Decreased Kidney Function Is a Significant Factor Associated with Silent Cerebral Infarction and Periventricular Hyperintensities

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Key Words

Magnetic resonance imaging • Chronic kidney disease • Silent cerebral lacunar infarction • Periventricular hyperintensities

Abstract

Background/Aims: Silent cerebral lacunar infarction (SCI) and periventricular hyperintensities (PVH) have been reported to be markers of ischemic cerebral small-vessel disease and risk factors for future cerebrovascular events in the general population. The relationship between CKD and SCI/PVH is examined. **Methods:** In this cross-sectional study, brain magnetic resonance imaging was performed with a 1.5-T system in 324 predialysis CKD patients and in 60 normal subjects. **Results:** SCI was found in 103 CKD patients (31.8%), and PVH was found in 174 CKD patients (53.7%). SCI/PVH were more prevalent in patients with higher blood pressure, advanced age and decreased kidney function. There was a significant association between the prevalence of SCI/PVH and the CKD stage, with greater prevalence of SCI/PVH as the CKD stage advanced ($p < 0.0001$). PVH grade also advanced as the CKD stage advanced. The estimated glomerular filtration rate was a significant factor associated with the presence of SCI/PVH, independent of any other factors. There was a strong association between the prevalence of SCI/PVH

($p < 0.0001$). **Conclusion:** In CKD patients, decreased kidney function is a significant factor associated with SCI/PVH, both of which are significantly associated with each other. These results suggest that CKD patients with SCI/PVH are at greater risk of future cerebrovascular events.

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Introduction

Chronic kidney disease (CKD) is recognized as a risk factor for accelerated atherosclerotic disease, compared with normal subjects [1–5]. Epidemiological studies have shown that CKD is a risk factor for cardiovascular events and all-cause mortality [6–8]. Several reports have indicated that CKD is associated with a high prevalence of clinically-overt stroke [9–12].

Silent cerebral lacunar infarction (SCI), which can be observed as a silent small lacunar infarction with magnetic resonance imaging (MRI), is associated with higher rates of subsequent clinical cerebral infarctions [13]. In the general population, the incidence of SCI has been reported to be 12.9–24% [14, 15], and the risk factors of SCI have been reported to include age, hypertension, atrial fibrillation, diabetes [13, 16], and decreased renal function [17–19]. In chronic hemodialysis patients, SCI has

been reported to be more highly prevalent [20, 21]. However, there are few reports that have examined the prevalence of SCI in all stages of CKD patients [22], in whom SCI has been reported to be a risk factor for cardiovascular events and advanced kidney dysfunction [23, 24].

White matter lesions (WMLs) of the brain, as detected on T₂-weighted MRI, are considered to be related to vascular risk factors [15, 25], and are associated with age, hypertension, diabetes mellitus, a history of stroke, and a history of heart disease [26]. In the general population, WMLs can be a predictor of dementia [27], depression [28], mood disorder [29], future symptomatic stroke [30–32] and gait disturbances [28, 33], and also occur more frequently in neurologically normal people with multiple risk factors for stroke than in those without [34]. WMLs show evidence of ischemia, representing loss of cells and axons from the lesion with the associated influx of these glia and macrophages [35]. Of WMLs, periventricular hyperintensities (PVH) have been identified using long repetition and echo times in MRI of patients with white matter disease as a result of local demyelination and in hydrocephalic patients as a result of transependymal migration of the spinal fluid [36]. PVH preexists in more than 60–70% of first-ever ischemic stroke patients [30]. It has been reported that there is a significant association of the presence of PVH with SCI [37]. WMLs have been reported to be prevalent in subjects with decreased renal function in community-based cohorts, compared to normal renal function [5, 38]. WMLs are frequently seen in chronic hemodialysis patients [39], and in patients with CKD stage 3 and 4 [40]. However, there have been no reports in which the prevalence of PVH is examined in relation to all stages of CKD patients with proteinuria. It is also unknown whether and how decreased renal function in CKD patients affects the incidence and degree of PVH.

In the present study, we investigated the prevalence of SCI and PVH in CKD patients with proteinuria without dialysis therapy, and examined the relationship between the prevalence of SCI/PVH, renal function, and the clinical factors.

