Effect of Hypoglycemia on Brain Structure in People With Type 2 Diabetes: Epidemiological Analysis of the ACCORD-MIND MRI Trial

Zi Zhang,[1] James Lovato,[2] Harsha Battapady,[1] Christos Davatzikos,[1] Hertzel C. Gerstein,[3] Faramarz Ismail-Beigi,[4] Lenore J. Launer,[5] Anne Murray,[6] Zubin Punthakee,[3] Amilcar A. Tirado,[7] Jeff Williamson,[2] R. Nick Bryan,[1] and Michael E. Miller[2]

Diabetes Care 2014;37:3279–3285 | DOI: 10.2337/dc14-0973

PATHOPHYSIOLOGY/COMPLICATIONS

OBJECTIVE

The effect of hypoglycemia related to treatment of type 2 diabetes mellitus (T2DM) on brain structure remains unclear. We aimed to assess whether symptomatic severe hypoglycemia is associated with brain atrophy and/or white matter abnormalities.

RESEARCH DESIGN AND METHODS

We included T2DM participants with brain MRI from the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial. Symptomatic severe hypoglycemia was defined as blood glucose <2.8 mmol/L or symptoms resolved with treatments that required the assistance of another person or medical assistance (hypoglycemia requiring assistance [HA]). Standardized brain MRI was performed at baseline and at 40 months. Total brain volume (TBV) and abnormal white matter (AWM) volume were calculated using an automated computer algorithm. Brain MRI scans of hypoglycemic participants were also reviewed for local disease.

RESULTS

Of the 503 T2DM participants (mean age, 62 years) with successful baseline and 40-month brain MRI, 28 had at least one HA episode during the 40-month follow-up. Compared with participants without HA, those with HA had marginally significant less atrophy (less decrease in TBV) from baseline to 40 months (−9.55 [95% CI −15.21, −3.90] vs. −15.38 [95% CI −16.64, −14.12], $P = 0.051$), and no significant increase of AWM volume (2.06 [95% CI 1.71, 2.49] vs. 1.84 [95% CI 1.76, 1.91], $P = 0.247$). In addition, no unexpected local signal changes or volume loss were seen on hypoglycemic participants' brain MRI scans.

CONCLUSIONS

Our study suggests that hypoglycemia related to T2DM treatment may not accentuate brain pathology, specifically brain atrophy or white matter abnormalities.

As a common side effect of treatment for diabetes, hypoglycemia is a constant threat and can have far-reaching and potentially devastating consequences, from irreversible coma and infarction to cognitive decline and dementia, although the relationship between treatment-related hypoglycemia and cognition remains unclear. One of the priority research areas defined by a recent workgroup of the American Diabetes Association and the Endocrine Society is to better understand the mechanisms of the associations between hypoglycemia and long-term outcomes, such as cognitive

[1]*University of Pennsylvania, Philadelphia, PA*
[2]*Wake Forest University, Winston Salem, NC*
[3]*McMaster University, Hamilton, Ontario, Canada*
[4]*Case Western Reserve University, Cleveland, OH*
[5]*National Institute on Aging, Bethesda, MD*
[6]*Hennepin County Medical Center, Minneapolis, MN*
[7]*Columbia University, New York, NY*

Corresponding author: R. Nick Bryan, nick.bryan@uphs.upenn.edu.

Received 16 April 2014 and accepted 2 September 2014.

Clinical trial reg. no. NCT00182910, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0973/-/DC1.

dysfunction (1). Previous studies have reported a relationship between diabetes and dementia and between a history of severe hypoglycemia and impaired cognitive function in people with diabetes (2,3). Severe hypoglycemic episodes, with or without coma, were associated with impaired cognitive function in children and young adults with type 1 diabetes and a greater risk of dementia among older patients with type 2 diabetes mellitus (T2DM) (4–9). Whether these effects are due to the hypoglycemia or to some related factor, however, remains unclear. In contrast, the Diabetes Control and Complications Trial (DCCT) study found no significant correlation between diabetes treatment–related hypoglycemic events and neuropsychological function (10).

