

Diabetes-related cognitive dysfunction: Hyperglycemia in the early stage might be a key?

Type 2 diabetes mellitus has been an established risk factor for cognitive decline, which has recently been recognized as a new type of diabetes-related complication¹. Although a wide range of cognitive domains are impaired in type 2 diabetes mellitus patients, executive function and processing speed are the most frequently reported to be impaired in older type 2 diabetes mellitus patients². The mechanisms by which type 2 diabetes mellitus affects cognitive function, however, largely remain to be elucidated. Type 2 diabetes mellitus is a complex syndrome that consists of high serum glucose, insulin resistance, impaired function of vascular endothelial cells, atherosclerosis and so on. Among the various features of type 2 diabetes mellitus, hyperglycemia is of course a central feature. Classical complications of diabetes elicited by microangiopathy (nephropathy, retinopathy and neuropathy) are closely associated with hyperglycemia, and glucose-lowering therapies have been shown to prevent the development of these complications. However, surprisingly enough, many past studies have denied an association of hyperglycemia with cognitive dysfunction in type 2 diabetes mellitus, or found only a weak contribution of hyperglycemia to cognitive decline².

Recently, Geijselaers *et al.*³ published a very interesting report associated with the Maastricht Study. The characteristics of the study are summarized in Table 1. They found that diabetes-associated

differences in processing speed and executive function/attention were largely explained by hyperglycemia-related composite variables (Table 1). Using cross-sectional data, the mediating effects for processing speed and executive function were as large as 79.6 and 50.3%, respectively. They also found that decreased processing speed was also explained by blood pressure-related variables (Table 1), to a lesser extent (mediating effect of 17.7%), but that insulin resistance (IR) did not explain cognitive dysfunction at all. Memory was associated with none of the factors in the current study.

The most intriguing feature of this report by Geijselaers *et al.*³ is that they found a strong association of hyperglycemia with cognitive impairment, which largely disagrees with past studies, as aforementioned. Several reasons for this discrepancy can be conjectured. First, the study used a composite index of fasting glucose, post-load glucose, glycated hemoglobin and tissue advanced glycation end-products to assess hyperglycemia (Table 1) instead of using only fasting glucose or glycated hemoglobin, as many of the past studies did. Some reports suggested that fluctuations in blood glucose contribute to cognitive impairment in type 2 diabetes mellitus. Including both fasting and post-load glucose might allow the composite index to reflect at least somewhat the fluctuations of blood glucose. Furthermore, including assessment of tissue advanced glycation end-products might also be important. They used skin autofluorescence to assess tissue advanced glycation end-products (AGEs) accumulation, and included it in the index. AGEs are products resulting from non-enzymatic chemical reactions between reduced sugars and proteins;

they accumulate during natural aging, and type 2 diabetes mellitus enhances the process. AGEs are markers of both hyperglycemia and tissue damage. Including AGEs in the composite index in the current study could allow the index to represent longer-term effects of hyperglycemia compared with using merely glycated hemoglobin, which is a relatively short-term indicator of blood glucose status, and to reflect the extent of tissue damage by hyperglycemia over the long term. AGEs have also been implicated in the pathogenesis of Alzheimer's disease, the most prevalent dementia-developing disease. Second, the study included relatively young (aged 60 ± 8 years) patients with an early stage of disease compared with studies that reported a null association of hyperglycemia with cognitive dysfunction. For example, the Japanese Elderly Diabetes Intervention Trial recruited older participants (>75 years) and found no association of glycated hemoglobin values⁴. Brain pathologies, including Alzheimer's disease or vascular disease, increase in terms of their varieties and severity with aging. As aging advances, a greater variety of factors affect the brain to impair its function. The relative contribution of hyperglycemia to brain dysfunction might be lower in older type 2 diabetes mellitus patients, even if the absolute effects are the same and difficult to detect. Hyperglycemia might influence brain function, even at an early stage. If so, blood glucose management as early as possible, even in the prediabetes stage, has the potential to prevent cognitive decline. Longitudinal and/or prospective studies to assess this possibility would be warranted. Given the disappointing results of both the interventional Action

