Association of Kidney Dysfunction With Asymptomatic Cerebrovascular Abnormalities in a Japanese Population With Health Checkups

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Background: Cerebrovascular disease is a major cause of mortality and morbidity. Chronic kidney disease (CKD) is prevalent in stroke patients. This study evaluated the correlation between kidney dysfunction and asymptomatic findings on carotid ultrasonography (US) and brain magnetic resonance imaging (MRI) in a Japanese population with health checkups.

Methods and Results: In total, 1,716 subjects aged 40–80 years, who received health checkups from January 1 to December 31, 2015, were included. Common carotid artery intima–media thickness (CCA-IMT) and carotid plaques by US, and the presence of old non-lacunar infarctions, lacunar infarctions, white matter lesions (WMLs), cerebral microbleeds (CMBs), and atrophy by brain MRI were evaluated. After adjusting for cardiovascular risk factors, multiple regression analyses revealed that an eGFR ranging from 15 to 44 mL/min/1.73 m² was independently associated with CCA plaques and hypoechoic or heterogeneous plaques. Proteinuria was associated with CCA or internal carotid artery plaques, the number of carotid plaques, and the presence of old non-lacunar infarctions and CMBs.

Conclusions: Decreased eGFR and proteinuria were independent risk factors for asymptomatic abnormalities on carotid US and brain MRI, which are surrogate markers for cerebrovascular diseases. Evaluation of these abnormalities may be useful for prevention of symptomatic cerebrovascular events in CKD patients.

Key Words: Carotid plaque; Cerebral microbleeds; eGFR; Proteinuria

Chronic kidney disease (CKD) has become a major health problem throughout the world, with a global increase in prevalence to greater than 10% as reported in 2009,¹ and resulting in almost 1 million deaths worldwide in 2013.² In recent years, CKD has been shown to be a potent cardiovascular and cerebrovascular risk factor.^{3,4} The prevention of these complications is one of the main goals in treating CKD patients.

Cerebrovascular diseases, such as stroke, are major causes of mortality and morbidity. The importance of prevention has been increasingly recognized in aging societies, such as Japan, to extend healthy life expectancy. CKD is prevalent in stroke patients,⁵ and CKD patients show poor functional outcome after ischemic stroke.⁶ Recently, the relationship between kidney dysfunction and neuroimaging findings (e.g., magnetic resonance imaging (MRI))⁷ has been investigated. Abnormal MRI findings, including lacunar infarcts, white matter lesions (WMLs), cerebral microbleeds (CMBs), and brain atrophy, have not

always been associated with apparent symptoms. However, these abnormalities have been correlated with cognitive dysfunction and symptomatic cerebrovascular diseases.⁵ Abnormal findings on carotid ultrasonography (US), including carotid artery intima-media thickness (IMT) and plaques, are also considered surrogate measures of cerebrovascular diseases. Recently associations between kidney dysfunction and the results of carotid US have been investigated, and it was reported that albuminuria and decreased estimated glomerular filtration rate (eGFR) were associated with the presence of carotid plaques.^{8,9}

Many studies have reported that abnormalities in brain MRI or carotid US were observed in patients on hemodialysis (HD) or with endstage renal disease (ESRD); however, the correlation between kidney dysfunction and these abnormalities in the general population remain to be fully examined. Moreover, CKD patients often have complications, such as hypertension, diabetes, and dyslipidemia, which are independent risk factors for cerebrovascular

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diseases. Therefore, only a small number of studies have evaluated whether kidney dysfunction is an independent risk factor for symptomatic and asymptomatic cerebrovascular diseases.

The aim of this study was to investigate in a general population whether decreased eGFR and proteinuria were independently associated with abnormal findings on carotid US or brain MRI, using a multiple regression analysis adjusted for other risk factors for cardiovascular and cerebrovascular diseases.

Methods

Study Population

Individuals aged 40–80 years who had received thorough medical examinations at Keio University Hospital between January 1 and December 31, 2015, were enrolled. We excluded participants without essential data, including age, sex, body mass index (BMI), systolic blood pressure (BP), diastolic BP, serum chemistries, a self-administered questionnaire and carotid artery US. Individuals with ESRD with an eGFR <15 mL/min/1.73 m² were also excluded. In total, data from 1,716 participants (1,175 males, 541 females) were included and analyzed.