In a recent American Diabetes Association–sponsored research symposium, "Diabetes and the Brain," several hypotheses were proposed regarding how diabetes could affect learning and memory (11). An area that has not been well studied is the relationship between severe hypoglycemia and chronic anatomical changes in the brain that are known to correlate with cognitive decline. Specifically, it is unclear whether hypoglycemia in patients with T2DM is associated with chronic brain changes such as atrophy and increased abnormal white matter (AWM). Brain atrophy, whether measured by total brain volume (TBV) or regionally, is a sensitive and powerful correlate of cognitive function and decline (12–16). AWM tissue volume is indicative of diffuse and focal ischemic, demyelinating, and inflammatory processes related to small vessel disease, and increased AWM tissue volume is associated with diabetes and impaired cognition (17,18). Thus, the specific aim of our study was to determine whether severe symptomatic hypoglycemic events in treated T2DM patients are associated with loss of TBV and/or increase of AWM.

RESEARCH DESIGN AND METHODS

Study Population

We conducted a cohort analysis of the Memory in Diabetes (MIND) study (19), which was done in 51 clinical sites in North America as part of Action to Control Cardiovascular Risk in Diabetes (ACCORD), a randomized trial of standard compared with intensive management of glycemia in people with T2DM. Participants aged 45–79 years with T2DM and who had a current glycosylated hemoglobin (HbA_{1c}) level at 7.5–11.0% (58–97 mmol/mol) and were at high risk for cardiovascular disease events suggested by atherosclerosis, left ventricular hypertrophy, albuminuria, or at least two additional cardiovascular risk factors, were enrolled between 21 August 2003 (34 months after the start of ACCORD) and 16 December 2005.

Participants were randomly assigned to an intensive strategy, aiming to achieve an HbA_{1c} <6.0% (42 mmol/mol), or to a standard strategy, aiming to maintain an HbA_{1c} level between 7.0 and 7.9% (53 and 63 mmol/mol). In addition, in a double two-by-two factorial design, all participants were enrolled in a randomized blood pressure trial comparing an intensive with a standard blood pressure treatment strategy or in a randomized lipid trial comparing treatment with fenofibrate versus placebo while maintaining good control of LDL cholesterol, mainly with simvastatin.

Key exclusion criteria of the ACCORD study included frequent or recent serious hypoglycemic events (hypoglycemic coma or seizure within the past 12 months or symptomatic, severe hypoglycemia requiring medical or any other third-party assistance [HA]) in the past 3 months with a concomitant glucose concentration of less than 3.3 mmol/L [60 mg/dL]), unwillingness to do home glucose monitoring or inject insulin, a BMI of more than 45 kg/m^2, a serum creatinine concentration of more than 133 μmol/L (1.5 mg/dL), or other serious illness. In addition, participants younger than 55 years of age were excluded in the MIND study; details have been described elsewhere (19).

Within MIND, a subset of participants from 4 clinical center networks (28 clinics) were recruited for the MRI substudy. Initially, only participants randomized to the glycemic and blood pressure trials were enrolled, but halfway through the study, the recruitment was extended to participants in the lipid trial to meet the sample size goals. We excluded participants with standard MRI exclusions (20). To enhance retention, recruitment focused on participants living within 2 h of an MRI scanner.

Exposure

The exposure of interest was reporting any episode of HA before the MRI targeted to occur at 40 months postrandomization (21,22). At each 4-month follow-up visit, participants were asked if they had experienced an episode of HA. HA was defined as a blood glucose concentration of less than 2.8 mmol/L (50 mg/dL) or recovery with carbohydrate treatment in which the participant reported receiving medical care or assistance from another individual.

Outcomes

Brain MRI scans were performed at baseline and were targeted for 40 months after randomization based on the standardized MRI scan protocol (19). The standardized MRI scan protocol was run on 1.5-T scanners and included 3D spoiled gradient recalled acquisition T1, 2D axial fast spin echo fluid-attenuated inversion recovery, and proton density/T2 weighted sequences. An operator at each center ran the standardized MRI sequences that were programmed into the scanner, and these did not change during the study. Digital images acquired at each center were sent to the MRI quality-control center for in-house review on an as-received basis (23). According to American College of Radiology's phantom analyses for MRI quality control, MRI scanner performance was stable across the MRI sites over the duration of our study.

An automated multispectral computer algorithm was used to calculate the primary and secondary MRI outcome variables (24,25) of TBV, total gray matter volume (TGM), total white matter volume (TWM), AWM, and abnormal deep gray/white matter volume (ADGW), which was operationally defined as basal ganglia, thalamus, and internal capsules. The primary MRI outcomes were defined as the changes of TBV and AWM volume on brain MRI scans from baseline to the 40-month follow-up. Secondary MRI outcomes included TGM, TWM, and ADGW volumes. Two neuroradiologists, who were blinded to treatment arms and each other's readings, reviewed the baseline and 40-month follow-up brain MRI scans from all the hypoglycemic participants for evidence of local insult reflected by volume loss or MRI signal change.

