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Impact of diabetes on cognitive function and brain structure

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Both type 1 and type 2 diabetes have been associated with reduced performance on multiple domains of cognitive function and with structural abnormalities in the brain. With an aging population and a growing epidemic of diabetes, central nervous system–related complications of diabetes are expected to rise and could have challenging future public health implications. In this review, we will discuss the brain structural and functional changes that have been associated with type 1 and type 2 diabetes. Diabetes duration and glycemic control may play important roles in the development of cognitive impairment in diabetes, but the exact underlying pathophysiological mechanisms causing these changes in cognition and structure are not well understood. Future research is needed to better understand the natural history and the underlying mechanisms, as well as to identify risk factors that predict who is at greatest risk of developing cognitive impairment. This information will lead to the development of new strategies to minimize the impact of diabetes on cognitive function.

Keywords: type 1 diabetes mellitus; type 2 diabetes mellitus; cognitive dysfunction; brain; memory

Introduction

Diabetes mellitus is associated with decrements in cognitive function and changes in brain structure. People with both type 1 and type 2 diabetes have been shown to have mild-to-moderate reductions in cognitive function as measured by neuropsychological testing compared to non-diabetic controls. Type 2 diabetes (T2DM) has also been associated with 50% increased risk of dementia.[1] Whether such an association is true for people with type 1 diabetes (T1DM) is not yet known.

Interestingly, diabetes has been known to have an effect on the brain for more than 100 years. In the early 20th century, researchers and clinicians recognized that people with diabetes frequently complained of poor memory and attention. In 1922, Mile *et al.*[2] showed that people with diabetes performed poorly on cognitive tasks examining memory and attention. The term diabetic encephalopathy was introduced in 1950 to describe central nervous system–related complications of diabetes.[3] Other terms like functional cerebral impairment and central neuropathy have also been used in the literature to describe diabetes-related cognitive dysfunction.[4] Mijnhout *et al.*[4] have proposed the term diabetes-associated cognitive decline (DACD) to describe diabetes-related mild-to-moderate reductions in cognitive function.

With the growing epidemic of diabetes and the ever-increasing number of people who live to old age, diabetes-related cognitive dysfunction could have challenging future public health implications. In this review, we will examine the research that has been done over the past two decades to increase our understanding of how diabetes affects brain function and structure. At the conclusion, we will make suggestions for future research that could help us address the challenges we may face as more people live longer with diabetes than ever before.

Cognitive dysfunction in type 1 diabetes

Longitudinal studies

In the Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of

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Diabetes Interventions Complications (EDIC) study, patients with T1DM underwent comprehensive batteries of cognitive tests at study enrollment (at the mean age of 27 years) and 18 years later. The results demonstrated that patients with worse metabolic control (glycated hemoglobin values > 8.8%) showed moderate declines in motor speed and psychomotor efficiency as compared to those with better control (glycated hemoglobin < 7.4%).[5] Frequency of severe hypoglycemia was not associated with decline in any cognitive domain in this population. Similar results were seen in the Stockholm Diabetes Intervention Study (SDIS), where at 10-year follow-up cognitive function was similar in both treatment groups, and was not related to the number of severe hypoglycemic episodes.[6]

T1DM is commonly diagnosed during childhood and adolescence. This is a period of rapid developmental changes in the central nervous system and there has been concern that the younger brain may be more susceptible to extremes of glycemia.[7] In a subanalysis of the DCCT cohort where only participants who were 13–19 years old at the time of entry in the DCC were included, Musen *et al.*[8] reported that severe hypoglycemia was not associated with cognitive decline, and higher A1C values were associated with declines in psychomotor and mental-efficiency domains, as was found in the population as a whole. In another prospective study, Ryan *et al.*[9] found that at 7-year follow-up, adults with T1DM (age 34 at entry) showed significant declines on measures of psychomotor efficiency compared to non-diabetic controls. No differences were seen in domains of learning, memory, or problem-solving tasks. Proliferative retinopathy, autonomic neuropathy, and duration of diabetes were associated with cognitive decline.

