Untreated Type 2 Diabetes and Its Complications Are Associated With Subcortical Infarctions

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OBJECTIVE — To investigate the association of type 2 diabetes with subcortical infarctions.

RESEARCH DESIGN AND METHODS — We investigated this association in subjects with type 2 diabetes (case subjects; $n = 93$) and without type 2 diabetes (control subjects; $n = 186$), matched by age, sex, and years of education. Participants were a subset of the Mayo Clinic Study of Aging (median age 79 years) who had undergone magnetic resonance imaging.

RESULTS — The frequency of subcortical infarctions was 39% in case subjects and 29% in control subjects (odds ratio 1.59 [95% CI 0.91–2.75]). The association was stronger in case subjects without treatment (2.60 [1.11–6.08]) and in case subjects with diabetes-related complications (1.96 [1.02–3.74]) compared with control subjects.

CONCLUSIONS — These findings suggest that untreated type 2 diabetes and type 2 diabetes with complications are associated with subcortical infarctions.

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Type 2 diabetes is associated with an increased risk of stroke (1), silent infarctions (2), cognitive impairment (3,4), and dementia (5). Few studies have examined the associations with magnetic resonance imaging (MRI) measures of cerebrovascular disease among individuals randomly selected from the population (2,6). The objective of our study was to investigate the association of type 2 diabetes with subcortical infarctions.

RESEARCH DESIGN AND METHODS

— The study design and methodology are published (7). Briefly, Mayo Clinic Study of Aging participants were Olmsted County residents aged 70–89 years on 1 October 2004, who were randomly selected from the population to investigate risk factors for mild cognitive impairment (MCI) and dementia. In a subset of 432 study participants who had undergone imaging, we matched 93 individuals with type 2 diabetes by age, sex, and years of education to 186 control subjects without type 2 diabetes. Study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Criteria for type 2 diabetes were *1*) treatment (oral antidiabetic agents, insulin) or *2*) fasting blood glucose >126 mg/dl on two separate occasions or *3*) a physician diagnosis, using information from participant medication bottles and from the participant medical record (3). Individuals who only met the latter two criteria were considered as having type 2 diabetes without treatment; they had very mild disease (median glycosylated hemoglobin [HbA1c] was 5.8% [range 5.1–6.7%]). Diabetes-related complications were defined as self-reported physician-diagnosed diabetic nephropathy, retinopathy, or neuropathy (3).

Demographic factors were assessed by interview, and vascular risk factors (hypertension, coronary heart disease, and dyslipidemia) were assessed from the medical record. Height and weight were measured, and apolipoprotein (apoE) ε4 genotyping was performed. Cognitive status was evaluated by a nurse, a neurologist, and by cognitive testing for a diagnosis of cognitively normal, MCI, or dementia as previously described (7).

Acquisition of MRI

MRI studies were performed on a 3-T system (Signa; GE Healthcare, Waukesha, WI), with an eight-channel phased-array head coil and a fluid-attenuated inversion recovery sequence (8). A trained technician assessed presence of white matter hyperintensities (WMHs), hemispheric cortical infarctions (>10 mm), and subcortical infarctions (lacunar infarctions in the central gray or capsular region or in the hemispheric white matter; areas >3 mm, dark in the center, bright rim, and not a perivascular space) as previously described (9).

Statistical analyses

We compared subcortical infarctions (present or absent) in case subjects and control subjects using logistic regression methods with adjustment for age, sex, years of education, and apoE ε4 allele carrier status (model 1) and with additional adjustment for potential confounders or covariates (model 2).

RESULTS

— Consistent with the matched case-control design, the distributions of age (median 79 years), sex (41% female), years of education (median 12 years), and apoE ε4 allele carrier status (26%) were similar in case subjects and control subjects. Case subjects (vs. control subjects) had a higher frequency of hypertension (94 vs. 68%; $P < 0.01$), BMI

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>30 kg/m^2 (33 vs. 21%; $P = 0.03$), coronary heart disease (40 vs. 27%; $P = 0.04$), dyslipidemia (88 vs. 70%; $P = <0.001$), and median HbA1c levels (6.0 vs. 5.0%; $P < 0.01$) but did not differ from control subjects in the frequency of smoking (57 vs. 56%; $P = 0.86$), MCI (25 vs. 22%; $P = 0.49$), or WMH (15 vs. 16 cm^3; $P = 0.86$).

Of the 90 subjects with subcortical infarctions, 55 subjects had one, 20 had two, and 5 had three to nine subcortical infarctions detected. The frequency of subcortical infarctions was higher in case subjects (39%) than in control subjects (29%; odds ratio [OR] 1.59 [95% CI 0.91–2.75]; $P = 0.10$). Compared with control subjects, the OR was elevated for case subjects without treatment for type 2 diabetes, case subjects with diabetes-related complications, and case subjects diagnosed with type 2 diabetes in late life (Table 1). Hypertension was not associated with subcortical infarctions, and there was no interaction of hypertension with type 2 diabetes.

When restricted to case subjects only, the OR of subcortical infarctions was elevated in case subjects without treatment (OR 2.34 [95% CI 0.84–6.54]; $P = 0.10$), case subjects treated with insulin (1.51 [0.43–5.26]; $P = 0.52$) compared with case subjects treated with oral antidiabetic agents (reference group), case subjects with complications versus no complications (1.75 [0.61–5.05]; $P = 0.30$), case subjects with diagnosis at aged ≥65 years versus aged <65 years (1.75 [0.61–5.05]; $P = 30$), and case subjects with shorter versus longer duration of diabetes (2.61 [1.01–6.75]; $P = 0.05$).