Statistical Analysis

Mann-Whitney-Wilcoxon rank sum tests and χ^2 tests were performed to evaluate for an association between

covariates and reporting of HA. Linear regression was used to model the associations between HA and change in TBV, TGM, TWM, AWM, and ADGW. We log-transformed the AWM and ADGW volumes so that the residuals from the linear models were approximately normally distributed. Change in these two outcomes was analyzed as the difference of log-transformed baseline and follow-up values; thus, when taking the exponent of the adjusted means, the resulting values are interpreted as the ratio of the geometric mean at follow-up to the geometric mean at baseline. In contrast, adjusted means of change for untransformed variables are differences of arithmetic means.

Initially, unadjusted Wilcoxon tests were used to determine whether changes in MRI outcomes from baseline to follow-up were significantly different between participants who did and did not report HA during follow-up. Subsequently, a series of linear regression models adjusted for baseline intracranial volume (ICV) and randomization factors were used to relate HA to the change in each MRI volumetric outcome. ICV was controlled for in all models because it was taken as a constant for each participant over time, as confirmed in this study as part of the quality-control analysis. In addition, the following factors used to stratify randomization were included in each model: glycemia treatment group, assignment to the blood pressure or lipid control trial, random assignment to the intensive blood pressure treatment, randomization to fenofibrate, clinical center network, and prior history of cardiovascular disease.

We used a series of models to control for potential baseline confounders in addition to ICV and randomization factors. The potential confounders included demographic and anthropometric characteristics (age, sex, ethnicity, education level, and BMI), laboratory measures (serum creatinine levels, LDL concentration, HDL concentration), medication use (any use of hypertension medications and statins), clinical measures (systolic blood pressure, baseline cognitive scores measured by digit symbol substitution test [DSST]), severity of diabetes (duration of diabetes, previous amputation, history of peripheral neuropathy, visual acuity, HbA_{1c} level, glucose level), and any insulin use (basal insulin, bolus insulin, and premixed insulin). The initial model controlled for only the ICV and randomization factors. Model 1 added demographic, laboratory, and medication use covariates to the covariates in the initial model. Model 2 added severity of diabetes to the covariates in model 1. Model 3 added insulin use to the factors in model 2. Because the level of covariate control did not alter qualitative conclusions about the relationship between HA and change in MRI outcomes considered, we present adjusted means for HA and non-HA groups based on model 3.

Multiple imputation was used to explore the sensitivity of final conclusions regarding the association between HA and change in MRI outcomes to missing outcome data. Initially, for the baseline factors listed above, multiple logistic regression analysis was used to explore the relationship between the baseline covariates and a missed follow-up MRI. Subsequently, we produced imputed data sets using regression-based imputation and models that included baseline ICV and factors predictive of missing MRIs.

Additional sensitivity analyses were performed by fitting the models within the intensive glycemia treatment group to explore whether the results were qualitatively similar when focused only on participants who underwent similar glycemia treatment. Note that in the models containing both glycemia groups, we did not test for interactions between the glycemia intervention and HA because such a test of interaction would only have good power to detect extremely large effects. We tested all hypotheses at the two-sided 0.05 level. All statistical analyses were performed using SAS 9.3 software.

RESULTS

Table 1 reports the baseline characteristics of the T2DM participants in this study. Of the 632 ACCORD-MIND participants with successful baseline brain MRI scans, TBV and AWM were successfully measured in 614 (97%), and 503 (82%) had successful 40-month follow-up brain MRI scans. These participants were included in the final analyses, with 273 in the standard treatment group and 230 in the intensive treatment group. Participant characteristics associated with missing scans were reported previously, and 18 participants died before the 40-month follow-up (23). The number of missed 40-month follow-up MRI scans was significantly different between participants with and without HA (18 of 46 [39%] vs. 93 of 567 [16.4%], $P < 0.001$ using χ^2 test). HA, age, sex, race, education level, baseline TBV, baseline history of statin use, DSST cognition score, visual acuity score, and HbA_{1c} level were significantly associated with missing MRI scans at the 40-month follow-up and thus were entered in regression-based imputation models (Supplementary Table 1).