Clinical Evaluation and Laboratory Measurements

All participants completed a self-administered questionnaire that documented medical history, medications, and lifestyle, including smoking habit. Serum markers, including triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, and hemoglobin A1c (HbA1c), were measured. Blood samples were collected after fasting overnight and immediately analyzed using an automated clinical chemical analyzer. Urinary protein excretion was examined using dipstick testing. BP was measured in the right upper arm after subjects had rested at least 5 min in a seated position in the hospital, using an automatic device BP-900 with the combination of Korotkoff sounds method and oscillometric technique (TANITA Co., Tokyo, Japan).

Carotid US

Common carotid artery IMT (CCA-IMT) and the location and characteristics of carotid plaques were assessed by trained examiners using high-resolution US with a 10.0-MHz linear transducer (LOGIQ S8, GE Healthcare, UK). IMT was defined as the distance between the leading edge of the first echogenic line and that of the second echogenic line of the far wall. The thickest point between the carotid bulb and the CCA was measured as the CCA-IMT, as previously described.^{8,10} CCA-IMT values >1.0 mm were considered significant.¹¹ A plaque was defined as a focal thickening lesion with an IMT >1.0 mm.¹⁰ The presence and characteristics of carotid plaques were evaluated in the CCA, carotid bulb, internal carotid artery (ICA), and right subclavian artery. The numbers of plaques in these arteries were counted. Plaque intensity was categorized as hyper-echoic, isoechoic, hypoechoic, or heterogeneous.^{12,13} These findings were reviewed by experienced radiologists.

MRI

MRI was performed using a 3.0-T scanner (SIGNA HDxt3.0T, GE Healthcare, USA). A standardized imaging protocol produced axial T2-weighted images, T1-weighted images, fluid attenuated inversion recovery (FLAIR), and

T2*-weighted images by gradient-recalled echo. CMBs were defined as discrete or isolated punctate hypointense lesions, smaller than 10 mm on T2*-weighted images.¹⁴ The association of kidney dysfunction with the presence of CMBs was investigated. Brain atrophy was classified as normal or advanced for age, and the association between kidney dysfunction and presence of advanced atrophy for age was examined. WMLs, including periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH), were classified into 5 grades (0–4) according to the Shinohara grading;¹⁵ grade 1 was considered mild, grades 2–3 as moderate, and grade 4 as severe WML. We adopted the higher grade if the PVH and DSWMH grades were different. The association between kidney dysfunction and WML with moderate or severe grade was investigated. These findings were double-checked by 2 experienced radiologists.

Definitions

Urinary protein was examined using dipstick testing and categorized into 5 degrees: –, ±, 1+, 2+, and 3+. Proteinuria was defined as urine protein ≥1+. eGFR (mL/min/1.73 m²) was calculated using the following equation: $=194 \times \text{serum creatinine (mg/dL)}^{-1.094} \times \text{age (years)}^{-0.287} \times 0.739$ (for women).¹⁶ Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg or if the patient had indicated use of antihypertensive drugs in the questionnaire. Diabetes was defined in accordance with the guidelines of the American Diabetes Association as a fasting glucose concentration ≥126 mg/dL, HbA1c level ≥6.5%¹⁷ or use of antihyperglycemic drugs in the questionnaire. Dyslipidemia was defined as HDL-C <40 mg/dL and/or LDL ≥140 mg/dL and/or TG ≥150 mg/dL or use of a lipid-lowering medication in the questionnaire.

Statistical Analysis

Multiple logistic or linear regression analyses were used to investigate associations between abnormal findings on carotid US or brain MRI and eGFR category (eGFR ≥60, eGFR 45–59 or eGFR 15–45 mL/min/1.73 m²) or albuminuria, adjusted by age, sex, BMI, smoking status, hypertension, diabetes, and dyslipidemia. The 45–59 mL/min/1.73 m² category of eGFR included CKD stage G3a. The 15–45 mL/min/1.73 m² category of eGFR included CKD stages G3b and G4, because the population in each stage was small. For univariable analyses, analysis of variance (ANOVA) followed by Scheffé's post-hoc test and Pearson's test were used for continuous and categorical variables, respectively. Continuous variables are expressed as the mean ± standard deviation (SD). The significance level for all tests in this study was two-sided 5%. All statistical analyses were performed using JMP version 12 (SAS Institute Inc., Cary, NC, USA).

