Association Between Diabetes and Gray Matter Atrophy Patterns in a General Older Japanese Population: The Hisayama Study

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OBJECTIVE

To examine the association between diabetes and gray matter atrophy patterns in a general older Japanese population.

RESEARCH DESIGN AND METHODS

In 2012, a total of 1,189 community-dwelling Japanese aged ≥65 years underwent brain MRI scans. Regional gray matter volumes (GMV) and intracranial volume (ICV) were measured by applying voxel-based morphometry (VBM) methods. The associations of diabetes and related parameters with the regional GMV/ICV were examined using an ANCOVA. The regional gray matter atrophy patterns in the subjects with diabetes or elevated fasting plasma glucose (FPG) or 2-h postload glucose (2hPG) levels were investigated using VBM.

RESULTS

Subjects with diabetes had significantly lower mean values of GMV/ICV in the frontal lobe, temporal lobe, insula, deep gray matter structures, and cerebellum than subjects without diabetes after adjusting for potential confounders. A longer duration of diabetes was also significantly associated with lower mean values of GMV/ICV in these brain regions. The multivariable-adjusted mean values of the temporal, insular, and deep GMV/ICV decreased significantly with elevating 2hPG levels, whereas higher FPG levels were not significantly associated with GMV/ICV of any brain regions. In the VBM analysis, diabetes was associated with gray matter atrophy in the bilateral superior temporal gyri, right middle temporal gyrus, left inferior temporal gyrus, right middle frontal gyrus, bilateral thalami, right caudate, and right cerebellum.

CONCLUSIONS

The current study suggests that a longer duration of diabetes and elevated 2hPG levels are significant risk factors for gray matter atrophy in various brain regions.

Recent epidemiological studies have reported that diabetes is associated with the risk of developing dementia (1). Some population-based studies have also reported that diabetes is associated with morphological changes in the brain. However,

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many of these studies have only investigated the association between diabetes and total brain and hippocampal volume (2,3).

The recent progress in image analysis enables us to measure the brain volume of each anatomical region quantitatively based on brain MRI. Several epidemiological studies have reported that diabetes is associated with the atrophy of some brain regions, such as the temporal lobe, hippocampus, and so on (4–6). In addition, voxel-based morphometry (VBM) is also a powerful tool to detect subtle structural changes in brain regions that are associated with neurological and psychiatric dysfunction in a variety of diseases (7). VBM is considered to be useful to elucidate the pathological mechanisms of diabetes-related dementia. However, there are no population-based studies examining the relationship between diabetes and morphological changes in the brain using VBM in a community.

The Hisayama Study is a population-based observational study of cardiovascular disease and dementia in Japan. In this study, we conducted a survey of older residents using brain MRI in 2012. Using these brain MRI data, we previously reported that diabetes, particularly higher 2-h postload glucose (2hPG) levels, was significantly associated with lower hippocampal volume (5) in a general Japanese older population. However, the previous study did not include a detailed examination of the influence of diabetes on the brain volumes of various brain regions. In the current study, we used the brain MRI data collected from a general older Japanese population in the Hisayama Study to evaluate: *1*) the association of diabetes and hyperglycemia (i.e., elevated fasting plasma glucose [FPG] and 2hPG levels determined by a 75-g oral glucose tolerance test [OGTT]) with the gray matter volume (GMV) of various brain regions, such as the frontal lobe, temporal lobe, parietal lobe, occipital lobe, insula, cingulum, deep gray matter structures, and cerebellum; and *2*) the association of diabetes and hyperglycemia with the pattern of gray matter atrophy determined using VBM.