Subjects and Methods

Patients

All patients in this study were admitted to the Departments of Endocrinology, Metabolism, Molecular Medicine and Nephrology or Urology of Osaka City University Hospital, for treatment and education for CKD from January 2008 to July 2010. During the period, 345 CKD patients without dialysis therapy and without neurological abnormalities were admitted. In all patients,

neurological abnormalities were denied by physical examination by attending physicians, and absence of the history of stroke was confirmed by them. Of them, 324 CKD patients gave written informed consent, and were enrolled in this study. They had no past history or symptoms of stroke based on their medical records. There were 144 patients with diabetes, and 180 without. In this study, all patients had hematuria, proteinuria and/or albuminuria, as determined by dip-stick examination or turbid immunoassay of the urine, for at least 3 months. In all patients, serum creatinine was measured at least three times during admission, and the levels of serum creatinine at the time of the MRI were entered for the statistical analysis. CKD was defined as patients with kidney damage, as reported by KDIGO [41]. Patients with vasculitis, rapidly progressive glomerulonephritis, polycystic kidney disease, acute kidney injury, postrenal failure and malignancy were excluded from this investigation. As a control, 60 healthy subjects, who were admitted to our hospital for a medical check-up during the study period, were consecutively examined by MRI. None of the healthy control subjects exhibited proteinuria or had any past history of kidney diseases or stroke. This study protocol was approved by the ethics review committee of Osaka City University Hospital (No. 1415).

Blood pressure was measured with the patients resting in a supine position for at least 10 min on the day of MRI, using a standard mercury sphygmomanometer and cuffs appropriate to their arm circumference. The systolic blood pressure was taken as the point of appearance of Korotkoff sounds, and the diastolic blood pressure was the point at which the sounds disappeared. In this study, hypertension was defined by (1) administration of antihypertensive agents or a history of hypertension, (2) systolic pressure ≥ 140 mm Hg, or (3) diastolic pressure ≥ 90 mm Hg. Diabetes mellitus was defined by (1) administration of insulin or oral antidiabetic agents, (2) prior diagnosis according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the American Diabetes Association [42]. In the present study, peripheral artery disease was defined as a past history or symptoms of arteriosclerosis obliterans or thromboangiitis obliterans in medical records. 24-Hour urine was collected, and amount of urinary protein excretion was measured. Blood samples were obtained from patients after overnight fasting. Total protein, serum albumin, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol, blood urea nitrogen (BUN), C-reactive protein, and hemoglobin (Hb) were measured by routine laboratory methods. Information on smoking behavior, angina pectoris, and treatment with anticoagulation or antiplatelet agent were collected by attending physicians' interview and medical records. Pulse pressure was calculated using the following formula:

$$\text{Pulse pressure [mm Hg]} = \text{Systolic blood pressure [mm Hg]} - \text{Diastolic blood pressure [mm Hg]}$$

Body mass index (BMI) was calculated using the following formula:

$$\text{BMI [kg/m}^2\text{]} = (\text{body weight [kg]})/(\text{height [m]})^2 \times 22$$

Estimated glomerular filtration rate (eGFR) was calculated using the following formula:

$$\text{eGFR [ml/min/1.73 m}^2\text{]} = 194 \times (\text{serum creatinine})^{-1.084} \times (\text{age})^{-0.287}$$

Fig. 1. PVH examined by FLAIR MR images. The images clearly demonstrate the presence of PVH. The severity of PVH was classified according to Fazekas et al. [44] as follows: grade 0, absent; grade 1, caps or pencil-thin lining; grade 2, smooth halo; grade 3, irregular and extending into the deep white matter.

The value was multiplied by 0.739 for women. This formula represents the eGFR for Japanese reported by Japanese Society of Nephrology [43]. We stratified eGFR into the following ranges (in ml/min/1.73 m²): ≥90 (stage 1), 60–89 (stage 2), 30–59 (stage 3), 15–29 (stage 4), and <15 (stage 5), according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) classification and staging system [41].

Brain Magnetic Resonance Imaging

All participating patients underwent a brain MRI that used a superconducting magnet at a field strength of 1.5 T (Signa Horizon LX EchoSpeed 1.5 T; General Electric, Conn., USA) on proton density, T₁-weighted, T₂-weighted, and fluid-attenuated inversion recovery (FLAIR) images in axial planes at 5-mm-thick slices with an interslice gap of 1.5 mm. FLAIR images were obtained using a short spin-echo pulse sequence with a repetition time of 8,500 ms, an echo time of 140 ms and inversion time of 2,200 ms. SCI as lacunar infarctions were defined as an area of low signal intensity that measured >3 mm and <15 mm on T₁-weighted images and were also visible as hyperintense lesions on T₂-weighted images. High signal intensity lesions adjacent to the lateral ventricles on FLAIR images were defined as PVH. The severity of PVH was classified according to Fazekas et al. [44] as follows: grade 0, absent; grade 1, caps or pencil-thin lining; grade 2, smooth halo; grade 3, irregular and extending into the deep white

matter (fig. 1). The MR images were assessed independently by two neuroradiologists who had not been informed of the clinical information. When different results between two radiologists were obtained, the results were re-examined by them, and final results agreed by them were included in the analysis.

