Diabetes

A risk factor for cognitive impairment and dementia?

Archana Singh-Manoux, PhD
Reinhold Schmidt, MD

Correspondence to Prof. Singh-Manoux: archana.singh-manoux@inserm.fr

Neurology® 2015;84:2300–2301

Hyperglycemia, caused by impaired insulin sensitivity or secretion, is the hallmark of diabetes. In epidemiologic studies, diabetes has been related to cognitive impairment and both vascular and neurodegenerative forms of dementia.[1] As diabetes and dementia are more common at older ages, it is possible that their association is attributable to common causes. It is also possible that type 2 diabetes affects cognitive function only at older ages when the brain undergoes neurodegenerative changes associated with ageing.[2] In this issue of *Neurology*®, data from the Framingham Heart Study show diabetes to be associated with subtle brain injury and poor performance on tests of memory, visual perception, and attention.[3] Although fasting glucose was not associated with performance on cognitive tests, it was associated with gray matter atrophy and reduced white matter integrity. These results are striking because the mean age of participants was 40 years at the glycemic assessment and 47 years at cognitive assessment and brain imaging. Recent studies have also reported accelerated cognitive decline in middle-aged adults with longer exposure to type 2 diabetes.[4,5] These results, considered together, suggest that the diabetes-cognition association is not confined to old age.

Besides the age of participants, 3 features of the current study are noteworthy. First, by including data on cognitive tests along with brain imaging, the authors were able to show effects of diabetes in a comprehensive multimodal manner. Second, associations were evident for both memory and nonmemory domains of cognition, even though the clinical importance of the small effect sizes found in the study remain to be determined. Third, the authors were able to show that statistical adjustment for hypertension did not fully attenuate associations. As vascular complications of diabetes are worse in the presence of hypertension, results from the current study provide further evidence of the importance of both vascular and nonvascular pathways. The association of memory was mediated through frontal, occipital, and hippocampal atrophy, suggesting that degenerative processes in the brain are involved in the development of cognitive impairment in young adults with diabetes.

The natural history of type 2 diabetes involves impaired glucose regulation, which may predate clinically manifest diabetes by several years. The mechanisms underpinning its association with dementia remain unclear. Diabetes is associated with metabolic and hemodynamic defects that cause microvascular and macrovascular damage, leading to reduced cerebral flow and impaired vascular reactivity. Peripheral hyperinsulinemia may be highly relevant. It downregulates blood–brain barrier insulin receptors leading to reduced insulin transport to the brain followed by decreased acetylcholine transmission and cerebral blood flow.[6] Hyperglycemia itself contributes to neuronal apoptosis via increased generation of free radicals, enhanced glycation end products, and elevated lipid peroxidation.[6] Other possible mechanisms are hyperglycemia-related vascular lesions and microstructural tissue damage that can be noninvasively detected by diffusion tensor imaging.[7] Because a recent study using ultra-high-field MRI did not find increased burden of cerebral microvascular damage in patients with type 2 diabetes, compared to controls, there is additional support for the hypothesis that type 2 diabetes induces nonvascular dysfunction.[8] Thus, further research is needed to assess whether the core mechanisms underlying the association between diabetes and dementia are primarily neurodegenerative or cerebrovascular.

By demonstrating structural brain damage and related cognitive impairment in young diabetic patients, the present results from the Framingham Heart Study reinforce the importance of early prevention. Therapeutic strategies that improve glycemic control could mitigate the effects of diabetes on the brain. However, results from intervention studies, carried out mostly on older adults, have been disappointing so far. The Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD MIND) intervention compared the effects of an

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From INSERM (A.S.-M.), Epidemiology of Ageing and Age-related Diseases, Hôpital Paul Brousse, Villejuif Cedex, France; the Department of Epidemiology and Public Health (A.S.-M.), University College London, UK; and the Department of Neurology (R.S.), Clinical Division of Neurogeriatrics, Medical University Graz, Austria.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

intensive glycemic therapeutic strategy to standard strategy and showed no benefit of intensive therapy for cognitive function, although small positive effects were seen on total brain volume.[9] The trial was stopped prematurely due to higher rate of hypoglycemic events and death in the intensive treatment group. The adverse effects of hypoglycemic events, particularly in older adults, are poorly understood and may have contributed to the null findings; these events can lead to brain injury, offsetting the benefits of reduced exposure to hyperglycemia. The use of several drugs to reduce HbA1c to less than 6% in the intensive treatment arm of the ACCORD trial also raises the possibility of adverse drug interactions. The ACCORD MIND results do not rule out the possibility that intervention to lower glucose at younger ages or early in the disease process may be beneficial. Longitudinal studies suggest greater cognitive decline in participants with poorly controlled diabetes.[4,5] Early-stage diabetes is amenable to control via improvements in lifestyle, with some evidence that intensive lifestyle modification programs may work better than the administration of metformin, an antidiabetic medication.[10]

Understanding the association between diabetes and dementia is important because of the epidemic of type 2 diabetes: the International Diabetes Federation (http://www.idf.org/diabetesatlas/update-2014) estimates 387 million cases of diabetes globally; by 2035 this will rise to 592 million. Rapid urbanization, changes in dietary habits, increasingly sedentary lifestyles, and the rising tide of obesity explain this epidemic. It is urgent to determine the feasibility and benefit of various strategies to prevent or delay the onset of type 2 diabetes. Strategies to promote cardiometabolic health when implemented from early life might help to delay the onset of dementia. The benefits of routine testing for cognitive impairment in patients diagnosed with type 2 diabetes also need to be investigated. Another area of interest is the possible neuroprotective effect of antidiabetic medication. Despite these gaps in knowledge, we agree with the authors of the present study that the brain is indeed an important end organ of vascular disease.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

A. Singh-Manoux receives research support from the US NIH (R01AG013196; R01AG034454) and the European Union H2020 programme (643576). R. Schmidt receives research support from the Austrian Science Fund (P20545-P05, P13180, P20103, and I904). Go to Neurology.org for full disclosures.

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