Table 1—*Association of type 2 diabetes and diabetes-related measures with subcortical infarctions**

		Subcortical infarctions			
		Model 1		Model 2	
Parameter	*n*	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Treatment					
No type 2 diabetes	186	1.00 (reference)	—	1.00 (reference)	—
With treatment	65	1.27 (0.67–2.39)	0.47	1.38 (0.70–2.73)	0.35
Without treatment	28	2.60 (1.11–6.08)	0.03	2.70 (1.11–6.55)	0.03
Type of type 2 diabetes treatment					
No type 2 diabetes	186	1.00 (reference)	—	1.00 (reference)	—
With oral treatment	46	1.13 (0.55–2.32)	0.73	1.25 (0.58–2.69)	0.56
With insulin treatment	19	1.72 (0.58–5.03)	0.33	1.78 (0.59–5.52)	0.30
Without treatment	28	2.60 (1.11–6.10)	0.03	2.72 (1.12–6.61)	0.03
Type 2 diabetes-related complications					
No type 2 diabetes	186	1.00 (reference)	—	1.00 (reference)	—
No complications	37	1.12 (0.50–2.52)	0.78	1.26 (0.54–2.94)	0.59
With complications	56	1.96 (1.02–3.74)	0.04	2.10 (1.04–4.23)	0.04
Age at diagnosis of type 2 diabetes (years)					
No type 2 diabetes	186	1.00 (reference)	—	1.00 (reference)	—
Aged <65 years	28	1.06 (0.41–2.74)	0.91	1.20 (0.45–3.22)	0.72
Aged ≥65 years	65	1.84 (1.00–3.38)	0.05	1.95 (1.01–3.73)	0.05
Duration of type 2 diabetes					
No type 2 diabetes	186	1.00 (reference)	—	1.00 (reference)	—
≥8 years	46	0.97 (0.46–2.07)	0.95	1.00 (0.44–2.24)	1.00
<8 years	47	2.44 (1.22–4.87)	0.01	2.67 (1.29–5.53)	<0.01

*Case subjects were matched to control subjects without type 2 diabetes by age, sex, and years of education. Model 1 includes adjustment for age, sex, years of education (as a continuous variable), and apoE ε4 allele carrier status to account for any residual confounding. Model 2 includes model 1 variables in addition to hypertension, dyslipidemia, coronary heart disease, BMI, and smoking. When we examined associations with subcortical infarctions as an ordinal variable (0, 1, and ≥2), the magnitude of the associations were attenuated but remained in the same direction as in the table. With subjects without type 2 diabetes as the references groups, the estimates for model 1 are as follows: oral antidiabetic agents (OR 1.03 [95% CI 0.51–2.08]; $P = 0.93$), insulin use (1.64 [0.58–4.61]; $P = 0.35$); without treatment (2.03 [0.91–4.53]; $P = 0.08$); without diabetes-related complications (1.03 [0.47–2.27]; $P = 0.95$) and with complications (1.68 [0.90–3.13]; $P = 0.10$); age at diagnosis <65 years (1.10 [0.44–2.75]; $P = 0.84$) and ≥65 years (1.52 [0.84–2.74]; $P = 0.16$); short duration of diabetes (0.93 [0.45–1.94]; $P = 0.86$); <8 years (1.94 [1.00–3.74]; $P = 0.05$).

CONCLUSIONS— In this elderly sample, subjects with untreated type 2 diabetes, diabetes-related complications, and later age at diagnosis were more likely to have subcortical infarctions. Treatment with insulin was associated with an elevated OR. Untreated type 2 diabetes may contribute to subclinical microvascular disease and undetected large vessel atherosclerotic disease (10). In a stroke registry, type 2 diabetes was associated with multiple lacunar infarctions (11). Insulin treatment, a marker for disease severity, has been associated with micro- and macrocerebrovascular disease including subcortical infarctions (12). The present findings are consistent with a role of subcortical infarctions as a mediator of cognitive impairment in patients with type 2 diabetes. The nonsignificant association for insulin-treated diabetes may be due to survival bias and underrepresentation of subjects with insulin-treated diabetes in our study, given the increased risk of mortality and stroke in subjects with severe diabetes or to limited power due to small numbers.

Consistent with our study, type 2 diabetes was associated with an increased risk of lacunar infarctions in the Honolulu-Asia Aging Study (6), the Utrecht Diabetic Encephalopathy Study (13), and the Cardiovascular Health Study (14). In contrast, others have not found associations of type 2 diabetes with lacunar infarctions (15) or have observed associations with WMH (13).

Potential limitations of our study include the cross-sectional design, potential nonparticipation bias, underrepresentation of subjects with early onset of diabetes, and inadequate power to assess associations of type 2 diabetes with cortical infarctions.

In summary, our findings suggest that untreated type 2 diabetes, diabetes-related complications, and insulin treatment are associated with subcortical infarctions.

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R.O.R. originated the study concept and design; analyzed and interpreted data; wrote the manuscript; provided administrative, technical, and material support; supervised the study; and revised/edited the manuscript. K.K. originated the study concept and design, acquired data, analyzed and interpreted data, wrote the manuscript, and revised/edited the manuscript. Y.E.G. acquired data and revised/edited the manuscript. D.S.K. acquired data; provided administrative, technical, and material support; and revised/edited the manuscript. S.A.P. analyzed and interpreted data, provided statistical analysis, and wrote the manuscript. S.D.W. analyzed and interpreted data and provided statistical analysis. R.C.P. originated the study concept and design, obtained funding, acquired data, and provided administrative, technical, and material support. C.R.J. obtained funding, acquired data, analyzed and interpreted data, provided study supervision, and revised/edited the manuscript.

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