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Table 1 | Characteristics of the Maastricht study

<i>n</i>	2,531 (52% male)
Glucose metabolism status (<i>n</i>)	Normal (1,479), prediabetes (386), diabetes (666)
Age (years)	60 ± 8
Cognitive assessments	
Memory	Verbal learning test (immediate and delayed recalls)
Processing speed	Stoop Color Word Test I and II, Concept Shifting Test A and B, Letter-Digit Substitution Test
Executive function and attention	Stoop Color Word Test III, Concept Shifting Test C
Hyperglycemia-related variables	Fasting and post-load plasma glucose, glycated hemoglobin, tissue advanced end-product accumulation
Hypertension-related variables	24 h ambulatory blood pressure (systolic, diastolic, and standard deviations)
Insulin resistance-related variable	HOMA-IR

HOMA-IR, homeostatic model assessment of insulin resistance.

to Control Cardiovascular Risk in Diabetes Memory in Diabetes study⁵ and its extension study, the Action to Control Cardiovascular Risk in Diabetes Follow-On Memory in Diabetes study⁶, which failed to show any effects of antihyperglycemic treatment on cognitive preservation in type 2 diabetes mellitus patients, intervention at an earlier stage, perhaps the prediabetes stage, might be the key to success.

The study also found an important role of hypertension in terms of cognitive dysfunction. Regarding the role of hypertension in diabetes-related cognitive dysfunction, the authors proposed a very interesting hypothesis in the article. They hypothesized that hyperglycemia creates a physiological context of vulnerability, and that hypertension causes deterioration of brain function in this context. Hyperglycemia may largely contribute to the development rather than progression of brain dysfunction. This hypothesis at least partly agrees with past observations. Several longitudinal studies found cognitive decline at baseline, but the rates of the decline were not significantly different between type 2 diabetes mellitus patients and non-diabetes individuals⁷. Comprehensive management, focused not solely on hyperglycemia, but also on hypertension, is as important as the management of other complications, such as retinopathy or nephropathy.

Another interesting point of the study is that it failed to find any contribution of IR to cognitive decline. Many past studies have suggested that IR was associated with cognitive decline. Several lines

of evidence have also suggested that IR is associated with Alzheimer's disease. The association between IR and cognition has been found mainly in the general population, not exclusively diabetes mellitus patients or diabetes patients with lower IR. The null association of IR in the current study was reported in the analysis for only diabetes mellitus patients, whereas the analysis including non-diabetic individuals in the present study found a significant association of IR. In this regard, prevention of obesity would contribute to the prevention of cognitive dysfunction. Also, the capacity of exercise and active lifestyle to increase insulin sensitivity would also be important.

Advances in pharmacological therapeutics and expanded knowledge of disease mechanisms for diabetes mellitus have improved the life expectancy of type 2 diabetes mellitus patients worldwide, which has led to greater numbers of older diabetes mellitus patients. This produces a new perspective in this field. Older diabetes mellitus patients tend to have 'geriatric syndrome,' marked by dementia, sarcopenia, frailty and so on. Now we need to confront these emerging complications of older diabetes mellitus patients. The objective of diabetes mellitus treatment is to prevent diabetes mellitus-related complications and maintain quality of life in patients. In past decades, we have accomplished a great deal of success in the field of classic diabetes mellitus-related complications, such as nephropathy, and have thereby contributed to patients' well-being. Now, we need to step forward to confront

emerging diabetes mellitus-related complications, such as cognitive impairment, in the older stage. The current study provides us with many useful suggestions in this regard, one of which is the potential importance of early intervention by anti-hyperglycemic treatment on cognitive preservation. Now we need to deepen our insights into the prevention of diabetes mellitus-related geriatric syndrome to help patients maintain good quality of life throughout their lifetimes.

DISCLOSURE

The author declares no conflict of interest.

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