Original Article

A Newly Estimated Glomerular Filtration Rate Is Independently Associated with Arterial Stiffness in Japanese Patients

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Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease, and thus is a major worldwide public health problem. Recently, an estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation for Japanese patients was proposed by the Japanese Society of Nephrology. However, the role of eGFR in the assessment of atherosclerosis is not well understood in Japanese patients. We analyzed the relationship between eGFR and severity of arterial stiffness using brachial-ankle pulse wave velocity (baPWV) in 647 adult Japanese patients. baPWV correlated significantly and positively with age, hypertension, diabetes, prior cardiovascular disease, blood pressure, pulse pressure and heart rate, and negatively with eGFR ($r=-0.405$, $p<0.0001$). A multiple regression analysis revealed that baPWV correlated independently with eGFR. Furthermore, there was a stepwise increase in baPWV, corresponding to advances in CKD through stages 1 to 5. When CKD stage 3 was divided at eGFR 45 mL/min/1.73 m^2, the baPWV of stage 3b (eGFR 30 to 44) was significantly higher than that of stage 3a (eGFR 45 to 59) independent of traditional risk factors, suggesting that an eGFR of 45 mL/min/1.73 m^2 may be a critical cut off value to predict arterial stiffness in CKD. In conclusion, the newly proposed eGFR is significantly associated with arterial stiffness, independent of traditional risk factors for cardiovascular disease. (*Hypertens Res* 2008; 31: 193–201)

***Key Words*: chronic kidney disease, estimated glomerular filtration rate, arterial stiffness, cross-sectional studies, Japanese patients**

Introduction

Chronic kidney disease (CKD) is a major worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease (CVD), and premature death (*1–3*). A number of prospective epidemiologic studies have shown that patients with CKD are at increased risk for CVD, independent of conventional cardiovascular risk factors (*4–6*). Thus, the National Kidney Foundation formed a task force to heighten awareness of CVD in CKD (*7*), and defined CKD as either 1) kidney damage for ≥3 months, confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in glomerular filtration rate (GFR), or 2) GFR <60 mL/min/1.73 m^2 for ≥3 months, with or without kidney damage (*8*). Pulse wave velocity (PWV) is known to be an indicator of arterial stiffness (*9*, *10*), and an independent predictor of cardiovascular events in patients with end-stage renal disease (*11*, *12*). A simple and noninvasive method to automatically measure brachial-ankle PWV (baPWV) was recently developed to

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Table 1. Baseline Characteristics

	Men	Women	Total
N	318	329	647
Age (years)	65.9±12.4	66.6±11.0	66.3±11.7
BMI (kg/m^2)	25.6±3.7	26.3±4.3	25.9±4.0
Hypertension (*n* (%))	251 (79)	265 (81)	516 (80)
Diabetes (*n* (%))	117 (37)	112 (34)	229 (35)
Dyslipidemia (*n* (%))	163 (51)	223 (68)	386 (60)
Smoking (*n* (%))	153 (48)	40 (12)	193 (30)
Prior CVD (*n* (%))	81 (25)	32 (11)	113 (18)
baPWV (cm/s)	1,782±376	1,768±374	1,775±375
Systolic BP (mmHg)	142±19	144±18	143±19
Diastolic BP (mmHg)	83±10	81±10	82±10
Pulse pressure (mmHg)	59±13	63±14	61±14
Mean BP (mmHg)	103±12	102±12	102±12
HR (bpm)	68±12	70±11	69±12
Hb (g/dL)	14.3±1.7	13.1±1.3	13.7±1.6
Total cholesterol (mg/dL)	180±34	188±32	184±33
Triglycerides (mg/dL) (*n*=607)	151±120	125±65	138±96
HDL-C (mg/dL) (*n*=606)	53±15	59±16	56±16
LDL-C (mg/dL) (*n*=605)	104±26	110±28	107±28
Uric acid (mg/dL) (*n*=604)	5.9±1.4	4.8±1.3	5.3±1.4
HbA1c (%) (*n*=278)	6.3±1.4	6.3±1.2	6.3±1.3
Serum creatinine (mg/dL)	0.97±0.79	0.72±0.33	0.84±0.61
eGFR (mL/min/1.73 m^2)	66.1±16.1	60.9±12.7	63.4±14.5

Variables are presented as mean±SD, or number and percentage. BMI, body mass index; CVD; cardiovascular disease; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate.

screen large populations (*13*, *14*). In several reports that included patients with different stages of CKD, PWV increased proportionally to decreased estimated GFR (eGFR) or creatinine clearance (*15–17*). Recently, an eGFR for Japanese patients was proposed by the Japanese Society of Nephrology (*18*); however, its clinical usefulness has not yet been fully established. In this study, we investigated for the first time the significance of eGFR as an index and predictor of arterial stiffness in Japanese patients to clarify whether CKD is related to the progression of arterial stiffness in such patients.

