Haptoglobin 1-1 Genotype Modulates the Association of Glycemic Control With Hippocampal Volume in Elderly Individuals With Type 2 Diabetes

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Recent evidence suggests that glycemic control is associated with cognitive function in older patients with type 2 diabetes who are carriers of the haptoglobin (Hp) 1-1 genotype compared with noncarriers. We assessed whether poor glycemic control in Hp 1-1 carriers is more strongly associated with smaller hippocampal volume than in noncarriers. Hippocampal volume was generated from high-resolution structural T1 MRI obtained for 224 participants (28 Hp 1-1 carriers [12.5%] and 196 noncarriers [87.5%]) from the Israel Diabetes and Cognitive Decline (IDCD) study, who had a mean (SD) number of years in the Maccabi Healthcare Services (MHS) registry of 8.35 (2.63) and a mean (SD) HbA_{1c} level of 6.66 (0.73)% [49 mmol/mol]. A stronger negative association between right hippocampal volume and HbA_{1c} was found in patients with the Hp 1-1 genotype, with a 0.032-mL decrease in right hippocampal volume per 14% increase in HbA_{1c} ($P = 0.0007$) versus a 0.009-mL decrease in Hp 1-1 noncarriers ($P = 0.047$), after adjusting for total intracranial volume, age, sex, follow-up years in the registry, and cardiovascular factor (interaction, $P = 0.025$). This indicates that 29.66% of the total variance in right hippocampal volume is explained by HbA_{1c} levels among Hp 1-1 carriers and that 3.22% is explained by HbA_{1c} levels among Hp 1-1 noncarriers. Our results suggest that the hippocampus of Hp 1-1 carriers may be more vulnerable to the insults of poor glycemic control.

Type 2 diabetes (T2D) is associated with a lower level of cognitive function, a faster rate of cognitive decline, and an increased risk of dementia—both Alzheimer disease (AD) and vascular dementia (1). Serum HbA_{1c} is the gold standard measure for glycemic control, reflects mean blood glucose levels, and has also been consistently associated with poorer cognitive outcomes (2). While the association of T2D with late-life cognitive impairment may be explained in part based on its association with cerebrovascular disease (3) and brain imaging abnormalities (4,5), the underlying mechanisms for the increased dementia risk associated with T2D remain to be elucidated.

Haptoglobin (Hp) is a hemoglobin-binding protein acting as an antioxidant, expressed by a genetic polymorphism as three major genotypes: Hp 1-1, Hp 2-1, and Hp 2-2 (6). Each has structural and functional differences (7). The Hp polymorphism has been shown to be associated with the prevalence and incidence of adverse health outcomes in T2D (6). Hp 2-2 genotype is associated with an increased risk of peripheral and coronary artery disease and increased

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incidence of micro- and macrovascular complications (7,8). Hp 1-1 genotype has been implicated with increased prevalence of small lacunar strokes (9) and white matter hyperintensities (10). We have recently reported that cognitively normal elderly individuals with T2D carrying the Hp 1-1 genotype have lower cognitive function than both Hp 1-2 and Hp 2-2 carriers (11). Moreover, the association of glycemic control with cognitive function was primarily observed for individuals with Hp 1-1 but not for Hp 1-2 and Hp 2-2 carriers. These findings suggest that individuals with the Hp 1-1 genotype may be more susceptible to the deleterious effects of poor glycemic control (12). We examined the interrelationship of Hp genotype, HbA_{1c} levels, and regional volume of the hippocampus obtained from MRI of the brain in older individuals with T2D. In line with our findings on cognition, we hypothesized that the negative association of HbA_{1c} with regional brain volume would be stronger among elderly T2D patients carrying the Hp 1-1 genotype compared with the other genotypes.

