Brain Aging in Very Old Men With Type 2 Diabetes

The Honolulu-Asia Aging Study

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OBJECTIVE — Type 2 diabetes leads to cognitive impairment and dementia, which may reflect microvascular and macrovascular complications as well as neurodegenerative processes. There are few studies on the anatomical basis for loss of cognitive function in type 2 diabetes. The objective of this study was to investigate the association between type 2 diabetes and markers of brain aging on magnetic resonance images, including infarcts, lacunes, and white matter hyperintensities as markers of vascular damage and general and hippocampal atrophy as markers of neurodegeneration in Japanese-American men born between 1900 and 1919 and followed since 1965 in the Honolulu-Asia Aging Study.

RESEARCH DESIGN AND METHODS — Prevalent and incident dementia was assessed. Associations between magnetic resonance imaging markers and diabetic status were estimated with logistic regression, controlling for sociodemographic and other vascular factors.

RESULTS — The prevalence of type 2 diabetes in the cohort is 38%. Subjects with type 2 diabetes had a moderately elevated risk for lacunes (odds ratio [OR] 1.6 [95% CI 1.0–2.6]) and hippocampal atrophy (1.7 [0.9–2.9]). The risk for both hippocampal atrophy and lacunes/infarcts was twice as high in subjects with compared with those without type 2 diabetes. Among the group with type 2 diabetes, those with the longest duration of diabetes, those taking insulin, and those with complications had relatively more pathologic brain changes.

CONCLUSIONS — There is evidence that older individuals with type 2 diabetes have an elevated risk for vascular brain damage and neurodegenerative changes. These pathological changes may be the anatomical basis for an increased risk of cognitive impairment or dementia in type 2 diabetes.

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Subjects with type 2 diabetes are at increased risk for cerebral complications, including stroke (1,2), cognitive impairment (3,4), and dementia (5–7). This may partially reflect the systemic microvascular (retinopathy, nephropathy, and neuropathy) (8) and macrovascular (coronary heart disease and peripheral arterial disease) (9–11) complications that characterize type 2 diabetes. Characteristics of subjects with type 2 diabetes, such as hyperglycemia, elevated blood pressure, hyperinsulinemia, and dyslipidemia may also directly affect neuronal viability. In type 2 diabetes, the phosphorylation of tau may be enhanced (12), the breakdown of amyloid might be diminished (13,14), and advanced glycated end products may contribute to the formation of neurofibrillary tangles (NFTs) and neuritic plaques (15), which are markers of Alzheimer's disease, a major neurodegenerative disease in the elderly. Autopsy data based on the Honolulu-Asia Aging Study (HAAS) cohort show a significant association of type 2 diabetes with infarcts as well as hippocampal NFTs and neuritic plaques (6).

Taken together, the evidence suggests that type 2 diabetes may contribute to cognitive disorders not only via vascular lesions but also via neurodegeneration. To test this hypothesis, we investigated the association between type 2 diabetes and magnetic resonance imaging (MRI) findings of infarcts, lacunes, and white matter hyperintensities (WMHs) as markers of vascular damage and general and hippocampal atrophy (16) as markers of neurodegeneration. Data are from the population-based HAAS.

RESEARCH DESIGN AND METHODS

— The design of the HAAS has been described elsewhere (17). Briefly, the cohort consisted of Japanese-American men born between 1900 and 1919 and living on the island of Oahu, Hawaii, who were enrolled in 1965 as a part of the Honolulu Heart Program. After the first examination (1965–1968), the men were reexamined in 1968 through 1970 (examination 2) and in 1971 through 1974 (examination 3). In 1991–1993, the HAAS was established with the aim of investigating neurodegenerative diseases in the cohort. Of the survivors, 3,734 men (80% response) underwent a complete examination (examination 4). The cohort was reexamined in 1994 through 1996 (examination 5), with an 84% participation rate among those with a previous cognitive screen. At each examination, clinical measurements were made and sociodemographic and medical conditions were assessed. At examinations 4 and 5, cognitive status was tested and subjects with prevalent (examination 4) and incident (examination 5) dementia

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Abbreviations: ABI, ankle-brachial index; apo, apolipoprotein; CHD, coronary heart disease; FOV, field of view; HAAS, Honolulu-Asia Aging Study; IDE, insulin-degrading enzyme; IGT, impaired glucose tolerance; MRI, magnetic resonance imaging; NFT, neurofibrillary tangle; TICV, total intracranial volume; WMH, white matter hyperintensity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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were identified. The Kuakini Medical Center Institutional Review Board approved this study. All respondents signed informed consent forms, except those who had dementia. For these subjects, an informed caretaker signed the consent.