Methods

Subjects

Subjects were 647 consecutive patients (318 men and 329 women; aged 15 to 92 years), who underwent baPWV at Hokkaido Prefectural Haboro Hospital from January 2005 to April 2006. Patients on hemodialysis or with an ankle brachial pressure index (ABI) of ≤0.9 were excluded. Age, gender, lipid parameters, and conventional cardiovascular risk factors were recorded. Body weight and height were measured during the examination in light indoor clothing without shoes. baPWV, ABI, heart rate (HR), and blood pressure (BP) were measured with a pulse pressure analyzer (model: BP-203RPE II; Nihon Colin, Tokyo, Japan) as described previously (*13*, *14*). PWV was expressed in cm/s. Fasting or non-fasting blood samples were drawn from the antecubital vein of seated participants with minimal tourniquet use. Samples were collected into vacuum tubes containing ethylenediaminetetraacetic acid for Hb and HbA1c measurement, or a serum separator gel for serum creatinine, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and uric acid measurement. A history of smoking was defined as >10 pack-years. Hypertension was defined as either systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg, or current use of antihypertensive medications. Diabetes was defined as one of the following: fasting blood sugar ≥126 mg/dL; non-fasting blood sugar ≥200 mg/dL or HbA1c ≥6.5%; or current use of insulin or an oral hypoglycemic agent. Dyslipidemia was defined as: TC ≥220 mg/dL; HDL cholesterol ≤40 mg/dL; triglycerides ≥150 mg/dL; or current use of an anti-hyperlipidemic medication. The dipstick urinalysis (Bayer, Tokyo, Japan) for proteinuria was performed on spontaneously voided fresh urine. Urine test results were interpreted by the physicians and recorded as −, ±, 1+, 2+, and 3+. Results recorded as − and ± are defined as the absence of proteinuria; others are defined as the presence of proteinuria (7.3% of total

Table 2. Univariate Relationship to baPWV

	r	*p*
Sex	0.020	n.s.
Age	0.609	<0.0001
BMI	−0.127	0.0012
Hypertension	0.212	<0.0001
Diabetes	0.092	0.0193
Dyslipidemia	−0.013	n.s.
Smoking	−0.057	n.s.
Prior CVD	0.096	0.0144
Systolic BP	0.441	<0.0001
Diastolic BP	0.240	<0.0001
Pulse pressure	0.425	<0.0001
Mean BP	0.366	<0.0001
HR	0.200	<0.0001
Hb	−0.235	<0.0001
Total cholesterol	−0.096	0.0147
Triglycerides (n=607)	−0.051	n.s.
HDL-C (n=606)	−0.072	n.s.
LDL-C (n=605)	−0.071	n.s.
Uric acid (n=604)	−0.006	n.s.
HbA1c (n=278)	−0.002	n.s.
Serum creatinine	0.231	<0.0001
eCcr	−0.555	<0.0001
eGFR	−0.405	<0.0001

HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; eCcr, estimated creatinine clearance. Other abbreviations are the same as Table 1.

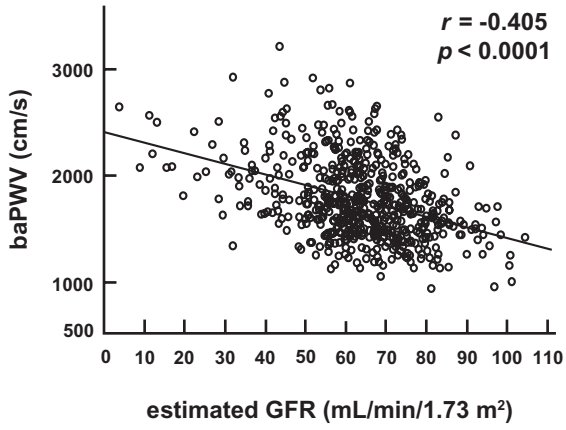

Fig. 1. *Relationship between baPWV and eGFR in all 647 subjects. GFR was estimated using the MDRD equation for Japanese proposed by the Japanese Society of Nephrology. baPWV was correlated significantly and negatively with eGFR ($r=-0.405$, $p<0.0001$). baPWV, brachial-ankle pulse wave velocity; GFR, glomerular filtration rate.*

subjects). Body mass index (BMI) was calculated as weight divided by height squared.