RESEARCH DESIGN AND METHODS

Study Population

The Hisayama Study is an ongoing population-based observational study of cardiovascular diseases established in 1961 in the town of Hisayama, a suburban community of the Fukuoka metropolitan area in the southern part of Japan. In addition, comprehensive screening surveys of dementia in the elderly residents of this town have been conducted every 5–7 years since 1985 (8,9). In 2012, a total of 1,906 individuals (93.6%) among 2,036 residents aged ≥65 years participated in the screening survey of dementia, and 1,342 of them (70.4%) underwent brain MRI scanning. After excluding 1 individual who refused to participate in the study, 41 without available data of diabetic status, 8 with no plasma glucose data, 44 with errors in the MRI scans (25 without T1-weighted three-dimensional images, 8 without fluid attenuated inversion recovery images, 4 with metal artifacts, and 7 with excessive motion artifacts), and 59 with cortical or cerebellar infarcts that might affect the assessment of GMV by VBM, the remaining 1,189 individuals (510 men and 679 women) were eligible for the main analysis of the current study (Supplementary Fig. 1).

Brain MRI Analysis

For brain MRI scans, three-dimensional T1-weighted images, conventional T1- and T2-weighted images, fluid-attenuated inversion recovery, T2*-weighted images, and magnetic resonance angiography of the brain were obtained by using a 1.5-Tesla MRI scanner (Intera Pulsar; Philips Medical Systems, Best, the Netherlands) with a multichannel head coil as described previously (5). The MRI images were processed and examined using VBM8 Toolbox version 435 (University of Jena, Jena, Germany; https://dbm.neuro.uni-jena.de/vbm/) in SPM8 (University College London, London, U.K.; https://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB (MathWorks Inc, Natick, MA). The default settings were used, except that affine regularization was performed with the International Consortium for Brain Mapping template for East Asian brains. The T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid. We also created subject-specific binarized white matter hyperintensity (WMH) masks, as previously described (10). Given that WMH are often misclassified as gray matter on T1 scans, the gray matter and white matter maps were corrected using the binarized WMH. Segmented gray matter images were normalized and modulated to compensate for the volumetric effects of expansion or shrinking that occur in spatial normalization. Lastly, the images were smoothed with an 8 mm full-width, half-maximum isotropic Gaussian kernel. The intracranial volume (ICV) was calculated as the sum of the gray matter, white matter, and cerebrospinal fluid volumes. The GMV of the frontal lobe, temporal lobe, parietal lobe, occipital lobe, insula, cingulum, deep gray matter structures (defined as the total volume of the thalamus, caudate, putamen, accumbens, and globus pallidus), and cerebellum from modulated images were calculated using the Neuromorphometrics atlas, which is available in SPM12 (Neuromorphometrics, Inc.; https://neuromorphometrics.com). Each gray matter voxel that was not assigned to any label was labeled according to the nearest gray matter label with a 5-mm distance limit. In the current study, the frontal, temporal, parietal, occipital, insular, cingulate, deep, and cerebellar GMV/ICV (percentage) were calculated as indicators of regional gray matter atrophy. The cortical thickness of the left and right hemispheres was automatically estimated by CAT12 Toolbox version 12.8 (University of Jena; https://dbm.neuro.uni-jena.de/cat/) based on the projection-based thickness method, and the images were smoothed with a 12-mm full-width, half-maximum Gaussian kernel (11).

Definition of Diabetes

In the 2012 health examination, subjects aged 40–79 years without contraindications (i.e., severe hyperglycemia defined as a recently measured hemoglobin A1c [HbA_{1c}] of ≥9.4% or the use of insulin treatment) were encouraged to undergo the OGTT. The OGTT was also conducted for subjects aged ≥80 years who requested it. Consequently, among the total 1,189 eligible subjects, 887 (74.5%) underwent the OGTT, and the remaining 302 (25.4%) had a single measurement of fasting or postprandial plasma glucose concentrations. Plasma glucose levels were determined by the hexokinase method. Diabetes was defined as an FPG ≥7.0 mmol/L,

2hPG or postprandial plasma glucose ≥11.1 mmol/L, and/or the use of antidiabetic medications. Diabetes was further classified into newly diagnosed and known diabetes by a self-administered question-naire, and the subjects with known diabetes were further subclassified into tertiles according to the duration of diabetes (≤9, 10 to 16, and ≥17 years), as described previously (5).

