Original Article

Association Between Renal Vasculature Changes and Generalized Atherosclerosis: An Autopsy Survey

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***Aim*: To examine the association between renal vasculature changes and generalized atherosclerosis using autopsy cases.**
***Methods*: We histologically examined 107 autopsy patients (mean age, 68.4 years; 64% men; 81% non-CVD) to investigate the association between renal vasculature changes and generalized atherosclerosis. We measured the intima/media (I/M) ratio for the renal, intrarenal and systemic arteries (coronary, cerebral, common carotid and common iliac), calculated the rates of arteriolar hyalinization and global glomerulosclerosis and evaluated the frequency of advanced lesions (AHA classification ≥ IV) in the systemic arteries.**
***Results*: The I/M ratios of the renal and intrarenal arteries and the rate of global glomerulosclerosis increased with age, while the rates of arteriolar hyalinization and global glomerulosclerosis were associated with diabetes and hypertension (all $p<0.05$). The I/M ratio of the coronary artery was independently associated with the rate of global glomerulosclerosis ($p<0.05$). The frequency of advanced atherosclerotic lesions in the coronary and cerebral arteries was also correlated with the I/M ratio of the renal artery and rates of arteriolar hyalinization and global glomerulosclerosis (all $p<0.05$). The frequency of advanced lesions in the cerebral and common carotid arteries was independently associated with the I/M ratio of the renal artery and the rate of renal arteriolar hyalinization (odds ratio (OR) with [95% confidence interval]; 5.09 [1.15-27.9] and 4.11 [1.38-13.9], respectively).**
***Conclusions*: The results of this study demonstrated that pathological changes in four portions of the renal vasculature differ. Renal vasculature changes except the intrarenal arteries were significantly associated with those observed in the cerebral, common carotid and coronary arteries.**

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Key words: Renal artery, Cardiovascular disease, Atherosclerosis, Autopsy

Introduction

Cardiovascular disease (CVD) is a major cause of mortality worldwide. The impact of CVD risk factors, such as diabetes mellitus, hypertension and aging, has been established. Recently, a decline in the kidney function and the development of early-stage chronic kidney disease (CKD) have been recognized as novel risk factors for CVD[1-4]. In Japan, CKD has become a major public health problem. Patients with early-stage CKD are more likely to die of CVD than those who progress to end-stage renal disease (ESRD)[2, 5].

Atherosclerosis is a systemic disease that affects the entire body. Schwartz *et al.*[6] reported that coronary plaques in patients with ESRD exhibit thickened media and marked calcification. However, it is unclear whether changes in the renal vasculature are associated with the severity of generalized atherosclerosis in

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Table 1. Characteristics of the autopsy subjects ($n=107$)

Age, years	68.4 ± 11.7
Male, n (%)	68 (63.6)
Diabetes, n (%)	21 (19.8)
Hypertension, n (%)	36 (40.0)
Hyperlipidemia, n (%)	7 (6.6)
Smoking, n (%)	52 (48.6)
Cause of death	
Malignancy, n (%)	51 (47.7)
Cardiovascular disease, n (%)	19 (17.8)
Infection, or sepsis, n (%)	13 (12.2)
Collagen disease, n (%)	2 (1.9)
Others, n (%)	22 (20.6)

The data are presented as the mean ± SD or number (%).

patients without ESRD. We investigated this issue using autopsy cases.