MRI substudy

Sample. In examination 5, a MRI study was conducted on a subsample of the cohort selected on the basis of information from both examinations 4 and 5 (18). The sample included a ~10% random sample of examination 5 participants and a randomly selected oversample of those with prevalent dementia (excluding those with severe dementia, who might not be able to undergo the procedure), those who scored poorly on the Cognitive Abilities Screening Instrument (19) but did not meet criteria for dementia, those with the apolipoprotein (apo)E ε4 genotype, and those with clinical stroke.

Dementia was ascertained in a multistep procedure, described in detail elsewhere (17). Diagnosis was made in a consensus conference: DSM-IIIR criteria (20) were applied for dementia, the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association (21) criteria for Alzheimer's disease, and the California Alzheimer's Disease Diagnostic and Treatment Centers criteria for vascular dementia (22). Stroke was identified from the first examination through to the MRI examination as a part of the ongoing Honolulu Heart Program hospital surveillance system in which multiple sources of information are used to complete a consensus diagnosis. ApoE genotyping based on samples collected at examination 4 was performed with restriction isotyping using a polymerase chain reaction (23).

Of the 845 men invited for the procedure, 621 MRI scans were acquired, and 543 MRI scans could be processed successfully for all relevant data. Nonparticipation was due to death, refusal to participate, and technical problems. Compared with the 302 subjects not included in the analyses, the included subjects had more years of education (P = 0.01) but the same prevalence of type 2 diabetes, hypertension, and stroke; by design they had the apoE ε4 allele more frequently (36 vs. 29%, P = 0.04).

Imaging protocol. Scans were acquired with a GE Signa Advantage 1.5-T machine at Kuakini Medical Center, Honolulu, Hawaii. The acquisition protocol typically required 20 min and included four pulse sequences: sagittal, 24-cm field of view (FOV), repetition time (TR) = 5,000, time to echo (TE) = minimum, 5-mm contiguous interleaved sections, 192 views, one repetition; three-dimensional coronal spoiled gradient echo sequence, 22 cm FOV, minimum TR and TE, 1.6-mm slice thickness, 124 slices, one repetition, 45° flip angle; axial proton density–weighted fast-spin echo sequence, 3-mm interleaved sections, minimum TE, TR = 2,300 ms, 24 cm FOV, 256 views, one repetition, four echo train length, minimum interecho spacing; another axial fast-spin echo sequence, T_2-weighted, 3-mm interleaved sections, TR ≥4,000 ms, 24 cm FOV, 256 views, one repetition, echo train length equal to 8, minimum interecho spacing.

MRI readings

WMHs, infarcts, and lacunes. Semiquantitative readings based on a protocol developed for the Cardiovascular Health Study were performed at the Johns Hopkins Neuroradiology Reading Center by readers blinded to subject risk factors and health. Scans were evaluated for the number of lacunes and infarcts as defined by Longstreth et al. (24). In short, infarcts or lacunes are defined as lesion at least 3 mm in diameter, visible on both the T_1-weighted images and the proton density/T_2-weighted images and approach cerebrospinal fluid density. Infarcts in the cortical gray matter and basal ganglia may only be cerebrospinal fluid–like on the proton density/T_2-weighted images. The location of lacunes is exclusively subcortical (including the basal ganglia), and they are between 3 and 20 mm in all dimensions. Infarcts are larger than 20 mm or located cortically. WMHs appear isointense compared with the white matter on the T_1-weighted images and hyperintense on the axial proton density–weighted images. They are rated on a 10-point scale that ranges from no white matter signal abnormalities to all white matter involved (25).