To investigate the associations of FPG and 2hPG levels with regional gray matter atrophy, 887 subjects (393 men and 494 women) who underwent the OGTT among the total 1,189 individuals were included in the analysis (Supplementary Fig. 1, a subpopulation with OGTT data). The FPG and 2hPG levels were each divided into three categories (FPG: <6.1, 6.1–6.9, and ≥7.0 mmol/L; and 2hPG: <7.8, 7.8–11.0, and ≥11.1 mmol/L) according to the 2006 World Health Organization criteria of glucose tolerance status (12).

Midlife and Late-Life Diabetes

For estimating the influence of diabetes diagnosed in midlife and late life on regional gray matter atrophy in late life, 816 subjects (327 men and 489 women) who participated in the health examination in 1988 (aged 41–64 years in 1988) among the 1,156 participants aged 65–88 years in 2012 (33 subjects aged ≥89 years were excluded) were included in the analysis (Supplementary Fig. 1, a subpopulation for the analysis of midlife diabetes). As reported previously (5), the subjects were classified into three categories: *1*) the subjects without diabetes in both the 1988 and 2012 health examinations (no diabetes); *2*) the subjects who had not been diagnosed as having diabetes in 1988 but were diagnosed as having diabetes in 2012 (late-life diabetes); and *3*) the subjects who had already been diagnosed as having diabetes in 1988 (midlife diabetes).

Definitions of the Covariates and Dementia

Detailed definitions of the covariates used in the multivariable model and dementia status are provided in the Supplementary Materials and Methods.

Statistical Analysis

The differences in the frequencies and the mean values of potential confounding factors between the subjects with and without diabetes were examined using a *t* test and χ^2 test, respectively. An ANCOVA was used to estimate and compare the age- and sex-adjusted or multivariable-adjusted means and 95% CIs of the frontal, temporal, parietal, occipital, insular, cingulate, deep, and cerebellar GMV/ICV. In the multivariable-adjusted models, age, sex, low education, hypertension, serum total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, cerebrovascular lesions on MRI, and/or antidiabetic medication were included. For a sensitivity analysis based on propensity score matching, age, sex, low education, hypertension, serum total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on MRI were used to generate the propensity score by a logistic regression model. Then, the subjects with diabetes ($n = 269$) and those without diabetes ($n = 269$) were matched with the use of a 1:1 matching protocol without replacement (greedy-matching algorithm), with a caliper width equal to 0.2 of the SD of the logit of the propensity score (Supplementary Fig. 1). In this analysis, we used the paired *t* test to compare the regional GMV/ICV between the subjects with and without diabetes. These statistical analyses were performed using the SAS version 9.4 (SAS Institute, Cary, NC). *P* values <0.05 were considered significant.

For voxel-based and vertex-based intergroup analysis, statistical parametric mapping was generated using an ANCOVA between the subjects with and without diabetes after adjustment for other confounding factors. ICV was also controlled as a covariate in the VBM analysis. For voxel-based correlation analysis, the association of GMV with FPG and 2hPG levels was analyzed using multiple regression, covarying for other confounding factors and ICV. In the VBM analysis, we applied explicit masking using a gray matter template included in the VBM8 Toolbox (Template_6_IXI550_MNI152.nii) with gray matter values of >0.05 and voxel-wise absolute masking with a threshold of 0.01. Both VBM and surface-based morphometry statistical maps were thresholded at uncorrected $P < 0.001$ at the voxel or vertex level combined with a

Table 1—Baseline characteristics of the study subjects with and without diabetes in 2012

