Relationships among Renal Function Loss within the Normal to Mildly Impaired Range, Arterial Stiffness, Inflammation, and Oxidative Stress

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Background and objectives: This study was conducted to clarify whether individuals with mildly impaired renal function show increased arterial stiffness, microinflammation, and oxidative stress as compared with those with normal renal function and also to examine the association of these parameters with the degree of GFR loss in middle-aged Japanese men with a low cardiovascular risk.

Design, setting, participants, & measurements: The brachial-ankle pulse wave velocity and plasma levels of C-reactive protein and lipid peroxides were measured in 1873 men (42 ± 9 yr of age).

Results: The brachial-ankle pulse wave velocity but not the plasma C-reactive protein or lipid peroxides, was increased in individuals with mildly impaired renal function. The GFR was significantly correlated with the brachial-ankle pulse wave velocity but not with the log-transformed values of C-reactive protein or lipid peroxides. Multivariate linear regression analysis demonstrated a significant relationship between the brachial-ankle pulse wave velocity and the GFR, independent of the conventional atherosclerotic risk factors. This relationship was significant even in individuals with GFR values within the "normal renal function" range. Thus, GFR loss seems to be more closely associated with arterial stiffness than with microinflammation and/or oxidative stress.

Conclusions: A weak but significant relationship was observed between the degree of GFR loss and arterial stiffness, even in individuals with GFR values within the normal renal function range. Therefore, increased arterial stiffness may underlie, at least in part, the elevated cardiovascular risk in individuals with mildly impaired renal function.

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Chronic kidney disease (CKD) is a major and serious risk factor for cardiovascular disease, and screening for CKD is recommended in all patients with cardiovascular disease (1,2); however, increased arterial stiffness is also known to be associated with an elevated risk for cardiovascular disease (3). Some studies have demonstrated that even mild CKD (GFR 60 to 89 ml/min per 1.73 m^2 body surface area) is a risk factor for cardiovascular disease (4,5), and other studies have demonstrated the existence of a relationship between the degree of GFR loss and arterial stiffness, as assessed by the pulse wave velocity (PWV) or pulse pressure, even in individuals with GFR values in the "normal to mildly impaired renal function" range (GFR ≥60 ml/min per 1.73 m^2 body surface area) (6–12), suggesting a cause–effect relationship and/or common underlying mechanisms. Microinflammation and/or oxidative stress contributes to the progression of atherosclerosis and arterial stiffening, and both have been shown to increase in severity with the progression of renal dysfunction (13); however, it still remains unclear whether microinflammation and/or oxidative stress is increased in individuals with only mildly impaired renal function. It remains to be clarified whether they are involved in the relationship between the degree of GFR loss and arterial stiffness in individuals with GFR values in the normal to mildly impaired renal function range. Furthermore, no study has examined the relationships among GFR loss, arterial stiffening, inflammation, and oxidative stress in individuals with GFR values within the normal renal function range.

This study was conducted to clarify the following in middle-aged Japanese men with a low cardiovascular risk: (*1*) Do individuals with mildly impaired renal function show increased arterial stiffness, microinflammation, and oxidative stress as compared with individuals with normal renal function? (2) Are inflammation and/or oxidative stress involved in the association between the degree of GFR loss and arterial stiffness in individuals with GFR values in the normal to mildly impaired renal function range? (*3*) Are the relationships among the mentioned four pathophysiologic abnormalities significant even in individuals with renal function parameters within the normal range?

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Concise Methods

Design and Participants

This cross-sectional study was performed on the employees of a single large construction company, all of whom underwent a routine annual health checkup between May and July 2004. The data obtained from this cohort have been reported in part elsewhere (14,15). In addition to the routine tests, measurements of the brachial-ankle PWV (baPWV) and of the plasma levels of C-reactive protein (CRP) and products of lipid peroxidation (LipOX) were conducted on the participants enrolled for this study. The routine annual health checkup included evaluation of the atherosclerotic risk factors (body mass index [BMI] and measurements of the serum levels of triglyceride [TG], HDL cholesterol and total cholesterol [TC], fasting blood glucose [FBG], and BP).