Atrophy. The inner table distance and the bifrontal distance (largest diameter between the left and right frontal horn of the lateral ventricles) were measured on the most superior T_1-weighted axial image where the lateral ventricles were indented by the thalami. The central sulcus width was the largest perpendicular diameter of the right central sulcus, also measured on the T_1-weighted axial sequence. As a measure of cortical volume, the central sulcus width was divided by the inner table distance; cortical atrophy was defined as the highest quartile of this measure. As a measure of subcortical volume, the bifrontal distance was divided by the inner table distance; subcortical atrophy was defined as the lowest quartile of this measure. General atrophy was defined as the presence of cortical and/or subcortical atrophy.

Hippocampal volume. The coronal spoiled gradient echo sequence was reformatted to oblique coronal, perpendicular to the long axis of the left hippocampus. Using MEDx version 3.41 software (Sensor Systems, Sterling, VA), one rater, blind to subjects' characteristics, measured the left and right hippocampi as described in an earlier report (26). The hippocampal formation, including the subiculum, dentate gyrus, cornu ammonis, fimbria, and alveus, was measured in its total length from anterior until the crux of the fornix was seen. The intraclass correlation coefficient for the intrareader agreement was 0.97.

Hippocampal volumes were corrected for head size, estimated on the axial proton density sequence, by measuring the intradural area (total intracranial volume [TICV]). For each subject, hippocampal volume was multiplied by the mean TICV of the sample and divided by the TICV of the subject (26).

Assessment of type 2 diabetes

Type 2 diabetes was assessed at the fourth examination. Subjects with a self-reported doctor's diagnosis of type 2 diabetes and those using oral hypoglycemic medications or insulin were classified as having type 2 diabetes. In addition, we identified those with diabetes from fasting and 2-h glucose levels taken after administration of a 75-g glucose drink (27); this was done for those who were not known to have type 2 diabetes and did not have a gastrectomy, an active peptic ulcer, or stomach cancer. On the basis of the recommendations of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (28), individuals with fasting blood glucose ≥126 mg/dl (≥7.0 mmol/l) or 2-h postload glucose ≥200 mg/dl (≥11.1 mmol/l) were classified as having type 2 diabetes, individuals with fasting glucose between 5.1 and 7.0 mmol/l or 2-h postload glucose between 7.8 and 11.1 mmol/l were classified as having impaired glucose tolerance (IGT), and subjects with fasting glucose ≤5.1 mmol/l and 2-h postload glucose ≤7.8

Table 1—*Characteristics of the MRI sample by diabetes status: HAAS*

Variable	No diabetes	IGT	Type 2 diabetes
n	204	137	202
Age (years)	81.3 ± 4.9	81.8 ± 5.0	81.7 ± 5.1
Education (years)	10.2 ± 3.3	10.4 ± 2.8	10.3 ± 3.2
SBP (mmHg)	131 ± 16	133 ± 18	134 ± 17
DBP (mmHg)	83 ± 9	83 ± 9	83 ± 10
BMI (kg/m^2)	23.5 ± 2.7	23.5 ± 2.2	24.3 ± 2.7
Antihypertensive drugs (%)*	41	47	55
Total cholesterol (mg/dl)	215 ± 31	220 ± 30	222 ± 32
Fasting glucose (mg/dl)†	98 ± 6	107 ± 8	132 ± 37
Fasting insulin (μIU/ml)*	12.6 ± 9.3	14.0 ± 7.4	18.6 ± 15.8
Smoking (%)			
Former	34.3	31.4	55
Current	25.0	19.0	2.5
ApoE ε4 (%)	36.8	38.0	35.1
ABI	1.04 ± 0.15	1.04 ± 0.15	1.03 ± 0.19
CHD (%)*	12.3	10.2	18.3
Stroke (%)	6.9	11.7	9.4
Dementia (%)	21	20	22
Alzheimer's disease (%)	9.8	8.8	8.9
Alzheimer's disease with cardiovascular disease (%)	2.5	5.1	5.4
Vascular dementia	2.9	3.6	5.4
Hippocampal volume (mm^3)*	5,406 ± 856	5,430 ± 855	5,348 ± 805
Hippocampal atrophy (%)	22	23	27
Lacunes (%)*			
0	61.8	61.3	47.5
1	19.6	16.1	24.8
≥2	18.6	22.6	27.8
WMHs (%)			
0–3	73.5	69.3	74.8
4–9	26.5	30.7	25.2
Infarcts (%)	9.8	13.0	13.4
General atrophy (%)	41.1	41.6	46.0