	No diabetes ($n = 917$)	Diabetes ($n = 272$)	*P* value
Age, years	74 (7)	74 (6)	0.55
Men	38.7	57.0	<0.001
Formal education ≤9 years	37.5	37.5	>0.99
Systolic blood pressure, mmHg	133 (19)	137 (18)	0.005
Diastolic blood pressure, mmHg	76 (11)	76 (11)	0.93
Antihypertensive medication	49.0	73.9	<0.001
Hypertension	65.5	84.6	<0.001
FPG, mmol/L	5.6 (0.5)	7.4 (1.5)	<0.001
2hPG, mmol/L	7.4 (1.7)	13.8 (4.1)	<0.001
Antidiabetic medication	—	52.2	—
Serum total cholesterol, mmol/L	5.20 (0.91)	4.86 (0.95)	<0.001
Lipid-modifying medication	31.3	44.5	<0.001
Hypercholesterolemia	54.1	58.1	0.25
BMI, kg/m^2	22.8 (3.2)	24.0 (3.5)	<0.001
Smoking habits	7.9	11.1	0.10
Alcohol intake	38.6	47.4	0.01
Regular exercise	18.3	22.6	0.11
Cerebrovascular lesions on MRI	31.1	43.8	<0.001

Data are means (SD) or percentages unless otherwise indicated.

familywise error-corrected $P < 0.05$ at the cluster level.

RESULTS

The clinical characteristics of the study subjects by diabetes status are summarized in Table 1. Of the total 1,189 subjects, 272 (23%) had diabetes. Among them, 271 subjects had type 2 diabetes and 1 subject had type 1 diabetes. The mean values of BMI and the proportions of men and subjects with hypertension, lipid-modifying medication, alcohol intake, and cerebrovascular lesions on MRI scans were significantly higher, whereas the mean total cholesterol levels were significantly lower in subjects with diabetes than in those without diabetes.

Table 2 shows the adjusted means of the total and regional GMV/ICV by diabetes status. In model 1 with adjustment for age and sex, the subjects with diabetes had significantly lower values of the total, frontal, temporal, deep, and cerebellar GMV/ICV than subjects without diabetes. These results were robust after adjusting for confounding factors in model 2. In addition, the subjects with diabetes had significantly lower insular GMV/ICV than subjects without diabetes in model 2. Similar associations were observed in the following sensitivity analyses: *1*) an analysis excluding the 107 subjects with dementia (Supplementary Table 1); and *2*) an analysis based on propensity score matching (269 subjects with diabetes and 269 without diabetes) (Supplementary Table 2).

Supplementary Table 3 demonstrates the association between the duration of diabetes and regional gray matter atrophy. Of the 272 subjects with diabetes, 6 subjects were excluded from the analysis because the duration of diabetes was unknown in their cases, 82 had newly diagnosed diabetes, and the remaining 184 subjects had known diabetes. Longer duration of diabetes was significantly associated with lower total, frontal, temporal, insular, deep, and cerebellar GMV/ICV after adjusting for potential confounding factors (all P for trend <0.05).

Supplementary Table 4 shows the association of midlife and late-life diabetes with regional gray matter atrophy in the subgroup of 816 subjects who had participated in the health examination in 1988 (Supplementary Fig. 1). The subjects with midlife diabetes had significantly lower total, frontal, temporal, insular, deep, and cerebellar GMV/ICV than those without diabetes. In addition, these subjects had significantly decreased insular and deep GMV/ICV compared with subjects with late-life diabetes.

Table 3 shows the association of FPG and 2hPG levels with regional gray matter atrophy in the subgroup of 887 subjects who underwent the OGTT (Supplementary Fig. 1). The multivariable-adjusted mean values of the total, temporal, insular, and deep GMV/ICV decreased significantly with elevating 2hPG levels. The total, temporal, insular, and deep GMV/ICV were significantly lower in the subjects with 2hPG levels $\geq$11.1 mmol/L compared with those with 2hPG levels $<$7.8 mmol/L. In contrast, FPG levels were not significantly associated with gray matter atrophy in any regions.