There were 28 participants who reported having at least one episode of HA before the 40-month MRI exam, and 6 of them reported coma during the HA episode. Among the 28 participants with HA, 19 (67.86%) had one episode, 5 (17.86%) had two, 2 (7.14%) had three, and 2 (7.14%) had five. The mean time between HA and the 40-month MRI scans was 25.5 ± 11.7 months, with the median at 28 months (min 3.29, max 41.2). Compared with participants without HA, participants who developed HA were significantly more likely to be older (66.82 ± 6.37 vs. 61.91 ± 5.50 years, $P < 0.0001$), in the intensive glucose control group (78.57% vs. 43.79%, $P = 0.0003$), have a longer duration of diabetes (13.68 ± 8.13 vs. 9.67 ± 6.95 years, $P = 0.0035$), more neuropathy (85.71 vs. 39.79%, $P < 0.0001$), worse visual acuity (71.43 ± 12.20 vs. 76.84 ± 9.23, $P = 0.0038$), and any insulin use at baseline (64.29% vs. 28.63%, $P < 0.0001$).

The neuroradiological review of baseline and 40-month follow-up brain MRI scans from participants with hypoglycemia showed no unexpected local signal changes or volume loss. As reported in Table 2, the results from our final adjusted linear regression model (model 3) showed that T2DM participants with HA did not have increased brain atrophy or AWM compared with the group without HA group. The participants with HA had marginally significant less atrophy (less decrease of TBV) from baseline to the 40-month follow-up compared with participants without HA (difference = −9.554 [95% CI −15.21, −3.903] vs. −15.38 [95% CI −16.64, −14.12], $P = 0.051$). A visual comparison of results from all models is provided in Supplementary Fig. 1. We further investigated these

Table 1—Baseline characteristics between participants with and without hypoglycemia

Baseline characteristics	Total* (*N* = 503)	Hypoglycemia		*P* value
		No (*n* = 475)*	Yes (*n* = 28)*	
Age (years)	62.18 ± 5.65	61.91 ± 5.50	66.82 ± 6.37	<0.0001
Sex (female)	233 (46.32)	220 (46.32)	13 (46.43)	0.9907
Race				0.6996
Non-Hispanic white	341 (67.8)	321 (67.6)	20 (71.4)	
African American	89 (17.7)	83 (17.5)	6 (21.4)	
Hispanic	31 (6.2)	30 (6.3)	1 (3.6)	
Other	42 (8.3)	41 (8.6)	1 (3.6)	
Education level				0.0179
Less than high school	46 (9.1)	46 (9.7)	0 (0.0)	
High school graduate	122 (24.3)	112 (23.6)	10 (35.7)	
Some college	168 (33.4)	164 (34.5)	4 (14.3)	
College graduate or more	167 (33.2)	153 (32.2)	14 (50.0)	
Clinical center network				0.6622
A	236 (46.9)	220 (46.3)	16 (57.1)	
B	71 (14.1)	68 (14.3)	3 (10.7)	
C	68 (13.5)	64 (13.5)	4 (14.3)	
D	128 (25.4)	123 (25.9)	5 (17.9)	
DSST cognition score	54.67 ± 15.54	54.73 ± 15.50	53.63 ± 16.38	0.7218
BMI (kg/m^2)	32.59 ± 5.14	32.60 ± 5.14	32.40 ± 5.23	0.8411
<25	31 (6.2)	28 (5.9)	3 (10.7)	0.5783
≥25 to <30	140 (27.8)	133 (28.0)	7 (25.0)	
≥30	332 (66.0)	314 (66.1)	18 (64.3)	
History of cardiovascular disease	128 (25.45)	118 (24.84)	10 (35.71)	0.1993
Systolic blood pressure (mmHg)	134.6 ± 17.85	134.5 ± 17.77	136.3 ± 19.62	0.6139
Treatment assignment				
Intensive glucose control	230 (45.73)	208 (43.79)	22 (78.57)	0.0003
Intensive blood pressure control	153 (30.42)	146 (30.74)	7 (25.00)	0.5214
Lipid control with fibrate	89 (17.69)	82 (17.26)	7 (25.00)	0.2972
Severity of diabetes				
Duration of diabetes (years)	9.89 ± 7.08	9.67 ± 6.95	13.68 ± 8.13	0.0035
HbA_{1c} level (%)	8.14 ± 0.93	8.13 ± 0.94	8.24 ± 0.87	0.5399
HbA_{1c} level (mmol/mol)	65 ± 13	65 ± 13	67 ± 14	
Glucose level (mg/dL)	172.2 ± 52.05	172.6 ± 50.61	166.4 ± 73.32	0.5417
Amputation	6 (1.19)	5 (1.05)	1 (3.57)	0.2329
Neuropathy score**	213 (42.35)	189 (39.79)	24 (85.71)	<0.0001
Visual acuity***	76.54 ± 9.48	76.84 ± 9.23	71.43 ± 12.20	0.0038
Serum creatinine (mg/dL)	0.88 ± 0.20	0.88 ± 0.20	0.93 ± 0.20	0.1987
LDL (mg/dL)	101.2 ± 32.32	101.7 ± 32.32	92.50 ± 31.63	0.1422
HDL (mg/dL)	43.84 ± 12.02	43.94 ± 11.68	42.21 ± 16.95	0.4606
Medication use at baseline				
Any hypertension medication	425 (84.49)	401 (84.42)	24 (85.71)	0.8542
Any statin	363 (72.17)	343 (72.21)	20 (71.43)	0.9285
Any insulin	154 (30.62)	136 (28.63)	18 (64.29)	<0.0001
Basal insulin	120 (23.86)	108 (22.74)	12 (42.86)	0.0152
Bolus insulin	59 (11.73)	52 (10.95)	7 (25.00)	0.0247
Premixed insulin	34 (6.76)	27 (5.68)	7 (25.00)	<0.0001