Among a total of 2325 participants, those who were receiving anti-inflammatory drugs or medication for hypertension, dyslipidemia, diabetes, heart disease, and/or stroke ($n = 247$); atrial fibrillation ($n = 1$); and/or a ankle/brachial pressure index <0.95 ($n = 32$) were excluded from the study. In regard to the renal function abnormalities, individuals in whom the plasma CRP levels were >10.0 mg/L ($n = 25$) and/or the GFR as estimated using the Modification of Diet in Renal Disease (MDRD) equation (1) was <60 ml/min per 1.73 m^2 body surface area ($n = 3$) and/or the result of urine dipstick for analysis for proteinuria was >1+ (urinary protein concentration ≥ 30 mg/dl; $n = 138$) were also excluded from the study. In addition, individuals with serum creatinine levels <35 μmol/L ($n = 6$) were excluded, because this value was lower than the mean in individuals with GFR values within the normal renal function range minus 3 SD. Finally, a total of 1873 men were successfully enrolled in the study. Verbal informed consent was obtained from all of the participants before their participation in this study. The protocol of this study conformed to the principles of the Declaration of Helsinki, and the study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University.

Measurements

BP Measurement in the Office Setting. Before measurement of the baPWV, the BP was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer. These two measurements were performed on the same occasion after the participants had rested in the seated position for at least 5 min.

baPWV and Pulse Pressure. The baPWV was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd., Komaki, Japan), in accordance with a previously described method (14,15). Briefly, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached on the left chest. Electrocardiograms and phonocardiograms were used to provide timing markers for the device. Occlusion cuffs, which were connected to both the plethysmographic and the oscillometric sensors, were tied around both the upper arms and ankles while the participants lay in the supine position. The brachial and post-tibial arterial pressures were measured by the oscillometric sensor. The brachial and post-tibial arterial pressure waveforms determined by the plethysmographic sensor and recorded for 10 s were stored. The characteristic points of the waveforms were determined automatically according to the phase velocity theory. The pulse wave may travel in different directions from the heart; however, there is a mathematical logic for measurement of the baPWV, as follows: For the pulse wave traveling from the heart to the brachium, the time interval from the heart to the brachium is defined as Thb, and the path length from the heart to brachium is defined as the path length from heart to suprasternal notch + that from the suprasternal notch to the brachium (Lb). For the pulse wave traveling from the heart to the ankle, the time interval from the heart to the ankle is defined as Tha, and the path length from the heart to the ankle is defined as the path length from the heart to the suprasternal notch + that from the suprasternal notch to the ankle (La). Therefore, the time interval from the brachium to the ankle, as the time interval from the wavefront of the brachial waveform to the wavefront of the ankle waveform, is calculated as Tha − Thb, and the path length from the brachium to the ankle is calculated as La − Lb. La and Lb are obtained using the equations La = 0.8129 × height of the patients (in cm) + 12.328 and Lb = 0.2195 × height of the patients (in cm) + 2.0734 (15). Finally, the following equation is used to calculate the baPWV: baPWV = (La − Lb)/(Tha − Thb) (15).

The measurements were conducted after the participants had rested for at least 5 min in the supine position, in an air-conditioned room (24 to 26°C) earmarked exclusively for this purpose. In 55 volunteers, the intraclass correlation coefficient of reproducibility of the baPWV was determined to be 0.92 (14). The BP, determined using the oscillometric sensor, and the heart rate were measured simultaneously during measurement of the baPWV. The pulse pressure (systolic BP − diastolic BP) was determined on two occasions: One in the office setting and the other at the time of measurement of the baPWV.

