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Glycemic Status and Brain Injury in Older Individuals

The Age Gene/Environment Susceptibility–Reykjavik Study

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OBJECTIVE — To examine the association of glycemic status to magnetic resonance imaging indicators of brain pathological changes.

RESEARCH DESIGN AND METHODS — This was a cross-sectional, population-based study of 4,415 men and women without dementia (mean age 76 years) participating in the Age Gene/Environment Susceptibility–Reykjavik Study. Glycemic status groups included the following: type 2 diabetes (self-report of diabetes, use of diabetes medications, or fasting blood glucose ≥7.0 mmol/l [126 mg/dl]), impaired fasting glucose (IFG) (fasting blood glucose 5.6–6.9 mmol/l [36.2%]), and normoglycemic (52.7%). Outcomes were total brain volume, white and gray matter volume, white matter lesion (WML) volume, and presence of cerebral infarcts.

RESULTS — After adjustment for demographic and cardiovascular risk factors, participants with type 2 diabetes had significantly lower total brain volume (72.2 vs. 71.5%, P < 0.001) and lower gray and white matter volumes (45.1 vs. 44.9%, P < 0.01 and 25.7 vs. 25.3%, P < 0.001, respectively) and were more likely to have single (odds ratio 1.45 [95% CI 1.14–1.85]) or multiple (2.27 [1.60–3.23]) cerebral infarcts compared with normoglycemic participants. Longer duration of type 2 diabetes was associated with lower total brain volume and gray and white matter volume, higher WML volume (all P ≤ 0.05), and a greater likelihood of single and multiple cerebral infarcts (all P ≤ 0.01).

CONCLUSIONS — Type 2 diabetic participants have more pronounced brain atrophy and are more likely to have cerebral infarcts. Duration of type 2 diabetes is associated with brain changes, suggesting that type 2 diabetes has a cumulative effect on the brain.

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The prevalence of type 2 diabetes is increasing worldwide and the disease has become a significant public health problem in individuals of all ages (1). Previously a disease of middle-aged and older adults, type 2 diabetes is rapidly increasing among young people, paralleling increasing rates of obesity (2). The number of individuals worldwide with type 2 diabetes is expected to increase more than twofold in the next 30 years, creating a public health crisis of epidemic proportion (3). The increasing prevalence and prolonged survival of individuals with type 2 diabetes has led to an increase in the number of individuals developing complications of type 2 diabetes, including brain changes and associated cognitive impairment (4–6). Experimental studies have linked neurodegenerative and vascular damaging mechanisms to characteristics of type 2 diabetes (7–10). Epidemiological studies have reported evidence for an association of type 2 diabetes to brain changes but have not investigated the association of type 2 diabetes to brain volume tissue changes and number and location of cerebral infarcts (5,11). Here, we examined the association of glycemic status and MRI findings of brain tissue volumes and cerebral infarcts in a population-based cohort of older men and women who participated in the Age Gene/Environment Susceptibility–Reykjavik Study (AGES-Reykjavik).
eral Electric Medical Systems, Waukesha, WI). The image protocol has been described previously (12). In brief, it includes the following pulse sequences: a proton density/T2-weighted fast spin echo sequence and a fluid-attenuated inversion recovery sequence (FLAIR). The acquisition of these sequences was performed with 3-mm-thick interleaved slices. In addition, images were acquired with a T1-weighted three-dimensional spoiled gradient echo sequence with a slice thickness of 1.5 mm. All images were acquired to give full brain coverage, and slices were angled parallel to the anterior commissure-posterior commissure line to give reproducible image views in the oblique-axial plane.

Cerebral infarcts. A cerebral infarct was defined as a defect of the brain parenchyma with a signal intensity that is isointense to that of cerebrospinal fluid on all pulse sequences (i.e., FLAIR and proton density/T2-weighted) and that has a minimal diameter of 4 mm, with the exception of infarcts in the cerebellum, which had no size criteria. The size (millimeters) of each infarct was measured at the largest diameter of the defect irrespective of the orientation. Image analyses were performed in a two-step procedure. An experienced neuroradiologist (O.K.) examined the scan for clinical abnormalities that needed immediate attention. At the same time, the neuroradiologist recorded directly into a shared database the slice location of observed cortical and cerebellar infarcts because identification of these infarcts may be more difficult. Trained raters with access to the shared database identified subcortical infarcts and then characterized all of the infarcts in more radiological detail. Infarcts that spanned two areas were assigned to the area with the largest diameter of the infarct.

