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Relationship between Endothelial Dysfunction and Prevalence of Chronic Kidney Disease: The Circulatory Risk in Communities Study (CIRCS)

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Aims: Patients with chronic kidney disease (CKD) have a higher burden of cardiovascular morbidity and mortality than the general population. Endothelial dysfunction has been suggested to play a role in both glomerular filtration rate loss and cardiovascular damage. Thus, the present study aimed to evaluate the relationship between endothelial dysfunction and the prevalence of CKD in the general Japanese population.

Methods: We conducted a cross-sectional study of 1042 men and women aged 30–81 years in two communities under the Circulatory Risk in Communities Study between 2013 and 2017. Endothelial function was evaluated by percent change of brachial artery flow-mediated dilation (%FMD) before and after the cuff inflation.

Results: Among the total 1042 participants, there were 62 cases of CKD (~6%). The multivariable odds ratios (ORs) (95% confidence intervals [CIs]) of CKD according to quartiles of %FMD were 2.02 (0.68–5.99), 3.56 (1.27–9.94), and 3.14 (1.10–8.93) for the third to lowest quartile compared with the highest %FMD quartile; p for trend = 0.02. The respective multivariable ORs (95% CIs) of CKD in subjects without antihypertensive medication use (39 cases among 886 subjects) were 1.83 (0.46–7.33), 3.41 (0.92–12.61), and 4.60 (1.22–17.31); p for trend = 0.01, and that for one-point decrement in %FMD was 1.16 (1.00–1.35); p for interaction with the status of antihypertensive medication use was 0.12.

Conclusions: Our cross-sectional study suggested the relationship between endothelial dysfunction and the higher prevalence of CKD in the general Japanese population.

Key words: Chronic kidney disease, Endothelial dysfunction, General Japanese population

Introduction

Compared with the general population, patients with chronic kidney disease (CKD) have a higher burden of cardiovascular morbidity and mortality[1]. Mortality from cardiovascular disease in patients with

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chronic renal failure is approximately 9% per year, which is 10 to 20 times higher than in the general population in Western countries[2]. Detection and treatment of CKD is now a public health priority. Traditional risk factors could not adequately predict CKD, and non-traditional risk factors may play a role both in reduced glomerular filtration rate (GFR) and cardiovascular damage[3, 4].

Endothelial dysfunction, as indicated by reduced brachial artery flow-mediated dilation (FMD), is considered a key early disorder in the development of coronary atherosclerosis[5]. Previous case-reference studies[6-8] reported that endothelial dysfunction was common in patients with advanced CKD, but the evidence on endothelial dysfunction associated with the risk of early CKD has been limited. A 7.7 year Italian prospective study[9] of 500 never-treated uncomplicated hypertensive subjects (mean aged 47 years) reported that endothelial dysfunction (evaluated by strain gauge plethysmography during intra-arterial infusion of acetylcholine) was associated with reduced estimated GFR (eGFR): eGFR changed by 0.37 mL/min/1.73 m^2 for each 100% change in forearm blood flow after adjustment for other cardiovascular risk factors and the use of antihypertensive treatment. Furthermore, experimental evidence also suggested that endothelial dysfunction plays a key role in human CKD; reduction of the bioavailability of nitric oxide leads to the development and progression of experimental kidney disease[10, 11].

To the best of our knowledge, no study has reported that endothelial dysfunction measured by noninvasive FMD is associated with the risk of CKD in detail. Thus, the present study aimed to examine the association between endothelial dysfunction by estimated %FMD levels and the prevalence of CKD in the general Japanese population.

