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Type 2 diabetes mellitus and Alzheimer's disease

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Abstract

Epidemiological and biological evidences support a link between type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD). Persons with diabetes have a higher incidence of cognitive decline and an increased risk of developing all types of dementia. Cognitive deficits in persons with diabetes mainly affect the areas of psychomotor efficiency, attention, learning and memory, mental flexibility and speed, and executive function. The strong epidemiological association has suggested the existence of a physiopathological link. The determinants of the accelerated cognitive decline in DM2, however, are less clear. Increased cortical and subcortical atrophy have been evidenced after controlling for diabetic vascular disease and inadequate cerebral circulation. Most recent studies have focused on the role of insulin and insulin resistance as possible links between diabetes and AD. Disturbances in brain insulin signaling mechanisms may contribute to the molecular, biochemical, and histopathological lesions in AD. Hyperglycemia itself is a risk factor for cognitive dysfunction and dementia. Hypoglycemia may also have deleterious effects on cognitive function. Recurrent symptomatic and asymptomatic hypoglycemic episodes have been suggested to cause sub-clinical brain damage, and permanent cognitive impairment. Future

trials are required to clarify the mechanistic link, to address the question whether cognitive decline may be prevented by an adequate metabolic control, and to elucidate the role of drugs that may cause hypoglycemic episodes.

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Key words: Dementia; Alzheimer; Type 2 diabetes; Aging; Cognitive decline; Mild cognitive impairment; Insulin; Hypoglycemia; Hyperglycemia

Core tip: Epidemiological and biological evidences support a link between type 2 diabetes (DM2) and Alzheimer's disease (AD). Persons with diabetes have increased incidence of cognitive decline and AD. Increased cortical and subcortical atrophy is present after controlling for vascular disease and inadequate cerebral circulation. Recent studies confirmed the role of insulin as possible link between DM2 and AD. Altered insulin signaling may contribute to AD biochemical and histopathological lesions. Hyperglycemia and hypoglycemia also have deleterious effects on cognitive function. Future trials would clarify the mechanistic link, and if cognitive decline may be prevented by an adequate metabolic control, and avoiding hypoglycemia.

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INTRODUCTION

Type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD) are age-related conditions, both characterized by increased incidence and prevalence with aging^[1,2].

DM2 is one of the fastest growing epidemics at present, which is frequently associated with aging. Characteristic features of DM2 include impairments in insulin actions

and signaling. Insulin resistance in peripheral tissues results in hyperglycemia and hyperinsulinemia. AD is the most common neurodegenerative disorder, and its incidence increases with age^[5]. AD is characterized by the presence of several pathological hallmarks including neuronal loss, formation of senile plaques composed by extracellular deposits of amyloid beta, intracellular neurofibrillary tangles composed of aggregated hyperphosphorylated tau proteins in brain, proliferation of astrocytes, and activation of microglia. These features are accompanied by mitochondrial dysfunction and alterations in neuronal synapses^[3]. The molecular and pathophysiological mechanisms that underlie AD still have many dark sides. Although etiology and the exact mechanism that trigger the pathological alterations of AD are still not clear, most studies have suggested that the deposit of the toxic amyloid-beta peptide caused by an abnormal processing of amyloid-beta precursor protein (amyloid cascade hypothesis), may initiate and/or contribute to the pathogenesis of AD.

EPIDEMIOLOGICAL EVIDENCES

Mounting epidemiological and biological evidences support a link between these two aging related diseases. First and foremost, diabetes mellitus is associated with changes in cognition, and cognitive dysfunction.

Persons with diabetes have been reported to hold a higher incidence of cognitive decline and AD; DM2 has been strongly associated with an increased risk of developing all types of dementia, including AD^[2,4-6]. A systematic review including fourteen eligible longitudinal population-based studies of variable methodological quality found that in most studies the incidence of “any dementia” was higher in persons with diabetes than in those without diabetes^[7]. Although, in some studies there are methodological limitations, the association remains strong. Some studies have relied on self-reported diagnosis of diabetes, and in the elderly population many patients with diabetes may remain undiagnosed. For the same reason, the duration of diabetes is also difficult to ascertain in older adults^[8].

In a longitudinal cohort study, lasting up to 9 years, the risk of developing Alzheimer’s disease was 65% higher in persons with diabetes than in non-diabetic controls^[9]. In a community-based controlled study (Mayo Clinic Alzheimer Disease Patient Registry) the prevalence of diabetes and glucose intolerance was examined in patients with AD *vs* control participants without AD. The study suggested that frank diabetes (35%) or glucose intolerance (46%) might be present in up to 80% of patients with AD^[10].

Even with the limitations discussed above, several studies have suggested that longer diabetes duration is generally associated with a higher risk for developing dementia^[6,11,12]. In random effects models, DM2 was associated with lower levels of global cognition, episodic, semantic and working memory, and visuospatial ability

at baseline^[9]. Cognitive deficits in DM2 mainly affected the areas of psychomotor efficiency, attention, learning and memory, mental flexibility, and speed and executive function^[13,14].

