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Type 2 diabetes mellitus and risk of Alzheimer's disease

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Abstract
The evidences like biological and epidemiological support a link between type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD). Persons with diabetes have a higher rate of cognitive decline and an increased risk of developing dementia of all types. Cognitive deficits in diabetic people get mainly affect the psychomotor efficiency areas like attention, learning and memory, mental ability, flexibility and speed, and executive function. The concrete epidemiological association has suggested the existence of a pathophysiological link. The factors of increased cognitive decline in DM2, however, are less clear. Increased atrophy of cortical and subcortical areas had clearly shows after controlling for diabetic vascular disease and inadequate circulation in cerebral areas.
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.

Keywords: Dementia, Alzheimer, type 2 diabetes, aging, cognitive decline, mild cognitive impairment, insulin, hypoglycemia, hyperglycemia

Introduction
Type 2 diabetes mellitus (DM2) and Alzheimer's disease (AD) are the conditions that are age onset both are characterized by increased incidence and prevalence of age. DIabetes mellitus type 2 is one of the fastest growing epidemics of world at present, which is frequently associated with ageing. Characteristic features of DIabetes type 2 include impairments in insulin actions and signaling. Insulin resistance in peripheral tissues results in increased glucose. AD is the common neurodegenerative disorder, and its incidence increases with age. AD is characterized by the presence of several pathological indications 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. 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 not clear till date, 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 contribute to the pathogenesis of AD.

Epidemiological evidences
There are both epidemiological and biological evidences to support the age factor that relates these two diseases and role of diabetes mellitus type 2 in changes of cognition and cognitive dysfunction. Persons with diabetes have higher risk of cognitive dysfunction and AD; DM2 has strongly associated with an increased risk of developing dementia of all types including AD. Some studies have relied on self-reported diagnosis of diabetes, and in the elderly population many patients with diabetes may remain undiagnosed. For same reason, duration of diabetes is very difficult to ascertain in senior adults.

In a recent longitudinal cohort study, lasting up to 9 years, the risk of developing Alzheimer's disease was 65% higher in person's diabetic people when compared to normal adults who are non-diabetic. 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.

Even with the limitations above, several studies clearly suggested that longer diabetes duration is generally associated with a higher risk for developing dementia. In random effects models, DM2 was associated with lower levels of cognition, episodic, semantic and working memory, and visuospatial ability at baseline. Cognitive deficits in DM2 mainly affected the areas of psychomotor efficiency, attention, learning and memory, mental flexibility, and speed and executive function.

Recent studies also showed a positive association between DM2 and mild cognitive impairment (MCI), and an increased progression from MCI to dementia in DM2.

Pathophysiological link

The epidemiological association has clearly stated the existence of a pathophysiological connection. However, there are more factors for cognitive decline in DM2 are not so clear. The most common hypothesis proposes that the primary cause of the association may be connected to the diabetic vascular disease and inadequate cerebral circulation, with subsequent silent ischemic damage induced by diabetes. However, after controlling risk factors for cardiovascular disease several studies on the cerebral structure of diabetic patients with have clearly evidenced increased cortical and subcortical atrophy, besides increased leukoaraiosis, which were associated with cognitive performance dysfunction.

