in its tight glycemic control arm[120]. Although the outcome of this study was global cognitive decline, the strongest correlate of global cognitive function in a subset of patients with detailed neuropsychological testing was memory performance, a proxy of LOAD. This suggests indirectly that T2D control mostly affected LOAD. Furthermore, a mediation analysis demonstrated that better HbA1c, an AGE, was the main mediator for the association between improved control and cognitive performance, providing further evidence for the involved mechanism.

9. Future directions

The most important questions that remain about the link between T2D and cognitive impairment are the following: 1) Is the association between T2D and LOAD causal?; 2) are the mechanisms linking T2D and LOAD dependent on insulin, or on correlates of T2D such

as abnormal glucose, AGE, and inflammation?; 3) are the mechanisms cerebrovascular or neurodegenerative (e.g. Aβ driven)? In the short term, question (1) could be answered by the results of the clinical trials mentioned previously. Thus far, no clinical trial has established definitively that LOAD risk can be modified by the treatment or prevention of T2D. If all clinical trials were negative, serious consideration should be given to the possibility of that the association between T2D and LOAD is not causal. If causality is established, then question (2) must be addressed. Given that T2D has many tightly correlated factors (e.g. AGE, insulin, glucose, inflammation) with evidence of plausible roles in LOAD, clinical trials would have to be conducted that manipulate a single element (e.g. AGE) while maintaining the others constant. This proposition seems very difficult and perhaps would be unethical. The second best option is to gain insights from existing clinical trials. In terms of question (3), if causality is established, a logical next step is to determine conduct in-vivo studies with LOAD biomarkers. The best way to discriminate between AD and non-AD forms of cognitive impairment with current technology is to use PET with amyloid binders, such as Pittsburgh compound B (PIB), which better discriminates AD from non AD cognitive syndromes compared to FDG PET [91]. Clarifying whether T2D is related to Amyloid-driven cognitive impairment or to cerebrovascular disease is important to guide future therapies in a growing susceptible population.

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Table 1

Summary of representative prospective epidemiologic studies relating Type 2 diabetes (T2D) with dementia.

First author, Year of Publication	Setting	Findings
Leibson, 1997[121]	Rates of dementia in 1455 persons 45 years and older with T2D in Rochester, Minnesota were compared to population rates.	Relative risk (RR) relating T2D and all cause dementia was 1.66 (95% confidence interval (CI): 1.34–2.05), RR relating T2D with AD was 2.27 for men (95% CI:1.55–3.31) and 1.37 for women, (95% CI: 0.94–2.01).
Brayne [122], 1998	2609 persons 75 years and older in Cambridge, England	Odds ratios (OR) relating T2D with all cause dementia was 2.62 (0.89–7.75), and 1.44 (1.05–17.00) for AD.
Ott[123], 1999	6370 persons 55 years and older in Rotterdam, The Netherlands	T2D related to both all cause dementia [RR= 1.9 [95% CI = 1.3 to 2.8]) and AD (RR 1.9 [1.2–3.1]). Risk of dementia highest in persons treated with insulin (RR 4.3; 95% CI: 1.7–10.5]).
Curb, 1999[88]	3,774 Japanese American men in Hawaii, United States, aged 45 to 68 years at the time of T2D ascertainment and between 71 to 93 years at the time of dementia ascertainment.	RR relating T2D with VD was 1.48; 95%CI: 0.79, 2.78), and 0.98 (95% CI: 0.48, 1.99) for AD
Peila, 2002[89]	2,574 Japanese-American men aged 77 years on average enrolled in the Honolulu-Asia Aging Study, Hawaii, United States. T2D was ascertained in older age	RR for total dementia was 1.5 (95% CI: 1.01–2.2), 1.8 for AD (95% CI: 1.1–2.9), 2.3 for vascular dementia (95% CI: 1.1–5.0). Individuals with both T2D and the APOE ε4 allele had an RR of 5.5 (CI 2.2–13.7) for AD compared with those with neither risk factor.
Arvanitakis, 2004[124]	824 persons older than 55 years from the Religious Orders Study in the United States	Hazard ratio (HR) relating T2D with AD was 1.65 (95% CI: 1.10–2.47).
Luchsinger, 2004[125]	1138 persons aged 65 years and older from Northern Manhattan, United States	Hazard ratio relating T2D and AD was 2.4 (95% CI: 1.8–3.2).
Schnaider-Beeri, 2004[126]	1,892 male civil servants aged 40 to 65 at time of T2D ascertainment in Israel	OR relating T2D at midlife with dementia 30 years later was 2.83 [95% CI = 1.40 to 5.71]).
Xu, 2004[127]	1,301 persons aged 75 years and older in Stockholm, Sweden	HR for T2D were 1.5 (95% CI 1.0 to 2.1) for dementia, 2.6 (95% CI 1.2 to 6.1) for VaD, and 1.3 (95% CI 0.9 to 2.1) for AD.
Whitmer, 2005[128]	8,845 participants of a health maintenance organization in California, United States, who were between the ages of 40 and 44 at the time of T2D ascertainment	HR relating T2D with dementia was 1.46, (95% CI: 1.19 to 1.79)
Xu, [129]2007	1,173 persons without known T2D aged 75 years and older in Stockholm, Sweden	Borderline T2D diagnosed with plasma glucose was associated with adjusted hazard ratios (95% CIs) of 1.67 (1.04–2.67) for dementia and 1.77 (1.06–2.97) for AD.
Irie, 2008[130]	2547 persons 65 years and from the Cardiovascular Health Study in the United States.	RR for AD 1.42 (95% CI: 1.02–1.97) but was 4.53 (95% CI: 2.47–8.30) when the APOE-ε4 allele was also present. There was no association with vascular dementia.
Cheng, 2011[131]	1488 persons aged 65 years and older without dementia at baseline from New York City recruited between 1999 and 2001.	Self reported T2D prevalence was 17%. T2D was related to incident dementia (HR = 1.7; 95% CI = 1.4–2.9) and LOAD (1.6; 1.0– 2.6) but the association with LOAD was appreciably weakened when only cases with mixed dementia were excluded (HR = 1.3; 95% CI =0.8–2.2). The association with VD (including cases of VD) was very strong (HR = 4.7; 95% CI = 1.6–13.7)