Recent studies have also shown a positive association between DM2 and mild cognitive impairment (MCI), and an accelerated progression from MCI to dementia in DM2^[15]. A retrospective case-notes review of people with known diabetes who were resident in nursing homes in England showed very significant levels of disability and comorbidity, and in this setting, dementia was the most common comorbidity^[16].

PHYSIOPATHOLOGICAL LINK

The strong epidemiological association has suggested the existence of a physiopathological link. However, the determinants of the accelerated cognitive decline in DM2 are less clear. The most studied hypothesis proposes that the primary cause of the association may be linked to the diabetic vascular disease and inadequate cerebral circulation, with subsequent silent ischemic damage induced by diabetes. However, even after controlling for cardiovascular risk factors, several studies on the cerebral structure of patients with diabetes have evidenced increased cortical and subcortical atrophy, besides increased leukoaraiosis, which were associated with impaired cognitive performance^[17,18].

Most recent studies have focused on the possible role of insulin, and insulin action. Insulin resistance has been strongly implicated as a possible link between DM2 and AD. A condition of hyperinsulinemia, regardless of the presence of DM2, appears to be associated with a worse cognitive performance. There is a rapid growth in the literature pointing toward insulin deficiency and insulin resistance as mediators of AD-type neurodegeneration. De la Monte has even suggested that AD may be termed as “type 3 diabetes”, indicating that AD may represent a form of diabetes that selectively involves the brain with molecular and biochemical features that overlap with diabetes mellitus^[19].

The importance of the role of insulin in brain aging has long been known. Insulin has significant neurotrophic properties in the brain. The hormone is rapidly transported to the level of the central nervous system through the blood-brain barrier by a transport mechanism mediated by insulin receptors. It is interesting to note that these receptors are mainly localized at the level of the hippocampus, entorhinal cortex and frontal areas known to be involved in functions such as memory and learning. Insulin is also involved in the production of important neurotransmitters such as acetylcholine and norepinephrine. It is known that an acute increase in circulating levels of insulin, as it occurs in the post-prandial period, determines a physiological parallel increase of the concentrations of the hormone in the brain. A state of chronic hyperinsulinemia, as it occurs in insulin-resistance conditions and in DM2 may

determine a down-regulation of the insulin receptors at the blood-brain barrier, thus reducing the transport of insulin in the brain. Evidence is growing to link an alteration of metabolism and the deposition of precursors of amyloid in the brain that may occur in persons with diabetes, which is suggested as the pathogenesis of AD in DM2. The amyloid precursor protein is a transmembrane protein consisting of 770 amino acids; it is known to be the precursor of the amyloid beta involved in the etiopathogenesis of AD. Although the role of amyloid beta and its isoforms has yet to be elucidated, it seems to take part in numerous physiological processes. How can clinical hyperinsulinemia be a risk factor for AD even if insulin is an important neurotrophic factor? These two apparent paradoxical findings may be reconciled by the notion of insulin resistance. Whereas insulin is a neurotrophic factor at moderate concentrations, hyperinsulinemia with elevated concentrations of insulin in the brain may be associated with reduced amyloid-beta clearance due to competition for their common and main degrading mechanism—the “Insulin-Degrading Enzyme” (IDE). Insulin modulates metabolism of amyloid precursor protein decreasing intracellular accumulation. Insulin is degraded by the IDE, which is also involved in the metabolism and degradation of amyloid beta. This multifunctional enzyme degrades insulin and amylin, peptides related to the pathology of DM2, together with amyloid-beta peptide in the AD brain. Hyperinsulinemia may elevate amyloid beta through insulin’s competition with amyloid beta for IDE^[20]. Therefore, it has been suggested that the link between hyperinsulinemia and AD may be the IDE. Since IDE is much more selective for insulin than for amyloid beta, brain hyperinsulinemia may deprive amyloid beta of its main clearance mechanism, favoring its accumulation in the brain, and its consequent neurotoxic effects^[21].

Disturbances in brain insulin signaling mechanisms represent early and progressive abnormalities and could account for the majority of molecular, biochemical, and histopathological lesions in AD. Increasing insulin resistance and hyperinsulinemia were associated with more hippocampal and amygdalar atrophy on magnetic resonance imaging (MRI) in persons with DM2 when compared to matched non-diabetic controls, regardless of vascular pathology^[13,17]. Given these links, it has been suggested that may be a common underlying mechanism predisposes to amyloid deposition in the brain and in the pancreatic islet^[10].

Glucose levels itself are a risk factor for cognitive dysfunction and dementia. In a prospective, community-based cohort study, higher plasma glucose concentrations were associated with an increased risk of dementia in populations with and without diabetes, suggesting that higher levels of glucose may have deleterious effects on the aging brain^[22].

Although there is still limited knowledge concerning the association between impaired fasting glucose and/or impaired glucose tolerance and cognitive impairment,

there is increasing evidence that these prediabetic conditions may increase the risk of AD in elderly patients. The risk of incident dementia increased in diabetic and in non-diabetic persons according to the average glucose concentrations during the preceding 5 years^[22]. Hyperglycemia and hyperinsulinemia may accelerate brain aging also by inducing *tau* hyperphosphorylation and amyloid oligomerization, as well as by leading to widespread brain microangiopathy. Persons with diabetes are more prone to develop accelerated leukoaraiosis (white matter high-intensity lesions)^[23].