Cross-sectional studies

Cross-sectional studies have shown that, relative to non-diabetic controls, subjects with T1DM have performance deficits in multiple cognitive domains, including information-processing speed, psychomotor efficiency, memory, attention, visuospatial abilities, and executive function.[10–14]

Perantie *et al.*[11] reported that children with T1DM who experienced severe hypoglycemic episodes before the age of 5 had deficits in spatial intelligence and delayed recall, suggesting that the developing brain at very young ages may be susceptible to the effects of hypoglycemia. Other factors, including poor glycemic control and presence of microvascular complication like neuropathy and retinopathy, have also been associated with cognitive dysfunction in subjects with T1DM.[10,11]

Systematic reviews and meta-analysis

Brands *et al.*[15] performed a meta-analysis to examine the nature and magnitude of cognitive impairment in T1DM. This analysis included 33 studies with participants who were mostly less than 50 years of age. The authors reported that, compared to non-diabetic controls, people with T1DM had mild-to-moderate declines (effect size ranging from –0.3 to –0.7) in multiple domains, including intelligence, speed of information processing, psychomotor efficiency, attention, cognitive flexibility, and visual perception. Lowered cognitive performance in diabetic patients appeared to be associated with the presence of microvascular complications but not with the occurrence of severe hypoglycemic episodes or with poor metabolic control. Gaudieri *et al.*[16] preformed a meta-analysis that included data from 19 studies in children with T1DM. They found that children with T1DM had decrements in a broad range of domains; however, the magnitude of decrement was greater in children who were diagnosed with diabetes at less than 7 years of age compared with those with later onset. This observation again suggests that early age of onset may be an important variable of cognitive dysfunction in children with T1DM.

In summary, results from both longitudinal and cross-sectional studies show that T1DM is associated with mild-to-modest decrements in cognitive function. Domains of psychomotor speed, mental flexibility, attention, and general intelligence are most commonly affected. Data from prospective studies suggest that hypoglycemia is not a risk factor for cognitive decline; however, this may not be true for children with young age at the onset of diabetes. Early age of onset and presence of microvascular complications are important risk factors for cognitive decline. Longitudinal studies looking at cognitive function in elderly subjects with T1DM are lacking and necessary, because age and duration of diabetes are important contributors to the changes in cognitive function found in T2DM. More research is needed to understand the clinical implications of these mild-to-moderate decrements

in cognitive functioning in the daily lives of people with T1DM.

Cognitive dysfunction in type 2 diabetes

Longitudinal studies

Several longitudinal studies have evaluated the impact of T2DM on cognitive function. These studies have been done mostly in middle-age to older adults and have examined the magnitude and rate of change in cognitive function in non-demented subjects with T2DM compared to non-diabetic controls. All of these studies have included a relatively short follow-up period of less than 6 years.[17–21] The neuropsychological examination done as part of the research ranges from limited testing to extensive batteries that examined all major cognitive domains. Most studies attempted to control for confounding factors like age, education, stroke, hypertension, visual impairment, dyslipidemia, heart disease, exercise, and depression, but were unable to address the underlying mechanisms responsible for any differences they found between the subjects with diabetes and the controls without the disease.

Despite these limitations, data from these prospective studies have shown that people with T2DM perform less well than controls in the cognitive domains of information-processing speed, memory, attention, and executive function.[18–21] Mental flexibility and global cognitive function[17] have also shown to be affected in some, but not in all, studies.[18]

In the Utrecht Diabetic Encephalopathy Study cohort, Van den Berg *et al.*[21] reported that subjects with T2DM performed poorly in the cognitive domains of information-processing speed, attention, and executive functions, both at baseline and at the 4th year of follow-up compared to non-diabetic controls; however, there was no evidence of accelerated cognitive decline in subjects with T2DM. In contrast, other studies have found evidence of accelerated decline in cognitive function over a follow-up of 3–6 years in subjects with T2DM.[19,20] However, only one of these studies found reduced performance in patients with T2DM at baseline compared to controls,[19] raising questions about when in the course of diabetes and aging these reductions in cognitive function develop.