Results

Participant Characteristics

A total of 9,169 individuals had medical checkups between January 1 and December 31, 2015. Individuals aged 40–80 years were included in this study. We excluded individuals without essential data and those with an eGFR <15 mL/min/1.73 m², as described in the Methods section. A total of 1,716 participants (1,175 males, 541 females) aged 61.8 ± 9.9 years were eligible for this study. **Table 1** shows the general characteristics of the subjects and the

Table 1. Baseline Characteristics of All Participants in Health Checkups

	Total	eGFR (mL/min/1.73 m ²)			P value
		≥60	45–59	15–44	
n (%)	1,716 (100)	1,348 (79)	330 (19)	38 (2.2)	–
Age (years)	61.8±9.9	60.3±10.2	67.1±8.6	71.7±6.3	<0.0001
Sex (male) (%)	1,175 (68)	906 (67)	236 (72)	33 (87)	0.0154
BMI (kg/m ²)	23.4±3.4	23.4±3.5	23.7±3.2	22.6±2.8	0.1003
Systolic BP (mmHg)	122.0±18.4	120.9±18.1	125.0±19.3	120.6±20.6	0.0015
Diastolic BP (mmHg)	76.8±10.7	77.0±10.7	76.8±11.0	72.3±10.4	0.0286
TG (mg/dL)	114.9±81.2	114.1±83.4	116.1±71.4	134.0±79.5	0.3151
HDL-C (mg/dL)	56.9±14.8	57.5±15.0	55.2±13.6	50.2±16.1	0.0009
LDL-C (mg/dL)	117.3±28.9	117.6±28.7	117.9±29.6	100.7±29.3	0.0016
Glucose (mg/dL)	108.7±19.2	108.5±19.3	108.8±16.5	114.2±32.4	0.2010
HbA1c (%)	5.80±0.64	5.78±0.66	5.85±0.56	5.97±0.66	0.0495
eGFR (mL/min/1.73 m ²)	69.9±9.8	74.6±10.9	54.2±4.0	37.8±5.6	<0.0001
Proteinuria	45 (2.6)	32 (2.4)	7 (2.1)	6 (16)	<0.0001
Hypertension	718 (42)	519 (38)	168 (51)	31 (82)	<0.0001
Dyslipidemia	783 (46)	599 (44)	161 (49)	23 (61)	0.0639
Diabetes	273 (16)	213 (16)	51 (15)	9 (24)	0.4107
Current smoking	221 (13)	193 (14)	23 (7.0)	5 (13)	0.0017
Findings on carotid ultrasonography					
CCA-IMT ≥ 1 mm	453 (26)	324 (24)	108 (33)	21 (55)	<0.0001
Location of carotid plaques					
Subclavian artery	329 (19)	260 (19)	63 (18)	6 (16)	0.8635
CCA	174 (10)	115 (8.5)	44 (13)	15 (39)	<0.0001
ICA	445 (26)	316 (23)	109 (33)	20 (53)	<0.0001
Carotid bulb	1,255 (73)	946 (70)	275 (83)	34 (89)	<0.0001
Hypoechoic or heterogeneous	120 (7.0)	74 (5.5)	34 (10)	12 (32)	<0.0001
No. of carotid plaques	1.9±1.5	1.8±1.5	2.3±1.5	3.2±2.0	<0.0001
Findings on brain MRI					
Old non-lacunar infarctions	48 (3.5)	30 (2.8)	15 (5.9)	3 (11)	0.0050
Lacunar infarctions	64 (4.7)	44 (4.1)	17 (6.7)	3 (11)	0.0582
White matter lesions	239 (18)	184 (17)	52 (20)	3 (11)	0.2891
Cerebral microbleeds	73 (5.4)	54 (5.0)	13 (5.1)	6 (22)	0.0004
Atrophy	35 (2.6)	28 (2.6)	6 (2.4)	1 (3.7)	0.9120