Methods

Study Population and Design

Between 2000 and 2005, 301 autopsies were carried out at the University of Miyazaki Hospital, University of Miyazaki, Japan. We randomly selected 124 subjects 40 years of age and older with well-preserved autopsy specimens. Seventeen patients with the following conditions were excluded: dialysis ($n=11$); amyloidosis ($n=3$); granulomatosis with polyangiitis ($n=2$); and renal transplantation ($n=1$). A total of 107 patients were included in this study (mean age, 68.4 ± 11.7 years; 68% men) (**Table 1**). The causes of death were as follows: CVD (i.e., coronary artery disease, stroke, brain hemorrhage and congestive heart disease), $n=19$ (18%); malignancy, $n=51$ (48%); infection or sepsis, $n=13$ (12%); collagen disease, $n=2$ (2%); other causes (liver cirrhosis, amyotrophic lateral sclerosis or intestinal pneumonia), $n=22$ (20%). Hypertension was defined as a blood pressure of ≥ 140/90 mmHg or the use of an antihypertensive agent. Diabetes mellitus was defined as a fasting glucose level of ≥ 126 mg/dL; a random non-fasting glucose level of ≥ 200 mg/dL; a hemoglobin A1c level of ≥ 6.5%; or the use of an antihyperglycemic agent. Hyperlipidemia was defined as a total cholesterol level of ≥ 220 mg/dL; a low-density lipoprotein level of ≥ 140 mg/dL; a triglyceride level of ≥ 150 mg/dL; or the use of an oral lipid-lowering agent. The Ethical Committee of the University of Miyazaki approved the study protocol (No. 942), and the study was performed in accordance with the ethical standards of the Declaration of Helsinki.

Table 2. I/M ratios of the renal vasculature and systemic arteries and rates of arteriolar hyalinization and global glomerulosclerosis

Coronary artery, I/M ratio	4.57 (2.95-9.30)
Cerebral artery, I/M ratio	1.27 (0.38-3.51)
Common carotid artery, I/M ratio	2.30 (0.81-4.68)
Common iliac artery, I/M ratio	5.71 (2.32-10.87)
Renal artery, I/M ratio	0.82 (0.37-2.24)
Intra-renal artery, I/M ratio	1.58 (1.22-2.13)
Arteriolar hyalinization, %	0 (0-6.3)
Global glomerulosclerosis, %	6.5 (2.8-14.0)

The data are presented as the median (interquartile range).

Histological Examinations

The following vascular structures and organs were isolated from 10% formalin-fixed organs, as described elsewhere[7]: bilateral common carotid arteries; coronary arteries (main left coronary artery); cerebrovascular arteries (bilateral middle cerebral artery); bilateral common iliac arteries; and bilateral renal arteries. Kidney parenchyma samples measuring approximately 4 cm^2 of the renal cortex were obtained from the bilateral kidneys. The cerebral vessels were not examined in 55 subjects (51%) in whom craniotomy was not permitted at the time of autopsy. We cut the arteries or aortae longitudinally for macroscopic observation, and all arteries were fixed in immersion. The isolated arteries were cut transversely at 3 mm, and the segments of the vessels showing the most stenosis were selected for the histological examination.

Two pathologists (T.I. and Y.S.) unaware of the patients' characteristics performed the histological examinations of the arteries and kidney parenchyma. The histological sections were embedded in paraffin and stained with hematoxylin and eosin. To assess the severity of atherosclerosis in the vasculature, except for the small renal arterioles and glomeruli, we measured the maximum intima/media layer ratio (I/M ratio) within each vascular wall, as thinning of the medial layer associated with intimal thickening has long been recognized to be a valid marker of atherosclerosis[7]. The intima and media thicknesses were measured using an image analysis system (Win Roof, Mitani, Fukui, Japan). All arteries were measured under non-perfusion-fixed conditions. We also assessed advanced atherosclerotic lesions in the systemic arteries, classifying them into six types of atherosclerotic lesions in accordance with the definition proposed by the Committee on Vascular Lesions of the Council on Atherosclerosis, American Heart Association (AHA)[8]. The AHA classification defines advanced atherosclerotic

Table 3A. Univariate analysis of risk factors for renal vasculature changes

	Renal artery (I/M ratio)	Intrarenal artery (I/M ratio)	Arteriolar hyalinization	Global glomerulosclerosis
Age	NS	<0.01	NS	<0.001
Men	0.01	NS	NS	NS
Diabetes	NS	NS	<0.001	<0.01
Hypertension	<0.05	NS	<0.05	<0.01
Dyslipidemia	NS	NS	NS	NS
Smoking	NS	NS	NS	NS

The numbers represent *p* values. NS indicates not significant.