As shown in Fig. 1, the results of VBM analysis of gray matter loss showed the subjects with diabetes had more significant gray matter loss than those without diabetes in the following brain regions after adjustment for other confounding

Table 2—Adjusted mean values (95% CIs) of the total and regional GMV/ICV by diabetes status

	Model 1	Model 2
Total GMV/ICV		
No diabetes	38.6 (38.4–38.7)	38.6 (38.4–38.7)
Diabetes	37.9 (37.5–38.2)	38.0 (37.6–38.3)
P value	<0.001	0.004
Frontal GMV/ICV		
No diabetes	9.83 (9.77–9.88)	9.83 (9.77–9.88)
Diabetes	9.65 (9.55–9.75)	9.68 (9.58–9.79)
P value	0.003	0.02
Temporal GMV/ICV		
No diabetes	7.15 (7.11–7.20)	7.15 (7.11–7.20)
Diabetes	7.00 (6.92–7.08)	7.02 (6.94–7.10)
P value	<0.001	0.006
Parietal GMV/ICV		
No diabetes	6.11 (6.08–6.14)	6.10 (6.07–6.14)
Diabetes	6.04 (5.98–6.10)	6.06 (6.00–6.12)
P value	0.054	0.22
Occipital GMV/ICV		
No diabetes	4.57 (4.55–4.60)	4.57 (4.55–4.60)
Diabetes	4.53 (4.48–4.58)	4.54 (4.50–4.59)
P value	0.11	0.31
Insular GMV/ICV		
No diabetes	0.855 (0.849–0.861)	0.856 (0.849–0.862)
Diabetes	0.842 (0.830–0.853)	0.841 (0.829–0.853)
P value	0.052	0.03
Cingulate GMV/ICV		
No diabetes	1.77 (1.77–1.78)	1.77 (1.76–1.78)
Diabetes	1.77 (1.75–1.78)	1.77 (1.76–1.79)
P value	0.50	0.93
Deep GMV/ICV		
No diabetes	1.28 (1.26–1.30)	1.28 (1.26–1.30)
Diabetes	1.22 (1.19–1.25)	1.22 (1.19–1.25)
P value	<0.001	<0.001
Cerebellar GMV/ICV		
No diabetes	5.85 (5.81–5.90)	5.85 (5.80–5.89)
Diabetes	5.68 (5.60–5.77)	5.71 (5.62–5.80)
P value	<0.001	0.007

Data are percentages unless otherwise indicated. Model 1: adjusted for age and sex; model 2: adjusted for the covariates in model 1 plus low education, hypertension, serum total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, and cerebrovascular lesions on MRI.

Table 3—Multivariable-adjusted mean values (95% CIs) of the total and regional GMV/ICV according to the FPG and 2hPG levels

	FPG levels (mmol/L)				2hPG levels (mmol/L)			
	<6.1 (reference) (n = 583)	6.1–6.9 (n = 181)	≥7.0 (n = 123)	P for trend	<7.8 (reference) (n = 423)	7.8–11.0 (n = 306)	≥11.1 (n = 158)	P for trend
Total GMV/ICV	39.2 (39.0–39.4)	38.8 (38.4–39.1)	39.0 (38.6–39.5)	0.25	39.2 (38.9–39.4)	39.2 (38.9–39.5)	38.5 (38.1–39.0)*	0.049
Frontal GMV/ICV	10.01 (9.95–10.08)	9.88 (9.76–9.99)	10.00 (9.85–10.15)	0.33	10.01 (9.93–10.08)	10.02 (9.94–10.11)	9.84 (9.70–9.98)	0.13
Temporal GMV/ICV	7.31 (7.26–7.36)	7.19 (7.10–7.27)*	7.26 (7.14–7.38)	0.13	7.32 (7.26–7.37)	7.33 (7.26–7.40)	7.07 (6.96–7.17)*	0.004
Parietal GMV/ICV	6.16 (6.12–6.20)	6.17 (6.10–6.24)	6.15 (6.06–6.25)	0.92	6.15 (6.10–6.19)	6.17 (6.12–6.22)	6.17 (6.09–6.25)	0.53
Occipital GMV/ICV	4.60 (4.57–4.63)	4.60 (4.55–4.65)	4.60 (4.53–4.67)	0.89	4.60 (4.57–4.64)	4.61 (4.57–4.65)	4.58 (4.52–4.65)	0.76
Insular GMV/ICV	0.873 (0.866–0.881)	0.856 (0.843–0.869)	0.876 (0.858–0.893)	0.50	0.880 (0.871–0.889)	0.870 (0.860–0.880)	0.844 (0.828–0.860)*	<0.001
Cingulate GMV/ICV	1.79 (1.78–1.80)	1.78 (1.77–1.80)	1.82 (1.80–1.84)	0.22	1.79 (1.78–1.81)	1.80 (1.78–1.81)	1.80 (1.78–1.82)	0.80
Deep GMV/ICV	1.32 (1.30–1.34)	1.28 (1.25–1.32)	1.30 (1.26–1.35)	0.17	1.33 (1.30–1.35)	1.32 (1.29–1.35)	1.25 (1.21–1.29)*	0.01
Cerebellar GMV/ICV	5.94 (5.88–5.99)	5.86 (5.76–5.96)	5.87 (5.73–6.00)	0.21	5.95 (5.89–6.02)	5.90 (5.82–5.97)	5.83 (5.71–5.95)	0.07