Hypertension, diabetes, dyslipidemia were defined as described in the Methods section. BMI, body mass index; BP, blood pressure; CCA-IMT, common carotid artery intima media thickness; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; ICA, internal carotid artery; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Table 2. Association Between eGFR Category and Findings on Carotid Ultrasonography Analyzed by Multiple Regression Model

eGFR (mL/min/1.73 m ²)	≥60		45–59		15–44	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
CCA-IMT	1	–	0.85 (0.63–1.14)	0.2789	1.47 (0.72–3.05)	0.2841
Subclavian artery plaque	1	–	1.05 (0.76–1.45)	0.7563	0.95 (0.34–2.22)	0.9072
CCA plaque	1	–	1.06 (0.71–1.58)	0.7462	2.38 (1.10–5.00)*	0.0274*
ICA plaque	1	–	1.02 (0.76–1.36)	0.8755	1.21 (0.60–2.46)	0.5951
Carotid bulb plaque	1	–	1.13 (0.81–1.61)	0.4796	0.95 (0.35–3.34)	0.9239
Hypoechoic or heterogeneous	1	–	1.33 (0.84–2.08)	0.2247	2.99 (1.31–6.48)*	0.0100*

Multivariate logistic regression analyses were performed adjusted by age, sex, BMI, current smoking, hypertension, diabetes, dyslipidemia and proteinuria. *Significant differences. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

relationship between these characteristics and eGFR categories. In subjects with a low eGFR, age, systolic BP, HbA1c and the proportion of male participants, participants with proteinuria, and hypertension were higher and diastolic BP, HDL-C, and LDL-C, and the proportion of

current smokers were lower. Carotid US findings showed that the proportions of subjects with CCA-IMT, plaques in CCA, ICA and carotid bulb, hypoechoic or heterogeneous plaques and the number of plaques were significantly higher in the low eGFR category, whereas the

Table 3. Association Between Proteinuria and Findings on Carotid Ultrasonography Analyzed by Multiple Regression Model

	Proteinuria (–)		Proteinuria (+)	
	OR (95% CI)	P value	OR (95% CI)	P value
CCA-IMT	1	–	0.81 (0.37–1.69)	0.5839
Subclavian artery plaque	1	–	0.67 (0.23–1.59)	0.3892
CCA plaque	1	–	2.75 (1.24–5.84)*	0.0136*
ICA plaque	1	–	2.15 (1.07–4.27)*	0.0314*
Carotid sinus plaque	1	–	0.93 (0.44–2.02)	0.8455
Hypoechoic or heterogeneous	1	–	2.00 (0.78–4.60)	0.1396

Multivariate logistic regression analyses were performed adjusted by age, sex, BMI, current smoking, hypertension, diabetes, dyslipidemia and eGFR category. *Significant differences. Abbreviations as in Tables 1,2.

Table 4. Association Between eGFR Category and Findings on MRI Analyzed by Multiple Regression Model

eGFR (mL/min/1.73 m ²)	≥60		45–59		15–44	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Old non-lacunar infarctions	1	–	1.47 (0.73–2.84)	0.2708	1.75 (0.36–6.21)	0.4512
Lacunar infarctions	1	–	1.06 (0.56–1.93)	0.8478	1.20 (0.26–4.06)	0.7889
White matter lesions	1	–	1.18 (0.81–1.68)	0.3844	0.56 (0.13–1.68)	0.3233
Cerebral microbleeds	1	–	0.67 (0.33–1.26)	0.2199	1.73 (0.55–4.81)	0.3296
Atrophy	1	–	0.88 (0.32–2.12)	0.7931	1.44 (0.08–8.38)	0.7498

*Significant differences. Multivariate logistic regression analyses were performed adjusted by age, sex, BMI, current smoking, hypertension, diabetes, dyslipidemia and proteinuria. MRI, magnetic resonance imaging. Other abbreviations as in Tables 1,2.

Table 5. Association Between Proteinuria and Findings on MRI Analyzed by Multiple Regression Model

	Proteinuria (–)		Proteinuria (+)	
	OR (95% CI)	P value	OR (95% CI)	P value
Old non-lacunar infarctions	1	–	3.39 (1.04–9.20)*	0.0430*
Lacunar infarctions	1	–	2.23 (0.61–6.41)	0.2023
White matter lesions	1	–	0.71 (0.24–1.70)	0.4631
Cerebral microbleeds	1	–	3.85 (1.48–9.09)*	0.0071*

*Significant differences. Multivariate logistic regression analyses were performed adjusted by age, sex, BMI, current smoking, hypertension, diabetes, dyslipidemia and eGFR category. No subjects with proteinuria showed advanced atrophy for age. Abbreviations as in Tables 1,2,4.

proportion of subjects with subclavian artery plaque was not significantly different between the groups. The MRI findings showed that the presence of old non-lacunar infarcts and CMBs were significantly higher in the low eGFR group.