Materials and Methods

Study Population

We conducted FMD measurements in two communities: one urban, Minami-Takayasu district in Yao City, Osaka prefecture, and one rural, Ikawa town, Akita Prefecture, covered by the Circulatory Risk in Communities Study (CIRCS). The CIRCS is a dynamic community-based cohort study that covers five communities in Japan, including Yao and Ikawa. From January 2013 to June 2017 [12], we recruited a total of 1,042 participants (537 men and 505 women) without specified from the community of Yao (recruitment rate among the cardiovascular survey participants, 31.2%) and from Ikawa (33.2%) aged 30–81 years who underwent annual cardiovascular risk surveys. Informed consent for FMD measurement was obtained from each participant. The Ethics Committee of Osaka University and the Osaka Center for Cancer and Cardiovascular Diseases Prevention approved this study protocol.

Measurement of Endothelial Dysfunction

To measure FMD, all participants took a 5 min rest in a sitting position, using the standard protocol[13], and technicians used high-resolution ultrasonography and a forearm occlusive cuff according to current guidelines[14]. The right brachial artery diameter was measured using a high-resolution linear artery sensor (10 MHz) equipped with computer-aided analysis software (UNEXEF18G, UNEX Co., Nagoya, Japan)[15]. The brachial artery was imaged 5–10 cm above the elbow. When obtaining the clearest image of the anterior and posterior intimal interface between the lumen and blood vessels, the sensor is fixed at the same point during the whole scanning process. To standardize the position of the probe, we used specially designed handrails and probe holders. The system measures the diameter of the brachial artery at baseline and collects 30 s of baseline longitudinal images of the artery before the cuff was inflated to a 50 mm mercury column above SBP for 5 min and then deflated the cuff. Percent change of FMD (%FMD) was defined by the following formula: %FMD = ((maximal hyperemia diameter − baseline diameter)/baseline diameter) × 100, according to published guidelines for the determination of endothelial function[14]. Endothelial dysfunction was considered for the lowest quartile of %FMD value (< 5.3%) according to our previous study[16] and other studies that used receiver operating characteristic analysis[17, 18]. Based on a subsample of 43 participants, the coefficient of inter-operator variability among three operators for the FMD measurement in our laboratory was 5.7%, and those of intra-operator variability after 2 and 4 months were 11.1% and 10.8%, respectively[18].

Measurement of CKD

Serum creatinine levels were assayed using an enzymatic method. We calculated the eGFR (mL/min/1.73 m^2) based on the following formula, established by the working group of the Japanese Chronic Kidney Disease Initiative: eGFR (mL/min/1.73 m^2) = $1.94 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ for men and $1.94 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$ for women[19]. We defined CKD cases as an unexplained reduction in eGFR to less than 60 mL/min/1.73 m^2.

Measurement of other Factors

The body mass index (BMI) as weight (kg)

divided by the square of height (m^2) was also calculated. Blood pressures were measured by physicians and nurses with a standard mercury sphygmomanometer on participants' right arm[20]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or antihypertensive medication use. Serum glucose was determined by the hexokinase method, and hyperglycemia was defined as borderline or high serum glucose (fasting glucose ≥ 110 mg/dL or non-fasting glucose ≥ 140 mg/dL) and/or antidiabetic medication use. Serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined by an enzymatic assay. The use of antihyperlipidemic drugs was also ascertained. Menopausal status for women was asked by interview. All of them were measured using an automatic biochemical analyzer TBA–2000FR (Canon Medical Systems Corp., Tochigi, Japan) in Osaka Center for Cancer and Cardiovascular Disease Prevention. A face-to-face interview was conducted to ascertain alcohol consumption, smoking habits, and usual weekly physical activity.

Statistical Analysis

Mean values (standard deviations) and proportions of baseline characteristics were calculated according to quartiles of FMD levels. We tested the p for trend for the associations between baseline characteristics and FMD by the analysis of variance, using the median FMD value of each quartile.