This study was conducted in accordance with the guidelines of the ethics committee of Hokkaido Prefectural Haboro Hospital. Informed consent was obtained from each patient before entry into the study.

Measurement of Estimated GFR

GFR was estimated from the MDRD equation for Japanese patients, recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative (*18*):

$$\text{eGFR} = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (0.881 \text{ if Japanese}).$$

Serum creatinine was analyzed by the enzyme method (normal: 0.7–1.2 mg/dL for men, 0.5–0.8 mg/dL for women) using a Toshiba TBA-200FR automated analyzer (Toshiba, Tokyo, Japan). Serum creatinine was calibrated using the following formula: serum creatinine (Yaffe method) = 0.2 + serum creatinine (enzyme method) (*19*, *20*). eGFR was analyzed using the following five categories provided by the Kidney Disease Outcomes Quality Initiative (K/DOQI) (*8*): stage 1: GFR ≥90 mL/min/1.73 m^2; stage 2: GFR 60 to 89 mL/min/1.73 m^2; stage 3: GFR 30 to 59 mL/min/1.73 m^2; stage 4: GFR 15 to 30 mL/min/1.73 m^2: and stage 5: GFR <15 mL/min/1.73 m^2. Furthermore, we calculated estimated creatinine clearance (eCcr) using the Cockcroft-Gault equation, which is often used clinically, and examined correlations between eCcr and baPWV, and between eCcr and eGFR.

Statistical Analysis

Results were expressed as the means±SD or number (%). Univariate and multivariate linear regression was used for continuous variables. The unadjusted mean of baPWV was compared to the different CKD stages using eGFR, with one-way analysis of variance (ANOVA) followed by multiple comparisons using Tukey's Studentized Range Test. Furthermore, additional comparisons were made under the condition that category CKD 3 was divided into early stage 3a (GFR 45 to 59 mL/min/1.73 m^2) and late stage 3b (GFR 30 to 44 mL/min/1.73 m^2) as previously reported (*6*). The adjusted mean of baPWV was compared among the different CKD stages, with analysis of covariance (ANCOVA) for age, sex, systolic BP, BMI, HR, Hb, TC, prior CVD, smoking, medication for hypertension, medication for diabetes, and medication for dyslipidemia. For the analysis of the amount of proteinuria at each CKD stage, proteinuria was scored as follows: dipstick findings of − and ± were scored as 0, and findings of 1+, 2+, and 3+ were scored as 1, 2, and 3, respectively. p values <0.05 were considered statistically significant. All statistical analyses were performed with the SPSS software package Version 11.0 for Windows (SPSS Inc., Chicago, USA).

Table 3. Multiple Regression Analysis of the Correlation of baPWV

	β	*B*	95% CI	*p*
Age	0.498	15.92	13.92–17.91	<0.0001
Sex (man=1, woman=0)	0.053	40.42	−8.40–89.24	0.104
BMI	−0.148	−14.00	−19.36–8.64	<0.0001
Diabetes	0.058	46.62	1.64–91.60	0.042
Smoking	0.008	6.67	−42.89–56.23	0.792
Prior CVD	0.019	19.01	−38.55–76.56	0.517
Systolic BP	0.374	7.77	6.59–8.95	<0.0001
HR	0.220	7.21	5.40–9.03	<0.0001
Hb	0.016	3.64	−12.18–19.46	0.651
Total cholesterol	−0.037	−0.424	−1.10–0.24	0.213
eGFR	−0.125	−3.23	−4.97–1.50	<0.0001

Model r^2=0.595; p<0.0001. β, standardized coefficients; *B*, unstandardized coefficients; CI, confidence interval. Other abbreviations are the same as Table 1.