Association Between Kidney Dysfunction and Findings of Carotid US

The association between decreased eGFR or the presence of proteinuria and carotid US findings was investigated using multiple logistic regression analysis adjusted for various factors, including age, sex, BMI, current smoking status, hypertension, diabetes, and dyslipidemia (Tables 2,3). The analysis demonstrated that eGFR levels of 15–44 mL/min/1.73 m² were significantly associated with the presence of plaques in CCA (odds ratio [OR], 2.38; 95% confidence interval [CI], 1.10–5.00; P=0.0274) independent of proteinuria, whereas low eGFR levels were not associated with the presence of plaques in the subclavian artery, ICA or carotid bulb. eGFR levels of 15–44 mL/min/1.73 m² were also significantly associated with the presence of hypoechoic or heterogeneous plaques (OR, 2.99; 95% CI, 1.31–6.48; P=0.0100). Proteinuria was

significantly associated with the presence of CCA or ICA plaques (OR, 2.75; 95% CI, 1.24–5.84; P=0.0136, 2.15; 1.07–4.27; P=0.0314, respectively). In the multiple linear regression analysis, proteinuria correlated with the number of carotid plaques (coeff., 0.21; 95% CI, –0.01–0.41; P=0.0435). eGFR 15–44 mL/min/1.73 m² category marginally correlated with the number of carotid plaques (coeff., 0.25; 95% CI, –0.04–0.55; P=0.0955).

Association Between Kidney Dysfunction and Findings of Brain MRI

The association between decreased eGFR or proteinuria and brain MRI findings was investigated using a multiple logistic regression model adjusted for factors, including age, sex, BMI, current smoking, hypertension, diabetes, and dyslipidemia (Tables 4,5). Proteinuria was significantly associated with the presence of old non-lacunar infarctions and CMBs after adjusting for the confounding factors listed above (OR 3.39, 95% CI 1.04–9.20, P=0.0430; 3.85, 1.48–9.09, P=0.0071, respectively).

Discussion

We investigated the association between kidney dysfunction, including reduced eGFR and proteinuria, and asymptomatic abnormalities in the results of carotid US and brain MRI. Using multiple regression analyses adjusted for age, sex, BMI, smoking status, hypertension, diabetes, and dyslipidemia, this study demonstrated the following: (1) eGFR 15–44 mL/min/1.73 m² and proteinuria were independently associated with presence of CCA plaques, (2) eGFR 15–44 mL/min/1.73 m² was significantly associated with the presence of hypoechoic or heterogeneous plaques, and (3) proteinuria was associated with the number of carotid plaques and the presence of ICA plaques, old non-lacunar infarctions and CMBs.

Carotid US is widely performed to evaluate the status of atherosclerosis in patients with cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia. A number of clinical studies have demonstrated that carotid plaques and IMT are useful surrogate markers for predicting myocardial infarcts and stroke.^{18–22} Recently, CKD was recognized as a risk factor for these events. Previous studies have reported that low eGFR and albuminuria were associated with the presence of carotid plaque.^{8,9} We investigated the associations of eGFR and proteinuria not only with the presence of carotid plaques and CCA-IMT, but also with the location, number and characteristics of plaques. Decreased eGFR were significantly associated with the presence of CCA plaques and hypoechoic or heterogeneous plaques, and proteinuria was associated with the number of plaques and the presence of CCA or ICA plaques. It has been demonstrated that hypoechoic or echolucent plaques are associated with a high risk of ischemic cerebrovascular events.^{12,23} Plaque heterogeneity is also suggested to be associated with symptomatic cerebrovascular events.²⁴ Although there is to some extent a variety of evaluations among sonographers, examination of plaque characteristics may be useful to predict the risk of symptomatic cerebrovascular events in CKD patients. In this study both decreased eGFR and proteinuria were not associated with CCA-IMT, as previously reported.⁸ CCA-IMT has previously been considered as not representative for atherosclerotic conditions in atherosclerosis-prone lesions, such as the proximal ICAs or carotid bulbs.^{8,25} Our results suggested that evaluation of plaques, especially CCA and ICA plaques, may be useful in patients with proteinuria or with eGFR <45 mL/min/1.73 m² to consider treatment for asymptomatic atherosclerosis.

