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ORIGINAL ARTICLE

Interrelationship between brachial artery function and renal small artery sclerosis in chronic kidney disease

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Chronic kidney disease (CKD), characterized by senile inflammation, is a risk factor for cardiovascular disease. Conduit artery function and small artery structure relate to cardiovascular disease. We examined the correlations, determinants and interrelationships of arterial indices in association with CKD in a cross-sectional study of 139 patients (60% male; mean age 44 years) with CKD (stages 3–5, 39%) who underwent a renal biopsy. Conduit artery function and small artery sclerosis were assessed by brachial artery flow-mediated dilatation (FMD) and semiquantitative evaluation of small artery intimal thickening (SA-IT), respectively. The estimated glomerular filtration rate correlated with FMD ($r=0.31$, $P=0.0002$) and inversely correlated with SA-IT ($r=-0.54$, $P<0.0001$). Multiple regression analysis showed that FMD was inversely correlated with SA-IT and vice versa. In addition, high-sensitivity C-reactive protein (hs-CRP) was significantly correlated with SA-IT, but not FMD. Multiple logistic analysis revealed that higher hs-CRP concomitant with decreased FMD was further associated with the risk of severe SA-IT compared with their individual effects. These findings suggest that both conduit artery and small artery disease develop with mutual interaction in parallel with decreased kidney function. Coexistence of inflammation and conduit artery dysfunction may be closely related to renal small artery sclerosis in patients with CKD.
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Keywords: chronic kidney disease; conduit artery; flow-mediated dilatation; inflammation; small artery sclerosis

INTRODUCTION

The risk of cardiovascular disease (CVD) and end-stage renal disease increases with progression of chronic kidney disease (CKD).[1–3] Endothelial dysfunction is an early step in the progression to atherosclerosis that precedes structural vessel changes.[4] Accumulating evidence has demonstrated that endothelial dysfunction in large conduit arteries (that is, brachial) can predict CVD in the general population[5] as well as among elderly individuals[6] and patients with hypertension[7] and established atherosclerosis.[8,9] Moreover, endothelial dysfunction has been implicated as a major pathophysiological mechanism responsible for the CKD-associated risk of CVD.[10,11] Although brachial artery flow-mediated dilatation (FMD) is frequently used as a tool for the assessment of endothelial function, it reportedly reflects both endothelial-dependent and endothelial-independent vascular function in patients with cardiovascular risk burdens.[12] In CKD patients whose conditions are often complicated by various cardiovascular risk factors, decreased FMD is reportedly associated with carotid intima–media thickness[13] and an increased risk of CVD.[11]

In the past decade, many studies have shown that small artery disease also has a predictive value for CVD. Structural changes in the vascular wall of small arteries in the retina and abdominal subcutaneous fat can predict future CVD in patients with hypertension.[14–17] In addition, previous studies suggested a link between conduit artery disease and small artery disease in patients with hypertension.[18,19] However, it is not clear whether large conduit artery function and small artery structural changes in target organs develop in parallel with CKD progression and whether they mutually correlate with independent risk factors for arteriosclerosis. Moreover, a link between inflammation and both indices of vascular disease is unknown, although inflammation is suggested to be involved in the mechanism of CKD-associated CVD.[11]

In the present study, we conducted a retrospective cross-sectional review to examine whether large conduit artery dysfunction assessed by FMD and renal small artery sclerosis advanced in parallel with a decrease in the estimated glomerular filtration rate (eGFR) and identify their determinants in CKD patients who had undergone a renal biopsy. We further examined the interrelationship among indices of large and small vascular disease.

METHODS

Study participants

A total of 172 consecutive patients with CKD who underwent renal biopsy at University of the Ryukyus Hospital between 1 June 2010 and 31 March 2013

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were considered for this study. We routinely examined FMD as a vascular function from 1 June 2010. Both conduit artery function and small artery structural change are proposed to be confounded by primary diseases such as systemic vasculitis and amyloidosis and some drugs such as calcineurin inhibitors. Therefore, we excluded 33 patients because of treatment with steroids ($n=16$) and/or calcineurin inhibitors ($n=6$), vasculitis ($n=2$), amyloidosis ($n=3$), purpura nephritis ($n=1$), a transplanted kidney ($n=1$) and the absence of a small artery specimen ($n=1$). Data from the remaining 139 patients (84 men and 55 women) were analyzed in this study. The study protocol was approved by the ethics review board of University of the Ryukyus. All patients gave informed consent to participate in the study.