Laboratory Measurements. The TG, HDL, FBG, TC, and serum creatinine concentrations were measured using enzymatic methods (Falco Biosystems Co. Ltd., Tokyo, Japan). GFR was calculated using the MDRD equation: $186 \times [\text{serum creatinine concentration}]^{-1.154} \times [\text{age}]^{-0.203}$. The plasma levels of LipOX were measured as a marker of oxidative stress (16,17). The interassay coefficient of variation for this parameter was 1.2%. The plasma CRP level was determined using the latex-aggregation method (Eiken Co., Tokyo, Japan) (16,18), which is a high-sensitivity assay method with a detection threshold of <0.1 mg/L. The interassay coefficient of variation for this parameter was 2.9%. All of the blood samples were collected in the morning, after the participants had fasted overnight.

Statistical Analyses

Data were expressed as means ± SD. Figures are shown with error bars. The plasma levels of CRP and LipOX were skewed rightward; therefore, these variables were log-transformed for the analyses. The relationships of the GFR with the other variables were assessed by univariate linear regression analysis and multivariate linear regression analysis. The GFR values were divided into tertiles in participants with values within the normal renal function range. The differences in the variables among the four groups of participants classified according to the GFR values (*i.e.*, in either one of the three tertiles in the normal renal function range and in the mildly impaired renal function range) were assessed by one-way ANOVA. Then, under a general linear model, the differences in the baPWV among the four groups were also assessed by analysis of covariance after adjustments. All of the analyses were conducted using the SPSS software for Windows, version 11.0J (SPSS, Chicago, IL). $P < 0.05$ was considered to denote statistical significance.

Results

The analyses were conducted in four groups of participants classified according to the GFR values: One group with GFR in the mildly impaired renal function range (GFR 60 to 89) and three groups with GFR in one of the three tertiles in the normal renal function range, namely 90 to 108 (tertile 1), 109 to 126 (tertile 2), and 127 to 209 (tertile 3) ml/min per 1.73 m^2 body surface area. Table 1 shows the clinical characteristics of the four groups. ANOVA demonstrated that age, BMI, systolic and diastolic BP, TC, and FBG increased, whereas the HDL decreased with decrease of the GFR values.

Table 1. Clinical characteristics of the participants with GFR values in the mildly impaired renal function range and the three groups of participants with GFR values in the normal renal function range classified into tertiles[a]

Variables	Mild Impairment	Tertile 1	Tertile 2	Tertile 3
GFR (ml/min per 1.73 m^2 BSA)	60 to 89	90 to 108	109 to 126	127 to 209
No. of participants	95	591	594	593
Age	48 ± 8	45 ± 10[b]	41 ± 9[b,c]	40 ± 8[b,c,d]
BMI	24.0 ± 2.6	24.1 ± 2.9	23.7 ± 2.9[c]	22.5 ± 3.3[b,c,d]
Smoking	19 (20%)	126 (21%)	137 (23%)	143 (24%)
SBPoff (mmHg)	129 ± 15	127 ± 15	124 ± 13[b,c]	122 ± 13[b,c,d]
DBPoff (mmHg)	79 ± 11	77 ± 11[b]	75 ± 10[b,c]	72 ± 10[b,c,d]
PPoff (mmHg)	50 ± 10	50 ± 10	49 ± 9	49 ± 9
SBPpwv (mmHg)	130 ± 16	129 ± 15	126 ± 14[b,c]	123 ± 15[b,c,d]
DBPpwv (mmHg)	81 ± 12	78 ± 11[b]	76 ± 10[b,c]	74 ± 11[b,c,d]
PPpwv (mmHg)	49 ± 8	50 ± 7	50 ± 7	49 ± 7[c]
TC (mmol/L)	5.3 ± 0.8	5.2 ± 0.8	5.1 ± 0.8[b]	5.0 ± 0.9[b,c]
TG (mmol/L)	1.2 ± 0.5	1.3 ± 0.8	1.2 ± 0.9	1.2 ± 1.3[c]
HDL (mmol/L)	1.5 ± 0.3	1.5 ± 0.4	1.5 ± 0.3	1.6 ± 0.4[b,c,d]
FBG (mmol/L)	5.3 ± 0.6	5.1 ± 0.7[b]	5.1 ± 0.7[b]	5.0 ± 0.9[b]
Crnn (μmol/L)	77 ± 5	66 ± 4[b]	59 ± 4[b,c]	50 ± 5[b,c,d]