Postprocessing of MRI scans and brain tissue volumes. Total brain, white and gray matter, and white matter lesion (WML) volumes were computed automatically with an algorithm based on the Montreal Neurological Institute pipeline (14). The AGES-Reykjavik/Montreal Neurological Institute pipeline has been modified to accommodate full brain coverage including cerebellum and brainstem, multispectral images (T1-weighted three-dimensional spoiled gradient echo sequence, FLAIR, and proton density/T2-weighted fast spin echo sequences), high throughput, and minimal editing. Total brain volume (an indicator of atrophy) was derived as the percentage of the total tissue volume to the intracranial volume. The other brain tissue classes were similarly adjusted for total intracranial volume to give a percentage.

Quality control procedures. Every 6 months the intraobserver variability for each observer and every 3 months the interobserver variability for the whole group of observers were assessed. The intraobserver weighted $\kappa$ statistic was 0.92 for cerebral infarcts; the interobserver weighted $\kappa$ statistic was 0.66 for cerebral infarcts.

Glycemic groups. Glycemic groups were defined using American Diabetes Association cut points (15). Type 2 diabetes was based on self-reported doctor’s diagnosis of diabetes, use of diabetes medications (hypoglycemic medications and insulin), which was noted from medication vials brought to the clinic, or a fasting blood glucose level $\geq 7.0$ mmol/l at the baseline AGES-Reykjavik examination. The definition of impaired fasting glucose (IFG) followed American Diabetes Association criteria of no type 2 diabetes and a fasting blood glucose level between 5.6 and 6.9 mmol/l. In separate analyses we also defined IFG according to World Health Organization criteria (fasting glucose levels between 6.1 and 6.9 mmol/l) (16). Measurement of A1C was performed on a Hitachi 912 instrument, with a turbidimetric inhibition immunoassay for hemolyzed whole blood from Roche Diagnostics, traceable to the Diabetes Control and Complications Trial reference. To further identify factors that may moderate the association of diabetes to brain changes, we examined the effects of duration of disease, as assessed by questionnaire.

Diagnosis of dementia. Dementia was ascertained by use of a three-step process that has been described elsewhere (12). A consensus diagnosis of dementia based on the DSM-IV guidelines was made by a panel that included a geriatrician, neurologist, neuropsychologist, and neuroradiologist.

Potential confounders. Based on previous reports (4,11,17), a number of potentially confounding variables associated with brain atrophy, cerebral infarcts, and diabetes were examined as potential confounders. Factors that significantly differed among glycemic groups in univariate analyses were included as covariates in the final multivariate models. Demographic (age, sex, and education) and health-related confounding variables were assessed via questionnaire at the AGES-Reykjavik examination. High depressive symptomatology was classified as a score of $\geq 6$ on the 15-item Geriatric Depression Scale (18). We also controlled for vascular risk factors measured at the AGES-Reykjavik examination, including hypertension (self-reported doctor’s diagnosis of hypertension, use of hypertensive medications, or systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg); smoking status (ever smoker/never smoker) and physical activity (moderate or more versus less) assessed via questionnaire; BMI (calculated from measured height and weight); and myocardial infarction defined as a self-reported doctor’s diagnosis or detected on an electrocardiogram.

Analytic sample and strategy. Of the 5,764 participants, 281 were excluded based on standard MRI contraindications and an additional 834 had incomplete MRI data (due to claustrophobia, equipment failure, refusal, or ability to participate only in an in-home examination) or scans could not be processed successfully, giving a sample of 4,614 MRI scans. Dementia probably confounds the relationship between brain changes and type 2 diabetes (11). Therefore, we excluded subjects with dementia from the analysis. Of the 4,614 participants with complete MRI data, 4,415 did not have dementia and served as the sample for the present analysis.

