Chronic Kidney Disease and Carotid Atherosclerosis

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Chronic kidney disease is an independent risk factor for cardiovascular disease. The association between carotid intima-media thickness (IMT) and chronic kidney disease is controversial, however. In addition, whether renal dysfunction promotes vascular calcification in patients with chronic kidney disease is not clear. The study subjects were 1003 patients aged ≥50 years who underwent carotid ultrasonography in our hospital. Kidney function was evaluated based on the estimated glomerular filtration rate (eGFR) and the presence of proteinuria. Patients with end-stage renal failure were excluded. We measured the mean max-IMT (which indicates mean maximal wall thickness) at 12 carotid segments, and examined the characteristics of the maximal plaques by carotid ultrasonography. We evaluated the association between mean max-IMT and eGFR, and also evaluated the clinical factors associated with mean max-IMT and calcification of the maximal plaques. We found that eGFR was significantly correlated with mean max-IMT. Reduced eGFR, proteinuria, age, male sex, cardiovascular disease, hypertension, diabetes, and smoking were independently associated with mean max-IMT in multiple regression analysis. Kidney function was not associated with calcified plaque. Kidney dysfunction was associated with carotid atherosclerosis in patients with mild or moderate chronic kidney disease. **Key Words:** Kidney dysfunction—carotid ultrasound—intima-media thickness—vascular calcification.

Chronic kidney disease (CKD) has recently been shown to be an independent risk factor for cardiovascular disease, including stroke.[1-5] Carotid intima-media thickness (IMT) is a reliable marker of systemic atherosclerosis and a predictor of cardiovascular events.[6-9] Whether increased carotid IMT is associated with CKD is controversial, however. In addition, whether or not renal dysfunction affects the characteristics of carotid plaques is unknown. Although, for example, end-stage renal failure is known to promote vascular calcification, the association between vascular calcification and predialysis CKD is unclear. The purpose of the present study was to confirm whether carotid IMT is associated with CKD, and whether renal dysfunction is associated with calcified plaque in carotid arteries.

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Methods

Subjects

The study subjects were enrolled from 1198 patients aged ≥50 years who had consecutively undergone carotid ultrasound examination in the Department of Neurology at Osaka University Hospital between January 2001 and December 2008. Patients who had undergone carotid endarterectomy (n = 7) or carotid stenting (n = 17) were excluded, as were those with occluded carotid arteries (n = 37), because IMT could not be correctly determined in these patients. Patients with Takayasu's arteritis (n = 9) were excluded because the disease can affect kidney function and carotid IMT. Patients with end-stage renal failure (those who had undergone dialysis or those with an estimated glomerular filtration rate

[eGFR] of <15 mL/min/1.73 m^2; n = 8) were excluded, so as to focus on mild and moderate CKD. Patients also were excluded due to incomplete laboratory data (n = 117). Consequently, the study group comprised 1003 subjects (581 men and 422 women; mean age, 67.3 ± 8.1 years). The subjects' characteristics are summarized in Table 1, which demonstrates a higher prevalence of atherosclerotic risk factors in the study sample.

We next selected patients with carotid plaques to evaluate the association between kidney function and the presence of calcification in the maximal plaques. Based on the common definition of carotid plaque of a focal increase in IMT of ≥1.1 mm,[10] we selected patients with a maximal plaque thickness of ≥1.1 mm (n = 874). Nineteen of these patients were excluded because their plaque characteristics had not been evaluated. Subsequently, 855 patients (527 men and 328 women; mean age, 68.0 ± 7.9 years) were involved in the subgroup analysis for plaque characteristics.

Our institution's Ethical Committee approved this study, and written informed consent was obtained from all patients. The study conformed to the principles outlined in the Declaration of Helsinki.