*Results are presented as *n* (%) or mean ± SD. **Michigan Neuropathy Screening Instrument score >2 or any lower-extremity amputation. ***Letters, 75 equals visual acuity of 20/30.

associations for TBV among the 230 participants in the intensive glycemia treatment group only and found that although the adjusted mean change in TBV for those with HA remained similar to that reported in Table 2 (difference = −9.09 [95% CI −15.35, −2.839]), the adjusted mean for those without HA was somewhat less than reported in Table 2 (difference = −12.51 [95% CI −14.35, −10.68], *P* = 0.315 for comparison with HA group). The multiple imputation results focusing on the fully adjusted comparison of HA and non-HA groups provided very similar estimates: the estimates of change from baseline to the 40-month follow-up were −8.73 (95% CI −14.83, −2.63) in participants with HA versus −15.47 (95% CI −16.35, −14.03) in participants without HA.

Under model 3, there was no significant difference in the changes of AWM volume from baseline to the 40-month follow-up (ratio = 2.06 [95% CI 1.71, 2.49] for HA vs. 1.84 [95% CI 1.76, 1.91] for no HA, *P* = 0.247). When we focused on participants in the intensive

Table 2—Adjusted associations between hypoglycemia and brain MRI structure

Brain MRI outcome measure	Total (*N* = 503)	HA		*P* value
		No (*n* = 475)	Yes (*n* = 28)	
TBV				
Baseline[1]	925.36 ± 95.93	925.22 ± 94.55	927.87 ± 118.9	
40-month follow-up[1]	910.11 ± 95.57	909.66 ± 94.25	917.73 ± 117.5	
Change from baseline to 40 months[1,2]	−15.25 ± 16.46	−15.55 ± 16.41	−10.14 ± 16.76	0.064
Adjusted for ICV and randomization factors[3]		−15.23 (−16.53, −13.93)	−12.20 (−17.64, −6.769)	0.290
Adjusted for factors in the final model[3]		−15.38 (−16.64, −14.12)	−9.55 (−15.21, −3.903)	0.051
AWM				
Baseline[1]	2.10 ± 3.88	2.07 ± 3.90	2.55 ± 3.50	
40-month follow-up[1]	3.60 ± 5.72	3.51 ± 5.68	5.08 ± 6.29	
Change from baseline to 40 months[1,2]	1.50 ± 2.77	1.44 ± 2.75	2.53 ± 3.06	0.013
Ratio of baseline to 40-month geometric means adjusted for				
ICV and randomization factors[3,4]		1.84 (1.76, 1.92)	2.00 (1.67, 2.38)	0.378
Factors in the final model[3,4]		1.84 (1.76, 1.91)	2.06 (1.71, 2.49)	0.247

[1]Mean ± SD. [2]*P* value based on Wilcoxon test unadjusted for any other factors. [3]Adjusted mean (model-based 95% CI) and *P* value. [4]Because of skewness in the outcomes, change in these outcomes was analyzed as the difference of log-transformed baseline and follow-up *P* values. When exponentiating the resulting adjusted means from ANCOVA, the resulting values are interpreted as the ratio of the geometric mean at follow-up to the geometric mean at baseline.

glycemia group, our conclusions were unchanged under the fully adjusted model (ratio = 2.08 [95% CI 1.65, 2.62] for HA vs. 1.97 [95% CI 1.84, 2.10], *P* = 0.663). Finally, the multiple imputation results under the fully adjusted model provided an estimated ratio of baseline to follow-up means of 1.98 (95% CI 1.35, 2.89) in participants with HA versus 192 (95% CI 1.76, 2.10) in those without HA.