[a]BSA, body surface area; BMI, body mass index; BSA, body surface area; Crnn, serum creatinine; DBPoff, diastolic BP determined in the office setting; DBPpwv, DBP determined at the time of measurement of the brachial-ankle pulse wave velocity (baPWV); FBG, fasting blood glucose; PPoff, pulse pressure determined in the office setting; PPpwv, pulse pressure determined at the time of measurement of the baPWV; SBPoff, systolic BP determined in the office setting; SBPpwv, SBP determined at the time of measurement of the baPWV; TC, serum total cholesterol; TG, serum triglycerides.

[b]$P < 0.05$ *versus* the result in participants with GFR in the mildly impaired renal function range.

[c]$P < 0.05$ *versus* the result for the first tertile of GFR in the normal renal function range.

[d]$P < 0.05$ *versus* the result for the second tertile of GFR in the normal renal function range (assessed by one-way ANOVA with Bonferroni adjustment).

Figure 1 shows the means of the baPWV among the four groups classified according to the GFR values. The results of ANOVA demonstrated that the baPWV increased with decrease of the GFR. The results of analysis of covariance demonstrated that after adjustment for age, the baPWV in the group with GFR values in the third tertile of the normal renal function range was lower than that in the group with values in the mildly impaired renal function range and in the group with values in the first tertile of the normal renal function range; however, the difference in the values was significant only between participants with GFR values in the first tertile and those with GFR values in the third tertile referred to previously after adjustment for age, BMI, TC, TG, HDL, FBG, mean BP determined at the time of measurement of the baPWV, log plasma CRP levels, and log plasma LipOX levels (Figure 1).

Table 2 depicts the correlation coefficients determined by linear regression analysis. The GFR was correlated with the baPWV and pulse pressure measured at the time of measurement of the baPWV but not with the log plasma CRP or log plasma LipOX levels. Thus, the GFR was correlated with parameters of arterial stiffness. Then, multivariate linear regression analysis was conducted to clarify whether GFR might be an independent factor affecting the baPWV. This analysis demonstrated a significant relationship between the baPWV and the GFR, independent of age, BMI, TC, TG, HDL, FBG, mean BP determined at the time of measurement of the baPWV, log

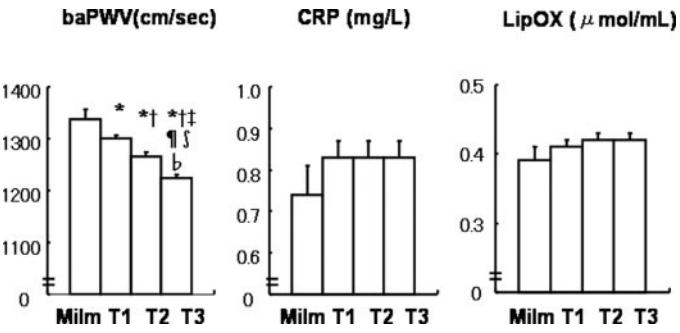

Figure 1. Mean values of the brachial-ankle pulse wave velocity (baPWV) in the groups classified according to the GFR. MiIm, mildly impaired renal function; T1, first tertile; T2, second tertile; T3, third tertile; CRP, plasma levels of C-reactive protein; LipOX, plasma levels of products of lipid peroxidation. *$P < 0.05$ *versus* the result for GFR in the mildly impaired renal function range; †$P < 0.05$ *versus* the result for T1 of GFR in the normal renal function range; ‡$P < 0.05$ *versus* the result for T2 of GFR in the normal renal function range (assessed by one-way ANOVA with Bonferroni adjustment); ∫$P < 0.05$ *versus* the result for GFR in the mildly impaired renal function range; ¶$P < 0.05$ *versus* the result for T1 (assessed by analysis of covariance with adjustment for age); b$P < 0.05$ *versus* the result for T1 of GFR in the normal renal function range (assessed by analysis of covariance with adjustment for age and other variables described in text).

