ORIGINAL ARTICLE

Silent cerebral infarction is associated with the development and progression of nephropathy in patients with type 2 diabetes

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Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease in patients with diabetes. The relationship between renal manifestations of CKD (albuminuria and decreased glomerular filtration rate) and silent cerebral infarction (SCI) has attracted attention; however, most studies examined the effects of components of CKD on prevalence of SCI. We sought to assess the relationship between SCI and the development and progression of nephropathy in type 2 diabetic patients. We studied 366 type 2 diabetic patients with normoalbuminuria (urinary albumin-to-creatinine ratio [ACR] $<30 \text{ mg g}^{-1}$, $N=246$) or microalbuminuria ($\text{ACR}=30\text{--}299 \text{ mg g}^{-1}$, $N=120$). SCI was defined by cranial MRI. The primary end point was progression from normo- to microalbuminuria or from micro- to macroalbuminuria. The cumulative incidence of the primary end point was estimated using the Kaplan–Meier method. Risk estimates for reaching the end point were calculated using Cox proportional hazard model analyses. During a median follow-up period of 3.9 years, 23 normoalbuminuric and 24 microalbuminuric patients reached the primary end point. Patients with SCI ($N=171$) had a greater incidence of reaching the end point than those without SCI ($N=195$, $P=0.020$ by the log-rank test), with a hazard ratio of 2.02 (95% confidence interval=1.09–3.72, $P=0.025$) in the multivariate Cox regression model. Although the common pathogenesis of SCI and albuminuria in diabetic patients is still unclear, SCI may be a predictor of progression of nephropathy in type 2 diabetic patients.

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INTRODUCTION

Chronic kidney disease (CKD)¹ is an independent risk factor for cardiovascular disease in both the general population² and diabetic patients.³ Albuminuria, one of the important components of CKD,¹ has been shown to be associated with incident cardiovascular disease^{3,4} and progression of renal impairment.⁵ It is, therefore, widely recommended that urinary albumin should be measured not only for the early detection of diabetic nephropathy,^{6,7} but also to evaluate the risk of incident cardiovascular disease.

Silent cerebral infarction (SCI), which has a predilection for the subcortical white matter and basal ganglia, is commonly observed on cranial MRI scans in the elderly and hypertensive patients.^{8,9} SCI is thought to be a clinical end-organ manifestation of arteriosclerosis in the brain, as well as retinal arterial sclerosis in the eyes and renal sclerosis in the kidneys,^{10,11} and the presence of SCI predicts incident clinically evident stroke,¹² cardiovascular disease¹³ and dementia.¹⁴ SCI has been also shown to be associated with albuminuria in community-dwelling elderly persons¹⁵ and diabetic patients.¹⁶ We have recently shown that (micro)albuminuria may be a predictor of

incident stroke in patients with type 2 diabetes.¹⁷ These studies suggest the organ cross-talk between brain and kidneys. A recent study indicated that SCI may predict progression to end-stage renal failure in patients with type 2 diabetes;¹⁸ however, there is limited understanding of whether patients with SCI are at increased risk of the development and progression of early stage of diabetic nephropathy. We, therefore, sought to determine the potential contribution of SCI to increased risk of development and progression of nephropathy in patients with type 2 diabetes.

METHODS

Study population

This study was conducted in accordance with the Declaration of Helsinki. We recruited consecutive patients with type 2 diabetes, 20 years or older, who underwent cranial MRI at the Diabetes Center, Tokyo Women's Medical University Hospital, Tokyo, Japan, during the period between 1 July 2003 and 30 April 2008. As the Japan Brain Dock Society recommends brain MRI scans in high-risk middle-aged or elderly persons (that is those with hypertension or diabetes) (<http://www.snh.or.jp/jsbd/pdf/guideline2008.pdf>),

we generally performed MRI for the purpose of screening for SCI in this study. Patients with type 1 diabetes, patients with macroalbuminuria (as defined later) and undergoing renal replacement therapy, pregnant women and patients with infectious or malignant diseases were excluded. Those who had clinical and laboratory missing data were also excluded. Type 2 diabetes was diagnosed according to the criteria of the World Health Organization definition.¹⁹

Participants underwent a routine medical history, physical examination and blood sampling. Information regarding smoking and family history of cardiovascular disease was obtained using a standard questionnaire. Smoking history was classified as either current smoker or non-smoker. Physical examination included blood pressure measurement and anthropometry; laboratory examinations included hemoglobin A1C, serum lipids and creatinine and urinary albumin excretion.