Decrements in cognitive function in subjects with T2DM have been associated with increased duration of diabetes[19] and poor glycemic control.[18] The ACCORD Memory in Diabetes (MIND) Study[22] sought to directly determine if the level of glycemic control affects cognitive performance over time in nearly 3000 subjects with T2DM. In this study, subjects were either randomized to intensive glycemic control, where the target was an HbA1c $< 6\%$, or to a standard strategy targeting HbA1c to 7–7.9%. At baseline, Cukierman-Yafee *et al.*[23] showed that there was an inverse relationship between cognitive function and glycemic control as measured by HbA1c. However, after 40 months of follow-up, there was no significant difference in cognitive function between the intensive and standard treatment arms. Interestingly, Hugenschmidt *et al.*[24] found that there was an association between the presence of diabetic retinopathy at baseline and changes in cognitive function over time in T2DM subjects participating in both the ACCORD–MIND and the ACCORD–Eye substudies. In this analysis, baseline diabetic retinopathy and severity of retinopathy were associated with decline in global cognitive function and processing speed over 40 months. Similar association was not seen for domains of executive function and memory. Retinal vessels and cerebral small vessels have similar embryology and anatomy,[25] raising the possibility that changes in the microvasculature may be responsible for both the retinopathy and the cognitive changes.

In another longitudinal study,[26] a cohort of healthy community-dwelling elderly subjects underwent an extensive battery of cognitive tests at baseline and after 4 years. Despite similar initial cognitive function, diabetic subjects tended to have an unfavorable evolution of cognitive performance over 4 years compared with subjects who had normal glucose or impaired fasting glucose. After 4 years, individuals with diabetes showed decrements in the cognitive domains of memory, attention, and psychomotor speed.

Dementia caused by either Alzheimer's disease or vascular disease has also been linked to T2DM in longitudinal studies. Rawkings *et al.*[27] recently reported that diabetes in midlife was associated with a 19% greater cognitive decline over 20 years compared with no diabetes in the Atherosclerosis Risk in Communities (ARIC) study cohort. In this study, cognitive decline was noted primarily in the domains of processing speed and executive function and was associated with duration of diabetes. In a large prospective population-based cohort study of

more than 6000 elderly subjects, the presence of T2DM almost doubled the risk of dementia.[28]

Cross-sectional studies

Cross-sectional studies have also shown that subjects with T2DM performed poorly in several cognitive domains including attention, executive function, information-processing, memory, psychomotor efficiency, verbal fluency, and learning.[29–33] These reductions have been associated with poor glycemic control,[29] longer duration of diabetes,[29,31] and the presence of microvascular complications such as diabetic retinopathy[34] and peripheral neuropathy.[35] Epidemiological studies have also shown that comorbidities such as hypertension, dyslipidemia, and depression[36–38] are associated with poor cognitive function in subjects with T2DM.

While long duration of diabetes appears to be an important risk factor for cognitive dysfunction, even patients in early phases of the disease including prediabetes appear to be affected.[33,39] Yau *et al.*[40] assessed cognitive function in adolescents (average age 16 years) with T2DM and found that adolescents with diabetes had lower performance in intellectual function, verbal memory, and psychomotor efficiency compared to non-diabetic controls. However, the type of cognitive deficits found in subject with T2DM also appear to be more pronounced in individuals aged 60 years and older.[41]

Systematic reviews and meta-analysis

Longitudinal and cross-sectional studies have clearly demonstrated an association between diabetes and mild-to-moderate cognitive dysfunction in T2DM, but less is known about the strength of association between diabetes and dementia. To address this question, investigators have performed systematic reviews and meta-analyses of small studies to increase the likelihood of finding an association. In one such systematic review, Biessels *et al.*[1] reported that risk of dementia was increased by 50–100% in people with T2DM relative to people without diabetes. This approach has also been used to identify the cognitive domains particularly affected by diabetes. One systematic review that included data from 27 studies found that processing speed, attention, memory, and cognitive flexibility were the most commonly affected domains in subjects with T2DM, with effect sizes ranging from 0 to 1.9.[42] Palta *et al.*[43] performed a meta-analysis of data from 24 studies in which cognitive function was compared between subjects with T2DM and controls. They found reductions of small-to-moderate effect size in people with T2DM, which ranged from –0.26 to –0.36 in the domains of motor function, executive function, processing speed, verbal memory, and visual memory.

In summary, T2DM is associated with mild-to-moderate cognitive deficits, mostly in the domains of memory, psychomotor speed, and executive function. Changes in cognitive function compared to non-diabetic controls can be seen early in the course of T2DM; however, duration of diabetes, glycemic control, and presence of microvascular complications are important risk factors. There is also an increasing body of evidence showing that, in the elderly population, T2DM increases the risk of dementia.

