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The association of diabetes and dementia and possible implications for nondiabetic populations

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Abstract

Diabetes and prediabetic states have consistently been shown to be risk factors for cognitive decline, mild cognitive impairment and dementia. The importance of these findings is that diabetes and diabetes-related factors are modifiable, potentially permitting interventions aimed at postponing or preventing dementia. However, diabetes control cannot yet be implemented universally in diabetic subjects as a strategy for dementia prevention since the mechanisms by which diabetes impairs brain function and cognition are not fully understood. It is not clear which of the diabetes-related factors is crucial to this relationship. In addition, strict diabetic control has been demonstrated to carry risk for certain diabetic populations. The aim of the current article is to discuss current understanding of the relationships of diabetes and some of its characteristics with dementia, and suggest future questions to be answered.

Keywords

advanced glycation end products; antidiabetic medications; cognition; dementia; diabetes; hypoglycemia; insulin resistance; mild cognitive impairment; neuropathology; vascular

Type 2 diabetes has consistently been shown to be associated with increased risk for cognitive decline [1], mild cognitive impairment (MCI) [2] and dementia [3–5]: both vascular dementia [6,7] and Alzheimer's disease (AD) [6,7]. Such results have been demonstrated for diabetes both in midlife [3,5] and in old age [8,9]. Even prediabetes stages, namely, insulin resistance, have been shown to be associated with increased risk for cognitive decline and with increased rates of brain atrophy [10], both of which are associated with dementia. Similarly, impaired fasting glucose has been associated with cognitive impairment [11]. The results of studies on the association of diabetes with the rate of cognitive decline vary, with the majority showing a higher rate or risk for cognitive decline in diabetic subjects compared with nondiabetic subjects [12–16], some showing no association between the rate of cognitive deterioration and diabetes status [17–19] and others even showing a slower rate of decline in diabetic AD patients [20]. Differences between studies may be attributed to the cognitive status and age range of subjects included, as well as to the tools used to measure cognitive status and the definition of cognitive

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decline [16]. These differences may also reflect different roles for diabetes as a risk factor for dementia and in the rate of disease progression.

The importance of these findings is that diabetes-related characteristics are modifiable, so that the degree of control of plasma glucose levels, prevention or treatment of insulin resistance and/or specific treatments in diabetic patients could potentially prevent dementia or delay its clinical onset. Since diabetes prevalence in the Western world is accelerating alarmingly, such treatments may affect a large proportion of the population. However, despite the fact that good glucose control has been proven and is being recommended for the prevention of most diabetes-related complications [21], its effect on the prevention or delay of dementia onset is not known. Furthermore, in addition to glucose control, there are numerous diabetes-related factors that could interact with clinical expression of dementia and neuropathology, as well as the rate of cognitive and functional decline; for example, age at onset of diabetes, diabetes duration, type and mechanism of action of antidiabetic medications, presence of other diabetes-related complications and comorbidities, and so on. Despite the robust and consistent studies demonstrating that diabetes is a risk factor for AD based on clinical assessment of dementia [22,23], some neuropathological studies have found results to the contrary, for instance, that diagnosis of diabetes is associated with less AD neuropathological hallmarks [6,24]. Better understanding of the mechanisms by which diabetes compromises brain function may facilitate disentangling the discrepancy between clinical and pathological studies. The specific strategies required for dementia prevention in this complicated context of diabetes have not been studied. It is also unknown whether specific diabetic subpopulations require different preventive strategies. The importance of such ‘personalized’ methods have been exemplified in studies aimed to assess the beneficial effect of vitamin E in the prevention of other diabetes-related complications, namely cardiovascular complications and death. In these studies, vitamin E was significantly beneficial only for diabetic patients who carried the haptoglobin 22 genotype [25–27]. The understanding of such interactions may enable development of specific preventive strategies in different diabetic subpopulations, and may shed light onto the mechanisms underlying the relationships between diabetes and dementia. The need for such a personalized approach is emphasized by the recent surprising results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, showing increased risk for morbidity and mortality associated with tight diabetes control in some diabetic populations [28–30].