For our secondary outcomes, there were no significant differences between participants with and without HA in the changes of TGM (difference = −17.13 [95% CI −24.87, −9.395] vs. −19.61 [95% CI −21.34, −17.89], *P* = 0.544), TWM (difference = 1.017 [95% CI 1.000, 1.034] vs. 1.009 [95% CI 1.006, 1.013], *P* = 0.414) and ADGW (ratio = 1.46 [95% CI 1.22, 1.76] vs. 1.33 [95% CI 1.27, 1.38], *P* = 0.303) from baseline to the 40-month follow-up.

CONCLUSIONS

Hypoglycemia, a common complication of intensive glycemic control, causes physical and psychological morbidity that ranges from unpleasant symptoms to impaired judgment, seizure, coma, and even death (26,27). Although the brain would seem central to these therapeutic complications, the effect of hypoglycemia on brain structure is not clear. To our knowledge, our study is the first to quantify the effect of symptomatic hypoglycemia on chronic brain structure changes in a large clinical cohort of treated older T2DM patients. Our study showed that T2DM patients with HA have the same general pattern of brain atrophy and increased AWM as those without HA but show no additional evidence of brain insult from the HA events. Because most of the hypoglycemic events happened in the intensive glycemic control group, we did a subanalysis in the intensive glycemic control group alone and found similar results.

Short-term hypoglycemia has been suggested to cause brain fuel deprivation that, if unchecked, results in functional brain failure that is typically corrected after the plasma glucose concentration is raised (27). Our study further addressed concerns about long-term structural brain damage associated with hypoglycemia in T2DM, and results indicate that typical clinically reversed hypoglycemia may not worsen the pathological effect of T2DM on brain structure. This apparent lack of chronic structural brain changes from hypoglycemic events in diabetic patients may reflect a general resilience of the brain to hypoglycemia or, perhaps, a greater resistance to hypoglycemic insult in the diabetic brain. van de Ven et al. (9) investigated the effect of hypoglycemia on cerebral glucose metabolism in patients with uncomplicated type 1 diabetes and found an increased flux through the tricarboxylic acid cycle and a possible increased metabolism of lactate and other nonglucose compounds compared with nondiabetic subjects. These results suggest that the brains of patients with type 1 diabetes are better able to endure moderate hypoglycemia than those of subjects without diabetes (9). Regardless of mechanism, the absence of incremental brain volume loss from treatment related hypoglycemic events probably bodes well for future cognitive function. Loss of brain volume correlates closely with decreased cognitive performance in healthy, at-risk, as well as demented populations, supporting its validity as a marker of brain function (13–16).

Previous case or small series reports have demonstrated dramatic MRI findings in severe, acute hypoglycemic coma, including reversible and irreversible hyperintensity on fluid-attenuated inversion recovery and diffusion restriction on diffusion-weighted imaging in gray matter (cerebral cortex, hippocampus, and basal ganglia) and white matter (posterior limb of the internal capsule, corona radiate, and centrum semiovale) structures (28–38). In contrast, our study did not find any unexpected MRI changes suggestive of ischemia, infarction, inflammation, or volume loss in patients with HA, beyond that seen in the nonhypoglycemic T2DM population. The blood glucose levels in most reported patients with abnormal MRI findings were less than 20 mg/dL, probably lower than that found in our patients. In addition, the median time between HA and 40-month follow-up MRI scans was 28 months (min 3.29, max 41.2), which suggest the effects of HA on brain structure in nonacute settings may be minimal.

In our ACCORD-MIND MRI study, 5.6% of participants with baseline and follow-up scans had at least one HA between baseline to the 40-month follow-up (i.e., 9.6% in the intensive therapy arm and 2.2% in the standard therapy arm), which was lower than the 10.5% observed over an average of 3.5 years of follow-up in the full ACCORD trial (i.e., 15.9% in the intensive therapy arm and 5.0% in the standard therapy arm) (22). This difference of HA incidence was partially because participants with HA were more likely to miss the 40-month follow-up MRI scans than participants without HA. Thus, we further compared the incidence of hypoglycemia and factors associated with hypoglycemia in our study with the other published studies. The UK Hypoglycaemia Study group found that prevalence of severe hypoglycemia was ~7% in T2DM patients treated with insulin for <2 years and ~25% in those with insulin for >5 years (39). Our study also found that hypoglycemia was significantly more likely to occur in older patients who had insulin, intensive glycemic control, longer duration of T2DM, more neuropathy and worse visual acuity scores. These findings are consistent with the ACCORD study and comparable with the studies of other T2DM populations (22,40,41).