Imaging studies on diabetes and brain structure

Various neuroimaging techniques have been employed to study the impact of diabetes on brain structure and function. This approach has also been used to define the structural correlates of cognitive dysfunction in diabetes and to provide insights into the mechanisms underlying the central nervous system complications of the disease. Here, we will review studies that have used magnetic resonance–based techniques including structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and functional MRI (fMRI) to assess brain structure and function in diabetes (Table 1).

Type 1 diabetes. Structural MRI techniques are most commonly used to examine the impact of diabetes on total and regional brain volumes. Structural MRI studies have shown lower gray and white volumes in subject with T1DM compared to non-diabetic controls. Musen *et al.*[44] used voxel-based morphometry to examine brain changes in 82 patients with T1DM. Compared to non-diabetic controls, patients with diabetes had lower gray matter density, primarily in the posterior, temporal, and cerebellar regions of the brain. Lower gray matter density was associated with poor glycemic control, higher frequency of severe hypoglycemic events, age of onset, and duration of diabetes. In another study, the frontal lobe appeared to be the location of reduced volumes in patients with T1DM

Table 1. Studies examining the relationship between diabetes and brain volume

Study	Groups: number	Mean age patients (years)	Study design	Outcome and results (diabetes compared to control)	Association with diabetes-related risk factors
Musen *et al.*	T1DM: 82 Controls: 36	33	Cross-sectional	Lower GMD primarily in the posterior, temporal, and cerebellar regions	Lower GMD associated with poor glycemic control and higher frequency of severe hypoglycemia
Hughes *et al.*	T1DM: 104 Controls: 151	49	Cross-sectional	Smaller GMV in the frontal lobe	No significant association between diabetes-associated variables and reduced GMV
Wessels *et al.*	T1DM: 13 DR, 18 NDR Controls: 21	42	Cross-sectional	Reduced GMD in the right inferior frontal gyrus and right occipital lobe	Reduced GMD seen in patients with diabetic retinopathy
Hershey *et al.*[3]	T1DM: 95 Controls: 49	12	Cross-sectional	No difference in hippocampal volumes between the groups	Greater exposure to severe hypoglycemia was associated with larger hippocampal volumes
Moran *et al.*	T2DM: 350 Controls: 363	67	Cross-sectional	Reduced GMV seen in hippocampal, frontal, cingulate, and temporal regions. Reduced WMV seen in the frontal and temporal regions	
den Heijer *et al.*	T2DM: 41 Controls: 465	77	Cross-sectional	Smaller hippocampal and amygdalar volumes	Insulin resistance associated with amygdalar atrophy in non-diabetic controls
Brundel *et al.*	T2DM: 56 Controls: 30	70	Cross-sectional	Reduced cortical gray matter, most pronounced in the temporal lobe	Atrophy in the hippocampal region associated with the presence of small vessel disease
Manschot *et al.*	T2DM: 122 Controls: 56	66	Cross-sectional	Increased cortical and subcortical atrophy	Retinopathy associated with more pronounced cortical atrophy
van Elderen *et al.*[1]	T2DM: 89 Controls: 438	75	Longitudinal	Reduced brain volume at baseline with increase rate of volume loss during follow-up	Fasting glucose level and insulin treatment associated with rate of brain volume loss
de Bresser *et al.*	T2DM: 55 Controls: 28	66	Longitudinal	Reduced brain volume at baseline with greater increase over time in lateral ventricular volume	Increasing age and hypertension associated with greater progression of cerebral atrophy

Abbreviations: T1DM, type 1 diabetes; T2DM, type 2 diabetes; GMD, gray matter density; GMV, gray matter volume; DR, diabetic retinopathy; NDR, no diabetic retinopathy; WMV, white matter volume.