Histological diagnoses based on renal biopsy specimens

On the basis of renal biopsy findings, the following diagnoses were made for the 139 study participants: immunoglobulin A nephropathy ($n=84$), membranous nephropathy ($n=11$), minor glomerular abnormalities ($n=4$), focal segmental glomerular sclerosis ($n=1$), membranoproliferative glomerulonephritis ($n=2$), nonimmunoglobulin A mesangial proliferative glomerulonephritis ($n=7$), benign nephrosclerosis ($n=12$), lupus nephritis ($n=1$), diabetic nephropathy ($n=6$), tubulointerstitial nephritis ($n=2$) and other miscellaneous diseases ($n=9$).

Semiquantitative assessment of renal small arteries

We studied renal small arteries, including the large interlobular artery, with more than three layers of smooth muscle cells and a lumen diameter of ~200–300 μm and the arcuate arteries of the kidney. The wall/lumen ratio of the small artery, which is often used as an index of small vessel disease,[14,15,20] is difficult to apply to renal biopsy specimens because it is not commonly available in the tangential view. Intrarenal arteriosclerosis with intimal thickening is often complicated in patients with hypertension[21] and in elderly patients.[22] Intimal thickening has been shown to be an early morphological change preceding atherosclerosis in humans.[23,24] Therefore, we examined the degree of intimal thickening compared with the thickness of the adjacent medial wall. Specifically, we semiquantitatively assessed intimal thickening in the small arteries of each specimen using the following grading system: grade 0 (G0), no thickening; grade 1 (G1), intimal thickening of less than half the adjusted medial thickness; grade 2 (G2), intimal thickening of more than half and/or less than the adjusted medial thickness; and grade 3 (G3), intimal thickening of more than the adjusted medial thickness. On the basis of this grading system, we calculated the mean grade of intimal thickening in the small renal arteries (small artery intimal thickening (SA-IT) index) in each patient according to the following formula: arteriolar wall thickening index $=(n0\times 0+n1\times 1+n2\times 2+n3\times 3)/N$.

The representative microphotographs of each graded SA-IT are shown in Figure 1. All histologic analyses were performed by one physician (KK) who was blinded to patient information.

Assessment of brachial artery vascular function

We routinely examined FMD as a vascular function from 1 June 2010. Subjects underwent noninvasive assessment of FMD to evaluate endothelial function using a standardized procedure.[21,25] We measured FMD in the morning before renal biopsy. All patients were requested to fast for at least 10 h, abstain from smoking and the consumption of alcohol and caffeine and withhold all medications. They were asked to rest in a quiet, dark, air-conditioned, temperature-controlled room (23–26 °C) for at least 15 min in a supine position before the examination. Ultrasound equipment and a high-resolution linear array transducer coupled to computer-assisted analysis software provided one longitudinal and two short-axis images using 10 MHz H-type probe (UNEXEF18G, UNEX, Nagoya, Japan). It was used to scan the brachial artery in B-mode 5 to 10 cm above the right elbow. When the clearest B-mode image of the intima–media complex was obtained, the transducer was held at the same point throughout the scan by a stereotactic probe holder. FMD was measured by the A-mode waves as a signal of the intima–media complex that was synchronized with the electrocardiographic R-waves and tracked automatically. After measuring baseline brachial artery diameter, we compressed the brachial artery (at least 50 mm Hg above systolic blood pressure) for 5 min using a blood pressure cuff placed around the forearm. After compression, maximum brachial artery diameter was measured after cuff release for 3 min.

The reproducibility of the FMD measurements using this system and the correlation coefficient between the data of two visits was reported to be 0.86, with a coefficient of variance of 11.2%.[26] We also assessed FMD measurement in 7 control subjects who were all healthy volunteers (28–38 years old, 57% male). We examined the first FMD and second FMD in 1 day with 2 h interval using this system. Pearson's correlation coefficient of the FMD between first FMD and second FMD was 0.93 ($P<0.005$), and the coefficient of variation was 17.4%. The mean value of the FMD in the control subjects was 7.1%, similar to those of general population aged 20–40 years.[27]

FMD was expressed as follows: (maximum brachial artery diameter after cuff release −baseline brachial artery diameter)/baseline brachial artery diameter $\times 100$. This dilating rate is referred to as the percentage FMD (%), an evaluation index for the vascular function of the brachial artery. All FMD examinations were performed by one experienced physician (TM).