Demographic and health characteristics were compared among the three glycemic groups (normoglycemic, IFG, and type 2 diabetes) with age-adjusted linear models for continuous variables and age-adjusted logistic regression for dichotomous outcomes. Linear regression was used to examine the association of glycemic groups to brain volume. Multinomial logistic regression was used to investigate the association of the glycemic groups and the presence of a single infarct or multiple infarcts compared with having no infarcts. Participants classified as normoglycemic were the reference group in these analyses. The models were adjusted for previously described demographic, health, and cardiovascular factors. In subsequent analyses, we examined the association between duration of type 2 diabetes and brain tissue volumes and the presence of cerebral infarcts. Among participants with type 2 diabetes, we exam-
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Table 1—Sample description according to glycemic group: AGES-Reykjavik

|                         | Normoglycemic | IFG | Type 2 diabetes |
|-------------------------|---------------|-----|----------------|
| n                       | 2,327         | 1,599 | 489            |
| Age (years)             | 76.4 ± 5.5    | 75.9 ± 5.4 | 76.0 ± 5.4 |
| Education (low)         | 23.3          | 22.7  | 19.0           |
| Sex (female)            | 65.0          | 52.5¶  | 47.2‡          |
| Depression              | 7.1           | 6.0   | 6.8            |
| MMSE total score        | 27 (26, 29)   | 27 (26, 29) | 28 (26, 29) |
| DSST (total correct)    | 29 (22, 36)   | 29 (22, 37) | 28 (20, 36) |
| Ever smoker             | 54.9          | 58.9*  | 60.7*          |
| Physical activity (no moderate activity) | 43.5       | 44.0   | 51.9‡          |
| BMI (kg/m²)             | 26.1 ± 4.1    | 27.7 ± 4.3¶ | 28.6 ± 4.5† |
| Hypertension            | 75.9          | 83.0  | 91.2‡          |
| Myocardial infarction   | 5.4           | 5.1   | 7.4            |
| A1C (%)                 | 5.5 (5.3, 5.7) | 5.6 (5.4, 5.8)¶ | 6.2 (5.9, 6.8)‡ |
| Fasting glucose         | 5.2 (5.0, 5.4) | 5.9 (5.7, 6.2)¶ | 7.4 (6.6, 8.5)‡ |
| Hypoglycemic medication use | —             | 0.1   | 50.9           |
| Insulin use             | —             | —     | 6.8            |
| Self-reported stroke    | 6.3           | 5.2   | 7.2            |
| Cerebral infarct on MRI | 28.0          | 29.5  | 43.7‡          |
| Brain volume (% of total intracranial volume) | 72.25 ± 3.8  | 72.23 ± 3.9 | 71.24 ± 3.7† |
| Total brain volume      | 45.18 ± 1.8   | 45.23 ± 1.9 | 44.66 ± 1.9¶ |
| Grey matter             | 25.74 ± 1.3   | 25.71 ± 1.3* | 25.12 ± 1.3‡ |
| White matter            | 1.32 ± 3.3    | 1.29 ± 3.2 | 1.46 ± 3.2*    |
| WMLs                    | 1.32 ± 3.3    | 1.29 ± 3.2 | 1.46 ± 3.2*    |

Data are means ± SD, median (25th percentile, 75th percentile), or percent. n = 4,415. Glycemic groups are based on current American Diabetes Association criteria (15). Depression was classified as a score of ≥16 on the 15-item Geriatric Depression Scale (18). *P < 0.05, ‡P < 0.01, for age-adjusted comparison with the normoglycemic group. DSST, Digit Symbol Substitution Test (24); MMSE, Mini-Mental State Examination (23).

In addition to the association of two markers of severity of disease, A1C levels and diabetes medication use, to brain tissue volumes and cerebral infarcts.