The intensive glycemia control intervention of the ACCORD trial was stopped early because of higher mortality in this study arm (42). Hypoglycemia is among the possible mechanisms to explain this result. However, although hypoglycemia was associated with an increased risk of death, no differences in glycemia-related mortality risk between participants in the two treatment arms were noted (22). The mechanism for the increased mortality in the intensive glycemia control arm of ACCORD therefore remains unknown. A cerebral mechanism is not supported by our study, which shows no incremental adverse effect of hypoglycemic events on TBV and AWM. This would be consistent with, but not proof of, the relative resilience of the brain to hypoglycemic insult; however, these brain MRI variables reflect only structure, not function.

The study has several limitations. First, even though this appears to be the largest MRI study of brain structural changes in hypoglycemic patients, the number of hypoglycemic events was relatively few in our study, and future studies with larger sample sizes may provide further evidence to support our findings. Second, not every T2DM patient had 40-month follow-up MRI scans, and thus, the factors associated with missing MRI scans were used in a multiple imputation procedure to explore the sensitivity of results to missing outcomes.

In conclusion, results from this small sample of events show that severe symptomatic hypoglycemic events in treated T2DM patients are not associated with accentuated loss of TBV and/or increase of AWM compared with T2DM patients without hypoglycemia. Although the undesirable effects of treatment-induced hypoglycemia are of increasing clinical concern, particularly when more aggressive management of hyperglycemia is contemplated, the lack of associated changes in gross brain structure suggests that there may be some fortuitous resilience of this organ. Further studies with more details of hypoglycemic events and longitudinal MRI scans before and after hypoglycemia can help to better specify whether the severity of hypoglycemia affects the longitudinal changes of MRI brain structure.

Funding. ACCORD-MIND was funded through an intra-agency agreement between the National Institute on Aging and the National Heart, Lung, and Blood Institute (AG-0002) and the National Institute on Aging Intramural Research Program. ACCORD was funded by the National Heart, Lung, and Blood Institute (N01-HC-95178, N01-HC-95179, N01-HC-95180, N01-HC-95181, N01-HC-95182, N01-HC-95183, N01-HC-95184).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. Z.Z., J.L., H.B., C.D., H.C.G., F.I.-B., L.J.L., A.M., Z.P., A.A.T., J.W., R.N.B., and M.E.M. performed research. Z.Z. and R.N.B. wrote the manuscript. All other authors contributed to discussion and reviewed the manuscript. R.N.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–1395
2. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA 2009;301:1565–1572
3. Jacobson AM, Musen G, Ryan CM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. N Engl J Med 2007;356:1842–1852
4. Draelos MT, Jacobson AM, Weinger K, et al. Cognitive function in patients with insulin-dependent diabetes mellitus during hyperglycemia and hypoglycemia. Am J Med 1995;98:135–144
5. Warren RE, Frier BM. Hypoglycaemia and cognitive function. Diabetes Obes Metab 2005;7:493–503
6. Kaufman FR, Epport K, Engilman R, Halvorson M. Neurocognitive functioning in children diagnosed with diabetes before age 10 years. J Diabetes Complications 1999;13:31–38
7. Wredling R, Levander S, Adamson U, Lins PE. Permanent neuropsychological impairment after recurrent episodes of severe hypoglycaemia in man. Diabetologia 1990;33:152–157
8. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. Diabetologia 2005;48:2460–2469
9. van de Ven KC, Tack CJ, Heerschap A, van der Graaf M, de Galan BE. Patients with type 1 diabetes exhibit altered cerebral metabolism during hypoglycemia. J Clin Invest 2013;123:623–629
10. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med 1993;329:304–309
11. Seaquist ER, Lattemann DF, Dixon RA. American Diabetes Association research symposium: diabetes and the brain. Diabetes 2012;61:3056–3062
12. Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 2010;6:67–77
13. Driscoll I, Davatzikos C, An Y, et al. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. Neurology 2009;72:1906–1913
14. Fox NC, Scahill RI, Crum WR, Rossor MN. Correlation between rates of brain atrophy and cognitive decline in AD. Neurology 1999;52:1687–1689
15. Sluimer JD, van der Flier WM, Karas GB, et al. Whole-brain atrophy rate and cognitive decline: longitudinal MR study of memory clinic patients. Radiology 2008;248:590–598
16. Schott JM, Crutch SJ, Frost C, Warrington EK, Rossor MN, Fox NC. Neuropsychological correlates of whole brain atrophy in Alzheimer's disease. Neuropsychologia 2008;46:1732–1737
17. van Harten B, de Leeuw FE, Weinstein HC, Scheltens P, Biessels GJ. Brain imaging in patients with diabetes: a systematic review. Diabetes Care 2006;29:2539–2548
18. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010;341:c3666
19. Williamson JD, Miller ME, Bryan RN, et al.; ACCORD Study Group. The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): rationale, design, and methods. Am J Cardiol 2007;99:112i–122i