Laboratory procedures and definition of comorbid conditions

Fasting blood samples were used to measure the serum levels of total cholesterol, high-density lipoprotein and low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, creatinine, high-sensitivity C-reactive protein (hs-CRP), hemoglobin A_{1c} (HbA_{1c}) and glucose. Urinary protein was measured in first spot morning urine samples. Blood and urine samples were collected on the day before FMD measurement. Diabetes mellitus was determined by fasting and postprandial glucose and HbA_{1c} levels in addition to a medical history of diabetes. Dyslipidemia was defined as hyper LDL cholesterolemia and/or hypertriglyceridemia and/or hypo high-density lipoprotein cholesterolemia and/or the use of medications for dyslipidemia. Hyperuricemia was defined as uric acid $\geqslant 7\,mg\,dl^{-1}$ among men and uric acid $\geqslant 6\,mg\,dl^{-1}$ among women and/or the use of medications for hyperuricemia. Ever smokers were defined as current or ex-smokers. The eGFR was calculated using a new equation for Japanese individuals: eGFR ($ml\,min^{-1}$ per $1.73\,m^2$) $=194\times$ serum creatinine$^{1.094}\times$ age$^{0.287}$ ($\times 0.739$ if female).[28]

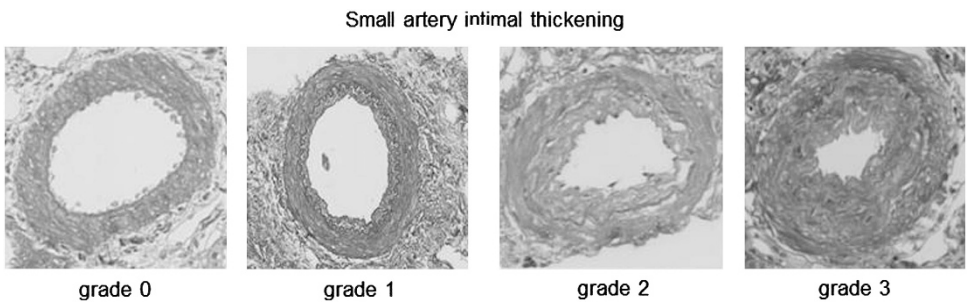


Figure 1 Representative microphotographs of small artery intimal thickening (grades 0–3). Masson's trichrome staining (magnification: grades 0, 2 and 3, ×400; grade 1, ×200). Small artery intimal thickening was semiquantitatively assessed as follows: grade 0 (G0), no thickening; grade 1 (G1), mild thickening; grade 2 (G2), moderate thickening without definite narrowing of the lumen; and grade 3 (G3), severe thickening with definite narrowing of the lumen. A full color version of this figure is available at *Hypertension Research* online.

We estimated eGFR in 7 patients aged <18 years using the Schwartz formula.[29]

Patient characteristics

Lifestyle information (that is, smoking habits), anthropometric parameters and medication information, including the use of antihypertensive drugs, statins, antidiabetic drugs and antiuricemic drugs, were obtained from medical records.

Statistical analyses

Continuous measures, categorical measures and ordered categorical measures were analyzed using analysis of variance, χ^2 tests and Kruskal–Wallis tests, respectively. Multivariate regression analysis was performed to identify independent predictors of either FMD or SA-IT. Some medications, including antihypertensive drugs, statins and antiuricemic drugs; uric acid; and inflammation can potentially affect the indices of vascular damage. Accordingly, we computed models of increasing complexity adjusted for basal status (age, sex, eGFR and medication for risk factors), traditional risk factors (mean blood pressure at FMD measurement, HbA_{1c}, low-density lipoprotein (LDL) cholesterol and ever smoking status) and potential nontraditional risk factors (uric acid and hs-CRP). Because of log-normality distribution of plasma hs-CRP, logarithmic-transformed hs-CRP (Log (hs-CRP)) was used in the analysis. Diabetes mellitus is thought to have an effect on both vascular indices. Therefore, to minimize the confounding effect of diabetes mellitus on the association between FMD and SA-IT, we also conducted multiple regression analysis for subjects without diabetes mellitus. We found that both FMD and hs-CRP were significantly correlated with SA-IT. Therefore, we further examined the interaction of FMD and hs-CRP with SA-IT. The data are expressed as means and s.d., medians and interquartile ranges or numbers and percentages. Statistical analyses were conducted using JMP 10 software (SAS Institute, Cary, NC, USA). The *P*-values of <0.05 were considered statistically significant.