**RESULTS** — Of the participants, 53% were classified as being normoglycemic (n = 2,327), 36% (n = 1,599) were classified as having IFG, and 11% (n = 489) were classified as having type 2 diabetes. Compared with normal glycemic participants, those with IFG and type 2 diabetes were more often men, were more likely to be smokers, and had higher average BMI (Table 1). Participants with diabetes had a higher prevalence of hypertension, were more likely to have a cerebral infarct, and were less likely to engage in physical activity than normoglycemic participants. Participants with type 2 diabetes had more brain atrophy, a lower percentage of gray matter, and a higher percentage of WMLs than normoglycemic participants (Table 1). Those with type 2 diabetes and with IFG had a lower percentage of white matter compared with those who were normoglycemic.

**Glycemic groups and brain tissue volumes and cerebral infarcts**

In models adjusted for demographic characteristics and cardiovascular risk factors, participants with type 2 diabetes had significantly lower average total brain and gray and white matter volumes compared with normoglycemic participants (Table 2). Participants with type 2 diabetes also had a higher average percentage of WMLs compared with normoglycemic participants, but the association was attenuated when adjusted for demographic and cardiovascular risk factors (1.45 [1.12–1.88]), but the association was slightly attenuated when adjusted for subcortical and cortical infarcts and was no longer significant (1.30 [0.99–1.69]).

IFG was not significantly associated with the measures of brain tissue volume or the presence of cerebral infarcts. Results were similar when World Health Organization cut points were used for IFG (data not shown).

**Duration of diagnosed diabetes**

Of the 489 participants with type 2 diabetes, diabetes was diagnosed in 8.5% (n = 41) within the past year, in 19.8% (n = 97) from 1 to 6 years, in 18.2% (n = 89) from 7 to 14 years, and in 24.7% (n = 121) 15+ years before the AGES-Reykjavik examination; 28.8% (n = 141) had undiagnosed type 2 diabetes that was identified based on fasting glucose levels at the in-person examination (i.e., no self-reported history of type 2 diabetes or medication use but fasting glucose of ≥7.0 mmol/l). There was a significant trend for increasing duration of disease and lower percentage of total brain volume (P<sub>trend</sub> < 0.001), lower percentage of gray matter (P<sub>trend</sub> < 0.001) and white matter (P<sub>trend</sub> < 0.001), and higher percentage of WMLs (P<sub>trend</sub> = 0.05) (Table 3). A longer duration of type 2 diabetes was also associated with significantly higher odds of having single (P<sub>trend</sub> = 0.004) or multiple (P<sub>trend</sub> < 0.001) infarcts compared with having no infarcts (Table 3). Compared with normoglycemic participants, those whose type 2 diabetes was diagnosed based on fasting glucose at the AGES-Reykjavik examination (undiagnosed type 2 diabetes) also had lower percentages of total brain volume and gray matter and were more likely to have single and multiple infarcts (Table 3).
Among participants with type 2 diabetes, ~56% were taking either hypoglycemic medications or insulin. Compared with participants with type 2 diabetes who did not take diabetes-related medications, those who took medications had a significantly lower percentage of total brain volume (adjusted mean percentage 72.4 vs. 70.9; \( P < 0.001 \)) and lower percentage of gray matter (45.4 vs. 44.5; \( P = 0.01 \)) and white matter (25.6 vs. 24.9; \( P < 0.001 \)) volume. Medication use was not associated with WML volume or the presence of cerebral infarcts (data not shown).

**CONCLUSIONS** — We examined the association of type 2 diabetes and IFG to brain tissue volumes and the presence of cerebral infarcts in a population-based cohort of older adults that excluded individuals with in-study assessed cases of dementia. We found that type 2 diabetes was associated with lower total brain volume and with lower gray and white matter volume, and more cerebral infarcts. We also found that those who took medications to control diabetes, an indicator of disease severity, had lower brain volume than those diabetic participants not taking medication. These associations were independent of demographic and other cardiovascular risk factors.

Although the percent differences between normoglycemic participants and participants with type 2 diabetes are small, in this cohort, the average annual decrease in brain tissue volume is ~0.43% for total brain volume. Thus, the average differences in brain tissue volumes in participants with type 2 diabetes correspond to ~2 years of age for loss of total brain volume.