Table 2. Correlation coefficients determined by univariate linear regression analyses to assess the relationships of the GFR with other variables[a]

Variables	Mild Impairment to Normal (n = 1873)	P	Normal (n = 1778)	P
baPWV	−0.19	<0.01	−0.17	<0.01
PPoff	−0.01	0.62	0.01	0.93
PPpwv	−0.07	<0.01	−0.08	<0.01
logCRP	−0.02	0.48	−0.02	0.34
logLipOX	0.04	0.07	0.04	0.08
Age	−0.25	<0.01	−0.21	<0.01
MBPoff	−0.18	<0.01	−0.18	<0.01
MBPpwv	−0.21	<0.01	−0.19	<0.01
BMI	−0.24	<0.01	−0.25	<0.01
TC	−0.10	<0.01	−0.10	<0.01
HDL	0.17	<0.01	0.17	<0.01
TG	−0.08	<0.01	−0.08	<0.01
FBG	−0.08	<0.01	−0.05	0.02
Smoke	−0.01	0.73	0.01	0.89

[a]logCRP, log-transformed value of the plasma level of C-reactive protein; logLipOX, log-transformed value of the plasma level of products of lipid peroxidation; MBPoff, mean BP determined in the office setting; MBPpwv, mean BP determined at the time of measurement of the baPWV.

plasma CRP levels, and log plasma LipOX levels not only in participants with GFR values in the normal to mildly impaired renal function range but also in those with values within the normal renal function range (Table 3).

Discussion

Several studies have demonstrated a significant relationship between degree of GFR loss and arterial stiffness in individuals with GFR values in the normal to mildly impaired renal function range (6–10); however, a recent study (19) demonstrated a significant relationship between the serum level of cystatin C and markers of inflammation in elderly individuals without CKD. It remains unclear, though, whether the GFR loss has a more close relationship with arterial stiffness than with microinflammation and/or oxidative stress in individuals with GFR values in the normal to mildly impaired renal function range. This study is the first to demonstrate that the baPWV but not the plasma levels of CRP or LipOX was higher in individuals with GFR values in the mildly impaired renal function range than in those with values in the normal renal function range. It should be noted that the MDRD equation systematically underestimates the GFR and also that larger discrepancies are found between the GFR estimated using this equation and that estimated by the inulin clearance method in healthy individuals than in those with impaired renal function (20,21). Even so, this study demonstrated that the GFR was correlated with the

Table 3. Results of multiple linear regression analysis to assess the significance of the relationship between the baPWV and GFR after adjustment for other variables[a]

Parameter	Normal to Mildly Impaired Renal Function (n = 1873, R^2 = 0.59)				Normal Renal Function (n = 1778, R^2 = 0.59)			
Variable	parR	β	t	P	parR	β	t	P
GFR	−0.05	−0.05	−2.10	0.04	−0.05	−0.05	−2.09	0.04
logCRP	0.05	0.05	3.15	<0.01	0.05	0.05	3.49	<0.01
logLipOX	−0.05	−0.05	−3.32	<0.01	−0.05	−0.05	−3.53	<0.01
Age	0.14	0.16	9.47	<0.01	0.14	0.16	8.88	<0.01
MBPpwv	0.55	0.66	37.55	<0.01	0.55	0.66	36.45	<0.01
BMI	−0.11	−0.13	−7.17	<0.01	−0.11	−0.13	−7.12	<0.01
TC	0.01	0.02	0.89	0.38	0.01	0.02	0.68	0.50
HDL	−0.03	−0.03	−1.90	0.06	−0.03	−0.03	−2.08	0.04
TG	0.06	0.08	4.37	<0.01	0.07	0.08	4.34	<0.01
FBG	0.05	0.05	3.09	<0.01	0.05	0.05	3.03	<0.01
Smoking	0.02	0.02	1.55	0.12	0.03	0.02	2.03	0.04

[a]parR, partial R.

baPWV but not with the plasma levels of CRP or LipOX, even in individuals with GFR values within the normal renal function range; therefore, mildly impaired renal function seems to be more closely associated with increased arterial stiffness than with microinflammation and/or oxidative stress. Furthermore, the relationship between the degree of GFR loss and arterial stiffness may begin even from the earliest stage of GFR loss.