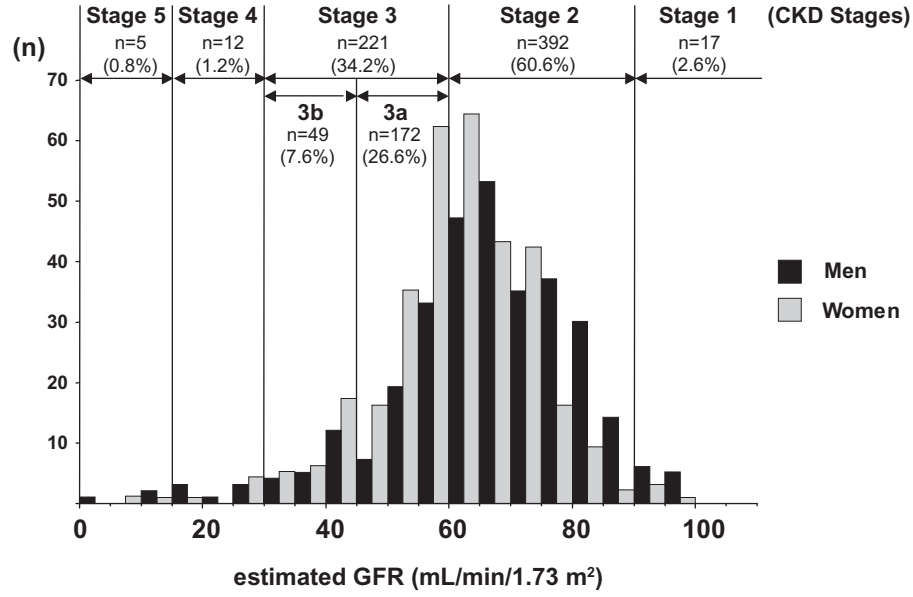

Fig. 2. *Distribution of eGFR and of CKD stages at baseline among the 647 subjects. eGFR peaked in the range of 65–70 mL/min/1.73 m² in men (black bar) and in the range of 60–65 mL/min/1.73 m² in women (gray bar). The prevalences of CKD stages 1–5 were 2.6, 60.6, 34.2, 1.9 and 0.8%, representing 17, 392, 221, 12 and 5 patients, respectively. The prevalence of eGFR < 60 mL/min/1.73 m² was 36.9%, representing 238 patients (90 or 28.3% men and 148 or 45.0% women).*

Results

The baseline characteristics of the subjects are outlined in Table 1. The mean age was 66.3±11.7 years (range, 15 to 92 years). The prevalence of hypertension and diabetes mellitus were about 80% and 35%, respectively. The mean BMI was 25.9 kg/m². The mean serum creatinine was 0.84±0.61 mg/dL (men, 0.97±0.79 mg/dL; women, 0.72±0.33 mg/dL). The mean eGFR using the MDRD equation for Japanese patients was 63.4±14.5 (men, 66.1±15.8; women, 60.9±12.7 mL/min/1.73 m²). The mean baPWV was 1,775±375 cm/s (range, 950 to 3,341), 1,782±376 cm/s for men, and 1,768±374 cm/s for women. Univariate correlations between baPWV and various parameters are listed in Table 2. baPWV correlated significantly and positively with age, hypertension, diabetes, prior CVD, systolic, diastolic and mean BP, pulse pressure, HR, and serum creatinine, and negatively with eGFR (r=−0.405, p<0.0001), eCcr, Hb, BMI, and TC in the univariate linear regression analysis. However, baPWV did not significantly correlate with sex, smoking, triglycerides, HDL cholesterol, LDL cholesterol, uric acid (in a subset of