Data are means ± SD unless otherwise indicated. Data for smoking are missing 40 subjects. apoE ε4 group includes 15 subjects with ε24. *P* values are adjusted for age: *$P < 0.05$; †$P < 0.001$. DBP, diastolic blood pressure; SBP, systolic blood pressure.

mmol/l were classified as normoglycemic. Subjects reporting diabetes (i.e., those with diabetes not newly detected by the study) were asked the duration of their disease and whether they had complications of type 2 diabetes, including amputation, retinopathy, nephropathy, or peripheral neuropathy.

Measures of confounding or mediating variables

We considered the following factors to be possible confounders or mediators of the association between type 2 diabetes and MRI measurements: age, education (years), history of coronary heart disease (CHD), ankle-brachial index (ABI), midlife smoking (never [reference], current, and past), systolic blood pressure, BMI, and total cholesterol as well as treatment with antihypertensive medication. CHD history was assessed at baseline in 1965 and throughout the entire follow-up to the MRI examination. ABI was measured at examination 4. Smoking status was collected by questionnaire at the midlife examinations (examinations 1–3). The values of BMI (weight in kilograms divided by the square of height in meters), total cholesterol (milligrams per deciliter), and systolic blood pressure (millimeters of mercury) are the average of these factors measured at the three midlife examinations. Treatment with antihypertensive medication was based on self-report (examinations 1–3) or by presentation of medication vials (examination 4).

Statistical analyses

Age-adjusted differences in subject characteristics were examined across glycemic subgroups using ANOVA if the characteristic was continuously distributed and the Mantel-Haenszel test if it was categorical. Logistic regression was used to estimate the association of the three glycemic categories (type 2 diabetes, IGT, and normoglycemia) with brain outcomes. For the analyses, we defined the brain outcomes as follows: lacunes (present/absent), infarcts (present/absent), substantial WMH (score ≥4 versus the rest), severe hippocampal atrophy (the lowest 25th percentile of hippocampal volume versus the rest), and general atrophy. To examine the simultaneous risk for both vascular damage and hippocampal atrophy, we created a polytomous four-level outcome: only hippocampal atrophy, only infarcts or lacunes, and both hippocampal atrophy and lacunes/infarcts. The reference group had no infarcts, lacunes, or hippocampal atrophy.

Three models were estimated: model 1, adjusted for age and education; model 2, also adjusted for MRI variables other than the lesion of interest; and model 3, adjusted for apoE genotype, dementia status, smoking, alcohol use, history of CHD and stroke, systolic blood pressure, antihypertensive drug use, cholesterol, BMI, and ABI. We also conducted subanalyses to investigate whether subjects with presumably more severe or long-standing type 2 diabetes were at higher risk for the MRI outcomes. Markers of disease history included whether insulin is used, duration of disease, and self-reported presence of diabetes-related amputation or eye, kidney, or peripheral neuropathic complications. Analyses were conducted with the Statistical Analysis System (version 8; SAS Institute, Cary, NC) (29).

RESULTS — In the sample, 38% had type 2 diabetes (65% of whom had known diabetes), 25% IGT, and 37% normoglycemia (Table 1). The mean ± SD age of the men was 81.6 ± 5.0 years. Proportionately more subjects with type 2 diabetes used antihypertensive drugs and had CHD, smaller hippocampi, and more lacunes ($P < 0.05$, age adjusted). Insulin levels and, by definition, fasting glucose levels were higher in subjects with type 2 diabetes or IGT ($P < 0.001$ and $P < 0.05$, respectively) compared with normoglycemic subjects.