The prognosis of patients with end-stage CKD is poor. Some studies have demonstrated that mildly impaired renal function is also a risk factor for cardiovascular disease (4,22). The PWV is an independent predictor of the prognosis not only in patients with end-stage CKD (23,24) but also in those with hypertension or in the general population (25,26). Several mechanisms, such as increased cardiac afterload, impaired coronary arterial blood supply, and direct induction of atherosclerotic arterial damage, are thought to be possible mechanisms underlying the increased cardiovascular risk associated with arterial stiffening (3,27). Although inflammation and oxidative stress may be the primary mediators or the "missing link" that could explain the mechanism underlying the elevated cardiovascular risk in patients with CKD, including those with severely impaired renal function (2,13), the results of this study suggested that increased arterial stiffness but not microinflammation/oxidative stress may underlie, at least in part, the increased cardiovascular risk in individuals with mild impairment of renal function.

The mechanisms underlying the relationship between the degree of GFR loss and arterial stiffness are not fully understood (27). In this study, the results of multiple linear regression analyses demonstrated that even after adjustment for age and other conventional atherosclerotic risk factors, this relationship remained significant; therefore, additional mechanisms might underlie this relationship. The increased plasma levels of asymmetric dimethylarginine and of homocysteine in individuals with mild renal insufficiency may increase arterial stiffness *via* endothelial dysfunction (28–32). Conversely, increased arterial stiffness may directly cause glomerular and/or tubular damage *via* increased intrarenal pulse pressure (25) and *vice versa* (33). In any event, it may be useful to prevent the onset and progression of renal dysfunction and to conduct further longitudinal studies to clarify the cause–effect relationship and/or common underlying factors between loss of GFR and arterial stiffness.

This study had some limitations. First, because of the underestimation of the GFR calculated using the MDRD equation and the large discrepancies between GFR values obtained using the MDRD equation and those estimated by the insulin clearance method, especially in cases with GFR $\geq$60 ml/min per 1.73 m^2 body surface area (20,21), further studies using more reliable methods to estimate the GFR, such as measurement of the plasma levels of cystatin C, and on a larger number of individuals are proposed to confirm our results (21). Second, although the baPWV has been shown to be closely correlated with the aortic PWV (14), it also includes peripheral muscular arterial stiffness. Recently, Pannier *et al.* (34) demonstrated that central, rather than peripheral, arterial stiffness is an independent risk factor for future cardiovascular events in individuals with ESRD. Further studies are proposed to clarify whether central arterial stiffness may be more closely related with GFR loss in the early stage than arterial stiffness as measured by the baPWV. Third, the urinary microalbumin-to-creatinine excretion ratio is another recommended parameter for estimating the severity of renal dysfunction (1). This ratio is related to endothelial function, which, in turn, is thought to affect the peripheral muscular arterial stiffness (31,35). In addition, microinflammation and oxidative stress affect endothelial function. Therefore, the relationship among the urinary microalbumin-to-creatinine excretion ratio, arterial stiffness (central and peripheral arterial stiffness), endothelial function, microinflammation, and/or oxidative stress must also be evaluated. Finally, the rate of progression of renal dysfunction seems to be related to the ethnicity (36); therefore, future studies are required to confirm the relationship between the GFR loss within the normal renal function range and increased arterial stiffness in elderly individuals, female individuals, and individuals of other ethnicities.

Conclusions

In middle-aged Japanese men with a low cardiovascular risk and GFR values in the normal to mildly impaired renal function range, the degree of GFR loss seems to be more closely associated with arterial stiffness than with microinflammation and/or oxidative stress. A weak but significant relationship was observed between the degree of GFR loss and arterial stiffness, even in individuals with GFR values within the normal renal function range; therefore, increased arterial stiffness may underlie, at least in part, the elevated cardiovascular risk in individuals with mildly impaired renal function. The next logical step would be to clarify whether the PWV is a more reliable marker to predict future cardiovascular events than parameters of microinflammation and/or oxidative stress.