The mechanisms by which diabetes affects cognition may also be applicable to nondiabetic populations. The definition of diabetes is based on glucose levels only and is diagnosed when fasting glucose levels exceed 126 mg/dl or when random or postglucose tolerance testing levels exceed 200 mg/dl. However, there are several underlying mechanisms consistently associated with diabetes and with prediabetes states (the metabolic syndrome components [31], obesity [32] and hypertension [33]), which, by themselves, are associated with increased risk for dementia and impaired cognition. Consistent with such an approach are studies demonstrating an association between hemoglobin A1c (HbA1c) levels in nondiabetic subjects, even in those with HbA1c considered to be within the normal range, and rate of brain atrophy in a cohort of elderly subjects free of dementia at baseline [34]. HbA1c levels also predicted conversion to dementia and MCI in a cohort of nondemented women at baseline, even after excluding subjects who were frankly diabetic at baseline [35].

Numerous mechanisms have been proposed for the association between diabetes and dementia: brain vascular lesions [36], insulin resistance [37], advanced glycation end products [38], inflammation [39], oxidative stress [40] and competition of insulin and β-amyloid on the insulin-degrading enzyme [41]. This article will focus on the first three, with emphasis on the potential applicability of these mechanisms in nondiabetic, as well as in

diabetic, subjects. We will also review potential antidiabetic treatments as a means for dementia treatment/prevention.

Vascular pathology

Since diabetes is strongly associated with vasculopathy and cerebro vascular disease, the mechanism most commonly suggested to play a role in the association between diabetes and dementia/cognition is cerebrovascular disease, which alone, or in combination with the neuropathological hallmarks of AD amyloid plaques (APs) and neurofibrillary tangles (NFTs), increase the risk for dementia. However, neuropathological studies have shown conflicting results. Midlife diabetes was associated with increased risk for clinical diagnosis of dementia, both AD and vascular dementia, in the Honolulu Asia Aging Study (HAAS). This association was strongest for APOE ε4 carriers. In contrast to the clinical findings, the neuropathological assessment in the HAAS showed higher loads of hippocampal neuritic plaques, cortical and hippocampal NFTs, and higher risk for cerebral amyloid angiopathy only in APOE ε4 carriers [7]. When the entire study population was included in the ana lysis, there was no association between diabetes and the neuropathological hallmarks of AD. In the clinicopathological follow-up study of the Vantaa cohort, in which the subjects were 85 years old and above, similar clinical results were obtained, for instance, diabetes at baseline doubled the risk for dementia, AD and vascular dementia. However, in contrast to some of the neuropathological findings of the HAAS, diabetic subjects, compared with nondiabetic subjects, were less likely to have NFTs and APs, but more likely to have cerebral infarcts [6]. In fact, many neuropathological studies evaluating the association of antemortem diabetes and AD pathology have concluded that diabetes is associated with less AD pathology but more cerebrovacular disease pathology [24,42]. Other studies have found no relationship between diabetes and AD neuropathology [7,8,43,44] or an association of diabetes only with cerebral infarction [45]. Although they are beyond the scope of this article, neuro imaging studies are also important contributors to the understanding of the effect of diabetes on brain structure and function. Structural techniques, such as brain computed tomography and MRI, have demonstrated cortical atrophy and lacunar infarcts, stressing the role of vascular pathology but potentially other mechanisms in diabetes-related cognitive decline [46,47]. The role of white matter lesions has been less consistently demonstrated [46]. Functional brain imaging techniques have shown impairments in cerebral blood flow and glucose utilization [46]. Discrepancies between studies may be attributed to the age of the population studied (the association of AD-related neuro pathology and dementia may be stronger in younger compared with older subjects [9,10]) or to the age and form of assessment of diabetes (self-report vs medical charts, use of antidiabetes medications and midlife vs diabetes in old age). The lower load of AD-related neuropathology and higher load of vascular lesions in the brains of demented diabetic subjects, as demonstrated by some studies [6,45] may suggest that in diabetic subjects, who have greater risk for vascular brain lesions, a relatively low load of AD-related neuropathology is required to produce dementia [48]. Alternatively, the lower load of AD-related neuropathology, at least in some diabetic subjects, may be an effect of antidiabetic medications: insulin in combination with other antidiabetic medications was associated with less AD neuropathology in a clinicopathological study of elderly subjects [49], and even in subjects with no overt cerebrovascular disease. The relationship of antidiabetic medications with AD will be discussed in detail later.