20. Sawyer-Glover AM, Shellock FG. Pre-MRI procedure screening: recommendations and safety considerations for biomedical implants and devices. J Magn Reson Imaging 2000;12:92–106
21. Bonds DE, Kurashige EM, Bergenstal R, et al.; ACCORD Study Group. Severe hypoglycemia monitoring and risk management procedures in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99:80i–89i
22. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909
23. Launer LJ, Miller ME, Williamson JD, et al.; ACCORD MIND investigators. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011;10:969–977
24. Goldszal AF, Davatzikos C, Pham DL, Yan MX, Bryan RN, Resnick SM. An image-processing system for qualitative and quantitative volumetric analysis of brain images. J Comput Assist Tomogr 1998;22:827–837
25. Lao Z, Shen D, Liu D, et al. Computer-assisted segmentation of white matter lesions in 3D MR images using support vector machine. Acad Radiol 2008;15:300–313
26. Cryer P. *Hypoglycemia in Diabetes: Pathophysiology, Prevalence, and Prevention*. Alexandria, VA, American Diabetes Association, 2009
27. Cryer PE. Hypoglycemia, functional brain failure, and brain death. J Clin Invest 2007; 117:868–870
28. Böttcher J, Kunze A, Kurrat C, et al. Localized reversible reduction of apparent diffusion coefficient in transient hypoglycemia-induced hemiparesis. Stroke 2005;36:e20–e22
29. Aoki T, Sato T, Hasegawa K, Ishizaki R, Saiki M. Reversible hyperintensity lesion on diffusion-weighted MRI in hypoglycemic coma. Neurology 2004;63:392–393
30. Chan R, Erbay S, Oljeski S, Thaler D, Bhadelia R. Case report: hypoglycemia and diffusion-weighted imaging. J Comput Assist Tomogr 2003;27:420–423
31. Maruya J, Endoh H, Watanabe H, Motoyama H, Abe H. Rapid improvement of diffusion-weighted imaging abnormalities after glucose infusion in hypoglycaemic coma. BMJ Case Rep 2009;2009
32. Hasegawa Y, Formato JE, Latour LL, et al. Severe transient hypoglycemia causes reversible change in the apparent diffusion coefficient of water. Stroke 1996;27:1648–1655; discussion 1655–1656
33. Kim JH, Roh JH, Koh SB. Reversible injury of internal capsule and splenium in a patient with transient hypoglycemic hemiparesis. Cerebrovasc Dis 2006;22:282–283
34. Gallucci M, Limbucci N, Paonessa A, Caranci F. Reversible focal splenial lesions. Neuroradiology 2007;49:541–544
35. Albayram S, Ozer H, Gokdemir S, et al. Reversible reduction of apparent diffusion coefficient values in bilateral internal capsules in transient hypoglycemia-induced hemiparesis. AJNR Am J Neuroradiol 2006;27:1760–1762
36. Maekawa S, Aibiki M, Kikuchi K, Kikuchi S, Umakoshi K. Time related changes in reversible MRI findings after prolonged hypoglycemia. Clin Neurol Neurosurg 2006;108:511–513
37. Lo L, Tan AC, Umapathi T, Lim CC. Diffusion-weighted MR imaging in early diagnosis and prognosis of hypoglycemia. AJNR Am J Neuroradiol 2006;27:1222–1224
38. Kang EG, Jeon SJ, Choi SS, Song CJ, Yu IK. Diffusion MR imaging of hypoglycemic encephalopathy. AJNR Am J Neuroradiol 2010;31:559–564
39. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–1147
40. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes 2008;57:3169–3176
41. Akram K, Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycaemia in insulin-treated type 2 diabetes: a cross-sectional survey. Diabet Med 2006;23:750–756
42. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559