It was reported that endothelial dysfunction may be related to the association between albuminuria and carotid plaques, because vascular endothelial damage may cause both atherosclerosis and albuminuria.²⁶ Decreased eGFR is a risk factor for cardiovascular disease,³ although the mechanism of the relationship between low eGFR and atherosclerosis has not been elucidated. Previous reports have suggested various possibilities in CKD, including increased calcium or phosphorous concentrations²⁷ or inflammation.²⁸

CMBs are indicative of hemosiderin deposits, which can remain in macrophages for years following a microhemorrhage. Growing evidence suggests a correlation between CMBs and increased stroke risk, especially intracerebral hemorrhage.²⁹ In the DECIPHER study, Ovbiagele et al³⁰ demonstrated that CKD was associated with the presence of CMBs and the number of CMBs in primary intracranial

hemorrhage patients when adjusted for confounding factors, including hypertension and diabetes. They defined CKD as an eGFR <60 mL/min/1.73 m²; therefore, the influence of proteinuria on CMBs was not clear. Recently, CKD has been associated with CMBs in neurologically normal subjects;³¹ however, the association was made using a multiple regression model adjusted only for age and sex, excluding hypertension and diabetes as confounding factors. This study demonstrated the associations of proteinuria with CMBs in asymptomatic subjects in this study, after adjustment for BMI, hypertension, diabetes, dyslipidemia and current smoking status, which are important risk factors in cerebrovascular diseases. The result suggested the importance of proteinuria as an independent risk factor for CMBs. Careful neuroimaging screening may be necessary in patients with proteinuria despite eGFR levels.

Proteinuria was significantly associated with the presence of old non-lacunar infarctions, and neither decreased eGFR nor proteinuria was associated with lacunar infarctions in this study. The relationship between kidney dysfunction and silent brain infarctions in previous studies is controversial. A Rotterdam scan study of a general population in the Netherlands reported that decreased eGFR levels were not significantly associated with asymptomatic lacunar infarcts.³² On the other hand, Kobayashi et al demonstrated in Japanese populations that subjects with CKD or essential hypertension with eGFR levels from 15 to 29 mL/min/1.73 m² were significantly associated with silent brain infarcts compared with subjects with an eGFR >60 mL/min/1.73 m².³³ Wada et al found that microalbuminuria was associated with lacunar infarction in brain MRI in a cohort of community-based elderly.³⁴ Further studies are needed to evaluate the association of low eGFR or proteinuria with various types of infarctions in general population.

Although previous studies have reported that low eGFR levels were associated with WMLs,^{32,35} significant associations were not shown in the present study. Prior studies estimated the volume of WMLs, whereas this study evaluated the presence of WMLs using a severity scale as described in the Methods section. Future studies are necessary to evaluate any associations between WML grade and kidney dysfunction in the Japanese population. Decreased eGFR has been reported to be associated with brain atrophy in a Japanese population with health checkups;³⁶ however, this was not the case in the Rotterdam scan study.³² In the present study, low eGFR values and proteinuria did not show significant associations with advanced brain atrophy for age when adjusted for other confounding factors related to cardiovascular diseases.

Study Limitations

First, this study was unable to observe specific cerebrovascular events. Instead, we observed indicators, including carotid US and brain MRI results. Second, the numbers of subjects with an eGFR 45–59 mL/min/1.73 m² and 15–44 mL/min/1.73 m² were small compared with the number of subjects with an eGFR >60 mL/min/1.73 m², because of the characteristics of the subjects who underwent annual health checkups. Third, single-morning spot urine collections were used instead of timed urine collections, which would have been preferable.

Despite these limitations, this study revealed that decreased eGFR and proteinuria were independent risk

factors for asymptomatic findings on carotid US and brain MRI, which are surrogate markers for cerebrovascular diseases. Evaluation of carotid US and brain MRI may be useful for prevention of symptomatic cerebrovascular diseases in CKD patients.

Disclosures

The authors declare no conflicts of interest related to this study.

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Ethical Statement and Informed Consent

General informed consent was obtained because this study was a non-invasive, retrospective study. The records of participants were made anonymous prior to analyses. The ethics committee of the Keio University School of Medicine approved the study protocol (No. 20140329).

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