We calculated age- and sex-adjusted, multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of prevalent CKD using the logistic regression analysis according to the quartiles of and one-point decrement of %FMD levels. We adjusted for the following potential confounding factors: age (year), sex, community, alcohol consumption (never drinkers, ex-drinkers, or current drinkers), smoking habits (never smokers, ex-smokers, or current smokers), BMI (< 18.5, 18.5–24.9, or ≥ 25.0 kg/m²), hypertension (high systolic blood pressure ≥ 140 mmHg and/or high diastolic blood pressure ≥ 90 mmHg and/or antihypertensive medication use), hyperglycemia (laboratory diagnosis and/or antidiabetic medication use), and baseline brachial artery diameter. Linear regression analysis predicting the level of eGFR by one-point decrement in %FMD was conducted for total sample, for those with and without antihypertensive medication use and for those with eGFR < 60 and ≥ 60 mL/min/1.73 m^2.

Using the Cochran–Armitage test, we calculated if the recruited sample size was enough to find a significant linear trend in the proportions tested. For the logistic regression analysis with four groups of equally spaced values (quartiles), with $\alpha = 0.05$ and power = 80%, the minimum required sample size in each group was 142 subjects with a minimum total sample of 568 subjects. In the present study, there was an average 260 subjects per group with a total sample of 1042 subjects; thus, at $\alpha = 0.05$, the estimated power was >97%. We further analyzed the association between %FMD levels and CKD, stratified by the use of antihypertensive medication status. P value for interaction was generated for an interaction term of the binary variable of the use of antihypertensive medication with the %FMD values by the likelihood ratio test. Sensitivity analyses were conducted considering the median, the lowest tertile, and the lowest quintile of %FMD as the cutoff points. We used SAS version 9.4 software (SAS Institute Inc, Cary, NC, USA) in all statistical analyses. Two-tailed P values of < 0.05 were considered statistically significant.

Results

The baseline characteristics of participants according to the quartiles of %FMD levels are shown in **Table 1**. The median values of %FMD in the lowest to highest quartiles were 3.9, 6.2, 7.8, and 10.4. Compared with participants in the lowest quartile of %FMD, those in the highest %FMD quartile were 6 year younger and were less likely to be men, rural residents, smokers, drinkers, diabetics, and hypertensives. eGFR and serum HDL-cholesterol levels were positively associated with %FMD, whereas systolic and diastolic blood pressure, serum triglycerides, and glucose levels were inversely associated with %FMD.

The association between %FMD levels and the prevalence of CKD are shown in **Table 2**. Among the total 1042 participants, compared with the highest %FMD quartile, the multivariable-adjusted ORs (95% CIs) of CKD were 2.02 (0.68–5.99) in the third quartile, 3.56 (1.27–9.94) in the second quartile, and 3.14 (1.10–8.93) in the lowest %FMD quartile of %FMD, p for trend = 0.02, and one-point decrement of %FMD levels was associated with OR of CKD = 1.09 (0.98–1.24). Further adjustment for serum total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), triglycerides (mg/dL), antihyperlipidemic drugs use (yes or not), and women menopausal status (yes or no) did not change the results materially (data not shown in **Table 2**). The positive association was primarily observed in subjects without medication use for hypertension; the respective multivariable-adjusted ORs (95% CIs) in the third to the lowest compared with the highest quartiles were 4.60 (1.22–17.31), 3.41 (0.92–12.61), and 1.83 (0.46–7.33), p for trend = 0.01, and one-point decrement of %FMD

Table 1. Mean values ± standard deviations and proportions of chronic kidney disease risk factors according to quartiles of %FMD levels