GLYCEMIC CONTROL AND THE ROLE OF HYPOGLYCEMIA

The effect of diabetes treatment and glycemic control on dementia risk are less clear. It has been suggested that glycemic control may have a role in preserving cognitive performance among patients with DM2. Using baseline cognitive measures collected in the Memory in Diabetes, sub-study of the Action to Control Cardiovascular Risk in Diabetes trial, the authors found that a 1% higher glycated hemoglobin A (HbA1c) value was associated with a significant lower test performance and memory score in patients with diabetes^[24].

HbA1c was also identified as an additional risk factor for a greater rate of brain atrophy. Enzinger *et al.*^[25], measuring the annual brain volume changes over 6 years with MRI in 201 participants in the Austrian Stroke Prevention Study, found significant differences in brain atrophy rates by quartiles of HbA1c levels^[25]. Clustering of factors associated with the so-called metabolic syndrome in persons with high HbA1c suggests a link between this syndrome, which is associated with insulin resistance and hyperinsulinemia, with late-life brain tissue loss^[25]. In diabetic patients, an inverse relationship was found between serum HbA1c and working memory, executive functioning, learning, and complex psychomotor performance, supporting the hypothesis that an inadequate glucose control may be associated with worsening cognitive function^[26,27].

However, an excessively tight glycemic control in older persons with DM2, and its related increased risk of hypoglycemia, may also have deleterious effects on cognitive function^[28]. In the presence of hypoglycemia, several responses occur within the brain, including activation of the central sympathetic nervous system; hypoglycemic symptoms include alterations of cognitive function, such as difficulty in concentrating and drowsiness, among others. Recurrent symptomatic and asymptomatic hypoglycemic episodes have been suggested to cause sub-clinical brain damage, and permanent cognitive impairment^[29]. In addition, hypoglycemic states may increase the action of the receptors through an arteriolar vasodilatation. Since chronic hyperglycemia in DM2 is associated with endothelial alterations^[30], this may cause in case of hypoglycemia a reduced vasodilating effect at the level of the blood-brain barrier, with a possible amplification of the brain

damage due to hypoglycemia itself. Among older patients with type 2 diabetes, a history of severe hypoglycemic episodes collected and reviewed using hospital discharge and emergency department diagnoses from 1980-2002 was associated with a greater risk of dementia^[31]. More recently, a 12 years prospective population-based study of 783 older adults who were participating in the Health, Aging, and Body Composition Study, found a bidirectional association between hypoglycemia and dementia^[32]. During the 12-year follow-up period, the participants who experienced at least one hypoglycemic event had a 2-fold increased risk for developing dementia, while older adults with DM2 who developed dementia had a greater risk for having a subsequent hypoglycemic event compared with participants who did not develop dementia^[32].

Therefore, it has been suggested that drugs that cause lower postprandial glucose excursions and minor risk of hypoglycemia may prevent cognitive decline in older diabetic persons^[33]. This data needs to be confirmed by future trials.

RESEARCH AND CLINICAL IMPLICATIONS

Cognitive function has not been included as an outcome in large scale randomized controlled trials of type 2 diabetes, and screening for dementia and cognitive impairment is still not included in routine diabetic patient care. There are sufficient epidemiological and clinical data to include an evaluation of cognitive complications in the clinical practice of persons with diabetes, in particular in those older than 70-75 years, and those with a long lasting history of diabetes.

There are some barriers in implementing a screening and diagnostic program for dementia in patients with diabetes. Neurocognitive testing in which an expert examiner administers a battery of tests to assess different aspects of cerebral function is still the gold standard for the diagnosis of dementia^[14], and a computed tomography (CT) scan or an MRI may be required. This evaluation requires substantial financial and human resources. Screening cognitive tests are time consuming and CT scans are expensive^[34]. However, diagnosis is even more important in older populations, because many older persons with diabetes nowadays live alone and self-manage their drugs. A mistake due to cognitive impairment may be extremely dangerous in particular in patients who need insulin, and self-practice insulin injections. Many hypoglycemic episodes may be due to errors in self-administration in undiagnosed subclinical demented patients.

CONCLUSION

There is convincing epidemiological evidence showing an increased risk of dementia in people with diabetes, but there are few mechanistic studies that provide a clear pathophysiological link, although the cause may be multifactorial. Cerebrovascular alterations, insulin action, in-

sulin resistance, altered amyloid metabolism, chronic hyperglycemia, and recurrent hypoglycemic episodes seem to play a major role. Future trials are required to clarify the mechanistic link and to address the question whether cognitive decline may be prevented by an adequate metabolic control, and to better define the role of drugs that may cause hypoglycemic episodes. Clinicians treating older persons with diabetes should start to routinely search for cognitive impairment as well as they search for cardiovascular, renal, or other common complications of diabetic disease. There is sufficient evidence to support the view that time is probably arrived to incorporate cognitive evaluation in future national and international diabetic guidelines.

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