This study has a number of strengths. Findings are based on a large, population-based cohort. Because the cohort is well characterized with respect to potential confounding factors, we could adjust our models with these factors to determine the direct relation of type 2 diabetes to brain changes. The use of an automated brain segmentation method enabled us to estimate accurate, reproducible, and sensitive volumetric assessments of the brain. Further, we were able to exclude patients with clinically diagnosed dementia, thus reducing the confounding effect of dementia pathology on the association of type 2 diabetes to brain pathological changes. However, these findings are based on cross-sectional data and should be replicated in longitudinal studies.

### Disease severity and brain tissue volumes and cerebral infarcts

As secondary analyses we examined two measures of disease severity, A1C levels and diabetes medication use (hypoglycemic medications or insulin), in relation to brain tissue volumes and presence of cerebral infarcts. Quartiles of A1C were not associated with WML volume or the presence of cerebral infarcts (data not shown).

Among participants with type 2 diabetes, ~56% were taking either hypoglycemic medications or insulin. Compared with participants with type 2 diabetes who did not take diabetes-related medications, those who took medications had a significantly lower percentage of total brain volume (adjusted mean percentage 72.4 vs. 70.9; \( P < 0.001 \)) and lower percentage of gray matter (45.4 vs. 44.5; \( P = 0.01 \)) and white matter (25.6 vs. 24.9; \( P < 0.001 \)) volume. Medication use was not associated with WML volume or the presence of cerebral infarcts (data not shown).

#### Table 2 — Association of glycemic groups to diffuse and focal brain changes: AGES–Reykjavik

| Tissue volume | Normoglycemic* | IFG | Type 2 diabetes |
|---------------|----------------|-----|----------------|
| Total brain volume | Model 1 72.19 | 72.27 | 71.45‡ |
| Grey matter | Model 1 45.10 | 45.28 | 44.86 |
| White matter | Model 1 25.77 | 25.68 | 25.11‡ |
| WMLs | Model 1 1.31 | 1.31 | 1.47† |
| Model 2 1.31 | 1.29 | 1.42 |

Data are adjusted mean percentage of total intracranial volume or ORs (95% CI). \( n = 4,415 \). Model 1 was adjusted for age, sex, and education. Model 2 included additional adjustments for myocardial infarction, smoking status, hypertension, BMI, and physical activity. *Reference group is normoglycemic subjects. †Reference group is normoglycemic subjects. ‡Reference group is normoglycemic subjects.

### Table 3 — Association of duration of diabetes to brain tissues volumes and cerebral infarcts: AGES–Reykjavik

| Duration of diabetes | Total brain volume | Grey matter | White matter | WMLs | Single infarct | Multiple infarcts |
|----------------------|-------------------|-------------|--------------|------|---------------|------------------|
| Nondiabetic          | 72.3 (ref)        | 45.2 (ref)  | 25.7 (ref)   | 1.3 (ref) | 1.0 (ref)     | 1.0 (ref)        |
| <1 year              | 73.0              | 46.0        | 25.4         | 1.6   | 1.56 (0.79–3.04) | 0.82 (0.19–3.54) |
| 1–6 years            | 71.7              | 45.0        | 25.1†        | 1.5   | 1.37 (0.84–2.21) | 2.70 (1.48–4.91)‡|
| 7–14 years           | 71.4*             | 44.9        | 25.1†        | 1.5   | 1.95 (1.22–2.21)§ | 2.25 (1.12–4.32)†|
| ≥15 years            | 70.9‡             | 44.3‡       | 25.2†        | 1.3   | 1.10 (0.70–1.72) | 2.02 (1.15–3.38)§|
| \( P_{trend} \)      | <0.001            | <0.001      | <0.001       | 0.048 | 0.004         | <0.001           |
| Undiagnosed diabetes| 71.3*             | 44.5‡       | 25.4         | 1.4   | 1.56 (1.05–2.32)§ | 2.20 (1.24–3.88)†|

Data are adjusted mean percentage (adjusted for age, education, sex, smoking status, myocardial infarction, hypertension, BMI, and physical activity) of total intracranial volume or ORs (95% CI). \( n = 4,415 \). \( P_{trend} \) excludes undiagnosed type 2 diabetes. *\( P < 0.05 \); †\( P < 0.01 \); ‡\( P < 0.001 \). ref, referent.
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Although evidence from clinical and epidemiological studies for the vascular and neurodegenerative effects of type 2 diabetes in the brain is increasing, findings are still mixed, particularly with respect to WML pathology (19,20). Differences in the measurement of WMLs in various studies (semiquantitative/visual scales versus quantitative/volumetric measurements) may, in part, explain inconsistencies in published studies. Furthermore, not all studies adjusted for confounding; we found that WML volume was higher in participants with type 2 diabetes, but this association was attenuated by other cardiovascular risk factors.