Most recent studies have well focused on the possible role of insulin, and insulin action. Insulin resistance has been strongly shown as a possible connection between DM2 and AD. A condition of hyperinsulinemia, even though Dm2 is absent appears to be associated with a worse cognitive performance. There is a rapid increase in the studies signalling toward insulin deficiency and insulin resistance as intermediary of AD-type neuro degeneration. Suzanne De la Monte a famous researcher claims as "type 3 diabetes" can be AD, indicating that AD may represent a form of diabetes that selectively involves the molecular and biochemical features of the brain that overlap with diabetes mellitus type 2. The importance of the insulin in the ageing of brain is well known. Insulin has significant neurothrophic properties and influences brain activity by regulating eating behaviour, energy storage, and aspects that related to memory and knowledge in the brain. Insulin hormone is rapidly transported to cns by BBB. It is very interesting to note that these receptors are mainly present at the level of the hippocampus lobe, and also the gateway for entering and leaving the hippocampus formation called entorhinal cortex and frontal areas are to be involved in functions such as memory and learning. Insulin hormone involved in the production of acetyl choline and nor epinephrine which are important neuro transmitters. It is known that in post pro dial period an acute increase in circulating levels of insulin, determines a physiological parallel increase of the hormonal concentrations in the brain. A state of chronic increased insulin levels that occurs in insulin-resistance conditions and in DM2 may determine a decreased-regulation of the insulin receptors at the BBB, thus reducing the transport of insulin hormone to the brain. Evidence is growing to connect an metabolic alteration and the deposition of amyloid precursors in the brain that may occur in diabetic type 2 persons, which is suggested as the pathogenesis of Alzheimers Disease in DM2. The amyloid precursor protein is a 770 amino acid containing Trans membrane protein; it is known to be the precursor of the amyloid beta involved in the etiology and pathogenesis of AD. Although the exact role of beta amyloid and isoforms of it has yet to be explained clearly. it can be clearly seen taking part in various physiological processes. How can clinically raised insulin hormone be a risk factor for AD, if insulin is an important neurotrophic factor? These two apparent opposite findings may be restored by the idea of insulin resistance. Whereas insulin is a neurotrophic factor at moderate or normal concentrations in brain, hyperinsulinemia with increased concentrations of insulin in the brain may be associated with reduced clearance of amyloid-beta due to competition for their "Insulin-Degrading Enzyme" (IDE). Insulin modulates the metabolism of amyloid precursor protein by decreasing its intracellular accumulation. Insulin is degraded by the IDE that is also involved in the metabolism and degradation of amyloid beta. This enzyme IDE which has multiple functions degrades insulin and amylin, peptides related to the pathology of DM2, together with amyloid-beta peptide in the brain of AD. Increased insulin levels may elevate amyloid beta through insulin's competition with amyloid beta for IDE. Hence, it has been suggested that the connection between hyperinsulinemia and AD may be the IDE. Since IDE is much more particular for insulin than for amyloid beta, brain hyperinsulinemia may deprive amyloid beta because of its main clearance mechanism, favoring its increased deposits in the brain, and its resultant neurotoxic effect

Disturbances in brain insulin signaling mechanisms shows 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 M.R.I in persons with DM2 when compared to match non-diabetic controls, regardless of vascular pathology. Given these links, it has been suggested that may be most common underlying mechanism predisposes to amyloid deposition in the brain and in the pancreatic islets of langerhans.

Increased Glucose levels itself are a risk factor for cognitive dysfunction and dementia. In a 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.

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 dementia increased in diabetic and in non-diabetic persons according to the average glucose concentrations during the past 5 years. Hyperglycemia and hyperinsulinemia may accelerate brain ageing also by inducing tau

hyperphosphorylation and amyloid oligomerization, as well as by leading to widespread brain micro angiopathy. Persons with diabetes are more prone to develop accelerated leukoaraiosis (white matter high-intensity lesions).

Glycemic control and the role of hypoglycemia

The effect of diabetic treatment and glycemic control on risk of dementia are not so evident. It has been suggested that glycemic control may have a role in preserving cognitive performance among diabetic patients. 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.

HbA1c was also identified as an additional risk factor for an increased rate of brain atrophy. Enzinger *et al*. 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. 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 hyper insulinemia, with late-life brain tissue loss. 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 decreasing cognitive function.

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. 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. 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, 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. 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. 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.

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. This data needs to be confirmed by future trials.

Research and clinical implications

Cognitive function has not been included as a result in large scale randomized controlled trials of type 2 diabetes, and screening for dementia and cognitive impairment is still not included in our routine outpatient 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 hurdles in implementing a screening and diagnostic program for dementia in patients with diabetes. Neurocognitive testing in which an expert examiner administers a series of tests to assess different aspects of cerebral function is still the gold standard for the diagnosis of dementia, and a computed tomography (CT) scan or an MRI may be required. This evaluation requires financial and human resources. Screening cognitive tests are time consuming and CT scans are expensive and sometimes not advisable on a frequent note. However, diagnosis is even more important in older populations, because many persons of golden age with diabetes nowadays live alone and self-manage their regimen of drugs. A mistake due to cognitive impairment may be extremely dangerous in particular in patients who need insulin, and people who self-practice insulin injections. Many hypoglycemic episodes may be due to errors in self-administration in undiagnosed subclinical dementia patients.

Conclusion

There is a satisfying epidemiological evidence showing an increased risk of dementia in diabetic people, but there are few mechanistic studies that provide a clear pathophysiological link, although the cause may be multifaceted. Cerebrovascular alterations, insulin action, insulin resistance, altered amyloid metabolism, chronic hyperglycemia, and recurrent hypoglycemic episodes seem to play a major role. Future trials are required to explain the mechanistic link and to address the question whether cognitive decline may be prevented by an proper metabolic control, and to better define the role of medicines that may cause sudden hypoglycaemic episodes. Physicians treating senior citizens 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 confirmation to support the view that this is the probable time to incorporate cognitive evaluation in future national and international diabetic guidelines.

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