Insulin resistance

Insulin resistance is another mechanism suggested to contribute to neuropathology and cognitive impairment. Understanding of this mechanism requires comprehension of the beneficial effects of insulin to the brain. Formerly, the brain was conceptualized as an

insulin-insensitive organ. However, insulin receptors have been detected in the brain with high concentrations in several brain areas, namely the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, septum and the medial temporal cortex [50–52]. The high concentrations of insulin receptors in the medial temporal cortex and hippo campus are consistent with its role in cognitive activity and memory. Insulin has been shown to have a role in aging-related processes [37], some of which may also be associated with brain aging and neurodegeneration [53]. In addition, intracerebro ventricular [54], intravenous [19] and intranasal [55] insulin administration in animal models [54] and in humans [55,56] have been demonstrated to improve memory. Learning has been shown to affect insulin signaling pathways in the hippocampus [57]. Although neurons possess mechanisms for influx of glucose that are not dependent on insulin, in certain brain regions, namely the hippocampus and hypothalamus, insulin has an effect on glucose uptake [58,59]. Others have shown that insulin is involved in long-term potentiation [60] and that it affects the levels of neurotransmitters involved in memory and learning [61,62]. In addition, downstream effectors and mediators of the insulin receptor signaling pathway have a role in reduction of tau phosphorylation [63–65] and NFT development [64]. Thus, insulin has beneficial effects in the brain that affect cognition. Therefore, it is reasonable to assume that when insulin levels in the brain are low or when tissue response to insulin is decreased (as in insulin resistance), cognitive processes would be compromised. Peripheral insulin resistance, which is associated with prolonged peripheral hyperinsulinemia and decrease in insulin transport through the BBB [50], may be one of the causes for reduced insulin levels in the brain. Previous studies in humans have consistently shown that peripheral insulin resistance *per se* and clinical entities characterized by insulin resistance, such as metabolic syndrome, are associated with cognitive compromise [10,66–69]. In postmenopausal women aged 50–65 years who were users of hormone replacement therapy, insulin resistance was associated with lower right and total hippocampal volume, and with worse overall cognitive performance and specific tests assessing verbal and nonverbal memory [10]. Metabolic syndrome was associated with poor cognitive performance in men aged 40–79 years [66] and with poor executive function in neurologically normal subjects aged 44–86 years of age, an effect that was independent of silent brain lesions [67]. Similarly, metabolic syndrome was associated with increased risk for cognitive impairment in a 4-year follow-up study of women who were cognitively intact at baseline [68]. In a longitudinal study of men who were 50 years old at study initiation, impaired acute insulin response at baseline was associated with an increased risk of AD up to 35 years later (median follow-up of 32 years) [69]. Insulin resistance was associated with reductions in cerebral glucose metabolic rate similar to those seen in AD, and in older adults (mean age of 74 years) who were not demented and did not meet criteria for MCI [70]. Hyperinsulinemia and hyperglycemia caused by insulin resistance were associated with accelerated neuritic plaque formation in a pathological follow-up study of a clinical cohort [71]. In animal models, diet-induced insulin resistance in the absence of diabetes was associated with lower cognitive performance manifested as inability to change contingency [72]. It is important to consider the fact that there is no simple dichotomy between insulin sensitivity and insulin resistance, but rather both exist along a continuum [73]. Since insulin resistance is thought to be an underlying cause of several clinical entities in addition to diabetes (metabolic syndrome, hypertension and cardiovascular disease) [50], therapeutic strategies aimed at the treatment of insulin resistance may have beneficial effects for the prevention of AD and dementia in populations other than diabetic subjects.