RESULTS

Clinical characteristics

The mean age of all patients at baseline was 44 years, and 60% were male (Table 1). The mean eGFR was $73 \pm 31\,ml\,min^{-1}$ per $1.73\,m^2$, whereas the prevalence of CKD stages 3–5 was 39% ($n=54$). Approximately 50% patients had hypertension, and 84% were being treated with renin–angiotensin system inhibitors. The prevalence of diabetes mellitus was only 9%. Age, prevalence of hypertension and hyperuricemia and the use of some drugs for cardiovascular risk factors, such as renin–angiotensin system inhibitors, increased with advancing CKD stage. There was a significant trend toward lower FMD and higher SA-IT with an advance in CKD stage.

Crude correlation of FMD and SA-IT with eGFR

The eGFR was positively correlated with FMD ($r=0.31$, $P=0.0002$) and negatively correlated with the SA-IT index ($r=-0.54$, $P<0.0001$; Figures 2a and b).

Crude correlation between potential risk factors for FMD and SA-IT

Age and all classic risk factors, uric acid and the SA-IT index showed an inverse correlation with FMD, whereas eGFR showed a positive correlation. Similarly, age, all classic risk factors except for LDL

Table 1 Clinical characteristics of subjects according to CKD stage

Variable	*Total* N = *139*	*CKD stage 1–2* n = *85*	*CKD 3a* n = *27*	*CKD 3b–5* n = *27*	P-*value for trend*
Age (years)	44 ± 17	37 ± 16	51 ± 10	57 ± 14	<0.0001
Male	84 (60)	46 (54)	20 (74)	18 (66)	0.13
Body mass index ($kg\,m^{-2}$)	24 ± 4	23 ± 4	24 ± 3	24 ± 4	0.4
Hypertension	69 (49)	29 (34)	20 (74)	20 (74)	<0.0001
Diabetes mellitus	13 (9)	6 (7)	2(7)	5 (18)	0.18
Dyslipidemia	83 (59)	46 (54)	19 (70)	18 (66)	0.23
Hyperuricemia	64 (46)	21 (24)	21 (77)	22 (81)	<0.0001
Ever smoking status	60 (43)	31 (36)	16 (59)	13 (48)	0.09
Mean blood pressure (mm Hg)	89 ± 10	85 ± 9	96 ± 9	93 ± 10	<0.0001
Serum creatinine ($mg\,dl^{-1}$)	1.0 ± 0.6	0.7 ± 0.1	1.0 ± 0.1	1.8 ± 1.0	<0.0001
eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	73 ± 31	92 ± 23	53 ± 3	31 ± 8	<0.0001
LDL cholesterol ($mg\,dl^{-1}$)	117 ± 53	119 ± 55	121 ± 56	108 ± 40	0.61
Fasting glucose ($mg\,dl^{-1}$)	105 ± 31	102 ± 27	106 ± 24	113 ± 44	0.24
HbA_{1c} (%)	5.5 ± 0.6	5.5 ± 0.6	5.5 ± 0.3	5.8 ± 0.9	0.09
UA ($mg\,dl^{-1}$)	6.3 ± 1.7	5.7 ± 1.4	7.0 ± 1.5	7.2 ± 1.9	<0.0001
hs-CRP($mg\,l^{-1}$)	0.9 (0.3–2.1)	0.6 (0.2–2.0)	1.5 (0.7–2.9)	1.4 (0.6–2.1)	0.05
FMD (%)	5.9 ± 2.9	6.6 ± 3.0	4.7 ± 2.6	5.0 ± 2.4	0.003
Baseline brachial artery diameter (mm)	3.8 ± 0.6	3.7 ± 0.6	4.1 ± 0.6	3.9 ± 0.5	0.001
SA-IT index	1.1 ± 0.9	0.8 ± 0.8	1.4 ± 0.8	1.7 ± 0.6	<0.0001
Antihypertensive drugs	65 (46)	26 (30)	19 (70)	20 (74)	<0.0001
Renin–angiotensin system inhibitors	58 (41)	24 (28)	15 (55)	19 (70)	0.0002
Calcium channel blockers	29 (20)	11 (12)	10 (37)	8 (29)	0.02
Diuretics	11 (7)	8 (9)	2 (7)	1 (3)	0.6
Others	12 (13)	4 (4)	4 (14)	4 (14)	0.1
Statins	19 (13)	8 (9)	3 (11)	8 (29)	0.02
Antiuricemic drugs	21 (15)	3 (3)	6 (22)	12 (44)	<0.0001

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilatation; HbA_{1c}, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SA-IT, small artery intimal thickening; UA, serum uric acid.
Data are expressed as mean ± s.d., medians (interquartile ranges) or numbers (%).
To convert serum creatinine in $mg\,dl^{-1}$ to $mmol\,l^{-1}$, multiply by 88.4; LDL cholesterol in $mg\,dl^{-1}$ to $mmol\,l^{-1}$, multiply by 0.0259; glucose in $mg\,dl^{-1}$ to $mmol\,l^{-1}$, multiply by 0.055; UA in $mg\,dl^{-1}$ to $\mu mol\,l^{-1}$, multiply by 59.48.