Data are percentages unless otherwise indicated. Adjusted for age, sex, low education, hypertension, serum total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, cerebrovascular lesions on MRI, and antidiabetic medication. *$P < 0.05$ vs. the reference group.

factors: the bilateral superior temporal gyri, right middle temporal gyrus, left inferior temporal gyrus, right middle frontal gyrus, bilateral thalami, right caudate, and right cerebellum. Montreal Neurological Institute (MNI) coordinates for this analysis are shown in Supplementary Table 5. No brain regions showed increased gray matter areas in the subjects with diabetes compared with those without diabetes. The regions that were negatively correlated with FPG and 2hPG levels are also shown in Fig. 1. MNI coordinates for this analysis are shown in Supplementary Table 6. There were no significantly decreased gray matter areas that were correlated with higher FPG levels. In contrast, the increased 2hPG levels correlated with atrophy of the bilateral superior, middle, inferior gyri, bilateral temporal poles, bilateral insulae, left parietal operculum, right opercular part of the inferior frontal gyrus, and right thalamus. There were no significantly increased gray matter areas that were correlated with higher FPG and 2hPG levels.

As shown in Supplementary Fig. 2, a surface-based morphometry analysis of cortical thickness revealed that the subjects with diabetes had significant cortical thinning in extensive portions of the frontal, temporal, parietal, and insular cortices compared with subjects without diabetes. MNI coordinates for this analysis are shown in Supplementary Table 7.

CONCLUSIONS

The current study demonstrated that subjects with diabetes, particularly those with a longer duration of diabetes or those who had onset of diabetes in midlife, had significantly lower frontal, temporal, insular, deep, and cerebellar GMVs compared with subjects without diabetes after adjustment for potential confounding factors in a general older Japanese population. Intriguingly, elevated 2hPG levels were associated with gray matter atrophy in extensive brain regions, but FPG levels were not significantly associated with gray matter atrophy of any region. The results from the current study suggest that longer duration of diabetes and postload hyperglycemia, rather than fasting hyperglycemia, are likely to play an important role in atrophy of the brain