Table 3B. Multivariate analysis of risk factors for renal vasculature changes

	Renal artery (I/M ratio)	Intrarenal artery (I/M ratio)	Arteriolar hyalinization	Global glomerulosclerosis
Age	NS	<0.0001	NS	<0.05
Men	<0.05	NS	NS	NS
Diabetes	NS	NS	<0.0001	<0.01
Hypertension	NS	NS	NS	<0.01
Dyslipidemia	NS	NS	NS	NS
Smoking	NS	NS	NS	NS

The numbers represent *p* values. NS indicates not significant.

lesions as type Ⅳ-Ⅵ. We evaluated the I/M ratios of the renal and intrarenal arteries (with a diameter between 90 and 500 μm) as well as the systemic arteries. To evaluate the arterioles and glomeruli, we assessed the rates of arteriolar hyalinization and global glomerulosclerosis in 100 arterioles and 100 glomeruli in each sample[9]. The interobserver correlation coefficients (ICCs) for measuring the I/M ratios of the arteries and the rates of arteriolar hyalinization and global glomerulosclerosis were $r=0.91$, 0.83 and 0.92, respectively. We also tested the ICC of categorization according to the AHA classification ($\kappa=0.93$). Disagreements between the observers were resolved by discussion to achieve a consensus.

Statistical Analysis

All statistical analyses were performed using the JMP version 8.0.1 (SAS, Cary, NC) and GraphPad Prism 5.01 software programs (GraphPad Software, San Diego, CA). Variables with a normal distribution are expressed as the mean±standard deviation (SD), whereas variables with a skewed distribution are expressed as the median with the interquartile range (IQR). The associations between the individual variables were calculated according to Spearman's correlation method using raw data. The clinical parameters of the patients with or without risk factors were compared using the unpaired *t*-test for variables with a normal distribution or the Mann-Whitney test for variables with a skewed distribution, and categorical parameters were compared with the chi-squared test or Kruskal-Wallis test. A multivariate analysis of the risk factors for renal vasculature changes was performed using a stepwise regression analysis. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a logistic regression analysis. A *p* value of <0.05 was considered to be statistically significant.

Results

The I/M ratios of the renal vasculature and coronary, cerebral, common carotid and common iliac arteries and the rates of renal arteriolar hyalinization and global glomerulosclerosis are shown in **Table 2**. The median I/M ratio of the renal arteries was lower than that of the systemic arteries. The rates of arteriolar hyalinization and global glomerulosclerosis were also lower in the renal arteries (median arteriolar hyalinization rate: 0%; median global glomerulosclerosis rate: 6.5%). Advanced atherosclerotic lesions (AHA Ⅳ-Ⅵ) were observed in the renal arteries in 10 (9%) subjects, while severe stenosis (>75%) was present in the renal arteries in one case. The I/M ratios of the intrarenal arteries and the rate of global glomerulosclerosis