Carotid Ultrasonography

All ultrasound examinations were performed using a SONOS 5500 equipped with a 7.5-MHz linear-array transducer (Philips Medical Systems, Massachusetts). Three different longitudinal (anterior oblique, lateral, and posterior oblique) and transverse images of the bilateral carotid arteries were obtained, and IMT was measured as the distance between the luminal-intimal interface and the medial-adventitial interface. IMT was measured using electronic calipers on the frozen frame of a suitable longitudinal B-mode image in which the putative maximal IMT was visualized. Thus, the severity of carotid atherosclerosis was evaluated by the mean max-IMT (which indicates the mean of maximal wall thickness) at 12 carotid segments: the near and far walls of the left and right common carotid arteries, carotid bifurcation, and internal carotid arteries (Fig 1).[11-13] We also measured the maximal plaque thickness in the two carotid arteries and evaluated the characteristics of the plaque by visual analysis. If a patient had more than one maximal plaque of the same size, we preferentially evaluated the plaque in the common carotid arteries. Calcified plaque was defined as a focal increase in echo density within the carotid plaque combined with a broad acoustic shadow.

Evaluation of Kidney Function and Other Atherosclerotic Risk Factors

Information on demographic characteristics and risk factors was collected using the clinical records at the time of ultrasound examination. Kidney function was estimated based on proteinuria and eGFR. Proteinuria was measured using urine strip devices and was considered present for a dipstick result of + or more. eGFR was estimated using the following equations suitable for the Japanese population: eGFR = 194 × (serum creatinine$^{-1.094}$) × (age$^{-0.287}$) × (0.739 for women).[14] CKD stage (0-4) was defined by eGFR and the presence of proteinuria.[15] CKD stage 5 (end-stage renal failure) was excluded as noted earlier. Hypertension was defined by a casual blood pressure measurement ≥140/90 mm Hg or the current use of antihypertensive agents. Diabetes mellitus was defined as fasting blood glucose level ≥126 mg/dL or current use of insulin or a hypoglycemic agent. Dyslipidemia was defined by fasting serum low-density lipoprotein cholesterol >140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or triglycerides ≥150 mg/mL, or current use of a cholesterol-lowering agent. Smoking status was evaluated based on self-report, with a smoker defined by a history of smoking as a score >50 on the Brinkman Index.[16] History of

Table 1. *Characteristics of the study participants (n = 1003)*

Age, years	67.3 ± 8.1
Sex (male/female), n	581/422
Hypertension, n (%)	773 (77.1)
Diabetes, n (%)	231 (23.0)
Dyslipidemia, n (%)	696 (69.4)
Hyper-LDL cholesterolemia	521 (51.9)
Hypertriglyceridemia	309 (30.8)
Hypo-HDL cholesterolemia	152 (15.2)
Smoking, n (%)	534 (53.2)
History of cardiovascular disease, n (%)	407 (40.6)
Ischemic heart disease	114 (11.4)
Stroke or transient ischemic attack	330 (32.9)
CKD, n (%)	
Stage 0	684 (68.2)
Stage 1	4 (0.4)
Stage 2	36 (3.6)
Stage 3	267 (26.6)
Stage 4	12 (1.2)
Proteinuria, n (%)	87 (8.7)

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

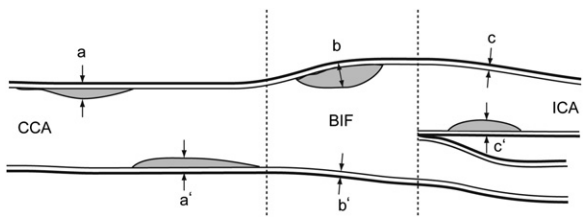

Figure 1. *Diagrams of carotid bifurcation and measurements obtained from B-mode ultrasonography. CCA, common carotid artery; BIF, carotid bulb; ICA, internal carotid artery. Mean max-IMT is defined as the mean of the maximal wall thickness at 12 points (near and far walls on both sides of the CCA, BIF and ICA), that is, a + a′ + b + b′ + c + c′ + contralateral sides/12).*

cardiovascular disease was defined by a history of stroke, transient ischemic attack or ischemic heart disease.

Statistical Analyses

All analyses were performed with SPSS 12.0J (SPSS Japan Inc., Tokyo). First, the association between mean max-IMT and eGFR was evaluated by linear regression analysis. Then multiple linear regression analyses were used to examine associations between kidney function and mean max-IMT, controlling for traditional atherosclerotic risk factors (forced entry method).

Next, the association between the presence of calcification in the maximal plaque and kidney function was evaluated by univariate analyses using the χ^2 test or Mann-Whitney *U* test. Logistic regression analysis (forced entry method) was used to assess the contribution of atherosclerotic risk factors to the calcified plaque. Probability values were two-tailed, and $P < .05$ was considered significant.