RESEARCH DESIGN AND METHODS

Participants were recruited from the Israel Diabetes and Cognitive Decline (IDCD) study (Fig. 1), a collaboration of the Icahn School of Medicine at Mount Sinai, NY, Sheba Medical Center, Israel, and Maccabi Healthcare Services (MHS), Israel. All three institutions provided institutional review board approval, and each participant provided informed consent. The IDCD study design has been previously described in detail (13). Briefly, community-dwelling elderly Israeli individuals with T2D (≥65 years old) were recruited from the MHS diabetes registry. Criteria for enrollment into the IDCD study were the following: *1*) having T2D; *2*) normal cognition at entry to the IDCD study; *3*) being free of any neurological (e.g., Parkinson disease, stroke), psychiatric (e.g., schizophrenia), or other diseases (e.g., alcohol or drug abuse) that might affect cognition; *4*) having an informant; *5*) fluency in Hebrew; and *6*) living in the area of Tel Aviv. Serum was extracted from blood samples, and Hp genotypes were determined by polyacrylamide gel electrophoresis from 10 μL of plasma using established methods (14) and dichotomized as Hp 1-1 carriers versus Hp 2-1 or Hp 2-2 carriers. We chose to use the dichotomy of Hp 1-1 carriers versus others because we found no difference between the Hp 1-2 and Hp 2-2 carriers in our prior studies assessing the association of Hp with cognition (11,12). Demographic details and T2D-related characteristics including longitudinal glycemic control based on repeated HbA_{1c} levels, systolic and diastolic blood pressure, LDL, HDL, total cholesterol, and creatinine were available for all participants. To obtain a measure of glycemic control, we used a multilevel mixed effects linear model with random intercepts to estimate the subject-specific mean HbA_{1c}, adjusting for the number of years in the IDCD registry. Using this type of model enabled us to take into account the degree of

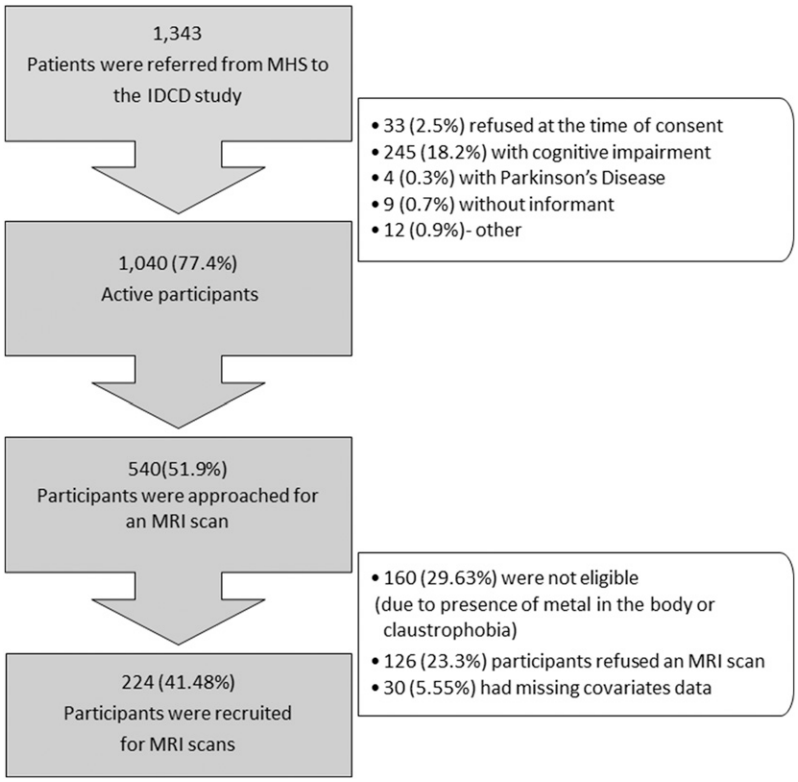

Figure 1—Flowchart of the study cohort.

correlation between the repeated measurements made within a patient as well as both the number of assessments (median [Q1, Q3] 14 [9, 20], range 3–57) and duration in the registry (mean [SD] 8.35 [2.63] years, range 1.46–13.47).

A subsample of participants from the IDCD cohort underwent an MRI scan. MRI scans were performed in the diagnostic imaging department at Sheba Medical Center with a 3T scanner (GE, Signa HDxt, v16VO2). High-resolution (1 mm^3) images were acquired using a 3-dimensional spoiled gradient-recalled echo (SPGR) T1-weighted sequence (TR/TE = 7.3/2.7 s, 20° flip angle, TI = 450 ms).

T1-weighted anatomical images for each subject were processed using the voxel-based morphometry (VBM [15]) toolbox developed by Gaser (http://www.fil.ion.ucl.ac.uk/spm/ext/#VBMtools) and implemented in Statistical Parametric Mapping (SPM8) software. This procedure included automated iterative skull stripping; segmentation of the images into gray matter (GM), white matter, and cerebrospinal fluid probability images; and spatial normalization of the GM images to a customized GM template in standard MNI (Montreal Neurological Institute) space. In order to optimize signal to noise, the GM maps were smoothed using an 8-mm Gaussian kernel. GM probability maps were thresholded at 0.1 to minimize inclusion of incorrect tissue types. Total intracranial volume (TICV) was calculated using the segmented and thresholded images (TICV = GM + white matter + cerebrospinal fluid). Based on our a priori hypothesis, we used a region of interest approach centered on the left and right hippocampus, identified by using the human Automated Anatomical Labeling (AAL) atlas (16) within the Wake Forest University PickAtlas (17) and extracted using the MarsBaR region of interest toolbox (18) as implemented in SPM8.