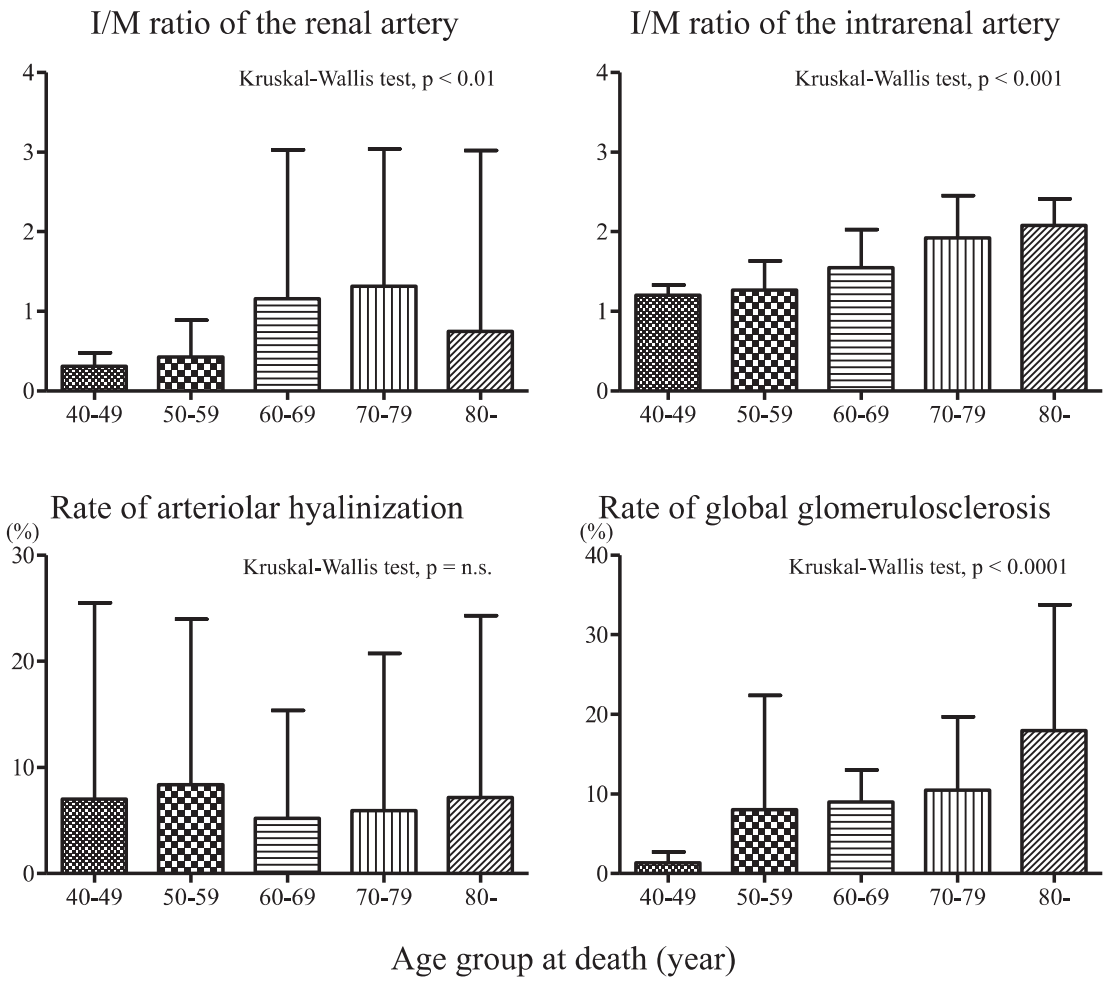

Fig. 1. Age-specific median values of the I/M ratios of the renal and intrarenal arteries and the rates of global glomerulosclerosis and arteriolar hyalinization.

The I/M ratios of the intrarenal arteries and the rate of global glomerulosclerosis increased with advancing age. In contrast, the rate of arteriolar hyalinization was not associated with age. The I/M ratios of the renal arteries tended to be higher with age.

rosis increased with advancing age, and the I/M ratios of the renal arteries also showed a trend to be higher with age (**Table 3A**, **B**, **Fig. 1**). However, the rate of arteriolar hyalinization was not associated with age. The I/M ratio of the renal artery and the rates of arteriolar hyalinization and global glomerulosclerosis were correlated with gender, diabetes and hypertension. The frequency of advanced lesions was higher in the coronary and common iliac arteries (50% and 62%) than in the cerebral and common carotid arteries (37% and 32%). We examined the correlations between renal vasculature changes and the I/M ratios of the systemic arteries. There were significant associations between the I/M ratios of the renal and intrarenal arteries and the I/M ratios of the coronary, cerebral, common carotid and common iliac arteries (all $p<0.05$, **Table 4A**). The rate of global glomerulosclerosis was correlated with the I/M ratios of the coronary, common carotid and common iliac arteries. The rate of arteriolar hyalinization was not associated with the I/M ratios of the systemic arteries. In addition, the microscopically evaluated common carotid IMT was correlated with the I/M ratio of the renal artery, the I/M ratios of the intrarenal arteries and the rate of global glomerulosclerosis (Spearman correlation coefficients=0.30, 0.22 and 0.28, respectively, all $p<0.05$). To clarify the relationship between renal vasculature changes and the I/M ratios in patients with generalized atherosclerosis, we examined several risk factors (age, gender, hypertension, diabetes, dyslipidemia

Table 4A. Correlations between renal vasculature changes and generalized atherosclerosis (I/M ratio)

