Diabetes and the Brain—An Overview of Existing Knowledge and Discussions and Future Implications

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Abstract

Diabetes affects many organ systems including the brain. Both type 1 and type 2 diabetes have been associated with reduced performance on multiple domains of cognitive function, including memory, psychomotor efficiency and executive function. In addition, structural abnormalities in the brain have been noted in subjects with both type 1 and type 2 diabetes using a variety of imaging techniques. The underlying pathophysiological mechanisms causing these changes in cognition and structure are not well understood but hyperglycemia, insulin resistance and vascular disease are likely to have key roles. Future research is needed to better understand of the natural history of the cerebral complications of diabetes and to identify the underlying mechanisms that lead to changes in brain function and structure.

Keywords

Cognitive dysfunction, diabetes, leukoaraiosis, cerebral complications of diabetes, brain

Diabetes is a complex metabolic disease that affects multiple organ systems in the body. Diabetes-induced complications in the kidneys, eyes, cardiovascular and peripheral nervous system have been well established. Diabetes-related complications in the central nervous system (CNS) are now being increasingly recognized and investigated. Diabetes is reaching epidemic proportions globally and with people living longer and better lives with diabetes, the CNS complications will likely have more clinical and public health implications in the future.

Both type 1 and type 2 diabetes mellitus have been associated with cognitive impairment (see *Table 1*) and structural changes in the brain (see *Table 2*). The underlying pathophysiological mechanisms causing these complications are not well understood, but various mechanisms linked to hyperglycemia have been proposed. This article reviews the clinical and epidemiological data regarding diabetes and cognitive dysfunction, the cerebral structural changes associated with diabetes and the possible pathophysiological mechanisms causing cognitive dysfunction in diabetes. It goes on to discuss the potential future direction of research in this field.

Diabetes and Cognitive Dysfunction

Type 1 Diabetes

Cognitive dysfunction in type 1 diabetes has been well described and was first reported by Miles in 1922.[1] Patients with type 1 diabetes have been shown to have performance deficits in multiple cognitive domains including:

- memory;[1]
- attention;[2]
- information processing;[2]
- psychomotor speed;[3,4]
- visuospatial abilities;[2]
- executive function; and[5]
- verbal and full scale IQ.[6]

Hyperglycemia has been shown to be associated with cognition changes in patients with type 1 diabetes. At the 18-year follow-up visit of the Diabetes Control and Complications Trial, subjects with worse metabolic control (glycated hemoglobin values >8.8%) performed significantly more slowly on measures of psychomotor efficiency than those with better control (glycated hemoglobin <7.4%).[7] Increased exposure to hyperglycemia was also associated with reduced performance on tests of verbal intelligence in children aged five to 16 years of age.[4]

The presence of diabetes complications appears to increase the risk of cognitive dysfunction in patients with type 1 diabetes.[2,8] Ryan et al. examined the relationship between diabetic complications and cognitive dysfunction in adults with longstanding type 1 diabetes.[2] They found that patients with polyneuropathy, background or proliferative retinopathy, or nephropathy performed more poorly on tests requiring sustained attention, rapid analysis of visuospatial detail and hand-eye coordination compared to non-diabetic control subjects. Further

regression analyses showed that the diagnosis of polyneuropathy was best predictor of performance on cognitive testing. Severe recurrent hypoglycemia was not found to be associated with cognitive dysfunction in this study.[2]

The age of diabetes onset appears to be an important variable in predicting cognitive dysfunction in children with type 1 diabetes. In a meta-analysis, Gaudieri et al. examined a sample of 2,144 children consisting of 1,393 study subjects with type 1 diabetes and 751 control subjects from 19 studies and found that cognitive changes were most pronounced for children with early-onset diabetes.[9] These children had slightly lower overall cognition with mild differences in learning, memory, attention and executive function skills compared to healthy controls.