Statistical Analysis

The skewedness and kurtosis for the adjusted HbA_{1c} mean levels were 1.28 and 2.72, respectively, suggesting the adjusted HbA_{1c} mean variable was not distributed normally. Therefore, we applied a natural log transformation to the HbA_{1c} mean variable, which improved skewedness and kurtosis to 0.87 and 1.53, respectively; we then used the natural log–transformed adjusted HbA_{1c} variable in all further analyses.

We assessed the relationship of mean levels of HbA_{1c} with left and right hippocampal volumes using a multiple linear regression analysis with backward selection. The selection criterion of $P < 0.1$ was used for elimination of a variable. The linear regression analysis allowed for control of TICV, age, sex, number of follow-up years in the registry (a surrogate of duration of T2D), and a cardiovascular risk score created from the first principal component of a factor analyses consisting of systolic and diastolic blood pressure, LDL and HDL, total cholesterol, creatinine, and albumin. The interaction of Hp genotype with HbA_{1c} was assessed.

Sociodemographic and medical characteristics of the two Hp genotype groups were compared using Student *t* test, Pearson χ^2 test, and nonparametric Mann-Whitney *U* test. A *P* value of 0.05 (two sided) was used to determine statistical significance level. For analysis, we used IBM SPSS Statistics for Windows (version 23.0; IBM, Armonk, NY).

RESULTS

Participants (*n* = 224; 28 Hp 1-1 carriers [12.5%] and 196 noncarriers [87.5%]) had a mean (SD) age of 71.30 (4.26) years. The mean (SD) number of years in the MHS registry was 8.35 (2.63), ranging from 1.46 to 13.47. Mean (SD) HbA_{1c} level was 6.66 (0.73)% [49 mmol/mol]. The majority of participants were males (61%). Hp 1-1 carriers did not differ significantly from noncarriers on any of the demographic, medical, or brain volume characteristics (Table 1).

In multivariable regression modeling of right hippocampal volume, there was a significant interaction observed between Hp genotype and HbA_{1c} level ($P = 0.025$) after adjusting for TICV, age, sex, follow-up years in the registry, and cardiovascular factor. Results indicate a stronger negative association between right hippocampal volume and HbA_{1c} in Hp 1-1 carriers, with a 0.032-mL decrease in right hippocampal volume per 14% increase in HbA_{1c} ($P = 0.0007$), than in Hp 1-1 noncarriers, who experienced a 0.009-mL decrease per 14% increase in HbA_{1c} ($P = 0.047$) (Table 2 and Fig. 2). For

Table 1—Demographics and clinical and brain measures of T2D patients by Hp genotypes

T2D patients	Hp 1-1 carriers (*N* = 28)	Hp 1-1 noncarriers (*N* = 196)	*P* value
Male, *n* (%)	16 (57)	121 (62)	0.681
Age (years)	71.24 (3.38)	71.31 (4.38)	0.922
HbA_{1c} (%)	6.73 (0.85)	6.65 (0.71)	0.658
Years in the registry	8.17 (2.96)	8.37 (2.59)	0.758
Number of HbA_{1c} measurements	14 [8, 19]	14 [9, 20]	0.479
Cardiovascular factor	−0.09 [−0.58, 0.94]	−0.01 [−0.67, 0.58]	0.416
TICV (mL)	1,316.18 (126.94)	1,337.66 (137.76)	0.413
GM volume (mL)	510.93 (43.17)	514.94 (51.67)	0.657
Hippocampal volume (ccs)	0.457 (0.04)	0.448 (0.04)	0.329

Data are mean (SD) or median [Q1, Q3] unless otherwise indicated. ccs, cubic centimeters.

Table 2—Slope estimates from multivariable linear regression model of right hippocampal volume regressed on natural log–transformed adjusted HbA_{1c} by Hp genotype carrier status

T2D patients	Unit increase	Slope	95% CI	*P* value†	*P* value‡
HbA_{1c} in Hp 1-1 carriers	14%**	−0.032	−0.050, −0.014	0.0007*	
HbA_{1c} in Hp 2-1/Hp 2-2 carriers	14%**	−0.009	−0.017, −0.001	0.0467*	
Age	5 years	−0.014	−0.021, −0.007	<0.0001*	
TICV	150 mL	−0.013	−0.021, −0.005	0.0012*	0.0249*
Cardiovascular factor	1 unit	0.008	0.001, 0.014	0.0155*	
Male		0.007	−0.008, 0.023	0.3422	
Years in the registry	5 years	−0.0017	−0.013, 0.010	0.7725	

