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

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Abstract

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 hemoglobin A1C levels.

Methods—This study examined non-demented 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=.006), semantic categorization (p=.019), attention/working memory (p=.011), and overall cognition (p=.006), such that the associations between duration of T2D and cognitive impairment increased as HbA1c levels increased—but not for episodic memory (p=.984).

Conclusions—Since 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.

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Keywords

cognitive performance; diabetes; hemoglobin A1c

Introduction

Type 2 diabetes (T2D) is a risk factor for cognitive decline, Alzheimer's 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 since T2D management may reduce the risk of cognitive decline and dementia (3).

Hemoglobin A1c (HbA1c), reflects glucose levels over the previous three 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). Since poor glycemic control over many years increases risk of T2D complications, we investigated whether the relationship of duration of T2D 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.

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 non-demented, above the age of 65, with at least three HbA1c assessments. The IDCD has recruited 1288 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 IRB 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 tests' 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 4 functions (see Supplemental Digital Content 1).

Statistical analysis

Partial correlations were performed to examine the association between duration of T2D and the cognitive factors. Socio-demographic (age, years of education, sex) and cardiovascular (HbA1c, BMI, creatinine, total, LDL, and HDL cholesterol, 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 socio-demographic 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. Since 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 (SD= 4.7), 59.3% male. Average education was 13.1 years (SD= 3.5), and average MMSE score was 28 (SD=1.8). Participants were in the Diabetes Registry for an average of 8.7 years (SD=2.6). Average cardiovascular variable levels were: HbA1c 6.8% (SD=.78%, range 4.0%-10.1%), glucose level 135.4 mg/dL (SD=21), creatinine 1.0 mg/dL (SD= .3), BMI 28.6 (SD=7.9), total cholesterol 180.6 mg/dL (SD=24.9), HDL cholesterol 47.8 mg/dL (SD=10.8), LDL cholesterol 101.5 mg/dL (SD=19.7), and triglycerides 157.3 mg/dL (SD=62.9). As expected for a diabetic sample, glucose, creatinine, BMI, and triglycerides were elevated. The majority of subjects (95%) received cholesterol lowering medications which is reflected in normal cholesterol panel values; 13.5% of the sample controlled their T2D solely by diet, 77.1% received hypoglycemic medication only, 0.7% received insulin only, and 8.7% received both insulin and hypoglycemic medications. No correlation was found between HbA1c and duration of T2D ($r=-.020$, $p=.550$, $N=880$).

Controlling for potential sociodemographic and cardiovascular confounders, partial correlations showed that longer duration of T2D was significantly associated with poorer

executive functioning ($r=-.072$, $p=.037$, $df=830$), and approached significance with overall cognition ($r=-.064$, $p=.064$, $df=832$), but not with semantic categorization ($r=-.021$, $p=.538$, $df=832$), attention/working memory ($r=-.033$, $p=.338$, $df=832$), or episodic memory ($r=-.047$, $p=.172$, $df=832$).

Partial correlations showed significant interaction between duration of T2D and HbA1c for attention/working memory ($r=-.088$, $p=.011$, $df=831$), executive functioning ($r=-.095$, $p=.006$, $df=829$), semantic categorization ($r=-.082$, $p=.019$, $df=831$), and overall cognition ($r=-.096$, $p=.006$, $df=831$), but not for episodic memory ($r=-.001$, $p=.984$, $df=831$) (see Table 1).

Partial correlations of duration of T2D with cognitive outcomes in tertiles of HbA1c showed that the relationship is strongest in the highest HbA1c levels, except for episodic memory (see Table 1). This confirmed the significance of the interaction analyses for all cognitive outcomes except episodic memory.

Secondary analysis including the inflammatory markers CRP and IL-6 as additional covariates had a negligible effect on the results (correlations changed by a magnitude of $< .005$, with no change of significance).

Discussion

In this sample, duration of T2D was associated with executive functions after controlling for socio-demographic and cardiovascular risk factors, similarly to other studies (6). This association was modulated by glycemic control so that the higher the levels of HbA1c (reflecting poorer glycemic control), the stronger the association between duration of T2D and the cognitive outcomes. These interactions were significant for all cognitive domains but episodic memory.

Duration of disease encompasses numerous systemic changes, including neuronal damage and brain atrophy via glucose toxicity, and vascular damage via infarcts and atherosclerosis. The relationship between duration of disease and cognition may represent an aggregate of the damage T2D causes (6). Longer duration of T2D increases the likelihood of experiencing numerous episodes of hyperglycemia. Hyperglycemia may directly impact cognitive functioning by increasing oxidative stress and producing glucose and glutamate toxicity, directly damaging neurons (3, 7). Microvascular, including cerebral, changes occur with hyperglycemia (6), potentially increasing the risk of cognitive decline. Higher levels of HbA1c may suggest impaired insulin action in the brain, which may impair cognition (3). Higher glucose levels are associated with a greater risk of cardiovascular disease (3), increasing the risk for impaired blood flow to the brain (6).