History of cerebrovascular disease was defined as earlier history of transient ischemic attack and/or stroke. History of coronary artery disease was defined as the presence of any of the following conditions: angina pectoris diagnosed by coronary angiography or myocardial scintigraphy, earlier myocardial infarction or earlier revascularization. History of peripheral artery disease was defined as earlier lower extremity peripheral artery disease according to American College of Cardiology/American Heart Association 2005 guideline.²⁰

Measurements

Cranial MRI scans were performed using a 1.5-T MR system (GyroScan Intere 1.5T master, Philips or MRT-2001/P3 excelart, Toshiba). T1- (repetition time, 400 ms; echo time, 10 ms) and T2-weighted images (repetition time, 3500 ms; echo time, 90 ms) were obtained in the transverse plane with 7-mm thick sections. SCI was defined by cranial MRI examinations as an area of low-signal intensity measuring at least 3 mm on T1-weighted images, which was also visible as a hyperintense lesion on T2-weighted images, according to the clinical guidelines by the Japanese Society for Detection of Asymptomatic Brain Disease.²¹ Hyperintense punctuate lesions evident only on T2-weighted images were excluded from the diagnosis of SCI. In each case, SCI was diagnosed by consensus of two neuroradiologists at the Tokyo Women's Medical University Hospital.

Classification of the degree of urinary albumin was assessed according to American Diabetes Association criteria, on the basis of at least two out of three albumin-to-creatinine ratio (ACR) measurements obtained from first morning urine specimens.⁷ Normo-, micro- and macroalbuminuria were defined as an ACR <30, 30–299 and ≥ 300 mg g⁻¹, respectively. Glomerular filtration rate (GFR) was estimated using the following modified three-variable equation for Japanese: $GFR = 194 \times SCr^{-1.094} \times age^{-0.287}$ ([if female] $\times 0.739$) ml min⁻¹ 1.73 m⁻².²² The primary end point was defined as transition from normo- to microalbuminuria or micro- to macroalbuminuria, confirmed on at least two consecutive urinary ACR measurements to reduce misclassification.

Hemoglobin A1C was measured by high-performance liquid chromatography (normal range: 4.3–5.8%), and total cholesterol and high-density lipoprotein cholesterol were determined enzymatically. Low-density lipoprotein cholesterol was calculated using the Friedewald equation when serum triglycerides level was <400 mg per 100 ml.²³

Statistical analyses

Data were expressed as percentage, arithmetic mean $\pm$ s.d. or geometric mean with 95% confidence interval (CI), as appropriate according to data distribution. Triglycerides and ACR were logarithmically transformed because of skewed distributions. For statistical analyses, Student's *t*-test or χ^2 test were conducted according to the appropriate situation. The cumulative incidence of the primary end point was estimated using the Kaplan–Meier method. Risk estimates for reaching the end point were calculated using univariate and multivariate Cox proportional hazard model analyses. The following variables were incorporated as covariates: age, gender, duration of diabetes, presence of proliferative diabetic retinopathy, smoking status, body mass index, systolic and diastolic blood pressure, use of renin–angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin type 1-receptor blockers), antiplatelet agents, statins, hemoglobin A1C, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin, uric acid, eGFR and urinary ACR at baseline. Prognostic factors were selected using the

stepwise procedure, specifying the significant levels for entering another explanatory variable into the model as 0.25, and that for removing an explanatory variable from the model as 0.15. A *P*-value <0.05 was considered significant. All statistical analyses were performed using the SAS version 9.13 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 366 type 2 diabetic patients had sufficient baseline and follow-up data to qualify for inclusion, including 149 women and 217 men, with a mean ($\pm$ s.d.) age of 64 ± 10 years (range: 29–89 years). At baseline, 246 patients had normoalbuminuria and 120 patients had microalbuminuria. SCI was detected in 171 patients (46.7%). Patients with SCI were older and had higher systolic blood pressure and urinary albumin excretion and lower body mass index, hemoglobin levels and eGFR than patients without SCI (Table 1).