Statistical Analysis

All data are expressed as the mean ± SD. Differences between groups were examined by unpaired Student's t-test. Categorical variables were compared using χ^2 test. Multiple logistic regression analyses were used to assess the combined influence of variables on the presence of SCI and PVH in CKD patients. In multiple logistic regression analyses, we chose variables which were significantly different between those with and without SCI/PVH, by either Student's t-test or χ^2 test. In the models, variables which are interrelated with each other, such as variables of creatinine, BUN and eGFR, and variables of systolic, diastolic and pulse pressure, were not included in the same model. A variable of eGFR, instead of serum creatinine or BUN, was chosen. Three models, in which either one of systolic, diastolic, and pulse pressure was included in a model, were constructed. Gender and diabetes mellitus were represented by dummy variables (0 = male, 1 = female; 0 = absence, 1 = presence) in logistic regression analyses. p values <0.05 were considered statistically significant. These results were determined on a Windows computer using the StatView V Statistical System (SAS Institute, Cary, N.C., USA).

Results

Prevalence of SCI in CKD Patients

Of the 324 CKD patients, SCI was found in 103 (31.8%). In table 1, the clinical characteristics are shown according to the presence or absence of SCI, in addition to those of the healthy subjects. In healthy subjects there were 8 patients with SCI. The patients with SCI were significantly older than those without. Both systolic and diastolic pressures and the prevalence of hypertension were significantly higher in patients with SCI than in those without. Pulse pressures were significantly greater in the former than in the latter group. The prevalence of SCI was significantly higher in patients with a history of hypertension, diabetes, smoking behavior, a history of peripheral arterial disease (PAD) and angina pectoris than in those without. BUN and serum creatinine were significantly higher in patients with SCI than in those without. The prevalence of SCI was significantly higher in patients with anticoagulation and/or antiplatelet therapy than in those without. eGFR was significantly lower in patients with SCI than in those without. Total cholesterol and LDL cholesterol levels were significantly lower in the former than in the latter group. There were no significant differences in the other clinical parameters.