HbA_{1c} was adjusted for number of years in registry. *P value <0.05. †P value testing the slope = 0. ‡P value testing for interaction between Hp genotype and natural log–transformed adjusted HbA_{1c}. **14% increase in HbA_{1c}, i.e., increasing from 7 to 8.

the Hp 1-1 carriers, the squared semipartial correlation coefficient for HbA_{1c} was 0.2969, and for the Hp 1-1 noncarriers, it was 0.0322; this indicates that 29.69% of the total variance in right hippocampal volume is explained by HbA_{1c} levels among the Hp 1-1 carriers and, in contrast, 3.22% of the right hippocampal volume total variance is explained by HbA_{1c} levels among the Hp 1-1 noncarriers. In multivariable regression modeling of the left hippocampal volume, we did not find a significant interaction between Hp genotype and HbA_{1c} level (P = 0.717) (Table 3) after adjusting for all covariates.

In secondary analyses of GM volume, the interaction between Hp genotype and HbA_{1c} level was not statistically significant after adjusting for TICV, age, sex, follow-up years in the registry, and the cardiovascular factor (P = 0.223), although the association of HbA_{1c} (per 14% increase) with GM volume was nominally stronger in the Hp 1-1 carriers (slope = −14.3; P = 0.04) than in noncarriers (slope = −4.84; P = 0.15).

DISCUSSION

We found a significant interaction of Hp genotype with HbA_{1c} in right hippocampal volume, indicating that in elderly patients with T2D, higher HbA_{1c} is associated with smaller right hippocampal volume in Hp 1-1 carriers but not in noncarriers, which may suggest that Hp 1-1 carriers may be more vulnerable to the harmful effects of high levels of HbA_{1c} on the hippocampus.

T2D patients exhibit brain volume loss (4) at an accelerated rate (more than the normal rate of age-related atrophy ([19]) and accelerated expansion of the ventricles (20). Previous studies have examined the association between T2D and hippocampal volume, revealing conflicting results. T2D has been associated with GM loss mainly in middle temporal gyrus (21,22), parahippocampal gyrus, cingulate cortex, precuneus, and insula (23), as well as in medial-frontal regions (21,23). Other studies found that T2D patients showed reduced total cortical volume in the right hemisphere (24) and in the hippocampal region (5,24). In contrast, a

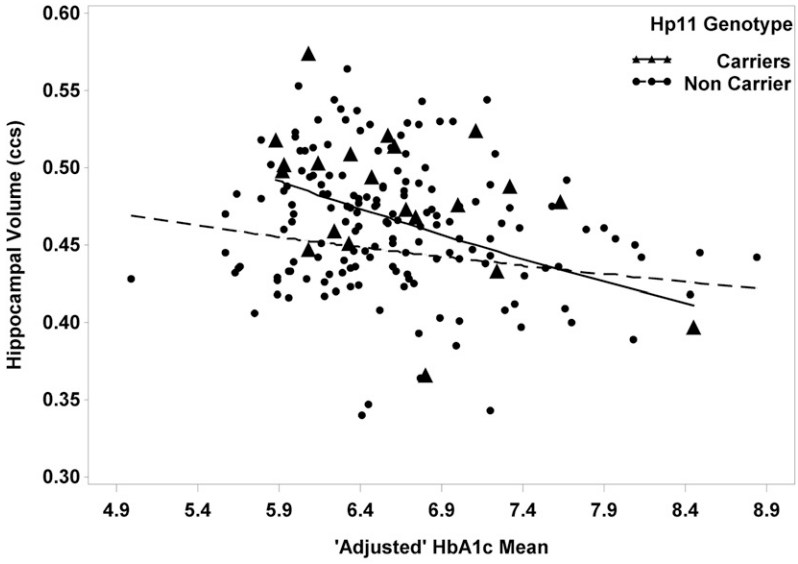

Figure 2—A negative association between right hippocampal volume and natural log–transformed adjusted HbA_{1c} in Hp 1-1 carriers (P = 0.0007) and in Hp 1-1 noncarriers (P = 0.0467) is shown; interaction between Hp genotype and HbA_{1c} level (P = 0.025) after adjusting for TICV, age, sex, follow-up years in the registry, and cardiovascular factor. ccs, cubic centimeters.