Compared with normoglycemic men, those with type 2 diabetes had an increased risk for lacunes (OR 1.6 [95% CI 1.0–2.6]) (Table 2). Subjects with type 2 diabetes had a risk for general atrophy

Table 2—*Association between diabetes and MRI outcome variables: HAAS*

	Model 1	Model 2	Model 3
General atrophy			
Normoglycemia	1	1	1
IGT	1 (0.6–1.5)	1 (0.6–1.5)	1 (0.6–1.6)
Type 2 diabetes	1.2 (0.8–1.8)	1.2 (0.8–1.7)	1.1 (0.7–1.7)
WMHs			
Normoglycemia	1	1	1
IGT	1.2 (0.7–1.9)	1.2 (0.7–1.9)	1.3 (0.8–2.3)
Type 2 diabetes	0.9 (0.6–1.4)	0.9 (0.6–1.4)	1.1 (0.7–1.9)
Infarcts			
Normoglycemia	1	1	1
IGT	1.4 (0.7–2.9)	1.6 (0.8–3.1)	1.0 (0.4–2.7)
Type 2 diabetes	1.5 (0.8–2.7)	1.5 (0.8–2.8)	1.9 (0.8–4.3)
Lacunes			
Normoglycemia	1	1	1
IGT	1.0 (0.6–1.6)	1.0 (0.6–1.6)	0.9 (0.6–1.6)
Type 2 diabetes	1.8 (1.2–2.6)	1.8 (1.2–2.6)	1.6 (1.0–2.6)
Hippocampal atrophy			
Normoglycemia	1	1	1
IGT	1.0 (0.6–1.8)	1.0 (0.6–1.7)	1.2 (0.7–2.3)
Type 2 diabetes	1.3 (0.8–2)	1.3 (0.8–2.1)	1.7 (0.9–2.9)

Data are OR (95% CI). Model 1: adjusting for age and education. Model 2: same as model 1, for atrophy and hippocampal atrophy also adjusting for WMHs, infarcts, and lacunes; for WMHs, infarcts, and lacunes also adjusting for general atrophy. Model 3: same as model 1, also adjusting for apoE genotype, dementia, smoking, alcohol, CHD, ABI, systolic blood pressure, blood pressure treatment, BMI, total cholesterol, and stroke. General atrophy indicates cortical atrophy (the highest quartile of the width of central sulcus/inner table distance) and/or subcortical atrophy (the lowest quartile of the bifrontal distance/ inner table distance); WMHs indicate a WMH score ≥4; infarcts indicate any cortical infarcts and/or any subcortical infarcts; lacunes indicate any lacunes; hippocampal atrophy indicates the lowest quartile of hippocampal volume.

that was similar to that of the normoglycemic group. In the fully adjusted model 3, the risk for hippocampal atrophy was moderately higher for type 2 diabetic subjects than for normoglycemic subjects (1.7 [0.9–2.9]). Subjects with IGT had essentially the same risk as did the normoglycemic subjects for all investigated MRI outcomes (Table 2).

Results from the combined groups on the basis of the presence or absence of vascular lesions and hippocampal atrophy (Table 3) suggest that those with type 2 diabetes have a two times increased risk for the mixed pathological condition of vascular lesions and hippocampal atrophy. However, the risk in the mixed profile group is similar to what would be expected if type 2 diabetes increased the risk for the two types of pathological changes in an additive manner. Compared with the normoglycemic subjects, the subjects with IGT did not have a significantly higher risk for these outcomes.

Only 10 subjects with type 2 diabetes (5% of type 2 diabetic subjects) used insulin. The mean hippocampal volume of these subjects was smaller than that for subjects with type 2 diabetes who did not take insulin or oral antidiabetic medication (4,778 ± 825 vs. 5,400 ± 833 mm^3, respectively), they had general atrophy more frequently (70 vs. 42.7%), 40% had hippocampal volumes in the lowest quartile, and 50% had lacunes; 3 of the 10 had dementia. There were 49 subjects with type 2 diabetes (24.2%) who used oral hypoglycemic drugs. The average hippocampal volume of these subjects was 5,312 ± 818 mm^3, 29% had small hippocampi, 59% had lacunes, and 18.3% had dementia.

Twelve subjects reported type 2 diabetes–related complications. Compared with diabetic subjects without complications, those with complications had slightly more brain atrophy (59 vs. 50%) and infarcts (25 vs. 10%), but the sample is very small. Compared with the subjects with diabetes for ≤5 years ($n = 53$), those with diabetes for >20 years ($n = 25$) had more lacunes (68 vs. 54.7%), hippocampal atrophy (44 vs. 28.3%), infarcts (20 vs. 15%), and WMHs (36 vs. 20.7%).