During a median follow-up period of 3.9 years (range: 0.3–6.0 years), 23 normoalbuminuric and 24 microalbuminuric patients reached the primary end point.

Twelve (8.5%) of 141 patients without SCI and 11 (10.5%) of 105 patients with SCI progressed from normo- to microalbuminuria. The progression from micro- to macroalbuminuria was observed in 6 (11.1%) of 54 patients without SCI and 18 (27.3%) of 66 patients with SCI. In contrast, the regression of nephropathy (from micro- to

Table 1 Demographic and laboratory data in type 2 diabetic patients with and without SCI at baseline

	Without SCI (N=195)	With SCI (N=171)	P-value ^a
Age (years)	61 $\pm$ 10	69 $\pm$ 8	<0.001
Gender (% men)	61.0	57.3	0.470
Current smoker (%)	22.6	14.6	0.053
Diabetes duration (years)	15 $\pm$ 10	15 $\pm$ 9	0.761
Body mass index (kg m ⁻²)	25.1 $\pm$ 4.0	24.1 $\pm$ 3.4	0.011
Systolic blood pressure (mm Hg)	134 $\pm$ 19	139 $\pm$ 19	0.008
Diastolic blood pressure (mm Hg)	77 $\pm$ 12	75 $\pm$ 14	0.112
Proliferative diabetic retinopathy (%)	16.4	18.7	0.563
<i>Medication (%)</i>			
OHA/insulin	54.9/39.5	55.6/40.9	0.778
RAS blockers (%)	45.1	55.6	0.048
Antiplatelet agents (%)	34.9	54.4	<0.001
Statins (%)	33.3	34.5	0.814
Hemoglobin A1C (%)	8.1 $\pm$ 1.6	7.9 $\pm$ 1.6	0.316
Triglycerides (mmol l ⁻¹) ^b	1.41 (1.31–1.52)	1.36 (1.26–1.48)	0.508
HDL cholesterol (mmol l ⁻¹)	1.31 $\pm$ 0.41	1.35 $\pm$ 0.43	0.414
LDL cholesterol (mmol l ⁻¹)	3.01 $\pm$ 0.85	2.97 $\pm$ 0.77	0.604
Uric acid (μ mol l ⁻¹)	304 $\pm$ 73	300 $\pm$ 85	0.649
Hemoglobin (g l ⁻¹)	141 $\pm$ 13	135 $\pm$ 15	<0.001
<i>ACR (mg g⁻¹)^b</i>			
<30 (%)	72.3	61.4	0.027
30–299 (%)	27.7	38.6	0.027
Serum creatinine (μ mol l ⁻¹)	65.6 $\pm$ 14.9	72.1 $\pm$ 22.5	0.001
eGFR (ml min ⁻¹ 1.73 m ⁻²)	77.9 $\pm$ 17.0	68.6 $\pm$ 16.8	<0.001

Abbreviations: ACR, albumin-to-creatinine ratio; CI, confidence interval; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OHA, oral hypoglycemic agent; RAS, rennin-angiotensin system; SCI, silent cerebral infarction. Data are expressed as mean $\pm$ s.d., geometric mean (95% CI), or percentage.

^aStudent's *t*-test or χ^2 test.

^bGeometric mean.

Figure 1 Cumulative incidence of the end point (transition to a more advanced stage of albuminuria) in Japanese type 2 diabetic patients with and without SCI. The difference between Kaplan-Meier estimates for the two groups was statistically significant by log-rank test ($P=0.020$).