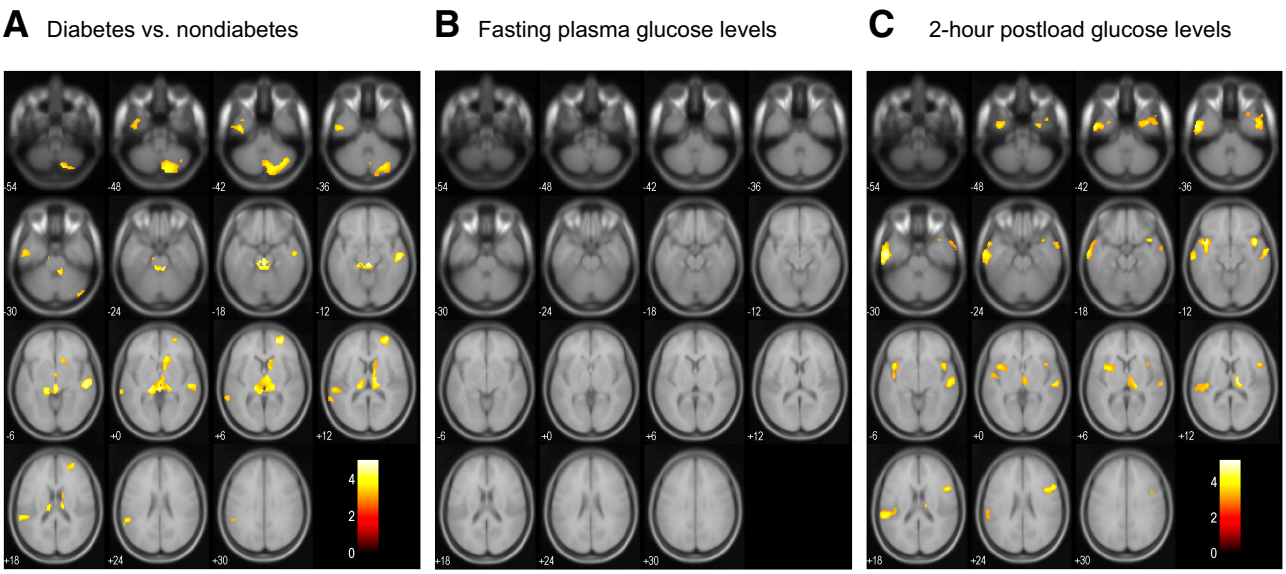

Figure 1—Gray matter regions that were inversely correlated with the presence of diabetes (*A*), FPG levels (*B*), and 2hPG levels (*C*). The regions of gray matter atrophy associated with diabetes mainly involved the bilateral superior temporal gyri, right middle temporal gyrus, left inferior temporal gyrus, right middle frontal gyrus, bilateral thalami, right caudate, and right cerebellum (*A*). There were no significantly decreased gray matter areas that were correlated with higher FPG levels (*B*). Those associated with elevated 2hPG levels included the bilateral superior, middle, and inferior gyri, bilateral temporal poles, bilateral insulae, left parietal operculum, right opercular part of the inferior frontal gyrus, and right thalamus (*C*). Values were adjusted for age, sex, low education, hypertension, serum total cholesterol, BMI, smoking habits, alcohol intake, regular exercise, cerebrovascular lesions on MRI, ICV, and/or antidiabetic mediation.

regions that were known to be associated with cognitive function.

Among the prior epidemiological studies of the general population, the Atherosclerosis Risk in Communities Neurocognitive (ARIC) Study demonstrated that participants with an HbA_{1c} of ≥7.0% had smaller frontal, temporal, occipital, and parietal volumes than those with an HbA_{1c} of <5.7% (4). The ARIC Study also reported that temporal and parietal volumes were lower in subjects who had diabetes for ≥10 years than in those who had diabetes for <10 years. The Rotterdam Study showed that diabetes was significantly associated with cerebellar atrophy (13). The whole-brain VBM meta-analysis of five case-control studies revealed that the subjects with diabetes had reduced GMVs in the left superior temporal gyrus, right middle temporal gyrus, right rolandic operculum, and left fusiform gyrus compared with the subjects without diabetes (14). Most of these previous structural MRI studies consistently revealed atrophy of temporal regions in patients with diabetes, which was in accordance with our present findings. In contrast, results for other brain regions have been inconsistent. Such conflicting results may be related to a difference in the methods for brain volume measurement, diagnostic criteria for diabetes, age distribution, race, duration of diabetes, and differences in the covariates included in the statistical models.