	Renal artery (I/M ratio)	Intrarenal artery (I/M ratio)	Arteriolar hyalinization	Global glomerulosclerosis
Coronary artery (I/M ratio)	0.216*	0.025	0.067	0.287**
Cerebral artery (I/M ratio)	0.415**	0.256	0.062	0.240
Common carotid artery (I/M ratio)	0.302**	0.254*	0.083	0.237*
Common iliac artery (I/M ratio)	0.340***	0.169	−0.0003	0.232*

The values indicate Spearman's rank correlation coefficients.
*$p<0.05$, **$p<0.01$, ***$p<0.001$

Table 4B. Multivariate adjusted correlations between renal vasculature changes and generalized atherosclerosis (I/M ratio)

	Renal artery (I/M ratio)	Intrarenal artery (I/M ratio)	Arteriolar hyalinization	Global glomerulosclerosis
Coronary artery (I/M ratio)	NS	NS	NS	<0.05
Cerebral artery (I/M ratio)	NS	NS	NS	NS
Common carotid artery (I/M ratio)	NS	NS	NS	NS
Common iliac artery (I/M ratio)	NS	NS	NS	NS

The values indicate *p* values

and smoking habits) and adjusted the correlations for these risk factors. The rate of global glomerulosclerosis was independently associated with the I/M ratio of the coronary artery (**Table 4B**).

Next, we examined the relationship between renal vasculature changes and the frequency of advanced atherosclerotic lesions in the systemic arteries. To estimate the fractional dimensions of these parameters, we selected a cutoff value for each median value of the parameters of renal vasculature changes. The I/M ratio of the renal artery was strongly associated with the presence of advanced lesions in the cerebral and common carotid arteries (OR [95% CI]; 5.42 [1.43-20.5] and 2.49 [1.10-5.62], respectively). The rate of arteriolar hyalinization was associated with the frequency of advanced lesions in the coronary and common carotid arteries (OR [95% CI]; 2.46 [1.10-5.52] and 2.95 [1.29-6.72], respectively). The rate of global glomerulosclerosis was also correlated with the frequency of advanced lesions in the coronary and common carotid arteries (OR [95% CI]; 2.81 [1.28-6.15] and 2.96 [1.30-6.76], respectively) (**Table 5A**). In addition, the frequency of advanced lesions in the cerebral and common carotid arteries was independently associated with the I/M ratio of the renal artery and the rate of renal arteriolar hyalinization according to a multivariate adjusted analysis (OR [95% CI]; 5.09 [1.15-27.9] and 4.11 [1.38-13.9], respectively) (**Table 5B**).

Discussion

We histologically examined the rates of renal and intrarenal arteriosclerosis, arteriolar hyalinization and global glomerulosclerosis and analyzed the effects of cardiovascular risk factors in autopsy cases. We showed that the I/M ratios of the intrarenal arteries and the rate of global glomerulosclerosis increased linearly with advancing age. In addition, diabetes and hypertension were found to be risk factors for arteriolar hyalinization and global glomerulosclerosis. Kubo *et al.*[10] reported that, in their study, the frequency of glomerulosclerosis was 2.9% in men and 3.5% in women in the 40- to 59-year-old age group and increased significantly to 24.3% and 38.5%, respectively, in the subjects ≥80 years of age. In the present study, hypertension and glucose intolerance were also found to be associated with renal vasculature changes. We confirmed that age, hypertension and diabetes are common risk factors for histological renal vasculature changes in the Japanese general population. Although dyslipidemia is generally recognized to be a strong risk factor for generalized atherosclerosis, it was not significantly associated with renal vascular changes in this study. The renal and intrarenal arteries of patients with dyslipidemia exhibit fibrous intimal thickening and less frequent fatty lesions than other systemic arteries[11, 12], which suggests that the renal and intrarenal arteries are unlikely to be affected by dyslipidemia.