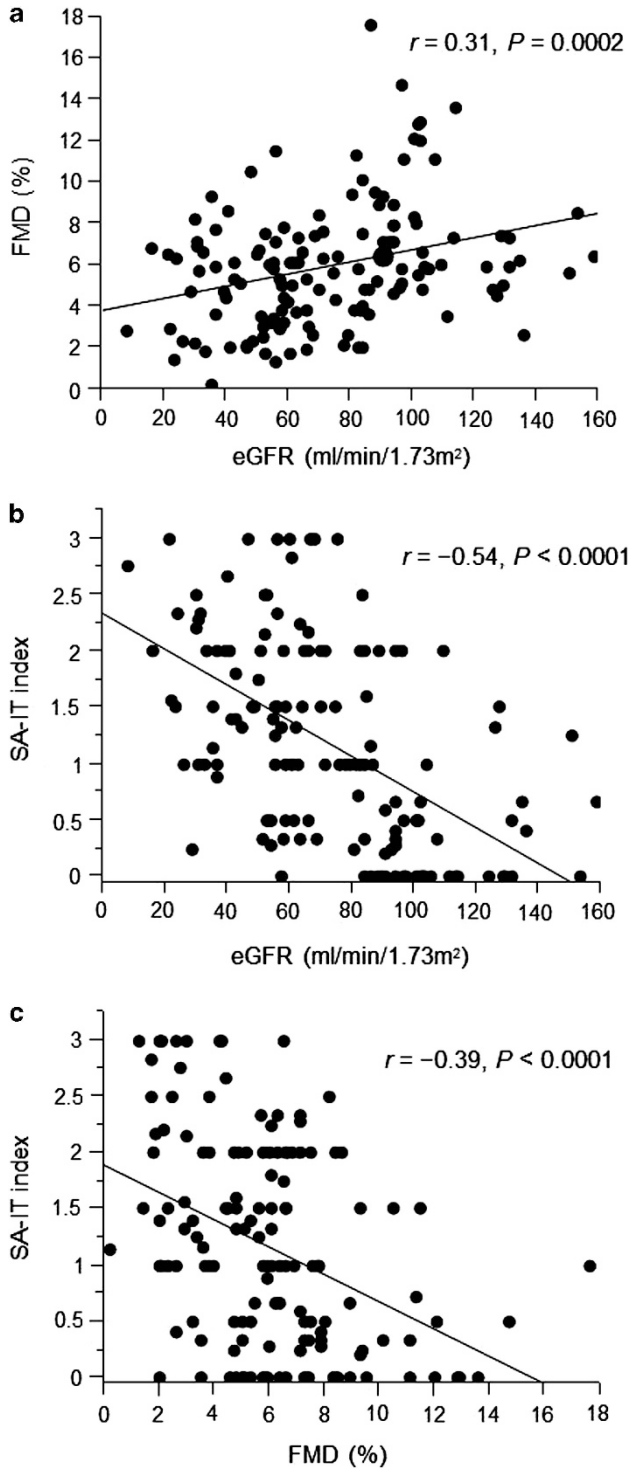


Figure 2 Relationship of estimated glomerular filtration rate (eGFR) with flow-mediated dilatation (FMD) (**a**) and the small artery intimal thickening (SA-IT) index (**b**). Relationship between FMD and the SA-IT index (**c**).

cholesterol, Log (hs-CRP) and uric acid showed a positive correlation with the SA-IT index, whereas eGFR and FMD showed an inverse correlation.

Correlation between FMD and renal small artery disease

FMD was inversely correlated with the SA-IT index ($r = -0.39$, $P < 0.0001$; Figure 2c).