normoalbuminuria) was also observed in 12 (10.0%) of 120 microalbuminuric patients during the follow-up period. The cumulative incidence of the primary end point, that is progression to micro- or macroalbuminuria, was significantly higher for patients with SCI than those without SCI (log-rank test, $P=0.020$; Figure 1). In the univariate Cox proportional hazard model, the hazard ratio of the end point for patients with SCI *vs.* those without SCI was 1.98 (95% CI=1.10–3.56, $P=0.023$). This statistical association remained significant even after adjustment for other covariates using the stepwise multivariate Cox regression analysis (hazard ratio=2.02, 95% CI=1.09–3.72, $P=0.025$). Other covariates finally included in the multivariate analysis were SCI, logarithmically transformed ACR, hemoglobin and proliferative diabetic retinopathy. SCI (hazard ratio=2.02, 95% CI=1.09–3.72, $P=0.025$), logarithmically transformed ACR (hazard ratio=4.61, 95% CI=2.65–8.02, $P<0.001$) and hemoglobin (hazard ratio=0.843, 95% CI=0.71–0.94, $P=0.016$) were selected as significant covariates.

DISCUSSION

Albuminuria is a strong risk factor for cardiovascular disease,^{3,4} however, limited data are available on the opposite relation, for example whether patients with cardiovascular disease have a great risk of incident albuminuria.^{18,24} In this study, we observed a higher incidence of the development and progression of nephropathy in type 2 diabetic subjects with SCI than without. This association remained significant after adjustment for covariates. To the best of our knowledge, this is the first study to show the significant association between SCI and the development or progression of albuminuria in a cohort of diabetic patients.

Concerning the cardio-renal association in diabetic patients, as we discussed earlier,¹⁷ albuminuria and cardiovascular disease share numerous risk factors that may help to explain the observed relationship between SCI and nephropathy in this study. Hemodynamic and anatomical aspects of renal and cerebral small vessels share many similarities,^{25,26} and a common pathogenesis may contribute to both SCI and incident nephropathy in patients with type 2 diabetes. Another possible mechanism that may contribute to the association of SCI with albuminuria involves asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, which was shown to be associated with prevalent SCI in the Framingham offspring study.²⁷

We have recently shown that elevated plasma asymmetric dimethylarginine is a significant predictor of the development and progression of nephropathy in diabetic patients.²⁸ Furthermore, Hashimoto *et al.*²⁹ cross-sectionally showed that large artery stiffness (pulse wave velocity) is an important factor, which explains the association between cerebral lacunar infarction and albuminuria. Stiffening of large arteries increases the pulsatile stress because of increased aortic characteristic impedance and early return of wave reflection, and it could eventually lead to microvascular damage of the brain (SCI) and kidneys (albuminuria). Therefore, the cerebro-renal association (SCI and albuminuria) in this study may be at least in part explained by stiffening of large arteries. Further studies are needed to better understand the common pathogenesis of SCI and albuminuria in diabetic patients.

In contrast to our study, Uzu *et al.*¹⁸ recently showed that SCI was not associated with the incidence of nephropathy, but progression to renal failure in Japanese diabetic patients. The differences of the impact of SCI on the renal outcomes between the study¹⁸ and ours are unclear. One possible explanation may be due to the differences in the patient characteristics. In our study, the prevalence of patients with microalbuminuria was nearly equal to that in the population-based study in Japan,³⁰ but smaller than that of the study by Uzu *et al.*¹⁸ In addition, patients in this study were older, probably explaining the higher prevalence of SCI because aging is a strong predictor of SCI.⁸ Further large prospective studies are needed to elucidate the association between SCI and incident albuminuria in diabetic patients.

Our study population was ethnically and socially homogeneous and, therefore, may not be generalizable to other ethnic groups or the general population. Furthermore, cranial MRIs in this study were mainly performed for the purpose of screening for SCI, yielding a strong selection bias. Therefore, the higher prevalence of SCI in this study may be overestimated. Second, the follow-up period is relatively short. Third, we never determined the impact of SCI on the progression to end-stage renal disease. Nevertheless, this study is the first to reveal the significant association between SCI and incident albuminuria in diabetic patients and may facilitate identification of diabetic patients carrying a higher risk of progression of nephropathy.

In conclusion, SCI may be a predictor of the development and progression of nephropathy in Japanese patients with type 2 diabetes.

ABBREVIATIONS

CKD, chronic kidney disease; SCI, silent cerebral infarction; MRI, magnetic resonance imaging; ACR, albumin-to-creatinine ratio; ADMA, asymmetric dimethylarginine; OHA, oral hypoglycemic agent; RAS, renin-angiotensin system.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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