We identified a direct relationship between renal

Table 5A. Odds ratios for renal atherosclerosis, arteriosclerosis, arteriolar hyalinization and global glomerulosclerosis according to the classification of advanced lesions in patients with generalized atherosclerosis (AHA)

	Renal artery (I/M ratio)	Intrarenal artery (I/M ratio)	Arteriolar hyalinization	Global glomerulosclerosis
Coronary artery (AHA advanced)	1.12 (0.52-2.39)	0.96 (0.45-2.05)	2.46 (1.10-5.52)*	2.81 (1.28-6.15)**
Cerebral artery (AHA advanced)	5.42 (1.43-20.5)*	2.08 (0.62-6.99)	1.48 (0.45-4.88)	2.73 (0.81-9.15)
Common carotid artery (AHA advanced)	2.49 (1.10-5.62)*	1.08 (0.49-2.39)	2.95 (1.29-6.72)**	2.96 (1.30-6.76)**
Common iliac artery (AHA advanced)	2.31 (0.97-5.50)	2.31 (0.97-5.50)	2.14 (0.85-5.40)	2.31 (0.97-5.50)

The values indicate odds ratios (95% confidence intervals). *$p<0.05$, **$p<0.01$. AHA, American Heart Association

Table 5B. Multivariate-adjusted odds ratios for renal atherosclerosis, arteriosclerosis, arteriolar hyalinization and global glomerulosclerosis according to the classification of advanced lesions in patients with generalized atherosclerosis (AHA)

	Renal artery (I/M ratio)	Intrarenal artery (I/M ratio)	Arteriolar hyalinization	Global glomerulosclerosis
Coronary artery (AHA advanced)	1.56 (0.64-3.98)	0.42 (0.15-1.09)	1.24 (0.47-3.22)	1.38 (0.55-3.42)
Cerebral artery (AHA advanced)	5.09 (1.15-27.9)*	1.27 (0.27-6.32)	1.50 (0.58-3.84)	2.93 (0.64-15.5)
Common carotid artery (AHA advanced)	1.47 (0.57-3.77)	0.51 (0.18-1.35)	4.11 (1.38-13.9)*	2.12 (0.89-6.91)
Common iliac artery (AHA advanced)	1.15 (0.41-3.24)	1.36 (0.47-3.96)	0.91 (0.29-2.90)	0.87 (0.29-2.55)

The values indicate odds ratios (95% confidence intervals). *$p<0.05$. AHA, American Heart Association

vasculature changes and atherosclerosis in the systemic arteries in autopsy samples obtained from the Japanese general population. Previous autopsy studies have shown severe atherosclerosis of the coronary arteries in patients with chronic renal failure or ESRD[6, 13-15]. Nakano *et al.*[16] reported that the progression of CKD is correlated with the severity of coronary atherosclerosis. Recently, Waheed S. *et al.*[17] demonstrated that a mildly decreasing glomerular filtration rate and/or mild albuminuria contribute to the development of coronary heart disease. In addition, we found that CVD risk factors, including age, gender, diabetes and hypertension, are associated with renal vasculature changes. A more recent study demonstrated that a reduction in the level of LDL cholesterol due to treatment with simvastatin reduces the incidence of major atherosclerotic events in patients with CKD[18]. These findings suggest the importance of managing CVD risk factors before the onset of ESRD in order to reduce the risk of coronary atherosclerosis.

Several angiographic studies have shown that more than 50% of CKD patients starting hemodialysis treatment have significant coronary artery stenosis[19, 20]. Kawai *et al.*[21] showed that the degree of coronary stenosis evaluated using computed tomography is significantly higher in patients with early-stage CKD than in those without CKD. Schwartz *et al.*[6] reported that the medial thickness of the coronary arteries is significantly higher in uremic patients and that the intima thickness tends to also be higher in such patients. We found that the I/M ratio of the coronary artery was significantly associated with the rates of renal arteriosclerosis and global glomerulosclerosis. We also found that the thickness of the intima of the coronary artery was significantly associated with the rate of global glomerulosclerosis; however, the thickness of the media of the coronary artery was not associated with renal vasculature changes (data not shown). In addition, the frequency of advanced coronary atherosclerotic lesions was significantly correlated with the rates of renal arteriolar hyalinization and global glomerulosclerosis. Schwartz *et al.*[6] demonstrated that advanced coronary lesions were more frequent in patients with ESRD than in those without renal disease (100% vs. 80%), similar to our results. Glomerular changes include signs of inflammatory glomerulopathy and noninflammatory glomerulopathy. Noninflammatory glomerular diseases comprise metabolic and systemic diseases, such as diabetes and hypertension. We found that noninflammatory glomerulosclerosis is largely affected by age, diabetes and hypertension. In addition, the rate of global glomerulosclerosis was independently associated with the I/M ratio of the coronary artery. The mechanism underlying the direct association between glomerular changes and the development of coronary artery disease is obscure; however, our findings suggest that glomerular changes are associated with the development of coronary heart disease.