	%FMD levels				
	Q4 (high)	Q3	Q2	Q1 (low)	*P* for trend
No. at risk	267	268	262	245	
Range of FMD, %	8.9-20.3	7.0-8.8	5.3-6.9	0.7-5.2	
Median FMD, %	10.4	7.8	6.2	3.9	
Estimated glomerular filtration rate (eGFR), ml/min per 1.73 mm^2	82.8 ± 13.3	82.2 ± 14.3	78.9 ± 15.3	79.1 ± 16.4	< 0.001
Age, years	49.3 ± 8.3	50.6 ± 9.1	52.4 ± 9.3	55.4 ± 8.8	< 0.001
Men, %	40.5	43.3	53.8	70.2	< 0.001
Rural residents, %	36.7	44.0	51.2	53.5	0.0004
Current smokers, %	19.2	26.0	25.1	29.7	< 0.001
Current drinkers, %	22.9	23.4	26.4	27.3	< 0.001
Body mass index, kg/m^2	22.7 ± 3.2	23.3 ± 4.7	23.6 ± 3.9	24.0 ± 3.8	< 0.001
Systolic blood pressure, mmHg	122 ± 16	122 ± 17	124 ± 17	128 ± 17	< 0.001
Diastolic blood pressure, mmHg	79 ± 11	79 ± 10	81 ± 12	81 ± 10	0.003
Antihypertensive medication use, %	12.4	8.6	13.4	26.5	< 0.001
Hypertension, %	34.8	37.3	39.3	63.7	< 0.001
Serum total cholesterol, mg/dL	208 ± 34	215 ± 45	209 ± 35	206 ± 35	0.355
Serum HDL-cholesterol, mg/dL	65 ± 17	65 ± 17	62 ± 16	60 ± 16	< 0.001
Serum non-HDL-cholesterol, mg/dL	143 ± 32	151 ± 45	147 ± 33	146 ± 33	0.449
Serum triglycerides, mg/dL	95 ± 64	113 ± 174	120 ± 113	127 ± 92	0.001
Antihyperlipidemic medication use, %	6.7	8.2	5.3	11.8	0.097
High serum glucose, %	5.6	6.0	10.3	13.1	0.006
Antidiabetic medication use, %	6.4	6.0	6.9	11.8	0.025
Diabetes, %	8.2	9.0	13.0	16.7	0.009
Baseline brachial artery diameter, mm	3.53 ± 0.65	3.75 ± 0.65	3.98 ± 0.69	4.32 ± 0.72	< 0.001

levels was associated with an OR of CKD = 1.16 (1.00–1.35). The respective multivariable-adjusted ORs (95% CIs) for subjects with medication use for hypertension were 2.36 (0.38–14.78), 6.51 (1.06–40.13), and 4.53 (0.67–30.51), p for trend = 0.53, and one-point decrement of %FMD levels was associated with an OR of CKD = 0.99 (0.81–1.23), P for interaction with the medication use was 0.12. Furthermore, the multivariable linear regression slopes (95% CIs) of eGFR (mL/min/1.73 m^2) by one-point decrement in %FMD were −0.14 (−0.47 to 0.19), $p = 0.40$ for total sample, 0.23 (−0.89 to 1.35), $p = 0.40$ for subjects with antihypertensive medication use, and −0.19 (−0.52 to 0.15), $p = 0.28$ for those without antihypertensive medication use. The respective slopes (95% CIs) were 0.16 (−1.04 to 1.37), $p = 0.79$ for subjects with eGFR < 60 mL/min/1.73 m^2, and −0.03 (−0.34 to 0.27), $p = 0.84$ for those with eGFR ≥ 60 mL/min/1.73 m^2 (data not shown in **Table**).

Discussion

In the present study of 1042 Japanese participants aged 30–81 years, we found that the endothelial dysfunction measured by %FMD value was associated with the increased prevalence of CKD. The association was evident for people who did not use antihypertensive medications.

Most of the previous studies were of a case-reference design to compare the endothelial function among advanced CKD patients (chronic renal failure, dialysis, and transplantation) and non-CKD controls; the prevalence of endothelial dysfunction was higher in CKD patients than controls[6-8]. However, little is known about whether endothelial dysfunction is associated with the prevalence of CKD in the general population samples. The Hoorn study of 613 Dutch men and women aged 50–70 years with mild to severe renal insufficiency (average eGFR of 68 mL/min/1.73 m^2) showed that endothelial dysfunction, estimated by plasma von Willebrand factor, soluble vascular cell adhesion molecule-1, and urinary albumin–creatinine ratio, was associated with reduced eGFR cross-sectionally [21]. In that study, %FMD was linearly and inversely associated with nephropathy (microalbuminuria) after adjustment for age, sex, baseline arterial