Perantie et al. studied the effects of hypoglycemia on cognitive function in youth (in children aged five to 16 years). They found the greatest deficits in spatial intelligence and delayed recall in those children who experienced severe hypoglycemic episodes before the age of five years.[4] These observations suggest that the developing brain may be particularly vulnerable to the effects of extremes in glycemia.

Type 2 Diabetes
Several large population-based studies have shown patients with type 2 diabetes have a significantly increased risk of developing both mild cognitive impairment, which is believed to be a predictor of Alzheimer's disease, and dementia when compared to controls without diabetes.[10–13] This increased risk pertains to both Alzheimer's and vascular-type dementias.[10,14]

In a prospective, population-based study of more than 6,000 subjects, the presence of diabetes mellitus almost doubled the risk of dementia.[10] In the Epidemiology of Vascular Aging study of community-dwelling elders with normal cognition at outset, only those subjects with diabetes showed deterioration in cognitive function over the four years of follow up.[11] While insulin use has been associated with the highest risk for dementia in some studies,[10] just the presence of the disease appears to greatly increase dementia risk in patients with type 2 diabetes.

The degree of chronic hyperglycemia may be an important determinant in the cognitive dysfunction seen in subjects with type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes (ACCORD-MIND) study included nearly 3,000 subjects. A strong inverse relationship was identified in this study between glycated hemoglobin (HbA_{1c}) and cognitive performance in the areas of:[15]

- visual motor function;
- attention;
- learning;
- working and verbal memory; and
- executive function.

Sustained improvements in glycemic control, as was achieved by Ryan et al. in their study, appear to lead to some improvement in a number of measures of cognition patients with type 2 diabetes.[16] Duration of diabetes[11,12,17] and diabetic complications, such as peripheral

Table 1: Changes in Cognition in Type 1 and Type 2 Diabetes

Impaired memory
Reduced psychomotor efficiency
Reduced executive function

Table 2: Changes in Cerebral Structure Seen in Type 1 and Type 2 Diabetes

Atrophy
Leukoaraiosis
White matter microstructural abnormalities

neuropathy,[18] both of which may be markers for greater exposure to hyperglycemia, have also been associated with cognitive dysfunction.

Epidemiological studies have also shown that comorbidities like hypertension,[19,20] dyslipidemia[19] and depression[21] are associated with increased risk of cognitive dysfunction in patients with type 2 diabetes. In a study of the Framingham cohort, subjects with type 2 diabetes and hypertension were at the greatest risk for poor performance on tests measuring visual organization and memory compared to subjects with only one of these conditions.[17]

Episodes of hypoglycemia may also play a role in the cognitive dysfunction identified in some patients with type 2 diabetes. This was shown in a longitudinal cohort study of more than 16,000 subjects with type 2 diabetes with a mean age of 65 years. Whitmer et al. found a 2.39% increase in absolute risk of dementia per year of follow-up for individuals with history of hypoglycemia sufficiently severe to require hospitalization compared with subjects without such a history. These findings were independent of glycemic control, type of diabetes treatment and diabetic comorbidities.[22] While it is tempting to speculate that the severe hypoglycemia contributed to the appearance of dementia, these observations could also be interpreted to demonstrate that individuals with dementia are at increased risk for hypoglycemia.

Multiple areas of cognition are altered by type 2 diabetes, with memory, psychomotor speed and executive function appearing to be most often affected.[23] Due to the variability in study design and how investigators control for factors such as age and comorbid conditions, however, not all studies have demonstrated abnormalities in these domains in patients with diabetes. In a recent report of the Victoria Longitudinal Study, subjects with type 2 diabetes were found to perform less well than healthy controls only on tests of executive functioning and semantic speed.[24]