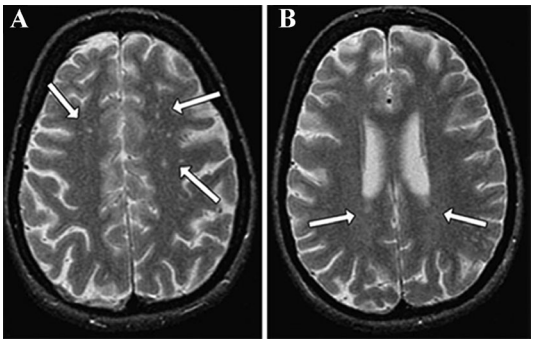

Figure 1. **Example of white matter hyperintensities on MRI images. (A) Arrows indicate deep white matter hyperintensities. (B) Arrows indicate periventricular hyperintensities. Reproduced from Ref. 51 with permission from Springer-Verlag.**

relative to controls.[45] Reduced white matter volumes were identified in subjects with T1DM by Wessels *et al.*, and this volume loss was associated with lower performances on tests for attention, speed of information processing, and executive function.[14] Age of onset, duration of diabetes, and presence of retinopathy have also been associated with structural changes in imaging studies in T1DM.[46,47] Patients with T1DM have also been shown to have increased white matter lesions (WMLs), which may represent vascular abnormalities in intraparenchymal cerebral arterioles (Fig. 1).[48,49] In patients with T1DM, increased severity of WMLs compared to controls has been reported in some[50] but not all studies.[51]

Compared to studies in patients with T2DM, there are limited data available on hippocampal volume in adults with T1DM. A small study in adults with T1DM did not find any difference in hippocampal volumes between adults with T1DM and controls.[52] Hershey *et al.* examined a large sample of young patients with T1DM and compared them with their siblings without diabetes.[53] Overall, there were no differences in hippocampal volumes between the groups, but hippocampal gray matter volume was larger in those children with T1DM with history of three or more severe hypoglycemic episodes in the past. Overall, studies show that T1DM is associated with reduction in brain volume compared to non-diabetic controls; the distribution of brain areas involved appears to be variable and the changes in brain structure have been associated with decline in cognitive performance.

DTI can identify white matter microstructural deficits by measuring the directionally restrained diffusion of water (anisotropy) within fiber tracts. Specifically, a reduction in fractional anisotropy (FA) because of the loss of restriction of water movement is expected when fiber bundles are damaged by the pathology. In a DTI study in patients who had diabetes for at least 15 years, Kodl *et al.*[54] reported white matter microstructural deficits in the posterior corona radiata and the optic radiation that correlated with lower performance in cognitive tests thought to be associated with white matter function. *In vivo* brain magnetic resonance spectroscopy (1H-MRS) can noninvasively quantify concentration of various metabolites. Mangia *et al.*,[55] using MRS, report lower *N*-acetylaspartate (NAA) and glutamate concentrations in gray matter–rich occipital lobes of patients with T1DM. Lower NAA is thought to be a marker of neuronal dysfunction.

In addition to providing invaluable information about tissue structure and microstructure, MRI is a method of choice to evaluate brain function and is being increasingly utilized in diabetes research. Current MRI approaches employed for functional brain mapping detect task-evoked energy requirements and accompanying hemodynamic responses. The most common fMRI technique is the blood oxygenation level–dependent (BOLD) contrast,[56] which detects signal changes induced by alterations in the local content of deoxyhemoglobin (dHb), which intrinsically acts as an endogenous contrast agent. Because the dHb content critically depends on a complex interplay of hemodynamic and metabolic parameters, caution is warranted when interpreting fMRI results in diabetes, as an altered neurovascular coupling cannot always be ruled out owing to the possible vascular complications of the disease.

Even during a so-called "resting-state (RS)" condition (i.e., in absence of external stimuli or tasks), there are physiological variations in brain activity and accompanying hemodynamic events that manifest as fluctuations in the BOLD signal. In fact, it has been long recognized that the engagement of brain areas to a task occurs on top of a complex baseline state. Synchronized neural activity exists between distinct brain locations in any given period of time, an observation that leads to the concepts of brain functional connectivity and RS networks. Such brain networks are remarkably

consistent across healthy subjects.[57] Some of these networks are clearly linked to neurobiologically relevant functions, as the visual, auditory, motor, sensory networks, whereas the interpretation of other networks still remains less clearly defined. Another network, referred to as the *default mode network* (DMN),[58–60] has attracted a considerable interest in the clinical neuroscience community for its possible interpretation as the baseline cognitive state of a subject and its link to memory and executive function in normal and pathological conditions. The DMN involves the anterior cingulate cortex and the posterior cingulate cortex (PCC), which are known to be involved in attention-related processes,[61] and a number of other regions that are transiently or consistently deactivated during different types of cognitive tasks.[62]