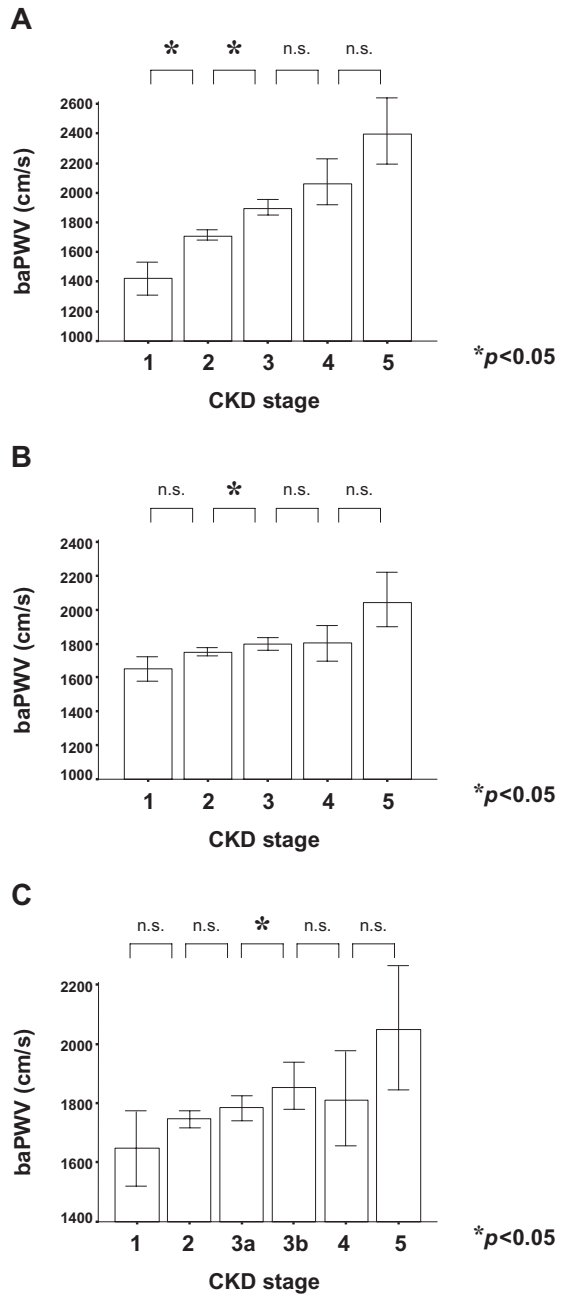

Fig. 3. *baPWV in patients with different stages of CKD. A: There was a stepwise increase in baPWVs, corresponding to advances of CKD through stages 1 to 5 ($p<0.0001$ for trend). B: After adjustment for age, sex, systolic BP, BMI, HR, TC, prior CVD, smoking, medication for hypertension, medication for diabetes, and medication for dyslipidemia, significant differences in baPWV were observed across the different CKD stages ($p<0.0001$). When CKD stage 3, moderately reduced GFR, was divided at eGFR 45 mL/min/1.73 m^2 (stage 3a: eGFR 45 to 59; stage 3b: eGFR 30 to 44 mL/min/1.73 m^2), C: the adjusted baPWV in stage 3b was found to be significantly greater than that in stage 3a ($p<0.0001$). The data are shown as the means±SD.*

607 subjects for whom triglycerides, HDL and LDL cholesterol data were available), or HbA1c (in a subset of 278 subjects for whom HbA1c data was available). Figure 1 shows the scatter chart of the relationship between baPWV and eGFR. An almost similar negative relationship between eGFR and baPWV was observed in both men and women (men, $r=-0.441$; women, $r=-0.390$; both $p<0.0001$) and in both diabetes and non-diabetes (diabetes, $r=-0.406$; non-diabetes, $r=-0.400$; both $p<0.0001$). Furthermore, eCcr calculated using the Cockcroft-Gault equation was associated significantly and negatively with baPWV ($r=-0.555$, $p<0.0001$) and positively with eGFR ($r=0.705$, $p<0.0001$). Although eCcr was also negatively associated with baPWV, we performed analyses using eGFR by the MDRD study equation modified for Japanese patients because eGFR provided a more accurate estimation of GFR than eCcr (*18*). The calculation of eGFR itself includes age, and age has a strong independent effect on baPWV. To exclude possible confounding problems of age, we performed a multiple regression analysis for baPWV. The multiple regression analysis revealed that baPWV was correlated independently with eGFR ($r=-0.125$, $p<0.0001$), age ($r=0.498$, $p<0.0001$), systolic BP ($r=0.374$, $p<0.0001$), HR ($r=0.220$, $p<0.0001$), BMI ($r=-0.148$, $p<0.0001$) and diabetes (diabetes=1, non-diabetes=0) ($r=0.058$, $p=0.042$) (Table 3), suggesting that eGFR was negatively correlated with baPWV independent of traditional risk factors.

