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Cognition in elderly with type 1 diabetes: Is there an interaction between glycemia and aging?



Researchers have spent decades studying cognitive functions in children and young to middle-aged adults with T1DM, and found them to perform somewhat poorer on measures of mental flexibility, attention, and executive functions compared to peers.^{1–3} Little is known about cognitive decrements in older T1DM patients, partly because life expectancy in this group had always been lower. With aging, however, and especially above the age of 65 years, cognitive functions become more vulnerable and the risk of mild to moderate cognitive deficits and dementia increases significantly.⁴ This could have serious consequences for the daily functioning of the adult individual with T1DM and complicate performance of the daily self-care tasks. Brands and colleagues showed that, compared to controls, T1DM patients with a mean age of 61 years and diabetes duration of 34 years, had mildly lower mental efficiency scores,⁵ although after a 4-year follow-up period no accelerated decline in patients compared with controls was found.⁶ However, within the patient group, those who had experienced one or more severe hypoglycemic events during the follow-up period and those with cardiovascular disease had lower scores on tests of general cognition and mental flexibility.⁶

In this issue of Journal of Diabetes and its Complications, in a large cross-sectional study, Chaytor and colleagues included 201 T1DM patients between 60 and 86 years of age and a diabetes duration between 20 and 73 years.⁷ No control group was included. A brief cognitive test battery covered the domains of memory, mental flexibility, and executive functions. Test performance was classified as impaired based on a score of 1.5 or more standard deviation below published normative data. Clinically significant cognitive impairment was then defined as two or more impaired test scores. This procedure that has been previously used in a study in middle-aged T1DM adults,⁸ and aligns with the diagnostic criteria for mild cognitive impairment, albeit cognition alone is not sufficient to diagnose mild cognitive impairment. Additionally, all patients carried a blinded continuous glucose monitor for 14 days, providing valuable information on glucose variability in relation to cognitive functioning. It was found that clinically significant cognitive impairment was present in 48% of the sample, which is high compared to 16% found in elderly without T1DM.⁹ Moreover, the number of patients with clinically significant cognitive impairment is almost twice as high as the 28% previously found in middle-aged T1DM patients with childhood disease onset.⁸

Such high levels of clinically significant cognitive impairment could raise concerns about progression to more severe cognitive deficits and

dementia. Therefore, this study also evaluated profiles of clinically significant cognitive impairment, according to the known profiles of mild cognitive impairment. In the general population, amnesic (solely memory) mild cognitive impairment is most prevalent,¹⁰ and also shows the highest conversion-rate to Alzheimer's disease compared to non-amnesic (no memory) and multiple-domain (memory and other functions) mild cognitive impairment.^{11,12} In this study, the large majority of individuals had non-amnesic (44%) or multiple-domain (44%) clinically significant cognitive impairment, compared to 12% having amnesic clinically significant cognitive impairment. This is somewhat reassuring and may indicate that the risk of Alzheimer's disease is not substantially increased in this population, although the risk of vascular dementia is higher in elderly with T1DM.¹³

Associated with a higher risk of clinically significant cognitive impairment were the presence of microvascular complications, higher HbA1c, higher blinded continuous glucose monitor measured average nocturnal glucose, hypoglycemia unawareness, and recent severe hypoglycemic events. Related to a lower risk of cognitive impairment was nocturnal time spent below 60 mg/dl, which might be related to those without cognitive impairment having stricter blood glucose targets. In a multivariate model including these variables, hypoglycemia unawareness, recent severe hypoglycemic events and nocturnal time spent below 60 mg/dl were independently associated with cognitive impairment. These associations corroborate results of the longitudinal study showing that elderly who experienced severe hypoglycemic events during follow-up had worse cognition.⁶ The mechanisms behind this relationship are unknown and need to be further studied, but could be direct (e.g. hypoglycemia-related cell death),¹⁴ or indirect (e.g. hypoglycemia-related hyperglycemic reperfusion damage).¹⁵ It does indicate that hypoglycemic events are related to cognition at times when the brain is most vulnerable, i.e. during childhood and older age, but not during more stable periods.¹ The idea that hypoglycemia can have serious long-term consequences on the aging T1DM-brain should be explored actively as it has been done in type 2 diabetes for some time now, where acute hypoglycemia has been associated with poorer cognition and dementia.^{16,17}

It is recognized that childhood T1DM onset, especially before the age of 7 years constitutes a critical period for T1DM-related brain damage.¹⁸ Of all patients in this study only 1% had an onset age < 7 years and 26% < 18 years. Consequently, the current study was not capable of capturing how aging affects those patients who were diagnosed with T1DM during childhood. However, as the patients included in cohort studies such as the DCCT and EDC are aging, they will hopefully be able to provide these much-needed data.

Conflicts of interest: The authors declare no conflict of interest.

In summary, Chaytor et al. have shown that clinically significant cognitive impairment is present in about half of elderly with T1DM, which is strongly related to hypoglycemic events and to a lesser extent to hyperglycemia. It is imperative that large-scale longitudinal studies are performed in this aging population of T1DM, to substantiate these findings. Clinically, it is important that health care providers are aware of the identified risk factors and make the prevention of hypoglycemic events in elderly a priority in setting glycemic goals. The prevalence of cognitive decrements in elderly with T1DM justifies monitoring of cognition in the context of diabetes self-management and lowering the cognitive demands of treatment where possible.

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