The impact of T1DM on brain functional connectivity is still poorly characterized as compared to T2DM. Few recent functional connectivity studies have been conducted on T1DM patients with neuropathic pain[63] with or without microangiopathy.[64] Such studies revealed abnormalities in networks involving attention,[63] working memory, auditory and language processing, and motor and visual areas.[64] In particular, reduced functional connectivity in the attention network was found in diabetics with microangiopathy compared to controls, but not in patients who did not have microangiopathy.[64] In a subsequent study by the same group,[65] subclinical macroangiopathy was also found to be a factor that likely contributes to development of diabetes-related cognitive changes in T1DM. More extensive studies aimed at establishing the impact of other clinical features of the disease, including hyperglycemia or hypoglycemia episodes, have yet to be performed.

Type 2 diabetes. People with T2DM have also been shown to have brain atrophy, including lower total and regional white and gray matter volumes compared to non-diabetic controls.[66] In a large cross-sectional study, Moran *et al.*[66] reported that patients with T2DM had lower total gray, white, and hippocampal volumes. Regions with loss of gray matter include the medial temporal, anterior cingulate, and medial frontal lobes. White matter loss was found in the frontal and temporal regions. These investigators determined that brain volume loss was associated with poor performance in cognitive testing in these patients with T2DM. Other studies have suggested that atrophy may be greater in the hippocampal region in patients with T2DM.[67,68] Patients with T2DM have also been shown to have increased WMLs.[66,69] Brain atrophy and WMLs have been associated with cognitive dysfunction in some[69] but not all studies.[70]

In prospective studies, subjects with T2DM showed an accelerated progression of brain atrophy and WMLs over 3–4 years[71–74] relative to controls. Diabetes-related risk factors, including hypertension, duration of diabetes, glycemic control, and retinopathy, have been associated with brain structural changes in this patient population.[24,69,74] However, in a more recent study using ultra-high-field MRI at 7 T, Brundel *et al.*[75] did not find any differences in the presence and number of microvascular lesions (microinfarcts and microbleeds) in patients with T2DM compared to controls, nor did they find that microvascular lesions were associated with performance on cognitive testing. As in T1DM, studies in T2DM also show that the distribution of volume loss across brain areas is variable, but the medial temporal lobe appears to be more susceptible. Future work will need to be done to determine if particular groups of patients with T2DM are at greater risk for changes in brain structure and function.

Using diffusion MRI, Reijmer *et al.* reported microstructural abnormalities and disruptions in the white matter network in individuals with T2DM compared with controls. These abnormalities were related to slowing of information-processing speed.[76,77] Reduced white and gray matter microstructural integrity has also been shown in obese adolescents with T2DM,[40] suggesting that these structural changes are related to diabetes-specific factors other than the atherosclerotic vascular disease–related changes seen in older people with diabetes.

Decreased connectivity of the PCC within the DMN is not only commonly observed in patients with Alzheimer's disease[78] and mild cognitive impairment,[79] but is also observed in subjects with T2DM.[80] Abnormal functional connectivity of the PCC to selected brain regions in patients with T2DM also appears to correlate with lower FA in the cingulum bundle and uncinate fasciculus[81] and with insulin resistance.[82]

Patients with T2DM not only demonstrate reduced functional connectivity within the resting state DMN, but also show abnormal involvement of the DMN during task performance,[83] including a reduced activation of the dorsolateral prefrontal cortex during encoding and reduced deactivation of the DMN during recognition, with these effects being possibly exacerbated by acute hyperglycemia.

Other alterations of brain functional connectivity have been reported in T2DM[84] that resemble those observed in individuals at risk for Alzheimer's disease[79] (including a reduced RS connectivity between the hippocampus and other brain regions[80,84]). In a study by Zhou *et al.*, the decline in cognitive performance in T2DM was associated with a reduction in functional connectivity of the hippocampus.[84] These are interesting observations, because patients with T2DM have an increased incidence of both Alzheimer's disease[85–89] and vascular-type dementia;[86,89,90] therefore, abnormal functional connectivity might constitute an early marker of subsequent cognitive decline for patients withT2DM. However, future longitudinal studies are necessary to determine whether these changes are predictive of cognitive dysfunction.