Next, we investigated the relationship between baPWV and the different CKD stages according to the K/DOQI category of kidney function. Figure 2 shows the distribution of eGFR and successive categories of kidney function (stage 1: GFR [mL/min/1.73 m^2] ≥90; stage 2: GFR 60 to 89; stage 3: GFR 30 to 59; stage 4: GFR 15 to 30; and stage 5: GFR <15). The average creatinine was 0.57 mg/dL, 0.70 mg/dL, 0.93 mg/dL, 2.16 mg/dL and 5.92 mg/dL in stages 1–5, respectively. eGFR distribution was shifted toward lower values in women compared to men. The prevalences of CKD stages 1–5 were 2.6, 60.6, 34.2, 1.9 and 0.8%, representing 17, 392, 221, 12 and 5 patients, respectively. Overall, the prevalence of eGFR <60 mL/min/1.73 m^2 was 36.9%, representing 238 patients (28.3% or 90 men and 45.0% or 148 women). Furthermore, there was a stepwise increase in baPWVs, corresponding to advances in CKD through stages 1 to 5 ($p<0.0001$ for trend) (Fig. 3A). After adjustment for age, sex, systolic BP, BMI, HR, Hb, TC, prior CVD, smoking, medication for hypertension, medication for diabetes, and medication for dyslipidemia, significant differences in baPWV were observed across the different CKD stages ($p<0.0001$) (Fig. 3B). When CKD stage 3, moderately reduced GFR, was divided at eGFR 45 mL/min/1.73 m^2 (stage 3a: eGFR 45 to 59 mL/min/1.73 m^2; stage 3b: eGFR 30 to 44 mL/min/1.73 m^2), the adjusted baPWV in stage 3b increased significantly compared to that in stage 3a (1,783 cm/s *vs*. 1,889 cm/s, $p<0.0001$) (Fig. 3C) independent of age, systolic BP and other traditional risk factors. Table 4 shows the differences in parameters at each

Table 4. Parameters According to CKD Stage

	CKD stage						*p* for trend
	1	2	3a	3b	4	5	
N	17	392	172	49	12	5	
Age (years)	48.6±15.2	63.9±11.3	70.4±9.0	76.4±8.8	70.4±10.5	65.0±11.1	<0.0001
Systolic BP (mmHg)	141.2±14.0	140.5±16.8	145.5±18.8	150.5±22.4	163.9±25.5	168.3±20.0	<0.0001
eGFR (mL/min/1.73 m^2)	95.5±3.7	70.7±7.4	54.8±3.8	39.7±4.3	24.2±4.9	9.6±3.7	<0.0001
baPWV (cm/s)	1,420±224	1,706±335	1,831±362	2,109±449	2,061±259	2,398±244	<0.0001
Prevalence of hypertension (%)	70.6	75.3	85.5	91.8	100.0	100.0	0.003
Prevalence of diabetes (%)	52.9	32.7	34.3	40.8	83.3	60.0	0.003
Prevalence of dyslipidemia (%)	35.3	56.4	72.1	44.9	83.3	60.0	<0.001
Prevalence of prior CVD (%)	5.9	15.8	19.8	24.5	8.3	60.0	0.042

BP, blood pressure; eGFR, estimated glomerular filtration rate; baPWV, brachial-ankle pulse wave velocity; CVD; cardiovascular disease.

Table 5. Parameters According to Dipstick Findings for Proteinuria

	Proteinuria			*p* for trend
	–	1+	≥2+	
N	539	25	25	
Age (years)	66.0±12.0	66.8±12.9	67.0±9.6	0.879
Systolic BP (mmHg)	142.6±18.2	147.4±18.6	158.7±23.9	<0.0001
eGFR (mL/min/1.73 m^2)	64.7±13.1	60.0±19.5	35.7±19.4	<0.0001
baPWV (cm/s)	1,757±377	1,918±359	2,033±331	<0.0001
Prevalence of hypertension (%)	78.5	88.0	96.0	0.059
Prevalence of diabetes (%)	36.0	64.0	76.0	<0.001
Prevalence of dyslipidemia (%)	58.8	40	84.0	0.006
Prevalence of prior CVD (%)	16.5	20	33	0.310

Abbreviations are the same as Table 4.

CKD stage. Significant differences in age, systolic BP, eGFR, baPWV, and the plevalence of hypertension, diabetes, dyslipidemia, and prior CVD were observed across the CKD stages. In addition, we also investigated the relationship between the prevalence of proteinuria and baPWV in a subset of 589 subjects for whom dipstick findings for proteinuria were available. Table 5 lists the ages, the systolic BP, eGFR, and baPWV values, and the prevalence of hypertension, diabetes mellitus, dyslipidemia, and prior CVD according to dipstick proteinuria findings. Higher proteinuria levels were associated with greater systolic BP, lower eGFR, greater baPWV, and greater prevalence of diabetes mellitus and dyslipidemia. The proteinuria score also increased with the progression of CKD stage ($p<0.0001$ for trend) and was significantly different between CKD stages 3a and 3b ($p<0.001$) (Fig. 4), suggesting that an eGFR of 45 mL/min/1.73 m^2 may be a critical cut off value not only to predict arterial stiffness progression, but also to predict the development of end-stage renal disease in CKD.

