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

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Running Title: Type 2 Diabetes and Subcortical Infarctions

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**Objective** – To investigate the association of type 2 diabetes with subcortical infarctions.

**Research design and methods** – We investigated the association in subjects with type 2 diabetes (cases; \(n = 93\)) and without type 2 diabetes (controls; \(n = 186\)), 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 cases and 29% in controls (odds ratio [OR] 1.59; 95% confidence interval [CI] 0.91–2.75). The association was stronger in cases without treatment (OR 2.60; 95% CI 1.11–6.08) and in cases with diabetes-related complications (OR 1.96; 95% CI 1.02–3.74) compared to controls.

**Conclusions** – These findings suggest that untreated type 2 diabetes and type 2 diabetes with complications are associated with subcortical infarctions.

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 persons 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 October 1, 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 persons 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 anti-diabetic 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). Persons 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 based (3).

Demographic factors were assessed by interview and vascular risk factors (hypertension, coronary heart disease, dyslipidemia) were assessed from the medical record. Height and weight were measured, and Apolipoprotein (ApoE) \(\varepsilon 4\) genotyping was performed. Cognitive status was evaluated by a nurse, a neurologist, and by cognitive testing, for a diagnosis of
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cognitively normal, MCI, or dementia as previously described (7).

**Acquisition of MRI.** MRI studies were performed on a 3T system (Signa, General Electric Healthcare, Waukesha, WI), with an 8-channel phased-array head coil and a fluid-attenuated inversion-recovery (FLAIR) 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 grey 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 cases and controls 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 cases and controls. Cases (vs. controls) had a higher frequency of hypertension (94% vs. 68%; \( P < 0.01 \)), body mass index >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 controls in the frequency of smoking (57% vs. 56%; \( P = 0.86 \)), MCI (25% vs. 22%; \( P = 0.49 \)), or WMH (15 cm\(^3\) vs. 16 cm\(^3\); \( P = 0.86 \)).

Of the 90 subjects with subcortical infarctions, 55 subjects had 1, 20 had 2, and 5 had 3–9 subcortical infarctions detected. The frequency of subcortical infarctions was higher in cases (39%) than in controls (29%; odds ratio [OR] 1.59; 95% confidence interval [CI] 0.91–2.75; \( P = 0.10 \)). Compared to controls, the OR was elevated for cases without treatment for type 2 diabetes, cases with diabetes-related complications, and cases diagnosed with type 2 diabetes in late life (Table). Hypertension was not associated with subcortical infarctions and there was no interaction of hypertension with type 2 diabetes.

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

**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 macro-cerebrovascular 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 non-significant association for insulin-treated diabetes may be due to survival bias and under-representation of subjects with insulin-treated diabetes in our study, given the increased risk of mortality and stroke in severe diabetics, 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 non-participation bias, under-representation of subjects with early onset of diabetes, and inadequate power to assess associations of type 2 diabetes with cortical infarctions.

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

Author Contributions – R.O.R. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. R.O.R. originated the study concept and design; analyzed and interpreted data; drafted/revised the manuscript; provided administrative, technical, and material support; supervised the study. K.K. originated the study concept and design; acquired data; analyzed and interpreted data; drafted/revised the manuscript. Y.E.G. acquired data; revised the manuscript. D.K.S. acquired data; revised the manuscript; provided administrative, technical, and material support. S.A.P. analyzed and interpreted data; drafted the manuscript; provided statistical analysis. S.D.W. analyzed and interpreted data; provided statistical analysis. R.C.P. originated the study concept and design; acquired data; obtained funding; provided administrative, technical, and material support. C.R.J. acquired data; analyzed and interpreted data; revised the manuscript; obtained funding; provided study supervision.

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REFERENCES


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Abbreviations: OR = odds ratio; CI = confidence interval. *Cases were matched to controls 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, body mass index, and smoking.

When we examined associations with subcortical infarctions as an ordinal variable (0, 1, ≥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 anti-diabetic agents (OR 1.03; 95% CI 0.51–2.08; P = 0.93); insulin use (OR 1.64; 95% CI 0.58, 4.61; P = 0.35); without treatment (OR 2.03; 95% CI 0.91–4.53; P = 0.08). Without diabetes-related complications (OR 1.03; 95% CI 0.47–2.27; P = 0.95); with complications (OR 1.68; 95% CI 0.90–3.13; P = 0.10). Age at diagnosis aged <65 years (OR 1.10; 95% CI 0.44–2.75; P = 0.84); aged ≥65 years (OR 1.52; 95% CI 0.84–2.74; P = 0.16). Short duration of diabetes (OR 0.93; 95% CI 0.45–1.94; P = 0.86); <8 years (OR 1.94; 95% CI 1.00–3.74; P = 0.05).