Findings for an association of type 2 diabetes to global atrophy and the presence of cerebral infarcts are more consistent than those of type 2 diabetes and WMLs (5,19,20). Few studies, however, are based on population-based samples, and many did not quantitatively estimate individual tissue class volumes. We found increased total brain atrophy, reduced white and gray matter volumes, and a higher likelihood of having one or more cerebral infarcts in participants with type 2 diabetes compared with normoglycemic participants. Our findings also suggest that type 2 diabetes may affect both subcortical and cortical brain tissue and thus may contribute to impairments in memory, processing speed, and executive function (6). Type 2 diabetic participants were also more likely to have infarcts in the cerebellum, which may contribute to impairments in motor function, although the association was attenuated when adjusted for the presence of cortical and subcortical infarcts.

There are a number of mechanisms through which type 2 diabetes may affect the brain. Disruption of the blood-brain barrier and microvascular changes in type 2 diabetes may contribute to neurodegeneration and vascular disease (8). Both cerebrovascular and neurodegenerative effects of type 2 diabetes have been reported from autopsy series (5,11). Endothelial dysfunction, as a result of oxidative stress and inflammation, may contribute to the development of cerebral infarcts (7,9). Atherosclerosis and hemodynamic changes in individuals with type 2 diabetes may lead to microvascular changes that are associated with cerebral infarcts and subcortical atrophy (10,17).

Disease-specific factors may also contribute to brain changes in type 2 diabetes. We found that duration of type 2 diabetes was associated with total brain atrophy as well as with smaller gray and white matter volumes and larger WML volumes, suggesting that prolonged hyperglycemic and other metabolic changes that occur in diabetes may contribute to pervasive diffuse brain atrophy as well as local lesions. In particular, we found that disease duration of >1 year was associated with the greatest differences in brain tissue volume. However, participants with diabetes diagnosed in the past year had tissue volumes similar to nondiabetic subjects.

Our findings on disease control and brain changes were mixed. We found that diabetes medication use, potentially a marker for severity of disease, was associated with lower total brain volume and lower gray and white matter volume but not with WML volume or cerebral infarcts. Further, A1C levels were not associated with any of the MRI outcomes. More work is needed to understand the association between control of type 2 diabetes and the brain, a question currently being investigated in the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND) trial (21).

These findings based on our population-based cohort of subjects without dementia, in conjunction with many studies based on smaller or clinical samples, argue for the adoption of diffuse cerebral disease as another complication of diabetes. These lesions may be the structural basis for the cognitive impairment in individuals with diabetes (6). Finally, the lack of association between pre-diabetic states (e.g., IFG and impaired glucose tolerance) and measures of brain atrophy and the presence of cerebral infarcts observed in our study and other studies (5) is in contrast with a dose-response hypothesis of hyperglycemia and brain changes in type 2 diabetes. However, our findings on duration of diabetes suggest that prolonged exposure to hyperglycemia is necessary to observe brain changes associated with type 2 diabetes. Duration of type 2 diabetes, pre-diabetic states such as IFG, and specific mechanisms for the association between hyperglycemia and brain changes warrant further investigation.

Our data suggest that type 2 diabetes has a cumulative effect on the brain. With the declining age at which individuals are developing type 2 diabetes and the increasing survival in patients with type 2 diabetes, more patients will be at risk for developing complications of type 2 diabetes including brain changes. The large increase in the type 2 diabetic population that is projected to occur over the next 30 years constitutes a significant public health problem. Brain changes and corresponding cognitive dysfunction (5,6) in type 2 diabetic subjects have implications for diabetes management and self-care, particularly as the complexity of disease management increases in the older patient (22).

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