Importantly, the presence of cognitive dysfunction in type 2 diabetes appears to be associated with substantial other comorbidities. In the Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial,[25] subjects with type 2 diabetes and mildly impaired cognitive function, as assessed by the mini-mental status exam, were at increased risk of cardiovascular events and death. In this cohort, more severe cognitive dysfunction was associated with an even greater risk of cardiovascular events. These subjects were also at increased risk of severe hypoglycemia.[25]
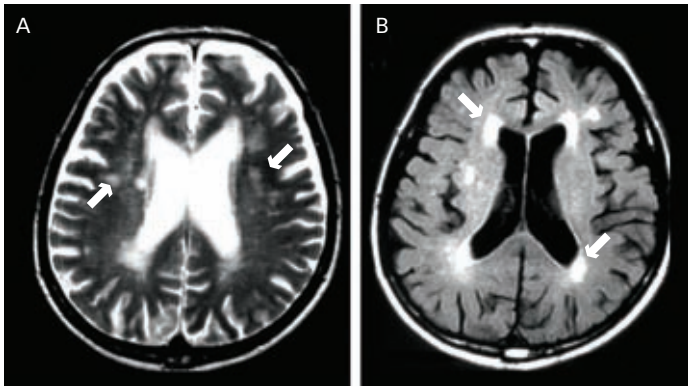
Source: Akisaki T, et al., 2006.[38] Reproduced with permission from the publisher, John Wiley and Sons.

Diabetes and Brain Structural Changes

Type 1 Diabetes

In recent years, magnetic resonance imaging (MRI) has been used to evaluate the impact of diabetes on brain structure. Using standard imaging techniques in an investigation of a small number of middle-aged adults with long-standing type 1 diabetes, Dejgaard et al.[26] found that 69% of diabetic patients had abnormal MRI scans. The scans of these patients showed an increased number of hyperintense white matter lesions in the brain. This high percentage of abnormal scans (69%) was compared to only 12% of healthy controls.

Termed leukoaraiosis, the white matter lesions are believed to represent vascular abnormalities, perhaps in the intraparenchymal cerebral arterioles.[27,28] They may represent the microvascular lesions seen in other organs of patients with diabetes. Not all studies, however, have found such lesions in patients with type 1 diabetes.[29]

Brain abnormalities are not restricted to white matter. Subjects with type 1 diabetes have also been found to have reduced gray matter density. In one report, this was localized to the bilateral frontal, left cerebellum and right occipital regions.[30] In another study it was noted in the left parietal, temporal and frontal and right parietal lobes.[31]

In a large cohort of children with type 1 diabetes, Hershey et al.[32] recently demonstrated that children with more frequent episodes of severe hypoglycemia had increased hippocampal volumes compared to children without severe hypoglycemia. Adults with longstanding type 1 diabetes have not been found to have similar changes,[33] raising the possibility that that the developing brain may respond differently than the adult brain to a hypoglycemic insult.

Seaquist's group has recently used diffusion tensor imaging to better define white matter microstructure in patients with long-standing type 1 diabetes and found evidence of damage in the regions of the posterior corona radiata and the optic radiations. The magnitude of the changes in microstructural integrity correlated with performance on cognitive tests of executive function.[34] No specific clinical characteristics—such as duration, presence of complications or history of severe hypoglycemia—could, however, be linked to the changes seen. The group suspects that a bigger sample size and a prospective study design will be necessary to understand more about the causes and effects of these white matter changes in patients with type 1 diabetes.

Single photon emission computed tomography (SPECT) has also been used to examine the brain in patients with type 1 diabetes. A useful tool to assess cerebral perfusion, SPECT methods revealed that cerebral blood flow was altered under normoglycaemic conditions in patients with diabetes as compared to healthy controls, with an increase in frontal and reduction in posterior cerebral blood flow. Interestingly, these changes were more pronounced in patients with a history of severe hypoglycemia.[35]

In another study of patients with type 1 diabetes, Salem et al. found significant hypoperfusion in basal ganglia and frontal regions using SPECT. These perfusion changes were not associated with measurable changes in cognitive function.[36]

Type 2 Diabetes

Patients with type 2 diabetes have also been found to have leukoaraiosis on magnetic resonance imaging[37,38] (see *Figure 1*). In patients with type 2 diabetes these white matter changes have been associated with reduced performance on tests of attention, executive function, information processing speed and memory.[37,38]