Table 1. Clinical characteristics of patients with and without SCI/PVH

	SCI		p	PVH		p	Healthy subjects (n = 60)
	patients			patients			
	without SCI	with SCI		without PVH	with PVH		
Number, male vs. female	128/93	64/39	0.1947	82/68	110/64	0.1183	SCI 8 (4/4) PVH 14 (8/6)
Age, years	57.5 ± 17.3	67.6 ± 10.3	<0.0001	51.6 ± 17.0	68.5 ± 10.2	<0.0001	56.7 ± 12.0
Body mass index	22.9 ± 4.3	23.4 ± 3.7	0.3768	23.3 ± 4.7	22.8 ± 3.6	0.2814	22.8 ± 3.0
Systolic pressure, mm Hg	125 ± 20	143 ± 23	<0.0001	121 ± 18	139 ± 23	<0.0001	120 ± 14
Diastolic pressure, mm Hg	69 ± 11	74 ± 11	0.0002	69 ± 10	72 ± 12	0.0247	66 ± 12
Pulse pressure, mm Hg	57 ± 17	70 ± 19	<0.0001	53 ± 15	68 ± 19	<0.0001	54 ± 9
History of hypertension, presence vs. absence	111/110	88/15	<0.0001	59/91	140/34	<0.0001	0/60
Diabetes, presence vs. absence	86/135	58/45	0.0033	54/96	90/84	0.0045	0/60
Smoking behavior, presence vs. absence	63/158	47/56	0.0024	41/109	69/105	0.0195	0/60
Angina pectoris, presence vs. absence	7/214	9/94	0.0320	3/147	13/161	0.0242	0/60
History of PAD, presence vs. absence	14/207	16/87	0.0078	8/142	22/152	0.0236	0/60
Treatment with anticoagulation or antiplatelet therapy, yes vs. no	53/168	43/60	0.0009	30/120	66/108	0.0003	0/60
Blood urea nitrogen, mg/dl	32.2 ± 25.7	42.6 ± 26.8	0.0010	26.2 ± 19.9	43.5 ± 28.7	<0.0001	14.2 ± 3.6
Creatinine, mg/dl	2.44 ± 2.39	3.53 ± 2.56	0.0002	1.92 ± 2.04	3.54 ± 2.61	<0.0001	0.73 ± 0.15
eGFR, ml/min	43.6 ± 33.8	24.6 ± 20.0	0.0005	52.5 ± 35.0	24.7 ± 20.6	<0.0001	77.5 ± 14.0
Proteinuria, mg/day	1,738 ± 2,396	2,248 ± 2,246	0.0686	1,749 ± 2,557	2,032 ± 2,109	0.2804	–
Total protein, g/dl	6.2 ± 1.0	6.1 ± 1.0	0.8202	6.1 ± 1.0	6.2 ± 1.1	0.8734	7.0 ± 0.4
Albumin, g/dl	3.3 ± 0.7	3.2 ± 0.7	0.4407	3.3 ± 0.7	3.2 ± 0.7	0.0679	4.2 ± 0.3
Total cholesterol, mg/dl	220 ± 92	201 ± 63	0.0050	225 ± 97	205 ± 70	0.0357	202 ± 31
Triglyceride, mg/dl	164 ± 112	148 ± 70	0.1978	170 ± 121	150 ± 78	0.0783	97 ± 42
LDL cholesterol, mg/dl	128 ± 57	112 ± 42	0.0159	128 ± 58	117 ± 47	0.0331	114 ± 24
HDL cholesterol, mg/dl	50 ± 18	50 ± 14	0.7275	51 ± 18	49 ± 16	0.4605	67 ± 19
Hemoglobin, g/dl	11.9 ± 2.5	11.3 ± 2.3	0.0274	12.4 ± 2.5	11.1 ± 2.3	<0.0001	13.7 ± 1.5
C-reactive protein, mg/dl	0.39 ± 1.31	0.41 ± 0.78	0.1351	0.28 ± 0.71	0.50 ± 1.44	0.0855	0.12 ± 0.11

Data are expressed as the number or means ± SD. SCI = Silent cerebral infarction; PVH = periventricular hyperintensities; PAD = peripheral arterial disease; eGFR = estimated glomerular filtration rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Prevalence of SCI according to CKD Stage

Table 2 shows the prevalence of SCI in CKD patients according to the CKD stages, and in healthy subjects. There were 8 healthy subjects with SCI, and 10 patients with SCI among those with CKD stage 1 and 2. The prevalence of SCI increased as the CKD stages advanced. In patients with CKD stage 5, 43 (46.3%) out of 92 exhibited SCI. χ^2 test revealed a significantly higher prevalence of SCI as the stages of CKD advanced ($p < 0.0001$).

Independent Association of Blood Pressure and Renal Function with SCI

Multivariate logistic analyses were performed to examine the independent association of several factors and blood pressure with the presence of SCI (table 3).

In Model 1 of the logistic regression analyses, age, LDL cholesterol, Hb and systolic blood pressure were significantly associated with the presence of SCI. eGFR tended

to be associated with the presence of SCI ($p = 0.0695$). Gender and diabetes were not associated with SCI.

In Model 2 of the logistic regression analyses, age, eGFR and diastolic blood pressure were significantly associated with the presence of SCI. Gender, diabetes and Hb were not associated with SCI.

In Model 3 of the logistic regression analyses, age, eGFR, LDL cholesterol, Hb and pulse pressure were significantly associated with the presence of SCI. Gender and diabetes were not associated with SCI.

Prevalence of PVH in CKD Patients

Of the 324 CKD patients, PVH were found in 174 (53.7%). In table 1, the clinical characteristics are shown according to the presence or absence of PVH, in addition to those of the healthy subjects. Among the healthy subjects, 14 exhibited PVH. The patients with PVH were significantly older than those without. Both systolic and di-