Table 2 Multiple regression analysis for determinants of FMD

	Unadjusted		*Model 1* ($R^2 = 0.25$)		*Model 2* ($R^2 = 0.26$)		*Model 3* ($R^2 = 0.29$)	
	r	P-*value*	β	P-*value*	β	P-*value*	β	P-*value*
SA-IT index	−0.39	<0.0001					−0.29	0.01
Age	−0.37	<0.0001	−0.17	0.1	−0.18	0.08	0.006	0.9
Male (yes)			0.20	0.01	0.16	0.05	0.22	0.01
eGFR	0.31	0.0002	0.02	0.8	−0.02	0.8	−0.03	0.7
Medication (yes)			0.18	0.07	0.17	0.09	0.20	0.04
HbA_{1c}	−0.28	0.0007	−0.08	0.3	−0.08	0.3	−0.06	0.4
LDL-C	−0.18	0.02	−0.15	0.04	−0.15	0.05	−0.15	0.05
Ever smoking status (yes)			0.04	0.63	0.03	0.7	0.02	0.7
Mean blood pressure	−0.20	0.01	0.005	0.9	0.01	0.8	0.04	0.6
Log (hs-CRP)	−0.16	0.05			0.02	0.7	0.09	0.2
UA	−0.30	0.0002			−0.13	0.1	−0.10	0.2

Abbreviations: eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilatation; HbA_{1c}, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SA-IT, small artery intimal thickening; UA, serum uric acid.
Medication: for hypertension, dyslipidemia and hyperuricemia.
Model 1: adjusted for age, classical risk factors and medication.
Model 2: adjusted for age, classical risk factors, medication, Log (hs-CRP) and uric acid.
Model 3: adjusted for SA-IT index, age, classical risk factors, medication, Log (hs-CRP) and uric acid.

Multiple regression analysis for determinants of FMD

In the multivariate analysis with forced entry of age, sex, eGFR, medications for traditional risk factors and traditional risk factors, male sex and LDL cholesterol were significant determinants of FMD (Table 2). After the addition of uric acid and Log (hs-CRP) to model 1, the significance of male sex and LDL cholesterol was attenuated and became marginal. Finally, addition of the SA-IT index to model 2 demonstrated that male sex and medication use were positively correlated with FMD, whereas the SA-IT index was negatively correlated.

Multiple regression analysis for determinants of SA-IT

In the multivariate analysis with force entry of age, sex, eGFR, medications for traditional risk factors and traditional risk factors, age and male sex were significant determinants of the SA-IT index (Table 3). After the addition of Log (hs-CRP) and uric acid (model 2), Log (hs-CRP), age and male sex were significant determinants. Finally, the addition of FMD to model 2 demonstrated that all significant factors in model 2 remained significant.

Therefore, there was a mutual interrelation between FMD and the SA-IT index, independent of various risk factors for CVD. This interaction remained significant even after additional adjustment for baseline brachial artery diameter (data was not shown). Moreover, even after the exclusion of 13 patients with diabetes, the mutual interrelation remained significant as follows: SA-IT for FMD ($\beta = -0.12$, $P = 0.04$) and FMD for SA-IT ($\beta = -0.27$, $P = 0.04$).

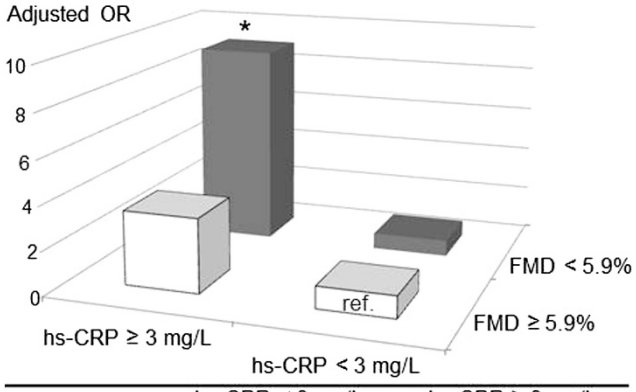
Combination effects of FMD and hs-CRP on SA-IT

Because multiple regression analysis revealed that both FMD and Log (hs-CRP) were significant determinants of SA-IT, we further examined their combined effects on SA-IT and found a significant interaction between these factors for SA-IT ($P = 0.02$ for interaction; Figure 3). Moreover, multiple logistic analysis revealed that the