Table 2. Multivariable odds ratios (ORs, 95%CI) of prevalence of chronic kidney disease according to quartiles of %FMD levels, and stratified by antihypertensive medication use

	%FMD levels				*P* for trend	1 point decrement of %FMD
	Q4 (high)	Q3	Q2	Q1 (low)		
Total						
No. at risk	267	268	262	245		
No. of e-GFR <60 ml/min per 1.73 mm²	5	12	22	23		
Model 1	ref	2.00 (0.68-5.89)	3.46 (1.26-9.55)	3.16 (1.13-8.78)	0.02	1.10 (0.99-1.23)
Model 2	ref	2.02 (0.68-5.99)	3.56 (1.27-9.94)	3.14 (1.10-8.93)	0.02	1.09 (0.98-1.22)
Subjects with antihypertensive medication						
No. at risk	33	23	35	65		
No. of e-GFR <60 ml/min per 1.73 mm²	2	5	9	7		
Model 1	ref	3.85 (0.61-24.13)	5.26 (0.94-29.28)	1.92 (0.35-10.55)	0.68	1.00 (0.84-1.21)
Model 2*	ref	4.53 (0.67-30.51)	6.51 (1.06-40.13)	2.36 (0.38-14.78)	0.53	0.99 (0.81-1.23)
Subjects without antihypertensive medication						
No. at risk	234	238	227	180		
No. of e-GFR <60 ml/min per 1.73 mm²	3	7	13	16		
Model 1	ref	1.80 (0.45-7.17)	3.36 (0.92-12.21)	4.19 (1.15-15.31)	0.01	1.15 (1.00-1.32)
Model 2*	ref	1.83 (0.46-7.33)	3.41 (0.92-12.61)	4.60 (1.22-17.31)	0.01	1.16 (1.00-1.35)
$P_{interaction}$					0.12	

Q4: 8.9-20.3, Q3: 7.0-8.8, Q2: 5.3-6.9, Q1: 0.7-5.2
Model 1: Adjusted for age, sex and community.
Model 2: Further adjusted for body mass index, hyperglycemia (high serum glucose and/or antidiabetic medication use), hypertension (systolic blood pressur
≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or antihypertension medication use) and brachial artery diameter.
*: Adjusted for the above variables except for antihypertensive medication use.
$P_{interaction}$ was calculated by the likelihood ratio between antihypertensive medication use status and the quartiles of %FMD levels.

diameter, and other potential confounders[22]. Similarly, a study of 334 patients with mild to severe renal insufficiency at a kidney clinic in Birmingham/UK reported that endothelial dysfunction, estimated by plasma von Willebrand factor and soluble P-selectin, was associated with the prevalence of CKD (serum creatinine concentration >1.47 mg/dL)[23]. However, in a more recent Japanese cross-sectional study[24] of 1,567 men and women aged 18–92 years who underwent health screening examinations or who visited the outpatient clinic, %FMD was not associated with the prevalence of CKD (eGFR <60 mL/min/1.73 m²) after adjustment for age, sex, and other cardiovascular risk factors; the OR of CKD for <1.7% compared with ≥ 1.7% in %FMD was 0.94 (95% CI: 0.70–1.27, p= 0.70). That result was different from our finding because of different definitions of endothelial dysfunction; they compared %FMD between the lowest quartile of %FMD (<1.7%) defined as endothelial dysfunction and the higher % FMD, whereas, in the present study, we divided %FMD into quartiles, and the lowest quartile %FMD defined as endothelial dysfunction was much higher (<5.3%). Many previous studies suggested a %FMD value of 6%–10% as healthy, 5%–6% as borderline, and 0%–5% as endothelial dysfunction[16, 18, 25-30]. Therefore, using a very low %FMD cutoff value (<1.7%) might have misclassified some cases of endothelial dysfunction. Another explanation is that 63.3% of participants in a previous Japanese study[24] were under antihypertensive medication that can affect the endothelial function by increased production or activity of nitric oxide[31, 32]. Antihypertensive agents such as ACE inhibitors and angiotensin II receptor blockers can increase more than two points of %FMD according to the review of 38 clinical trials[33]. By contrast, antihypertensive agents such as ACE inhibitors and calcium entry blockers can improve GFR[34].