Table 2. Number of patients with SCI/PVH according to CKD stages

CKD stage	Stage 1–2	Stage 3	Stage 4	Stage 5	Total number	Healthy subjects
Without SCI	74 (88.1%)	56 (70.9%)	42 (60.9%)	49 (53.3%)	221 (68.2%)	52 (86.7%)
With SCI	10 (11.9%)	23 (29.1%)	27 (39.1%)	43 (46.7%)	103 (31.8%)	8 (13.3%)
Total number	84	79	69	92	324	60
Without PVH	65 (77.4%)	41 (51.9%)	25 (36.2%)	19 (20.7%)	150 (46.3%)	46 (76.7%)
With PVH	19 (22.6%)	38 (48.1%)	44 (63.8%)	73 (79.3%)	174 (53.7%)	14 (23.3%)
Total number	84	79	69	92	324	60

$p < 0.0001$ (χ^2 test) in CKD patients.

systolic pressures and the prevalence of hypertension were significantly higher in patients with PVH than in those without. Pulse pressure was significantly greater in the former than in the latter group. The prevalence of PVH was significantly higher in patients with a history of hypertension, diabetes, smoking behavior and PAD. BUN and serum creatinine were significantly higher in patients with PVH than in those without. The prevalence of PVH was significantly higher in patients undergoing anticoagulation and/or antiplatelet therapy than in those without. eGFR was significantly lower in patients with PVH than in those without. Total cholesterol and LDL cholesterol levels and Hb were significantly lower in the former than in the latter group. There were no significant differences in the other clinical parameters.

Prevalence of PVH according to CKD Stage

Table 2 shows the prevalence of PVH in CKD patients, according to the CKD stages, and in healthy subjects. There were 14 healthy subjects with PVH, and 19 patients with PVH in those with CKD stage 1 and 2. The prevalence of PVH increased as the CKD stage advanced. Among the 92 patients with CKD stage 5, 73 patients (79.3%) exhibited PVH. χ^2 test revealed a significantly higher prevalence of PVH as the stages of CKD advanced ($p < 0.0001$).

PVH Grade according to Each CKD Stage

Table 4 shows the number of patients with each PVH grade and CKD stage. In the lower CKD stages (CKD stage 1–3), the PVH grades were low. As the CKD stage advanced, PVH grade increased. χ^2 test revealed a significantly higher PVH grade as the CKD stage advanced ($p < 0.0001$).

Independent Association of Blood Pressure and Renal Function with PVH

Multivariate logistic analyses were performed to examine the independent association of several factors and blood pressure with the presence of PVH (table 3).

In Model 1 of the logistic regression analyses, age, eGFR and systolic blood pressure were significantly associated with the presence of PVH. Gender, diabetes, LDL cholesterol and Hb were not associated with PVH.

In Model 2 of the logistic regression analyses, age, eGFR and diastolic blood pressure were significantly associated with the presence of PVH. Gender, diabetes, LDL cholesterol and Hb were not associated with PVH.

In Model 3 of the logistic regression analyses, age, eGFR and pulse pressure were significantly associated with the presence of PVH. Gender, diabetes, LDL cholesterol and Hb were not associated with PVH.

Association between SCI and PVH

Table 5 shows the prevalence of SCI and PVH among all patients. There was a significant association between the prevalence of SCI and PVH ($p < 0.0001$).

Discussion

In the present study, we examined the prevalence of SCI and PVH in predialysis CKD patients. We found that the prevalence of SCI was significantly higher as the CKD stage advanced. Multivariate logistic regression analyses revealed that factors significantly associated with SCI were older age, higher blood pressure, higher pulse pressure and lower eGFR. We also found that the prevalence of PVH was significantly higher as the CKD stage advanced, and that advanced PVH grade was significantly