Table 3 Multiple regression analysis for determinants of SA-IT

	Unadjusted		*Model 1 ($R^2 = 0.62$)*		*Model 2 ($R^2 = 0.66$)*		*Model 3 ($R^2 = 0.67$)*	
	r	P-*value*	β	P-*value*	β	P-*value*	β	P-*value*
FMD	−0.39	<0.0001					−0.14	0.01
Age	0.73	<0.0001	0.63	<0.0001	0.66	<0.0001	0.63	<0.0001
Male (yes)			0.12	0.03	0.19	0.002	0.22	0.0005
eGFR	−0.54	<0.0001	−0.07	0.3	−0.03	0.6	−0.03	0.6
Medication (yes)			0.05	0.5	0.11	0.1	0.13	0.06
HbA_{1c}	0.33	<0.0001	0.08	0.1	0.07	0.2	0.06	0.2
LDL cholesterol	0.13	0.1	0.01	0.7	−0.01	0.8	−0.03	0.5
Ever smoking status (yes)			−0.06	0.2	−0.02	0.6	−0.02	0.6
Mean blood pressure	0.38	<0.0001	0.11	0.08	0.09	0.1	0.09	0.1
Log (hs-CRP)	0.38	<0.0001			0.23	<0.0001	0.20	<0.0001
UA	0.28	0.0007			0.10	0.1	0.08	0.1

Abbreviations: eGFR, estimated glomerular filtration rate; FMD, flow-mediated dilatation; HbA_{1c}, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SA-IT, small artery intimal thickening; UA, serum uric acid.
Medication: for hypertension, dyslipidemia and hyperuricemia.
Model 1: adjusted for age, classical risk factors and medication.
Model 2: adjusted for age, classical risk factors, medication, Log (hs-CRP) and serum uric acid.
Model 3: adjusted for FMD, age, classical risk factors, medication, Log (hs-CRP) and serum uric acid.



	hs-CRP < 3 mg/L	hs-CRP ≥ 3 mg/L
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
FMD ≥ 5.9%	1.00 (reference)	3.37 (0.5–22.2)
FMD < 5.9%	0.72 (0.2–2.5)	9.39* (1.3–61.2)

Figure 3 Age, sex, medication use, traditional risk factors for cardiovascular disease (CVD) and hyperuricemia were included in the analysis. Adjusted odds ratios (ORs) for risk of higher-grade small artery intimal thickening (SA-IT) defined as the highest SA-IT index tertile according to higher ($\geqslant 3\,mg\,l^{-1}$) high-sensitivity C-reactive protein (hs-CRP) and lower (<5.9%) flow-mediated vasodilation (FMD). **vs.* subgroup hs-CRP$<3\,mg\,l^{-1}$/FMD$\geqslant$5.9% as a reference, $P = 0.018$. CI, confidence interval.

coexistence of a decreased FMD, defined as FMD lower than the mean value, and higher hs-CRP, defined as $>3\,mg\,l^{-1}$ of hs-CRP, was significantly associated with severe SA-IT, defined as the highest SA-IT index tertile independent of age, sex, medication use, traditional risk factors for CVD and hyperuricemia.

DISCUSSION

Decreased renal function is an independent risk factor for CVD among CKD patients.[10,11] The present study showed that large conduit artery dysfunction and small renal artery sclerosis progress in parallel with a decrease in kidney function. Although neither eGFR nor traditional risk factors correlated with both indices of vascular disease, hs-CRP correlated with SA-IT in multiple models. Moreover, interrelations between FMD and SA-IT existed independent of traditional risk factors.

Renal small vessel disease reportedly exists even in healthy kidney donors, and its prevalence increases with age.[22] In addition, renal function itself is suggested to be associated with endothelial dysfunction in large conduit arteries[11,13] and with small vessel disease in the retina[20] and kidney[30] among CKD patients. Similarly, we found a significant crude correlation among age, eGFR and both FMD (inverse relationship) and SA-IT. However, multiple regression analysis revealed that the contribution of either age or eGFR to both indices of large and small vessel disease was not clear, suggesting possible contribution by other factors.

FMD and associated factors

Several risk factors related to atherosclerosis were crudely correlated with conduit artery function assessed by FMD; however, these associations were not clear in multiple regression analysis. Therefore, the present study may not have enough power to elucidate the contributions of each risk factor or FMD may not be determined solely by individual risk factors. In contrast, SA-IT correlated with FMD independent of these risk factors. The degree of SA-IT may reflect the burden of measurable and unmeasurable CVD risk factors in CKD patients. Because FMD was reportedly improved after renal transplantation in hemodialysis patients,[31,32] uremia-related risk factors may play a significant role in the progression of large conduit artery dysfunction among CKD patients. A previous study of CKD patients demonstrated that hs-CRP increased in a linear manner with an advance in CKD stage and that it was significantly associated with FMD independent of traditional risk factors.[11] However, an independent association between hs-CRP and FMD was not confirmed in the present study. The greater proportion of patients with stage 4–5 CKD in the previous study compared with that in the present study may account for the differences in results. Alternatively, a higher prevalence of patients treated with renin–angiotensin inhibitors may have affected the results because these drugs reportedly improve FMD.[33]