Advanced glycation end products

Chronic exposure to high glucose levels contributes to the formation of endogenous advanced glycation end products (AGEs). This is a group of molecules formed by irreversible nonenzymatic reaction between sugars and free amino acids. The accumulation

of AGEs occurs during normal aging and is exacerbated in diabetes [74]. AGEs can also form from exogenous sources, such as tobacco smoke [75] and food [76]. The common consequence of exposure to all kinds of AGEs is covalent crosslink formation [77], leading to increased stiffness in protein matrix and resistance to proteolysis affecting tissue remodeling. This, in turn, results in sclerosis of renal glomeruli, thickening of capillary basement membrane, atherosclerosis [78] and endothelial dysfunction [77]. AGE-mediated crosslinking of proteins has been implicated in functional decline of tissues and cells with advancing age [79], vascular pathology [80], especially in diabetes and renal failure, and in AD [77,81,82]. Since glycation occurs over long periods of time, even at glucose levels considered to be normal, stable proteins, such as NFTs and APs, have been hypothesized to be ideal substrates for this reaction [83]. Indeed, in AD, AGEs can be detected in the pathological hallmarks of the disease (NFTs and APs) and at higher levels in CSF and plasma compared with normal controls [84–86]. These findings may explain, at least partially, some of the pathological neurobiological features of the disease, such as protein crosslinking, oxidative stress and cell death [83]. AGEs have been suggested to represent a driving force in accelerated β-amyloid deposition and plaque formation [83]. Both AGEs and β-amyloid are ligands for the receptors for AGEs (RAGE) – a transmembranotic protein and a soluble form circulating in the plasma, respectively. Soluble RAGE has been suggested to neutralize the detrimental effects of β-amyloid by acting as a decoy and preventing its ligation with trans membranotic RAGE. Lower plasma levels of soluble RAGE were detected in AD patients compared with vascular dementia patients as well as normal controls [87], and even in MCI patients [88]. These data formed the basis for suggesting the use of nonsoluble RAGE antagonists and antibodies, soluble RAGE and AGE inhibitors as treatment aimed to minimize the effect of AGE in aging and AD [83].

The role of antidiabetic medications in AD

The role of diabetes in increasing risk for cognitive decline and dementia leads to the exploration of the effect of antidiabetic medications on this association. To our knowledge, there are no published studies that have analyzed the association of the long-term effect of antidiabetic medications or long-term glucose control (over years) on cognitive function/dementia. Moreover, if antidiabetic medications are efficacious in dementia or dementia prevention, it is not known whether this effect is through diabetes control or other mechanisms. However, there is preclinical and clinical evidence demonstrating the potential beneficial effects of certain antidiabetic treatments in AD.

In epidemiological studies, the role of antidiabetic medication in altering risk for dementia is controversial: among diabetic subjects who participated in a population-based study, those treated with insulin, and to a lesser extent, those treated with oral hypoglycemics were at highest risk for dementia [9]. In the Kungsholmen project, diabetes diagnosis and to a larger extent, the use of oral hypoglycemics among diabetics, was associated with increased risk for dementia in general and for vascular dementia specifically [89]. In the Sacramento Area Latino Study on Aging (SALSA) study, among participants diagnosed with diabetes, antidiabetic medications – monotherapy (oral hypoglycemics or insulin), but more so combination therapy – were associated with less decline in cognitive function, especially among those with a longer duration of diabetes [90]. The apparent discrepancies among epidemiological studies are not necessarily contradictory from the mechanistic point of view. The type and number of prescribed antidiabetic medications may reflect difficulties in achieving glucose control, and therefore higher susceptibility to diabetes-related complications – with cognitive compromise being an additional complication.