In a population-based study of elderly patients without dementia, type 2 diabetes was associated with hippocampal and amygdala atrophy on MRI compared to control subjects. This association did not change after adjusting for blood pressure and vascular disease.[39] The hippocampus has high density of insulin receptors[40] and its role in memory formation makes it an area of great interest in diabetes. Interestingly, hippocampal and amygdala atrophy are also seen in Alzheimer's disease.[41]

In a recent study, Yau et al.[42] demonstrated that obese adolescents with type 2 diabetes had reduced whole brain volume, particularly in the frontal lobe. They also had diffuse reduced white and grey matter microstructural integrity on diffusion tensor imaging compared to controls. These adolescents with type 2 diabetes demonstrated significantly reduced cognitive performance in areas of intellectual functioning, verbal memory and psychomotor efficiency.[42] Given the youth of these subjects and the relatively short duration of diabetes, it is likely that these structural and cognitive changes are mediated by factors other than atherosclerotic vascular disease.

In a resting-state functional MRI study of elderly subjects with type 2 diabetes, Zhou et al. recently found that the hippocampus showed reduced functional connectivity bilaterally to widespread regions compared to healthy controls.[43] It was found that the regions with reduced connectivity included:

- fusiform gyrus;
- frontal gyrus;

- temporal gyrus;
- anterior cingulate gyrus;
- medial frontal gyrus;
- posterior cingulate gyrus; and
- precuneus and inferior parietal lobule.

These findings suggest that type 2 diabetes is associated with an impaired pattern of default network function that may be involved in the pathophysiology of cognitive dysfunction.

Potential Mechanisms for Diabetes-related Changes in Cognition and Cerebral Structure

The pathophysiology underlying the cognitive dysfunction and changes in cerebral structure in patients with diabetes are not completely understood. Several possible mechanisms have been postulated, including the roles of hyperglycemia, insulin resistance and vascular disease. It is likely that further research will reveal that, rather than a single cause, the underlying mechanism of cognitive dysfunction involves a combination of these factors.

Hyperglycemia

Poor glycemic control is associated with cognitive dysfunction in both type 1 and type 2 diabetes. Improving glycemic control in patients with type 2 diabetes has been shown to reduce cognitive dysfunction.[16] In other organs, the effects of chronic hyperglycemia are mediated through several pathways. These include:[44]

- the increased formation of advanced glycation end-products;
- polyol pathway activation;
- diacylglycerol activation of protein kinase C; and
- increased glucose shunting in the hexosamine pathway.

The same mechanisms may be involved in the cerebral complications seen in patients with diabetes.

Hyperglycemia has also been proposed to cause end-organ damage through increases in reactive oxygen species. In a cross-sectional study of young people with type 1 diabetes, Dominguez et al.[45] found markers of systemic oxidative stress to be present at the time of diagnosis of the disease. These markers were significantly increased compared to controls. Interestingly, the levels of these markers continued to rise over the course of disease, suggesting prolonged exposure to oxidative stress in patients with type 1 diabetes.[45]

In addition, hyperglycemia raises serum osmolality, which in turn has downstream effects on cerebral metabolism. Chronic hyperglycemia is associated with a chronically high demand for vasopressin. This has been shown to lead to several molecular changes within the vasopressin-producing hypothalamic neurons that may contribute to degeneration of these neurons in diabetic rats.[46]

In human patients with poorly controlled type 1 diabetes, the myoinositol content in the basal ganglia was found to be elevated compared to controls using magnetic resonance spectroscopy.[6] Myoinositol level was also noted to be high in another study of patients recovering from diabetic ketoacidosis.[47] Myoinositol is a marker of

changes in osmolarity. Increased levels of this marker have been associated with both gliosis and demyelination.[48]

Vascular Disease

As discussed above, type 2 diabetes has been associated with an increased risk for both Alzheimer's and vascular-type dementias. Vascular disease has been postulated to be a critical factor contributing to the functional and structural changes seen in the brains of subjects with diabetes.