Discussion

Our study demonstrated that increased baPWV is associated with decreased eGFR and advanced CKD stages, independent of traditional cardiovascular risk factors such as age, smoking, BMI, systolic BP, prior CVD, hypertension, diabetes and dyslipidemia, in patients living in rural Japan. Furthermore, to our knowledge, this is the first report to demonstrate an association between arterial stiffness and eGFR calculated using the MDRD equation for Japanese patients.

In the present study, we calculated eGFR using the MDRD equation, as proposed by the Japanese Society of Nephrology, which considers race in the calculation and has been adapted for Japanese subjects. Although the equation is now being assessed for validity, the Japanese Society of Nephrology has indicated that there is a good correlation between eGFR—particularly low eGFR (<60 mL/min/1.73 m^2)—and the actual GFR measured by inulin clearance, the gold standard for measuring GFR, in Japanese patients (*18*). Meanwhile, the Cockcroft-Gault equation is often used to estimate GFR in clinical settings, but this equation was originally used to

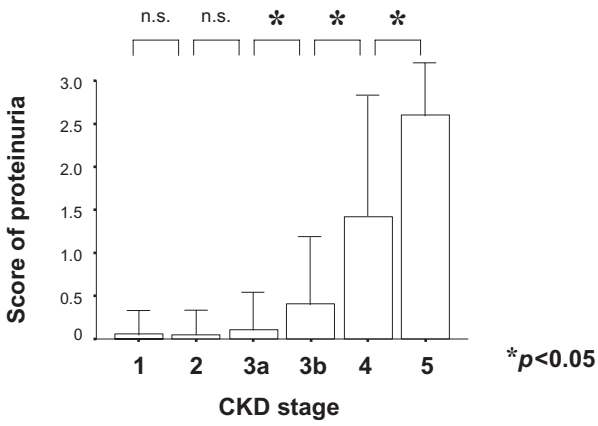

Fig. 4. *Score of proteinuria in patients with different stages of CKD. There was a stepwise increase in the score of proteinuria, corresponding to advances in CKD through stages 1 to 5 ($p < 0.0001$ for trend). The data are shown as the means ± SD.*

estimated creatinine clearance, not inulin clearance. Several studies have shown that the Cockcroft-Gault equation overestimates GFR, especially in patients with moderate and severe CKD, which was defined as GFR <60 mL/min/1.73 m^2 in the MDRD study (*18*, *21*, *22*). Furthermore, a recent advisory from the American Heart Association Kidney and Cardiovascular Disease Council formed in collaboration with the National Kidney Foundation revealed that CKD can be reliably detected with the combined use of the MDRD equation for eGFR and a sensitivity test to detect microalbuminuria (*22*). Thus, we used the MDRD equation for Japanese patients, which is suitable for routine clinical use or large screening programs for the detection of early stages of CKD.

Firstly, we demonstrated that age, hypertension (*i.e.*, systolic, diastolic and mean BP and pulse pressure), diabetes mellitus, and prior CVD had good positive correlations with baPWV, and that eGFR for Japanese patients had both a significant and negative association with baPWV, independent of other cardiovascular risk parameters. Surprisingly, our study revealed that the prevalence of moderate and severe CKD, defined as eGFR <60 mL/min/1.73 m^2, was 36.9% overall. The possible reasons for the high prevalence of CKD in our study are as follows. First, since the present study was performed at a hospital, it included many elderly patients, and thus the mean age was 66.3 years. The mean eGFR was 63.4 mL/min/1.73 m^2 for all patients, 66.1 mL/min/1.73 m^2 for men, and 60.9 mL/min/1.73 m^2 for women. Therefore, the prevalence of CKD defined as eGFR <60 mL/min/1.73 m^2 might have been high in our study. Second, GFR may be lower in Japanese than in Caucasians or African-Americans due to racial differences. Data from the U.S. NHANES (National Health and Nutrition Examination Survey) III study indicated that the prevalence of CKD defined as eGFR <60 mL/min/1.73 m^2 was 4.7% in the U.S. adult population aged 20 years or older, representing 8.3 million CKD patients (*3*). Most recently, the data from NIPPON DATA (National Integrated Project for Prospective Observation of Non-Communicable Disease and Its Trends in the Aged) 90 indicated that the prevalence of CKD defined as eGFR <60 mL/min/1.73 m^2 was 6.7% among the 7,316 participants in a community population in Japan (*23*). Although our results are not directly comparable with these population-based studies, the prevalence of moderate and severe CKD might be higher in Japan compared to the U.S. To confirm these relationships, a longitudinal study is needed.