The importance of glucose control in dementia prevention was exemplified in studies showing that uncontrolled diabetes was associated with higher risk for AD [91], while better

glucose control attenuated cognitive deterioration [92,93]. Moreover, even in subjects with HbA1c levels within the range considered to be normal, higher HbA1c is associated with higher risk for cognitive deterioration [94], MCI and brain atrophy [34]. On the other hand, certain antidiabetic medications, or combination of medications, may have a beneficial effect on cognition that is not necessarily related to glucose control.

The effect of antidiabetic medications on dementia has been assessed in several clinical trials of AD patients. When mild-to-moderate AD patients were randomized to rosiglitazone, an insulin sensitizer or placebo, rosiglitazone treatment was associated with improvement in cognition at 24 weeks in *APOE* ε4-negative subjects [95]. Intranasal insulin administration was associated with better performance in memory, attention and functional status compared with placebo in another trial [96]. In an observational follow-up study of subjects diagnosed at baseline as suffering from both AD and diabetes, participants were divided according to their baseline antidiabetic medication regimen (either oral hypoglycemic medications or a combination with insulin). At 12-month follow-up, the group treated with oral medications only performed significantly worse than the group treated with a combination of insulin and oral medication [97].

In animal models of AD, a drug that facilitates insulin signaling in the brain, liraglutide, demonstrated beneficial effects, for instance, prevention of memory impairment, synapse loss and deterioration of synaptic plasticity in the hippocampus, as well as lower β-amyloid plaque and amyloid olygomers counts [98]. Rosiglitazone mediated cognitive improvement in associative learning and memory in Tg2576 AD mouse models. Interestingly, this effect did not correlate with peripheral glucose regulation, but rather with age-related mechanistic differences that are the basis for cognitive decline in this mouse model [99].

In vitro studies demonstrated complex interactions between different antidiabetic medications and pathological hallmarks of AD. Insulin has been demonstrated to be a modulator of amyloid precursor protein metabolism in neurons by decreasing the intracellular accumulation of β-amyloid [100]. Excessive generation and accumulation of β-amyloid is considered to be the initiator of the pathological cascade in AD [101–103]. Interestingly, metformin, an oral hypoglycemic, significantly increased the generation of both intracellular and extracellular β-amyloid [104], but in combined use with insulin, metformin potentiated insulin's effect in reducing β-amyloid [104]. Similarly, rosiglitazone potentiated the effect of insulin in reversing downregulation of the brain insulin receptor by β-amyloid oligomers [105]. These *in vitro* studies are consistent with a neuropathological study in which significantly fewer neuritic plaques were found in the neocortex of diabetic subjects who received a combination of insulin and oral antidiabetic medication, as compared with diabetic participants with other medication statuses (none, insulin only or only oral antidiabetic medication) or nondiabetic subjects [49].

These results demonstrate the importance of studying the interaction of diabetes and cognition not only in the context of glucose control over time, but also in the context of medications used for diabetes and the possible interactions between these medications. Importantly, the beneficial effect on cognition of some antidiabetic treatment strategies may go further than their glucose-lowering effect, and may therefore extend to populations beyond diabetic subjects.

An additional consideration in the association of diabetes and antidiabetic treatment with dementia is hypoglycemia. Diabetic subjects, especially those treated with medications, are at increased risk for hypoglycemic episodes [29,30,106]. Severe hypoglycemic episodes in subjects who were not demented at baseline were demonstrated by some [107], but not all [108] to be associated with increased risk for dementia. Self-management of diabetes is

complicated, probably requiring complex cognitive abilities. Therefore, it is not easy to distinguish whether severe hypoglycemia induces permanent brain damage, or, as demonstrated by some, dementia is a risk factor for hypoglycemic episodes [108]. There are several possible explanations for the discrepancies between different studies, particularly the different strategies used to ascertain hypoglycemic episodes. An additional complexity in research on the association between hypoglycemia and cognition is that the majority of hypoglycemic episodes are not considered to be severe and are difficult to record, so understanding of their role in cognition is limited [109].