In a study by Manschot et al., macrovascular atherosclerotic disease appeared to be the most consistent determinant of impaired cognition and brain MRI abnormalities in type 2 diabetes patients.[37] In type 1 diabetes, the occurrence of microvascular disease has been associated with reduced cognitive function.[8] Thickening of capillary basement membrane, which is a distinctive feature of microangiopathy, has been seen in brains of patients with diabetes.[49]

In the Age Gene/Environment Susceptibility-Reykjavik Study, which is a large community-based cohort of older individuals, signs of retinal arteriolar changes, such as arteriovenoius nicking, microaneuryms and hemorrhages, were associated with the presence of multiple microbleeds in the brain.[50] These associations were stronger in subjects with diabetes than in healthy controls and were independent of potential confounders like high blood pressure, ischemic brain lesions and other vascular lesions. These observations suggest that there may be a diabetes-specific mechanism that contributes to microvascular changes in both the retina and brain.

Insulin and Insulin Resistance

A growing body of literature suggests that defects in cerebral insulin action may be linked to cognitive dysfunction.[51,52] Insulin receptors have been found to be widely distributed in the human brain, with higher concentrations located in the hypothalamus, cerebellum and cortex.[53]

The exact mechanisms through which insulin and insulin resistance affect cognitive function is not clear, but the hormone does not appear to play a role in the regulation of brain glucose metabolism.[54] Some have hypothesized that the mechanism involves alterations in cerebral insulin receptor signaling that lead to cerebral insulin resistance and downstream abnormalities in insulin-regulated pathways important to cognition.[55] Support for this possibility is the observation that insulin sensitizers have been shown to improve memory and attention in patients with Alzheimer's disease.[56]

Insulin has also been shown to have an important role in the secretion and degradation of beta-amyloid peptides.[57] These peptides contribute to the formation of the intracellular neurofibrillary tangles and extracellular senile plaques seen in Alzheimer's disease.[52] Perhaps defects in cerebral insulin action participate in the development of this dementing disease.

Insulin resistance may also be associated with hypercortisolemia, which has been linked with cognitive dysfunction.[58,59] In some studies, subjects with type 2 diabetes have been found to have upregulation of the hypothalamic-pituitary-adrenal axis, with increased serum cortisol

levels compared to controls. Whether this is a cause or an effect of the cerebral changes seen with diabetes is uncertain.

Future Directions

From the current evidence, it is clear that patients with both type 1 and type 2 diabetes have abnormalities in neurocognitive function and cerebral structure. The impact of these changes on the life of the patient generally appears to be subtle, but may be clinically significant in some individuals.

The number of patients with diabetes who experience the CNS complications of the disease may grow as the life expectancy of patients with diabetes is extended with better therapies. Consequently, future research must focus on more precisely identifying the natural history of the CNS complications of diabetes. Prospective studies will help identify the prevalence of this complication and determine the impact of age, diabetes duration and other clinical characteristics on the development of specific changes in brain structure and function.

In addition to this, future research needs to examine the mechanisms responsible for the development of changes in brain function and structure in diabetes. Hyperglycemia- and hypoglycemia-induced end-organ damage seem to play an important role. The presence of comorbidities, such as hypertension, and aging may also exacerbate the metabolic effects of hyperglycemia on the brain.

The biochemical pathways altered in the brain by exposure to diabetes and the specific cells affected by such exposure must be the topic of future research. Until it is understand how diabetes affects the brain on the molecular level, effective strategies to prevent and treat the cerebral complications of diabetes cannot be developed.

Conclusion

In conclusion, patients with both type 1 and type 2 diabetes have impairments in neurocognitive function and cerebral structural abnormalities. The specific mechanisms underlying these abnormalities are not clear, but multiple factors including poor glycemic control, insulin resistance and vascular disease may be involved. Future research must define the natural history and pathophysiology responsible for the CNS complications of diabetes. ■

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