The lack of association between endothelial dysfunction and the prevalence of CKD among participants under antihypertensive medication in the present study may be due to the low power to detect the association and also the effect of antihypertensive agents on endothelial function and GFR.

The biologic mechanisms for endothelial dysfunction and CKD are not well understood. Nitric

oxide, an important substance produced by the endothelium, plays a key role in vasodilation, inflammation, and reduction of oxidative stress mainly through the production of reactive oxygen species[35]. Several experimental studies[36-41] demonstrated that nitric oxide is an important regulator of renal blood flow, GFR, and salt and fluid balance. An experimental animal study using the 5/6 nephrectomy rat model of renal damage examined the endothelium-dependent vasodilatation of the interlobar artery at the time of nephrectomy and found that the endothelial release of nitric oxide protected rats from glomerular injury by reducing renal vascular resistance and glomerular hyperfiltration, preventing leukocyte adhesion and mesangial cell hyperplasia/hypertrophy, and inhibiting renal renin release[39]. Additionally, nitric oxide plays a role in reducing papillary blood flow and medullary blood flow that indirectly reduces urinary sodium and water excretion[40, 41].

The strength of the present study is the use of a noninvasive technique for measuring FMD values and the standardized measurements for other cardiovascular risk factors in community population-based study[20]. Second, we are the first to analyze the association between FMD and CKD in the general population.

The present study also has several limitations. First, we cannot guarantee causality because of a cross-sectional design. Second, the information on the specific types of administered antihypertensive or antidiabetic drugs that may affect brachial reactivity differentially[33, 42, 43] were not available. Third, the number of patients with CKD was small because we studied the association in apparently healthy general population; however, we had no power problem in the categorical analysis. Fourth, we used the cutoff value of the lowest %FMD quartile as an indicator of endothelial dysfunction, but other studies have used different cutoff points. However, using the value of lowest tertile (%FMD $<6.0\%$), quintile (%FMD $<5.0\%$), or dichotomizing FMD by median value (%FMD $=7.0\%$) did not change the observed association; the respective ORs (95% CIs) for the lowest category versus the highest were 2.06 (0.97–4.37); p for trend $=0.04$ in tertile analysis, 3.71 (1.00–13.73); p for trend $=0.04$ in quintile analysis; and 2.15 (1.15–4.02) in dichotomized analysis (data not shown in Table). Last, oxidative stress and inflammation play a critical role in the impairment of endothelial function[44, 45]. In the present study, oxidative stress markers and inflammation markers were not measured. Therefore, future studies should combine circulating biomarkers for endothelial function to verify our results.

In conclusion, our cross-sectional study suggested the relationship between endothelial dysfunction and the higher prevalence of CKD in the general Japanese population.

Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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Author Contributions

Yuting Li, Keyang Liu, Renzhe Cui, Ehab S. Eshak, Jia-Yi Dong, Meishan Cui and Masahiko Kiyama participated in the study design and data collection; Yuting Li, Renzhe Cui and Ehab S. Eshak analyzed the data; Yuting Li, Renzhe Cui, Ehab S. Eshak and Hiroyasu iso participated in interpretation of data and drafting of the manuscript; Yuting Li, Renzhe Cui and Ehab S. Eshak provided statistical expertise. Masahiko Kiyama, Isao Muraki, Takeo Okada, Akihiko Kitamura, Mitsumasa Umesawa, Kazumasa Yamagishi, Hironori Imano, Tetsuya Ohira and Hiroyasu Iso participated in the study concept and design, acquisition of data and interpretation of data, and critical revision of the manuscript.

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Appendix

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