Table 3. Multivariate logistic regression analysis for SCI/PVH

	Model 1			Model 2			Model 3		
	odds ratio	95% CI	p	odds ratio	95% CI	p	odds ratio	95% CI	p
<i>SCI</i>									
Age, years	1.030	1.004–1.056	0.0249	1.044	1.017–1.072	0.0014	1.022	0.998–1.048	0.0782
Gender, male vs. female	1.255	0.686–2.296	0.4602	1.163	0.645–2.095	0.6156	1.124	0.626–2.015	0.6959
eGFR, ml/min	0.986	0.972–1.001	0.0695	0.984	0.969–0.999	0.0319	0.981	0.967–0.996	0.0106
Diabetes, presence vs. absence	1.208	0.682–2.139	0.5167	1.252	0.716–2.191	0.4303	1.116	0.638–1.950	0.7009
Anticoagulation or antiplatelet therapy, yes vs. no	1.850	1.019–3.350	0.0154	1.916	1.067–3.430	0.0294	1.720	0.962–3.074	0.0674
LDL cholesterol, mg/dl	0.992	0.985–0.998	0.0258	0.994	0.988–1.000	0.0622	0.993	0.986–0.999	0.0232
Hemoglobin, g/dl	1.183	1.020–1.371	0.0431	1.080	0.932–1.251	0.3074	1.201	1.034–1.395	0.0162
Systolic pressure, mm Hg	1.038	1.023–1.054	<0.0001	–	–	–	–	–	–
Diastolic pressure, mm Hg	–	–	–	1.055	1.027–1.083	<0.0001	–	–	–
Pulse pressure, mm Hg	–	–	–	–	–	–	1.032	1.015–1.050	0.0002
<i>PVH</i>									
Age, years	1.074	1.045–1.103	<0.0001	1.083	1.054–1.114	<0.0001	1.064	1.037–1.092	<0.0001
Gender, male vs. female	0.960	0.515–1.708	0.9851	0.860	0.470–1.573	0.6245	0.867	0.472–1.592	0.6445
eGFR, ml/min	0.982	0.968–0.996	0.0119	0.980	0.966–0.993	0.0042	0.978	0.964–0.992	0.0020
Diabetes, presence vs. absence	0.752	0.412–1.375	0.5369	0.839	0.467–1.585	0.5552	0.731	0.402–1.327	0.3026
Anticoagulation or antiplatelet therapy, yes vs. no	1.677	0.876–3.210	0.1187	1.711	0.907–3.226	0.0969	1.601	0.844–3.030	0.1499
LDL cholesterol, mg/dl	0.996	0.990–1.003	0.2926	0.998	0.991–1.004	0.4967	0.996	0.990–1.003	0.2487
Hemoglobin, g/dl	1.094	0.943–1.271	0.2372	1.010	0.872–1.170	0.8966	1.123	0.963–1.310	0.1384
Systolic pressure, mm Hg	1.677	1.018–1.053	<0.0001	–	–	–	–	–	–
Diastolic pressure, mm Hg	–	–	–	1.042	1.013–1.071	0.0058	–	–	–
Pulse pressure, mm Hg	–	–	–	–	–	–	1.035	1.014–1.056	0.0011

Table 4. PVH grade according to each CKD stage

	CKD stage			
	1–2	3	4	5
PVH grade				
0	65	41	25	19
1	10	21	24	30
2	9	13	12	32
3	0	4	8	11
Total number	84	79	69	92

$p < 0.0001$ (χ^2 test). The severity of PVH was classified according to Fazekas et al. [44].

associated with advanced CKD stage. Multivariate logistic regression analyses revealed that factors that were significantly associated with PVH included older age, higher blood pressure, higher pulse pressure and lower eGFR. Prevalence of SCI was significantly associated with that of PVH. Taken together, we found that, in addition to older age and hypertension, decreased renal function was

Table 5. Association between SCI and PVH

	PVH		Total
	–	+	
SCI			
–	138	83	221
+	12	91	103
Total	150	174	324
$p < 0.0001$ (χ^2 test).			

significantly associated with the presence of both SCI and PVH which are subclinical cerebrovascular diseases.

In the general population, SCI has been reported to be related to older age and hypertension [45–48]. In the present study, older age and hypertension were also significantly associated with SCI in predialysis CKD patients. In hemodialysis patients, SCI was reported to be a risk factor for vascular events [23]. In a study of predialysis CKD patients, there was an independent association between eGFR and SCIs [22]. We have recently reported

that decreased renal function and hypertension were significantly and independently associated with the presence of cerebral microbleeds (CMB) [49]. SCI and CMB have been reported to occur via the same mechanism of vascular necrosis [9, 50–53]. In cases of obstruction of perforator arteries, SCIs are observed [9, 50–53]. Our results, which showed increased prevalence of both SCI and CMB as the CKD stage advanced among the predialysis CKD patients, suggest that the same factors may cause microangiopathy of cerebral small arteries during the predialysis CKD period, leading to a higher prevalence of SCI and/or CMB.