Several clinical studies have also shown that chronic renal failure or dysfunction is associated with carotid atherosclerosis[22, 23], cerebrovascular disease[24] and peripheral artery disease[22-25]. Patients with ESRD have a 4- to 10-fold greater risk of hospitalized ischemic and hemorrhagic stroke[26], an increased risk of cognitive impairment and dementia[27] and a poor long-term poststroke prognosis[28]. Histologically, we observed that renal vasculature changes were associated with the severity of atherosclerosis in the common carotid, common iliac and cerebral arteries. In addition, renal atherosclerosis was independently associated with the presence of advanced atherosclerotic lesions in the cerebral arteries. The cerebrovascular changes observed in patients with chronic kidney disease may be related to stroke or brain damage.

The carotid intima-media thickness (IMT) assessed using ultrasonography is a noninvasive measurement that is now widely used as an adjunct to traditional cardiovascular risk factors for assessing the atherosclerotic burden[29]. Zhang *et al.*[30] demonstrated that the carotid IMT values are significantly higher in subjects with early-stage CKD. Recently, we reported that the microscopically determined carotid IMT is associated with the I/M ratios of the coronary, cerebral and common iliac arteries[31]. In this study, the I/M ratio of the common carotid artery was associated with renal vasculature changes according to a univariate analysis, although there were no significant differences in a multivariate analysis. The microscopically evaluated common carotid IMT was also found to be correlated with atherosclerosis of the renal arteries, renal arteriolar hyalinization and global glomerulosclerosis. These findings suggest that the common carotid IMT is an indicator of renal vasculature changes.

Several potential mechanisms may explain the association between renal vasculature changes and generalized atherosclerosis. Age, gender, hypertension and diabetes are risk factors for the development of renal atherosclerosis and global glomerulosclerosis and are associated with generalized atherosclerosis[32]. In addition, a decreased renal blood flow and/or renal dysfunction are associated with increased levels of novel risk factors, such as inflammation, oxidative stress, anemia and abnormal calcium-phosphate metabolism[33, 34]. Animal studies using uremic apolipoprotein E knockout mice and Dahl salt-sensitive rats support these results[35, 36]. We were unable to assess the contribution of these factors in the present study.

In this study, pathological changes in four portions of the renal vasculature differed. Arteriosclerotic changes in the renal arteries, arterioles and glomeruli were found to be significantly associated with such changes in the cerebral, common carotid and coronary arteries, whereas changes in the intrarenal arteries were independent of systemic changes. Although we cannot clearly explain the mechanisms underlying these differences, variability in hydraulic pressure according to the site of the renal vasculature[37], local hemodynamic shear stress[38] and vascular smooth muscle cell diversity[39] may contribute to these changes.

There are several limitations to our study. First, albuminuria and proteinuria were not evaluated in this study. Second, the serum creatinine level can be affected by various factors, including cachexia, hydration and dehydration; therefore, we were unable to evaluate the correlation between the serum creatinine level and renal vasculature changes. Third, the number of cerebral arteries examined was less than half of that of other arteries.

Conclusion

Our results demonstrated that pathological changes in four portions of the renal vasculature differ, which suggests that different parts of the renal vasculature may be affected by different risk factors. On the other hand, renal vasculature changes except the intrarenal arteries were significantly associated with those observed in the cerebral, common carotid and coronary arteries. These results therefore support the concept that renal artery disease is associated with generalized atherosclerosis.

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Conflicts of Interest

None.

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