The Association of Duration of Type 2 Diabetes with Cognitive Performance is Modulated by Long-Term Glycemic Control

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Objectives: *It is unclear why duration of type 2 diabetes (T2D) is associated with increased cognitive compromise. High hemoglobin A1c (HbA1c) has also been associated with dementia, and is the primary contributor to T2D complications. Here we investigated whether the association of duration of T2D with cognitive functioning is modulated by HbA1C levels.* **Methods:** *This study examined nondemented community-dwelling T2D elderly (N = 897) participating in the Israel Diabetes and Cognitive Decline study, who were assessed with a broad neuropsychological battery. Subjects were all from the Maccabi Healthcare Services, which has a Diabetes Registry with complete HbA1c measurements since 1998. Partial correlations were performed to examine the modulating effect of HbA1c on the relationship of duration of T2D with five cognitive measures, controlling for sociodemographic and cardiovascular risk factors.* **Results:** *An interaction of duration of T2D with HbA1c was associated with executive functioning ($p = 0.006$), semantic categorization ($p = 0.019$), attention/working memory ($p = 0.011$), and overall cognition ($p = 0.006$), such that the associations between duration of T2D and cognitive impairment increased as HbA1c levels increased—but not for episodic memory ($p = 0.984$).* **Conclusions:** *Because duration of T2D was associated with cognition in higher HbA1c levels and overall no associations were found in lower HbA1c levels, our results suggest that individuals with T2D may limit their risk of future cognitive decline by maintaining long-term good glycemic control.* (Am J Geriatr Psychiatry 2014; ■:■−■)

Key Words: Cognitive performance, diabetes, hemoglobin A1c

Type 2 diabetes (T2D) is a risk factor for cognitive decline, Alzheimer disease (AD), and vascular dementia.[1] Duration of T2D and poor glycemic control are major contributors to the impact of T2D on cognitive impairment.[2] Disentangling the underlying basis of these associations is important because T2D management may reduce the risk of cognitive decline and dementia.[3]

Hemoglobin A1c (HbA1c) reflects glucose levels over the previous 3 months. Over time, poor glycemic control becomes a major factor contributing to T2D complications, via increased risk of cerebrovascular disease, oxidative stress, impaired insulin action, and glucose toxicity,[1,3] all associated with cognitive decline and dementia.[2,3]

With longer duration of disease there are more T2D complications, including cognitive compromise.[1] Because poor glycemic control over many years increases risk of T2D complications, we investigated whether the relationship of duration of T2D

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with cognitive function is modulated by long-term levels of glycemic control. We hypothesized that the relationship of duration of disease with cognitive function will be stronger with poorer glycemic control. We examined this in a large cohort of T2D elderly participating in the Israel Diabetes and Cognitive Decline (IDCD) study, a collaboration between the Mount Sinai School of Medicine, NY (MSSM), the Sheba Medical Center, Israel, and the Maccabi Healthcare Services (MHS), Israel, investigating the relationships of long-term T2D-related characteristics with cognitive decline. The design and methods of the IDCD are described in detail elsewhere,[4] and summarized in Supplemental Digital Content 1 (available online).

METHODS

Participants in the IDCD study were randomly selected from the approximately 11,000 T2D individuals in the MHS Diabetes Registry. Participants had confirmed T2D, were initially nondemented, above the age of 65 years, and with at least three HbA1c assessments. The IDCD has recruited 1,288 subjects; this study consisted of the 897 who completed a baseline evaluation, after exclusion of 8.5% who refused participation and 21.9% who were excluded by eligibility criteria (86% due to cognitive impairment). Excluded subjects and refusers were younger, had longer duration of T2D, and received more insulin than participants, but did not differ substantially on other demographic or clinical characteristics. The IDCD study is approved by the MSSM, Sheba, and MHS institutional review board committees.

Participants were assessed by a physician experienced in assessment and diagnosis of dementia and by a neuropsychologist, who administered a broad neuropsychological battery, which was the basis for the outcome measures. All neuropsychological test scores were transformed into Z scores. To reduce the number of correlations between duration of T2D, HbA1C, and the neuropsychological measures, factor analysis summarized the neuropsychological measures into four factors: episodic memory (immediate recall, delayed recall, and recognition), executive functioning (Trails A and Trails B, constructional praxis, and digit symbol), semantic categorization (similarities, letter fluency, category fluency), and attention/working memory (diamond cancellation, digit span forward, and digit span backwards). An overall cognition measure summed the scores of all four functions (see Supplemental Digital Content 1; available online).

Statistical Analysis

Partial correlations were performed to examine the association between duration of T2D and the cognitive factors. Sociodemographic (age, years of education, sex) and cardiovascular (HbA1c; body mass index [BMI]; creatinine; total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterols; triglycerides; diastolic and systolic blood pressure; and T2D medication) potential confounders were controlled for. The cardiovascular variables were defined as means over time of all data from the Diabetes Registry averaging 18 measurements. Duration of T2D was defined as the date from which a subject was included in the MHS Diabetes Registry. To further examine the modulation by HbA1c on the relationship of duration of T2D with cognitive outcomes, we examined the interaction between HbA1c and duration of T2D by creating the product of these two variables. The interaction was tested by its partial correlations with cognition variables controlling for HbA1c and duration of T2D, and also the other sociodemographic and cardiovascular variables. For concrete description of the change in the association of duration of T2D with cognition as HbA1c increases, partial correlations examined the relationships between duration of T2D and cognitive outcomes within tertiles of HbA1c. Because inflammation has been associated with both T2D and dementia,[5] a secondary analysis included as additional covariates the inflammatory markers CRP and IL-6 (which were assessed at the IDCD baseline). Each analysis included all subjects with available data, so numbers differed slightly (from 878 to 897).

RESULTS

Participants' average age was 72 years (standard deviation [SD]: 4.7), 59.3% were men. Average education was 13.1 years (SD: 3.5), and average Mini-Mental State Exam score was 28 (SD: 1.8). Participants were