Diabetes is an established risk factor for dementia, particularly Alzheimer disease (AD), and brain atrophy is known as a morphological feature of AD. The current study revealed that subjects with diabetes had lower GMVs of several brain regions related to cognitive impairment—namely, the extensive areas in the temporal lobe, insula, middle frontal gyrus, caudate, and thalamus—than subjects without diabetes. The superior temporal gyrus is involved in auditory processing and comprehension, including language, and is implicated in social cognition (15). The middle temporal gyrus and inferior temporal gyrus subserve semantic memory processing, visual perception, and multimodal sensory integration (16). The temporal pole is also associated with semantic memory and verbal fluency (17) and involved in social and emotional processing (18). The insula is a region that functions as a central brain hub characterized by widespread connections and diverse functional roles, and atrophy of the insula is known to be involved in various neurodegenerative diseases (19). The middle frontal gyrus is a region important for executive function and selective attention (20). The caudate is an important part of the system controlling learning and memory (21). The thalamus is a critical node in networks supporting cognitive functions, including component processes of memory and executive functions of attention and information processing (22,23). Previous epidemiological studies have reported that diabetes is associated with faster declines in executive function (24–26), processing speed (24,26), verbal fluency (24,26), and memory (24–26). The atrophy of brain regions that were associated with diabetes in the current study may have been related to an increased risk of loss of such brain functions. There was a strong tendency for GMVs of these regions to be decreased in the sensitivity analysis after excluding subjects with dementia, suggesting that gray matter atrophy in these regions is likely to occur before onset of dementia in the subjects with diabetes.

In the current study, elevated 2hPG levels were associated with gray matter atrophy of extensive brain regions, such as the superior temporal gyrus, middle temporal gyrus, temporal pole, and insula. Postload glucose levels are considered to reflect postprandial hyperglycemia. Our study group previously reported that elevated 2hPG levels

were significantly associated with total brain and hippocampal atrophy using brain MRI data (5), higher likelihood of neuritic plaques using autopsy data (27), and greater risk of development of AD using longitudinal data (9), but no significant association was observed between FPG levels and these outcomes. Thus, the findings from our series of studies suggest that the management of postprandial hyperglycemia may reduce the risk of morphological abnormalities in the brain and the subsequent risk of dementia in late life.

In the current study, longer duration of diabetes and younger onset of diabetes were significantly associated with atrophy in various brain regions, such as the frontal, temporal, and insular lobes. We previously reported similar results for total brain atrophy and hippocampal atrophy in this population (5). Thus, brain atrophy in these regions is likely to occur as the result of a long exposure to glucose toxicity, abnormal insulin metabolism, and microvascular disease.

The current study has several limitations. First, since the present analysis had a cross-sectional design, estimation of a causal association between diabetes and gray matter atrophy was difficult. However, we contend that diabetes causes gray matter atrophy, because a longer duration of diabetes or midlife diabetes was associated with more severe gray matter atrophy. Second, the diagnosis of diabetes and the measurement of FPG and 2hPG levels were based on a single measurement of glucose levels or a single 75-g OGTT at each health examination (in 1988 and 2012). This limitation might have resulted in misclassification of the diabetes diagnosis and FPG and 2hPG levels. Such misclassification could have weakened the association, biasing the results toward the null hypothesis. Thus, the true association may be stronger than that observed in the present analysis. Third, although the participation rate of the screening survey was fairly high, approximately one-third of the residents were not included in the current study. The individuals who did not participate in this study were more likely to be female and older and had a greater prevalence of dementia than those participating in the study, which may have caused the selection bias (28). In addition, the participants in this study were older people from a single suburban region in Japan. Thus, the generalizability of our findings may be limited.

In conclusion, the current study suggests that a longer duration of diabetes and a midlife onset of diabetes are significant risk factors for gray matter atrophy in various brain regions that are likely to play an important role in cognitive function. In addition, the significant association between elevated 2hPG levels and gray matter atrophy in various brain regions may suggest that careful control of postprandial plasma glucose levels is important to prevent gray matter atrophy and the subsequent development of dementia in individuals with diabetes. Further clinical and basic research is required to verify the findings from the current study.

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