CONCLUSIONS— Subjects with type 2 diabetes had an elevated risk for lacunar infarction and a borderline significantly increased risk for hippocampal atrophy. The risk for both infarcts and hippocampal atrophy was twice as high in subjects with type 2 diabetes as that in subjects without type 2 diabetes, after adjustment for other vascular factors. This risk estimate suggests that there is no synergism between the two pathological conditions. Compared with normoglycemic subjects, subjects with IGT, who are at high risk of developing type 2 diabetes, had no elevated risk for general atrophy, lacunes, infarcts, or hippocampal atrophy. These associations were independent of other vascular outcome measures and risk factors and also independent of each other.

This study had several strengths. It is based on a large sample of subjects with MRI of the brain and on cardiovascular data that were collected prospectively from midlife up through late life, when the MRI was performed. Also, we separated the subjects with IGT, who are at

Table 3—*Association of diabetes, hippocampus, and lacunes/infarcts: HAAS*

	Model 1	Model 3
Hippocampal atrophy only		
IGT	1.4 (0.7–2.7)	1.5 (0.7–3.1)
Diabetes	1.5 (8–2.7)	1.7 (0.8–3.4)
Lacunes/infarcts only		
IGT	1.22 (0.7–2.0)	1.2 (0.7–2.1)
Diabetes	1.9 (1.2–3.0)	1.8 (1.1–2.9)
Hippocampal atrophy and lacunes/infarcts		
IGT	0.9 (0.00.4–2.0)	0.9 (0.4–2.30
Diabetes	2.1 (1.1–4.11)	2.0 (0.9–4.4)

Model 1: adjusting for age and education. Model 3: same as model 1, also adjusting for apoE genotype, dementia, smoking, CHD, ABI, SBP, blood pressure treatment, and BMI. Hippocampal atrophy indicates lowest quartile of the hippocampal volumes without lacunes or infarcts; lacunes/infarcts indicate any lacunes or infarcts without hippocampal atrophy; hippocampal atrophy and lacunes/infarcts indicates the lowest quartile of the hippocampal volumes with lacunes or infarcts.

risk for type 2 diabetes, from the subjects with IGT and type 2 diabetes, so groups with different degrees of glucose regulation could be compared. The findings of very small hippocampi in insulin users and proportionately more brain pathological changes in those who had been diabetic for at least 20 years suggest that the amount of brain pathological changes may increase with disease severity or duration. However, this suggestion needs to be further investigated in a larger sample who are prospectively followed.

When these results are generalized to other cohorts, some characteristics of the sample should be noted. It has been reported that the prevalence of diabetes and glucose dysregulation in this cohort is comparatively high and that this finding may reflect differences in the relative contributions to the disease of insulin resistance, glucose overproduction, degree of impaired β-cell function, and genetics (30). Such differences may also account for the relatively low use of insulin and complications in this diabetic population. Other differences that might modify these results include that these men are relatively lean and that the mean age in the cohort is high [>80 years]. It is likely that many subjects with type 2 diabetes, who have severe complications of the disease, do not reach this age. If mortality is selective for men at risk for type 2 diabetes and cerebrovascular changes, this fact would change the estimates of the associations reported here. In this context, the risk estimates we found are of moderate size. It should also be noted that the MRI sample is not a random sample of the cohort but a sample selected on the basis of certain characteristics including dementia, poor cognitive performance, stroke, and the apoE genotype.