Table 3—Slope estimates from multivariable linear regression model of left hippocampal volume regressed on natural log–transformed adjusted HbA_{1c} by Hp genotype carrier status

T2D patients	Unit increase	Slope	95% CI	*P* value†	*P* value‡
HbA_{1c} in Hp 1-1 carriers	14%**	−0.014	−0.033, 0.005	0.1517	
HbA_{1c} in Hp 2-1/Hp 2-2 carriers	14%	−0.008	−0.017, 0.001	0.0806	
Age	5 years	−0.016	−0.023, −0.009	<0.0001	
TICV	150 mL	−0.019	−0.027, −0.011	<0.0001	0.5814
Cardiovascular factor	1 unit	0.006	−0.0008, 0.012	0.0834	
Male		−0.005	−0.021, 0.010	0.5024	
Years in the registry	5 years	0.0006	−0.012, 0.013	0.9218	

HbA_{1c} was adjusted for number of years in registry. †*P* value testing the slope = 0. ‡*P* value testing for interaction between Hp genotype and natural log–transformed adjusted HbA_{1c}. **14% increase in HbA_{1c}, i.e., increasing from 7 to 8.

recent pooled analysis of three studies showed that T2D patients had greater brain atrophy but not greater hippocampal atrophy compared with control subjects (4). The associations found between HbA_{1c} levels and brain volume in patients with T2D have also been inconsistent. Higher levels of HbA_{1c} have been shown to be associated with cortical atrophy in T2D patients (25). However, other studies have not found such associations (4,26). With regard to the hippocampus, HbA_{1c} was found to be a significant predictor of hippocampal volume (5), even when controlling for other variables commonly associated with T2D (27). However, a study examining the relationship between HbA_{1c} and GM volume of the right temporal lobe showed no significant correlation in older adults with T2D (22). Our results imply that these discrepancies might be, at least in part, explained by a potential moderating role of the Hp genotype in the relationship between glycemic control and hippocampal atrophy.

Hp has two polypeptide chains: β and α. Hp 1-1 expresses only α-1 chains, Hp 2-1 expresses α-1 and α-2 chains, and Hp 2-2 expresses only α-2 chains (6). Patients with AD and vascular dementia have greater levels of α-1 Hp chains in their cerebrospinal fluid (28), suggesting a possible role of Hp 1-1 in dementia. The hippocampus is robustly involved in AD and dementia (29), and this region is vulnerable to the accumulation of abnormally phosphorylated tau protein in the earliest stages of AD, decades before appearance of clinical symptoms (29). It is also one of the brain regions most susceptible to damage by several mechanisms of insults, including hypoglycemia and hypoxia (30). Participants of this study were cognitively normal, suggesting perhaps that the strong association between smaller right hippocampal volume and poorer glycemic control in Hp 1-1 carriers may reflect a preclinical signal of vulnerability to dementia in this subgroup of elderly individuals with diabetes. Unilateral volume changes in the right hippocampus were previously described in older adults at risk for cognitive decline; individuals with diabetes and low diastolic blood pressure had significantly smaller right hippocampal volumes (31). Consistent with this finding in cognitively intact middle-aged women at risk for AD, more insulin resistance was associated with smaller right hippocampal volume (32). Finally, in a study examining the reliability of hippocampal volumetry in the early diagnosis of AD, right hippocampal atrophy was the most strongly correlated with AD and mild cognitive impairment (33).

This study had several strengths, including a relatively large neuroimaging sample size of participants from the IDCD study. Our cohort is representative of elderly individuals with T2D in Israel, and we had access to numerous measurements of T2D characteristics for this cohort, including long-term data on HbA_{1c}, which allowed an average of 15 measurements, indicating a long-term mean level rather than a single observation.

One main limitation of the study is the cross-sectional design. Another limitation is that although our results on right hippocampal volume are significant, they are based on a relatively small sample size of Hp 1-1 carriers, hence necessitating further replication using a larger Hp 1-1 carrier group of T2D patients. Also, as Hp 2 carriers have a higher risk for myocardial infraction and mortality, our results may reflect a survival bias toward Hp 1-1 carriers.

The current study shows for the first time that the relationship of HbA_{1c} levels with hippocampal volume in T2D patients may depend on the Hp genotype. This may imply a common underlying mechanism for glycemic control (34) and Hp genotype (35) in hippocampal atrophy, such as endothelial dysfunction, leading to differential hippocampal vulnerability of T2D patients to the deleterious effects of poor glycemic control. Future studies should investigate whether glucose-lowering or insulin treatments in T2D patients may be more beneficial for Hp 1-1 carriers, thus reducing hippocampal atrophy, possibly contributing to reduction in risk for cognitive impairment.

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contributed to the discussion and reviewed the manuscript. I.C. and M.S.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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