In conclusion, epidemiological, clinical and preclinical data demonstrate a relatively consistent association between diabetes and dementia. The inconsistencies that do exist between studies may, at least partially, be attributed to different criteria for inclusion of diabetic subjects (based on self-report, medical charts and laboratory assessments at baseline) and different cognitive outcomes. Since the central characteristic of glucose control pertains to both diabetic and nondiabetic individuals, it may have broader implications for mechanisms and the treatment and for prevention of dementia. These complex relationships may be particularly relevant in subgroups of individuals (e.g., those carrying a particular genotype) rather than in the whole population. This has crucial implications for the design of clinical trials.

Further research is required to elucidate associations of pre-diabetes, diabetes, diabetes characteristics and their pattern of change over time with dementia, cognitive impairment and neuropathology. In an ideal world, such a study should follow a representative sample of the diabetic and prediabetic population (and not just those treated in tertiary referral centers or those suffering from diabetes-related complications), and longitudinally assess their cognitive performance in different cognitive domains, as well as their rate of conversion to MCI and dementia, while complementing these measurements with neuroimaging and, when possible, neuropathological assessments. Characteristics of diabetes (age of onset of diabetes, preclinical stages, presence of micro- and macro-vascular complications, long-term glucose control, medication, nutrition, physical activity, genes associated with risk for diabetes and dementia, comorbidities and so on) that may contribute to cognitive compromise should be measured, and when possible, also measured longitudinally, to permit investigation of cotemporaneous changes.

Expert commentary

The prevalence of both diabetes and dementia is increasing and will reach epidemic proportions. Diabetes and diabetes-related states have consistently been demonstrated to increase the risk for cognitive decline and dementia. Yet, the mechanisms for this association are not yet fully understood. Furthermore, type of dementia based on clinical assessment is not always consistent with neuropathological findings. Some of the discrepancies may rise from methological difference between studies; for example, age of population studied, duration of follow-up, diagnosis of diabetes (self-report vs medical charts), age and duration of exposure to diabetes, and cognitive end point. Although diabetes control has been demonstrated to prevent other diabetes complications, it cannot yet be implemented as a tool for dementia prevention since it is yet unknown which diabetes-related factors (glucose control, presence of complications, comorbidities, type of treatment or other) affects cognition. Better understanding of the relationships of diabetes and dementia is required. Since some diabetes-related factors are on a continuum extending to nondiabetic populations, the insights regarding the association of diabetes with cognition and dementia may extend to nondiabetic populations.

Five-year view

Data collected in presently ongoing and future studies, which longitudinally follow diabetic populations is expected to permit better understanding of the mechanisms by which diabetes affects brain function and cognition. The added value of these studies is that they not only analyze the association of diabetes diagnosis or glucose control at baseline with cognitive outcomes, but also diabetes-related factors (glucose control, diabetes complications, comorbidities, inflammation, oxidative stress, medications and so on), thus allowing better understanding of pathways through which diabetes affects brain function and cognition. Based on the findings of these studies, implementation of different prevention strategies and well-targeted clinical trials in diabetic subpopulations may evolve.

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Key issues

- Diabetes has consistently been shown to increase risk for cognitive decline, mild cognitive impairment and dementia.
- The mechanisms for this association are not understood.
- The importance of the association between diabetes and dementia is that diabetes is modifiable, thus, disentangling the mechanisms involved may offer prevention strategies for dementia.
- Different mechanisms have been discussed for the association of diabetes with dementia: vascular pathology, insulin resistance, advanced glycation end products, antidiabetic treatments and hypoglycemic episodes.
- Inconsistencies between different studies performed to date regarding the mechanisms of cognitive decline in dementia may rise from methodological heterogeneities, populations studied and cognitive end points, amongst others.
- Future studies should look into the relationship of dementia with multiple diabetes-related factors over time (age at onset, diabetes duration, glucose control, presence of complications, inflammation, oxidative stress, medications and hypoglycemic episodes) and not only diabetes diagnosis or glucose control at baseline.