Functional connectivity of other brain regions outside the DMN and the hippocampus has also been associated with cognitive dysfunction in T2DM. For example, in a recent study by Cui *et al.*,[91] a decreased amplitude of low-frequency fluctuations (possibly indicative of reduced functional connectivity) was observed in the postcentral gyrus and occipital lobe of patients with T2DM compared to controls. Interestingly, this finding was present in the absence of structural brain changes and was associated with worse memory performance and executive functioning. Disturbances of low-frequency fluctuations have been observed in several additional brain areas.[92,93] For instance, smaller fluctuations in the bilateral middle temporal gyrus have been associated with higher A1C values, impaired β-cell function, and poor neurocognitive performances.[92]

It is likely that the microvascular complications of diabetes largely contribute to the development of brain functional abnormalities, which possibly even precede the cognitive decline observed in T2DM. Indeed, when diabetics with or without microangiopathy were compared to non-diabetic controls, reductions of functional connectivity were observed only in patients with microangiopathy.[64] In addition, diabetic retinopathy is considered to be an independent risk factor for cognitive decline in diabetes.[94]

The pathophysiology underlying the cognitive decline and brain structural changes in subjects with diabetes is not well understood. Poor glycemic control, vascular disease, oxidative stress, genetic predisposition, insulin resistance, and amyloid disposition have been proposed as possible contributors; these proposed mechanisms are discussed in detail in other published reviews.[1,95,96]

Conclusions

Both type 1 and type 2 diabetes are associated with mild-to-moderate decrements in cognitive function. There are significant differences in the underlying pathophysiology of cognitive impairment between type 1 and type 2 diabetes. T1DM is usually diagnosed at an early age and may have effects on brain development. Chronic hyperglycemia and microvascular complications are important risk factors common to both type 1 and type 2 diabetes. T2DM is usually diagnosed at an older age and is commonly associated with obesity, insulin resistance, hypertension, and dyslipidemia, all of which can have a negative impact on the brain. The underlying mechanism and the risk factors that may lead to the development of more severe cognitive dysfunction like dementia in some but not all people with diabetes are not well understood. Large longitudinal studies, especially in older people with diabetes, are needed to better understand the impact, progression, and risk factors that drive the development of diabetes-related cognitive dysfunction. Both type 1 and type 2 diabetes have also been associated with structural and functional changes in the brain. However, the direct relationship between structural or functional changes seen in specific brain areas to specific cognitive tasks has not been well identified.

More studies are needed to understand the impact of mild-to-moderate decrements in cognitive function in the daily lives of people with diabetes. This mild-to-moderate degree of cognitive impairment likely does not cause clinically significant problems in the day-to-day activities of most people with diabetes. However, it may present problems during more stressful and challenging situations. People at the extremes of age are more likely to be at increased risk of developing clinically significant declines in cognitive function. Cognitive impairment in

children with early-onset T1DM appears to negatively affect their academic performance.[97] In elderly people with T2DM, cognitive dysfunction is associated with poor diabetes self-management, requiring more assistance with personal care and increased risk of hospitalization.[98] More research is needed to develop specific diagnostic criteria or severity scores to identify people who are at increased risk of developing accelerated or clinically significant cognitive decline. Specific therapeutic interventions or preventive measures to prevent cognitive decline have not been developed. The DCCT/EDIC study provides some evidence that good glycemic control has beneficial effects on cognitive decline in people with T1DM. However, the ACCORD MIND Study, with relatively shorter duration of follow-up, did not show benefits of intensive control on cognitive function in T2DM. It is also unclear if reduction of vascular risk factors in T2DM will have beneficial effects on cognitive function in T2DM. Overall, results of available studies do not support universal screening for cognitive impairment in all subjects with diabetes. Increased awareness about the risk of cognitive impairment in diabetes among medical providers is warranted, and screening may be considered if a treatment regimen is to be intensive to ensure the patient can adhere to the regimen. Patients and their families should be counseled about risk factors associated with cognitive decline. Screening for cognition dysfunction should be considered in subjects with cognitive complaints or in older subjects with T2DM, especially if there is evidence of deterioration in everyday functional ability. Large prospective intervention studies with long-term follow-up with neuroimaging and neuropsychological assessments are needed to develop strategies to prevent and treat this brain-related complication of diabetes.

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