Next, we demonstrated a stepwise increase in baPWV from CKD stages 1 to 5. Importantly, several studies across a broad spectrum of populations have shown that the risks of death and cardiovascular events are greatly increased in patients with an eGFR of less than 45 mL/min/1.73 m^2 (*2*, *6*). Therefore, we also investigated the findings when stage 3 was divided into two subsets: stage 3a, which included patients with an eGFR of 45 to 59; and stage 3b, which included those with an eGFR of 30 to 44 mL/min/1.73 m^2. The baPWV of stage 3b patients was significantly higher than that of stage 3a patients, independent of age, systolic BP and other traditional risk factors. eGFR 45 mL/min/1.73 m^2 may thus be a useful cut off value to predict arterial stiffness in CKD. These findings may explain, at least in part, why decreased eGFR is associated with greater risk for CVD and suggest that eGFR could be a useful surrogate end point for CVD.

The clinical significance of PWV is thought to relate not only to structural changes within the vascular wall but also to adverse hemodynamic effects (*24*, *25*). These include an increase in systolic BP and pulse pressure and, hence, an increase in dynamic left ventricular load. Meanwhile, decreased GFR may cause latent volume retention in patients with earlier stages of CKD. Furthermore, various factors that deteriorate vascular function, such as the renin-angiotensin-aldosterone system, homocysteine, oxidative stress, and inflammation, are also reportedly activated not only in patients with end-stage renal disease, but also those with earlier stages of CKD (*1*, *25–28*). Anemia is also a key factor to determine the prognosis not only of dialysis patients and patients with CKD, but also of patietnts with CVD. The published clinical and laboratory data suggest that anemia, CVD and CKD have a close interrelationship, each worsening the others to result in a "vicious cycle" of disease progression which Silberberg has named the Cardio-Renal-Anemia Syndrome (*29*). There was a significant and negative correlation between baPWV and Hb, although the statistical significance disappeared in the multiple regression analysis. Thus, decreased GFR may be associated with an increased level of traditional and nontraditional CVD risk factors.

Diabetic nephropathy is the leading cause of end-stage renal disease in the U.S., Europe and Japan. Diabetes mellitus is associated with an increased risk of CVD (*12*). In the present study, eGFR was negatively associated with baPWV in both a subgroup with and one without diabetes. Mean-

while, a multiple regression analysis revealed that the correlation between baPWV and diabetes was statistically significant but not strong. Although the severity of diabetes may determine both eGFR and baPWV, eGFR seems to be a useful predictive marker of baPWV both in diabetes and non-diabetes.

Proteinuria is known as a risk factor for the development of end-stage renal disease and CVD. In the present study, the prevalence of proteinuria was positively correlated with the progression of CKD stage. The presence of proteinuria was associated with increased baPWV; however, the statistical significance disappeared after adjustment for traditional risk factors. Many factors thus seemed to play a role in the appearance of proteinuria and in its association with baPWV.

Our study had several limitations. First, the MDRD equation also includes age, sex and serum creatinine, and baPWV is itself closely associated with age. To minimize the influence of age and gender, we performed a multivariate analysis adjusted for age, gender, and other conventional risk factors and showed that the independent contribution of eGFR to baPWV remained significant. Therefore, we believe that the decrease in eGFR was actually related to the increase in baPWV. Secondly, the MDRD equation for Japanese subjects, even after modification, has still not been completely approved for clinical use. Thus, it is crucial that the new equation proposed by the Japanese Society of Nephrology be validated. Thirdly, we did not measure certain metabolic parameters in all subjects, such as triglycerides, HDL cholesterol, LDL cholesterol, uric acid, HbA1c and fasting glucose. We did not include these parameters in the multiple regression analysis, and thus we could not conclude that there was an interaction between these parameters and baPWV. Finally, the present study was a cross-sectional study and only included patients from a rural population aged 15 to 92 years who underwent medical examinations. Future longitudinal studies with a larger number of subjects from the general population will be needed to determine the association between risk factors for increased arterial stiffness and the progression of CKD.

In conclusion, our study suggests that the new eGFR calculated using the MDRD equation for Japanese patients is closely associated with an increase in arterial stiffness, and is a useful predictive marker for the development of atherosclerosis and CVD.

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