Results

In linear regression analysis, eGFR was negatively correlated with mean max-IMT ($r = 0.203$; $P < .001$) (Fig 2). In multiple regression analysis (Table 2), decreased eGFR was correlated with mean max-IMT when controlling for age and sex (model 1), and also when controlling for traditional atherosclerotic risk factors and the presence of proteinuria (model 2). In contrast, eGFR and proteinuria were not associated with calcified plaque in the univariate and multivariate analyses. Older age and hypertension were independent factors associated with calcified plaque in the multivariate analysis (Table 3).

Discussion

Our findings show that kidney dysfunction was associated with increased carotid IMT independent of the classical atherosclerotic risk factors. A previous study reported

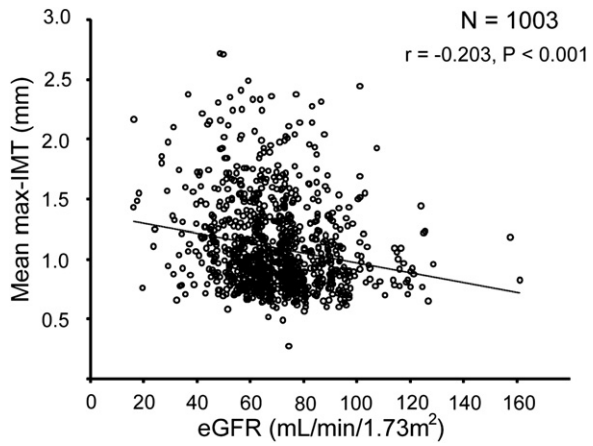

Figure 2. *Association between carotid IMT and eGFR.*

Table 2. *Multiple regression analyses for carotid IMT*

	Model 1		Model 2	
Variable	Coefficient	*P*	Coefficient	*P*
eGFR	−0.104	.001	−0.071	.018
Age	0.259	<.001	0.259	<.001
Male sex	0.274	<.001	0.160	<.001
Cardiovascular disease			0.152	<.001
Hypertension			0.111	<.001
Diabetes			0.058	.043
Dyslipidemia			0.053	.059
Smoking			0.119	.001
Proteinuria			0.061	.033
R^2	0.172	<.001	0.236	<.001

an association between reduced eGFR and carotid IMT,[8] but others found no independent association.[7,9] The subjects of the former study were outpatients with some cardiovascular risk factors, and those of the latter studies were from community-based epidemiologic studies. Our subjects included a high proportion of patients with some atherosclerotic risk factors, indicating that kidney dysfunction is an atherosclerotic risk factor, especially in patients at high risk for cardiovascular disease.

Our findings also indicate that proteinuria is an independent factor associated with carotid atherosclerosis. A previous community-based study also reported that albuminuria was associated with carotid IMT, although the association disappeared after adjustment for other atherosclerotic risk factors.[9] Our subjects had a higher rate of CKD than the general population, which might have led to a stronger association between proteinuria and atherosclerosis. CKD affects an estimated 12.9% of the adult population in Japan,[17] whereas 31.8% of our subjects had CKD. In general, proteinuria is detected even in the early stages of CKD. The study subjects had a high rate of slightly reduced kidney function, with a median eGFR of 67.9 mL/min/1.73 m^2. Meanwhile, many previous studies have demonstrated that proteinuria is a major risk factor for cardiovascular disease.[2,4,5] Carotid IMT may play a predictive role for cardiovascular disease that reflects the risk of CKD even in early stages.

On the other hand, our data reveal no association between kidney dysfunction and calcified plaque. Older age and hypertension were independent factors associated with calcified plaque. These factors are well-known promoters of vascular calcification.[15] It is also known that end-stage renal failure promotes systemic vascular calcification. Mechanisms involved in vascular calcification in end-stage renal failure include elevated levels of calcium-phosphorus product, elevated parathyroid hormone levels, exogenous vitamin D therapy, alkalosis, chronic inflammation, and reduced inhibitors of calcification.[15] The associations between these factors and vascular