Type 2 diabetes leads to both microvascular and macrovascular changes. Atherosclerosis of the large extra- and intracranial vessels decreased cerebral blood flow, impaired cerebrovascular reactivity, thickening of the capillary basement membrane, and endothelial cell degeneration of microvessels are all described in type 2 diabetes (rev. in 31). We found associations between type 2 diabetes and lacunes, which are markers for microvascular or small-vessel disease. In another community-based study, subjects with type 2 diabetes also had a higher risk for lacunes compared with normoglycemic subjects (25). A study with serial MRI scans also detected more new lacunes in the subjects with type 2 diabetes (32). The hypothesis that type 2 diabetes leads to small-vessel disease in the brain is supported by these studies. However, WMHs are also considered to be small-vessel disease, but we did not find an association between those lesions and type 2 diabetes. This finding might be due to the scoring system that was used. Although, as expected, the score is significantly associated with age, clinically silent stroke, higher systolic blood pressure, and impaired cognition (33), it does not evaluate the distribution of the lesions or provide a quantitative measure of lesion load. Further, we did not acquire a fluid-attenuated inversion recovery sequence, so WMHs may have been missed (34–36). However, the lack of association between type 2 diabetes and WMHs has also been reported in other studies (37,38), in which a semiquantitative method for estimating the WMH volume was used. These findings suggest that, in type 2 diabetes, WMHs may have a pathological basis different from that of lacunes, but this needs to be further investigated.

Cortical and subcortical infarcts are caused by macrovascular or large-vessel disease. We did not find a significant association between type 2 diabetes and infarcts, although risk ratios were increased. This finding is consistent with reports from other studies (37,38). This is a notable finding, as type 2 diabetes is a risk factor for stroke (2,39). The difference may be related to selective mortality of subjects with type 2 diabetes at risk for macrovascular disease.

Hippocampal atrophy is a general marker for neurodegenerative processes, particularly in Alzheimer's disease (16). Cerebral hypoxia-ischemic conditions can also lead to cell death and ensuing hippocampal atrophy (26,40). Subjects with type 2 diabetes had a moderately increased risk for hippocampal atrophy, particularly when infarcts and lacunes were also present. Adjusting for vascular risk factors (model 3) slightly attenuated the OR, suggesting some mediation by these factors. This is consistent with the findings in the HAAS autopsy study, which showed that both amyloid-related pathological changes and vascular pathological changes were more frequent in type 2 diabetic subjects than in the rest of the sample (6). In the present study, type 2 diabetes was not associated with general atrophy. The large community-based study Cardiovascular Determinants of Dementia (CASCADE) did find that type 2 diabetes was associated with an increased risk for cortical atrophy (38), particularly in those with hypertension. These subjects were much younger than those in the HAAS.

Several mechanisms can explain the effect of type 2 diabetes on neurodegeneration. Insulin has an inhibitive effect on the phosphorylation of tau. Tau is a phosphoprotein of the brain and normally has two or three phosphate groups. Hyperphosphorylation of tau can lead to NFTs, which are characteristic of Alzheimer's disease. As type 2 diabetes is characterized by signaling defects in insulin, the inhibition of phosphorylation of tau by insulin (12) may be diminished. Dysfunction of the insulin-degrading enzyme (IDE) may also be a possible pathologic link between Alzheimer's disease and type 2 diabetes. This enzyme is known to degrade insulin and β-amyloid. In type 2 diabetes, dysfunction of IDE causes high levels of insulin and β-amyloid. Deposition of β-amyloid into plaques is characteristic of Alzheimer's disease. In Alzheimer's disease, hyperinsulinemia is more prevalent than in control subjects, and the activity and amount of IDE are diminished (41,42). Interestingly, chromosome 10 contains the genes for IDE and potentially the genes for both late-onset Alzheimer's disease and type 2 diabetes (13,14,43). Another possible neurodegenerative mechanism is through neurotoxic advanced glycation end products, caused by hyperglycemia, which may contribute to the formation of NFTs and neuritic plaques (15,44).

We did not find an increased risk for MRI-detected brain changes in men who had IGT. A study of 30 volunteers without type 2 diabetes suggests (45) that fasting and 2-h glucose levels were negatively associated with hippocampal volume. However, studies based on larger, less-selected samples, are contradictory regarding the risk for cognitive impairment in those with IGT (46,47). Given the high prevalence of IGT, it will be important to further investigate this group in studies of brain aging.

In summary, we found that subjects with type 2 diabetes had a moderately elevated risk for vascular brain damage, such as lacunes, and for neurodegenerative changes, such as those indicated by hippocampal atrophy. Because of advances in treatment, subjects with type 2 diabetes are living longer. However, the pathological condition may cause cognitive impairment and subsequent difficulties in disease management. Further

studies on the changes in brain structure and correlation with cognition in type 2 diabetes are warranted.

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