Renal SA-IT and associated factors

Retinal artery caliber changes closely parallel microvascular structural changes elsewhere in the body, including the kidneys.[34] An Australian cohort study demonstrated that a small artery in the retina was narrowed with a decrease in eGFR; therefore, the authors implied that concurrent small vessel disease in the kidney may contribute to the progression of CKD.[20] Consistent with those observations, small artery sclerotic changes in the kidneys became more severe with a decline in kidney function in the present study. In addition, senile small artery disease may progress systemically with the progression of CKD. Previous studies demonstrated that hs-CRP was significantly associated with coronary artery atherosclerotic plaque and carotid artery intimal thickening. However, few clinical studies have reported the contribution of inflammation to small artery sclerosis in target organs such as the kidneys. The present study suggests that inflammation may be partially responsible for the development of small artery sclerosis. Moreover, the present study suggests that inflammation concomitant with vascular dysfunction may play a crucial role in small artery sclerosis.

Interrelationship between FMD and renal small artery sclerosis

Besides hs-CRP, FMD was found to be a significant factor for small artery sclerotic change along with conventional risk factors such as hypertension. Although we cannot conclude causality from the present study, these interrelationship may be involved in some underlying mechanisms. A previous report clearly showed that FMD closely correlated with the endothelial function of resistant small arteries of subcutaneous tissue.[35] Moreover, accumulation of asymmetric dimethylarginine, an endogenous nitric oxide inhibitor, was reportedly related to endothelial dysfunction in small vessels in patients with advanced CKD.[36,37] These observations suggest that local endothelial dysfunction may be related to renal SA-IT in CKD patients. Alternatively, conduit artery arterial wall stiffness, which can be reflected by decreased FMD, may contribute to small vessel disease as previously proposed.[19] Alternatively, renal small artery sclerosis may affect remote peripheral artery function because atherosclerotic renal artery stenosis has been suggested to cause peripheral conduit artery dysfunction.[38]

The association of decreased kidney function with large conduit artery dysfunction and renal small artery sclerosis may have some clinical implications. Previous studies increasingly suggest that small artery disease is involved in the progression of CVD and kidney dysfunction.[16,34] The present study suggests that inflammation may be responsible for small artery disease. Inflammation was consistently reported to be associated with an increased risk of CVD[11] and CKD.[39] The direct assessment of small artery disease in target organs is difficult in clinical settings. The results of the present study suggest that FMD may be a potent indicator of small artery sclerosis. In particular, decreased FMD accompanying elevated hs-CRP may be linked to the presence of renal small artery sclerosis among CKD patients. In addition, cross-talk between large vessel disease and small vessel disease is proposed to create a malignant circle and consequently play a crucial role in the progression of CVD.[19]

There are some limitations to the present study. First, measurement of FMD is highly dependent on technique in the conventional system[40] that often fails to detect peak diameter of brachial artery, resulting in underestimation of FMD. However, we used newly developed and semiautomated computerized ultrasonography (UNEXEF18G, UNEX) along with the protocol used in the FMD study conducted in Japan (FMDJ study), the ongoing multicenter study assessing clinical usefulness of FMD.[21] In this procedure, continuous edge-tracking system automatically detects and tracks the edges of the brachial artery at the same point throughout the study. In addition to technical issues, FMD at one point could vary because of several factors, including physiological variations and therapeutic effects. Therefore, FMD at one point does not always represent the steady state; however, the variability of FMD generally weakens the correlation of FMD with small artery sclerotic change. Second, we cannot conclude a cause–result relationship in the observed associations such as the correlation of FMD with renal small artery sclerosis. Third, we could not exclude the effects of sampling bias on the accuracy of the assessment of structural changes in the renal small arteries. However, the SA-IT index showed a linear correlation with age and classical risk factors. Moreover, if it had a profound impact on the results, such bias would tend to diminish the significance of specific associations. Fourth, the study sample included a small number of patients with hypertensive nephrosclerosis and diabetic nephropathy, and renal biopsies are generally not indicated in these patients. Therefore, it is not clear whether the observed association between FMD and small artery sclerosis in the kidney can be extended to all CKD etiologies.

In conclusion, large conduit artery dysfunction and renal small artery sclerosis progress in parallel with CKD progression. An interrelationship was found to exist between these indices independent of age, sex and various risk factors among the CKD patients evaluated. Inflammation, particularly when accompanied by vascular dysfunction, was significantly associated with renal small artery sclerosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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