Editorial

Is glycemic variability associated with a risk of Alzheimer's disease in older adults with diabetes mellitus?

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Alzheimer's disease (AD) is the most common form of senile dementia, accounting for more than half of all cases of dementia (1). This neurodegenerative disorder is the most common cause of death among older adults. Around 10% of elders over 70 years of age in the USA suffer from this type of dementia (2). Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that occurs when the body cannot effectively use the insulin it produces and when the pancreas does not produce enough insulin. The global prevalence of diabetes reached 8.5% of the adult population in 2016. The prevalence of T2DM in older adults is a global health issue, causing 1.5 million deaths in 2012 (3). T2DM has been considered as an important risk factor for AD (4-8). These two clinical conditions share underlying mechanisms that have a negative effect on older adults' cognition and independent living. These common mechanisms include inflammation, damage to the blood-brain barrier, hyperglycemia, insulin resistance and vascular dysfunction (5,9-12).

Poor glycemic control is negatively associated with cognitive functioning (13-15). Glycemic levels can be measured using different methods. The most common are: (I) fasting plasma glucose (FPG), consisting of measuring the level of blood glucose in the fasting body; (II) glycosylated hemoglobin (HbA1c), a long-term measure of glucose regulation; and (III) the glucose tolerance test consisting of measuring the time that the body needs to metabolize the sugar consumed.

Li and colleagues (16) recently published the results of a large retrospective cohort study investigating whether FPG coefficient of variation (CV) and HbA1c CV were independently associated with AD in T2DM patients. They used data from the Taiwan Diabetes Study, a retrospective population-based cohort study of Chinese patients with T2DM enrolled in the National Diabetes Care Management Program in Taiwan [2002–2004]. The authors considered that the use of these coefficients is more appropriate than other measures. They reasoned that HbA1c is a time-averaged mean glycemic level, but does not reflect acute glucose fluctuation. Trajectories in HbA1c over time have been associated with cognitive functioning (17). The authors used CV to measure glucose variation, a more feasible method in clinical settings than other methods. The main aim of Li and colleagues was to examine whether FPG CV and HbA1c CV are associated independently and significantly with AD in T2DM patients. The study included 16,706 participants, of whom 831 were diagnosed with AD during a follow-up period of 8.88 years. The study showed an association between glycemic variability, verified by FPG CV and HbA1c CV, and the risk of AD in T2DM patients. Given the connection between glycemic variability and AD, the authors of this large retrospective cohort study stress the importance of assessing the cognitive functions of diabetes mellitus patients, in particular those presenting with large glycemic variability.

Previous research has related HbA1c to cognitive functioning (6,13,14,18,19), but some studies have found conflicting results. For example, Huang (20) reported a positive relationship between elevated levels of HbA1c and cognitive functioning in very old diabetic patients (75 years of age or more), which could be explained by the adaptation

of metabolism processes in people with successful ageing. Although a large number of studies have investigated cognitive functioning in diabetic and AD patients, very few have examined in the same study the cognitive status of older adults suffering from these two chronic diseases, with the exception of the studies conducted by Redondo *et al.* (21,22). Their results showed that several important cognitive processes were negatively affected in both groups of patients (T2DM and AD) compared with healthy older adults. For example, in speed of processing (assessed with a choice reaction time task), episodic memory (measured with an "old-new" recognition task), and visuospatial and verbal working memory (assessed with *n*-back tasks), the T2DM patients performed midway between the healthy older adults and AD patients. However, cognitive control measured by the percentage of perseverations and percentage of perseverative errors in the Wisconsin Card Sorting Test (a frontal lobe test) was similarly impaired in the two clinical groups. T2DM patients performed significantly worse than healthy controls and as badly as AD patients. It is noteworthy that the group of diabetic older adults had no comorbidities such as cardiovascular disease or kidney disease. Moreover, their HbA1c levels were well controlled with a mean of 7.6±0.75% SD. It is important to mention that although their HbA1c levels were well controlled, the diabetic group showed impairments compared with healthy older controls in all cognitive functions and did not differ from AD patients in the decline of executive control. An exception was implicit (involuntary, unconscious) memory, as AD and T2DM patients did not differ from healthy controls. Similarly, Ruis and colleagues (23) did not find any relationship between performance and HbA1c level, especially when this was not above 7%.

The contribution of Li and colleagues is important because it highlights the variability in glucose levels as a main risk factor for AD in T2DM patients. As acknowledged by the authors, the study has some weaknesses, including a lack of information about education levels. Instead, the authors took income and occupational status as indicators of sociodemographic status to adjust for the potential confounding effect. The lack of validation for the diagnosis of AD in medical records was another concern, but the authors tried to ensure accurate diagnosis by including in the study only patients who received outpatient medical care (at least three times) or required hospitalization (at least once). Furthermore, AD could be underestimated because of the difficulty of diagnosing early-stage AD. Finally, as acknowledged by the authors, the assessment of glycemic variability is a complex matter, and there is no gold standard to assess it exactly.

This work sheds light on the apparently conflicting results of studies relating glucose levels with cognitive status. Mayeda and colleagues (12) reviewed a large number of studies and found no consistent results in memory, executive functions, and cognitive functioning in general. Huang *et al.* (20) found no impairments in very old diabetic people with high levels of HbA1c, while Ruis *et al.* (23) found impairments in diabetic patients in the early stages of T2DM. Bottiroli *et al.* (24) reported that diabetic patients scored lower than healthy controls only in the inhibition measure of executive control, but they found no differences in the other executive domains. By contrast, other studies (21,22) found that the episodic memory and executive functions of T2DM patients with good glycemic control were worse than those of healthy elders but better than those of AD patients, except in the Wisconsin Card Sorting Test, a frontal lobe test. The general agreement is that comorbidities and poor glycemic control lead to poor cognitive functioning and a greater risk of AD. It would be of great interest to measure the variability of glycemic levels exactly and relate it to performance in cognitive tests. This may provide a more clearly defined profile of diabetic patients at higher risk of developing AD.

In conclusion, the study confirms that glycemic variability, determined by FPG CV and HbAic CV, and is associated with the risk of AD and that this association is independent of mean FPG and HbA1c and other risk factors. We totally agree with the authors that important cognitive functions, especially episodic memory, working memory and executive control, should be assessed in T2DM patients. The assessment of these cognitive functions is even more necessary in patients presenting with large glycemic variability. More research is needed to confirm whether the variability in FPG and glycosylated hemoglobin are associated significantly with the risk of AD in diabetic patients.

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Footnote

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