In general, diabetes is an independent risk factor for cardiovascular disease [12]. Recently, however, several studies have reported that small cerebral vessel diseases, such as SCI and CMB, are not associated with diabetes [5, 9, 11, 22, 49, 53, 54]. In the present study, diabetes was not associated with the presence of SCI after adjustment for several confounders, which was consistent with these reports. Although dyslipidemia, particularly higher LDL cholesterol, is an independent risk factor for cardiovascular disease [12], small cerebral vessel diseases are not associated with dyslipidemia [5, 9, 49, 54]. Recently, it was reported that there were qualitative changes in LDL cholesterol in patients with CKD and dialysis patients [55]. In the present study, total cholesterol and LDL cholesterol were actually significantly lower in patients with SCI. Taken together with previous studies and our own, it is considered that decreased renal function is a significant risk factor for the prevalence of a subclinical cerebrovascular disease, SCI, independent of the presence of diabetes and dyslipidemia. In the present study, anticoagulation and/or antiplatelet therapies were more prevalent in patients with SCI. This may be due to the fact that, in patients with SCI, the prevalence of PAD and angina pectoris was significantly higher, leading to frequent administration of anticoagulant and/or antiplatelet agents.

In the present study, we examined the prevalence of PVH in predialysis CKD patients. PVH were more prevalent in predialysis CKD patients than in those with SCI (SCI 31.8% vs. PVH 53.7%). We found that the prevalence of PVH in predialysis CKD patients was significantly associated with decreased renal function, as represented by higher BUN and creatinine, and lower eGFR. There was a significantly higher prevalence of PVH as the advanced CKD stage. In multivariate logistic regression analyses, eGFR was a significant, independent factor associated with the presence of PVH. Furthermore, advanced CKD stage was significantly associated with higher PVH

grade. Recently, Khatri et al. [38] showed a significant association between white matter hyperintensity volume and CKD. The results of the present study were consistent with their study, although the method of examination was different. Our method, Fazekas grading [44], is clinically easy to perform to assess the degree of PVH. Our results showed that predialysis CKD patients had a higher risk of PVH, and that advanced CKD stage was significantly associated with subclinical cerebrovascular damages. In general, hypertension has been reported to be the strongest risk factor for ischemic lesions, such as SCI and PVH [30]. In multivariate logistic analyses in the present study, systolic blood pressure, diastolic blood pressure, and pulse pressures were significantly associated with PVH, after adjustment for other confounders. Several reports have suggested that PVH indicates ischemic changes in the cerebral white matter, which is supplied by deep penetrating arteries [56–58]. Both SCI and PVH comprise ischemic, cerebral changes [56–58]. In this study, there was a significant association between the prevalence of SCI and PVH (table 5). Taken together with previous studies [56–58] and our own, it is suggested that the presence of PVH is a risk factor for the presence of SCI, possibly leading to future cerebrovascular events.

As noted above, diabetes is known to be a significant risk factor for cardiovascular events [12]. In the present study, the prevalence of PVH was significantly higher in patients with diabetes than in those without. However, after adjustment for several confounders, diabetes was not a significant factor for the presence of PVH. These results are consistent with those of several studies, in which small cerebral vessel diseases were not associated with diabetes [5, 9, 11, 22, 53, 54]. In the present study, PVH was not associated with dyslipidemia, which is consistent with several studies, in which small cerebral vessel diseases are not shown to be associated with dyslipidemia [5, 9, 11, 22, 53, 54].

In the present study, there were no significant differences between levels of proteinuria and the presence of SCI/PVH. This may be due to the fact that patients with various kidney diseases were included in the present study. CKD patients in the present study had various levels of proteinuria, due to various causes of kidney diseases. Patients with focal segmental glomerulosclerosis and membranous glomerulonephritis usually had higher levels of proteinuria, while patients with hypertensive nephrosclerosis had lower levels of proteinuria. Patients with diabetic nephropathy had various levels of proteinuria, according to progression of the disease. In the anal-

yses of the present study, original kidney diseases of CKD patients were not adjusted. In the future study, it is needed to examine whether levels of proteinuria in each original disease of CKD patients are associated with the presence of SCI/PVH.

In conclusion, we demonstrated that decreased kidney function was significantly and independently associated with the presence of SCI and PVH in predialysis CKD patients. Our findings may suggest that CKD patients are considered as a high-risk population for future cerebrovascular events. Treatment of hypertension in predialysis CKD patients is considered to be very important for the prevention of SCI and PVH, and probably for prevention of clinically-overt strokes. T₁-weighted, T₂-weighted and FLAIR images are usually taken by MRI test in clinical

practice. Careful attention to the presence of SCI and PVH should be paid in predialysis CKD patients to prevent future cerebrovascular events.

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Disclosure Statement

There are no conflicts of interest to declare.

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