Table 3. *Univariate and multivariate analyses for carotid calcified plaque*

Variables	Plaque characteristic		Univariate analysis, *P*	Logistic regression analysis	
	Calcified (n = 138)	Noncalcified (n = 717)		Odds ratio	*P*
Age, years, median	72	68	<.001	1.08	<.001
Male sex, %	54.3	63.0	.05	0.91	.72
Cardiovascular disease, %	42.0	43.2	.79	-	
Hypertension, %	88.4	77.7	.01	2.08	.01
Diabetes, %	31.2	23.6	.06	1.40	.12
Dyslipidemia, %	71.0	69.6	.74	-	
Smoking, %	47.1	57.5	.03	0.73	.22
eGFR, median, mL/min/1.73 m^2	64.5	67.8	.12	1.00	.47
Proteinuria, %	11.6	7.7	.13	1.59	.15

calcification are not clear in patients with predialysis CKD, however. A study of nondialysis patients found much higher rates of coronary artery calcification in CKD patients than in controls (40% vs 13%).[18] The mean eGFR in the CKD patients in that study was 33 mL/min/1.73 m^2, much lower than that in our subjects. Our subjects included a high proportion of patients with mild renal insufficiency, and thus may demonstrate no significant association between vascular calcification and renal function. The main cause of vascular calcification is presumed to be disorders of bone and mineral metabolism, which tend to be associated with moderate to severe CKD.

The present study has several limitations. First, the study subjects were neurology outpatients, and patients with kidney disorders only were not included. The results might have differed had the study group included more patients with kidney disorders. Second, because microalbuminuria was not measured in all patients, patients without proteinuria according to urine strip measurements might have had a higher rate of CKD. Also, because the present study was cross-sectional, whether the kidney dysfunction itself caused atherosclerosis was not clear. However, a previous longitudinal study reported that changes in carotid IMT over 2 years occurred more rapidly in a group with worse kidney dysfunction prognosis.[7] Kidney dysfunction itself might have a certain effect on atherosclerosis.

In conclusion, in the present study, kidney dysfunction was associated with carotid atherosclerosis independent of traditional risk factors. Carotid IMT may be a predictive marker of cardiovascular disease that reflects early kidney dysfunction, especially in high-risk patients.

References

1. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285-1295.
2. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non insulin-dependent diabetes mellitus: A systematic overview of the literature. Arch Intern Med 1997;157:1413-1418.
3. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-1305.
4. National Kidney Foundation. National Kidney Foundation Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 2002; 39:S1-S266.
5. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney In Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003;108: 2154-2169.
6. Bui AL, Katz R, Kestenbaum B, et al. Cystatin C and carotid intima-media thickness in asymptomatic adults: The Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis 2009;53:389-398.
7. Desbien AM, Chonchol M, Gnahn H, et al. Kidney function and progression of carotid intima-media thickness in a community study. Am J Kidney Dis 2008;51:584-593.
8. Kawamoto R, Ohtsuka N, Kusunoki T, et al. An association between the estimated glomerular filtration rate and carotid atherosclerosis. Intern Med 2008;47:391-398.
9. Zhang L, Zhao F, Yang Y, et al. Association between carotid artery intima-media thickness and early-stage CKD in a Chinese population. Am J Kidney Dis 2007; 49:786-792.
10. Handa N, Matsumoto M, Maeda H, et al. Ischemic stroke events and carotid atherosclerosis: Results of the Osaka follow-up study for ultrasonographic assessment of carotid atherosclerosis (the OSACA study). Stroke 1995; 26:1781-1786.
11. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. Stroke 1992;23:1752-1760.
12. Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke 1993;24:1297-1304.

13. Sakaguchi M, Kitagawa K, Nagai Y, et al. Equivalence of plaque score and intima-media thickness of carotid ultrasonography for predicting severe coronary artery lesion. Ultrasound Med Biol 2003;29:367-371.
14. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982-992.
15. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: Effects on the cardiovascular system. Circulation 2007;116:85-97.
16. Brinkman GL, Coates EO Jr. The effect of bronchitis, smoking, and occupation on ventilation. Am Rev Respir Dis 1963;87:684-693.
17. Imai E, Horio M, Iseki K, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol 2007;11:156-163.
18. Russo D, Palmiero G, De Blasio AP, et al. Coronary artery calcification in patients with CRF not undergoing dialysis. Am J Kidney Dis 2004;44:1024-1030.