Our results also suggest that glycemic control may not impact all cognitive functions equally. In contrast to the relationship between other cognitive functions and duration of T2D, episodic memory was associated with duration of T2D only in those with the best glycemic control. Episodic memory, the primary cognitive domain affected by Alzheimer's disease neuropathology, did not diminish with longer duration of T2D even in poor levels of long-term glycemic control, suggesting that, although T2D, as well as insulin resistance,

have been found to significantly increase the risk of AD (9, 10), T2D could affect cognition through mechanisms other than AD neuropathology (8). This is consistent with evidence for lack of association of T2D with neuritic plaques and neurofibrillary tangles, the hallmark features of the AD brain (11). Although several studies have found episodic memory to be impacted by T2D (12-15), Hassing et al. (16) found episodic memory not to be impacted at baseline, but rather over time (at longitudinal follow-ups) suggesting that the lack of associations found in our study for episodic memory may change when the longitudinal portion of the IDCD is available. Alternatively, it may be the case that longer duration of disease is correlated with cognitive domains typically associated with cerebrovascular disease in those with poor glycemic control, since the latter is strongly associated with cerebrovascular disease (17), thus possibly masking associations with memory. The significant association of poor memory with long duration of disease only in the good glycemic control group (see Table 1), where cerebrovascular disease might be rarer, supports this interpretation.

Our study showed that the relationships of duration of T2D with cognitive domains other than episodic memory, i.e. executive functions, semantic categorization, and attention/working memory, became stronger with poorer glycemic control. These results suggest that duration of disease alone may not affect cognition if HbA1c is well controlled over many years. Cerebrovascular disease has been associated with executive functioning and attention (18), and poor glycemic control (17), suggesting cerebrovascular disease as a potential underlying mechanism.

Interpretation of results from this study must be done with caution, since it is cross-sectional and thus causation cannot be inferred—those with poorer cognitive performance might control less well their glucose. The ongoing longitudinal component of the IDCD may shed light into the contribution of glycemic control to the relationship of duration of T2D with cognitive decline. Additionally, participants included in this analysis were cognitively normal, and the relationships found in this study may change when cognitive impairment, particularly memory impairment, develops. Of note, the participants in this study exhibited a significant range of scores on all cognitive tests, providing the opportunity to find an interaction between duration of T2D and HbA1c with episodic memory if there was one. Since duration of T2D was defined as the time a subject was included in the Diabetes Registry, it is a conservative estimate of subjects' actual duration of T2D, such that there are likely subjects who have had a diagnosis of T2D for longer than is recorded in the Diabetes Registry. In a sensitivity analysis of the effect of truncation of duration of T2D comparing results when duration of at least 9 years was recoded as 9, 12, or 20 years (to represent underestimated, plausible, or overestimated T2D duration-- see Supplemental Digital Content 1), results were essentially unchanged. Finally, elderly subjects with T2D who have survived with normal cognition may be uniquely robust. Although effect sizes are small, in this population, we believe they are meaningful (19). This study is strengthened by a large sample, with strong validity for T2D diagnosis and of cardiovascular variables, and a broad cognitive assessment permitting examination of global and specific cognitive domains.

Our findings lend support to the literature suggesting glycemic control as an important factor in the relationship between T2D and cognitive functioning. Since in the low HbA1c levels

there were no associations between duration of T2D and executive functioning, attention/working memory, semantic categorization, or overall cognition, our results suggest that individuals with T2D may limit their risk of future cognitive decline in these cognitive domains by maintaining good long-term glycemic control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Associations of duration of type 2 diabetes and HbA1c with cognitive functions, for all participants and within HbA1c tertiles

	Interaction between duration of type 2 diabetes with HbA1c with cognition	Correlation of duration of type 2 diabetes with cognition within HbA1c tertiles		
Cognition variable	All participants r(p)	Lowest tertile (3.9500-6.4214%)	Middle tertile (6.4214-6.9962%)	Highest tertile (6.9962-10.1387%)
	df=831 (df=829 for Executive functioning)	df=269 (df= 268 for Executive functioning))	df=264 (df=263 for Executive functioning)	df=265
Overall cognition	-.096 (.006)*	.001 (.990)	-.060 (.331)	-.190 (.002)*
Semantic categorization	-.082 (.019)*	.028 (.645)	.002 (.973)	-.151 (.014)*
Attention/working memory	-.088 (.011)*	.067 (.274)	-.075 (.226)	-.116 (.058)
Executive functioning	-.095 (.006)*	.046 (.452)	-.125 (.042)*	-.182 (.003)*
Episodic memory	-.001 (.984)	-.133 (.028)*	.043 (.483)	-.061 (.319)

* indicates $p < .05$