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Disclosures

None.

References

1. Brosius FC 3rd, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, Pennathur S, Smith GL, Wilson PW, American Heart Association Kidney and Cardiovascular Disease Council, Council on High Blood Pressure Research, Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Quality of Care and Outcomes Research Interdisciplinary Working Group: Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: A science advisory from the American Heart Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working

Group—Developed in collaboration with the National Kidney Foundation. *Circulation* 114: 1083–1087, 2006
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 42: 1050–1065, 2003
3. Safar ME: Pulse pressure, arterial stiffness, and cardiovascular risk. *Curr Opin Cardiol* 15: 258–263, 2003
4. Henry RM, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD: Mild renal insufficiency is associated with increased cardiovascular mortality: The Hoorn Study. *Kidney Int* 62: 1402–1407, 2002
5. Schillaci G, Reboldi G, Verdecchia P: High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension. *Arch Intern Med* 161: 886–891, 2001
6. Schillaci G, Pirro M, Mannarino MR, Pucci G, Savarese G, Franklin SS, Mannarino E: Relation between renal function within the normal range and central and peripheral arterial stiffness in hypertension. *Hypertension* 48: 616–621, 2006
7. Gosse P, Safar M: Arterial stiffness and plasma creatinine in untreated hypertensive patients. *Am J Hypertens* 18: 1140–1145, 2005
8. Mourad JJ, Pannier B, Blacher J, Rudnichi A, Benetos A, London GM, Safar ME: Creatinine clearance, pulse wave velocity, carotid compliance and essential hypertension. *Kidney Int* 59: 1834–1841, 2001
9. Ohya Y, Iseki K, Iseki C, Miyagi T, Kinjo K, Takishita S: Increased pulse wave velocity is associated with low creatinine clearance and proteinuria in a screened cohort. *Am J Kidney Dis* 47: 790–797, 2006
10. Briet M, Bozec E, Laurent S, Fassot C, London GM, Jacquot C, Froissart M, Houillier P, Boutouyrie P: Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int* 69: 350–357, 2006
11. Peralta CA, Whooley MA, Ix JH, Shlipak MG: Kidney function and systolic blood pressure new insights from cystatin C: Data from the Heart and Soul Study. *Am J Hypertens* 19: 939–946, 2006
12. Verhave JC, Fesler P, du Cailar G, Ribstein J, Safar ME, Mimran A: Elevated pulse pressure is associated with low renal function in elderly patients with isolated systolic hypertension. *Hypertension* 45: 586–591, 2005
13. Kaysen GA, Eiserich JP: The role of oxidative stress-altered lipoprotein structure and function and microinflammation on cardiovascular risk in patients with minor renal dysfunction. *J Am Soc Nephrol* 15: 538–548, 2004
14. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 25: 359–364, 2002
15. Tomiyama H, Koji Y, Yambe M, Motobe K, Shiina K, Gulnisa Z, Yamamoto Y, Yamashina A: Elevated C-reactive protein augments increased arterial stiffness in subjects with the metabolic syndrome. *Hypertension* 45: 997–1003, 2005
16. Yamada J, Tomiyama H, Yambe M, Koji Y, Motobe K, Shiina K, Yamamoto Y, Yamashina A: Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. *Atherosclerosis* 189: 198–205, 2006
17. Yagi K, Kiuchi K, Saito Y, Miike A, Kayahara N, Tatano T, Ohishi N: Use of a new methylene blue derivative for determination of lipid peroxides in foods. *Biochem Int* 12: 367–371, 1986
18. Tomiyama H, Arai T, Koji Y, Yambe M, Hirayama Y, Yamamoto Y, Yamashina A: The relationship between high-sensitive C-reactive protein and pulse wave velocity in healthy Japanese men. *Atherosclerosis* 174: 373–377, 2004
19. Keller CR, Odden MC, Fried LF, Newman AB, Angleman S, Green CA, Cummings SR, Harris TB, Shlipak MG: Kidney function and markers of inflammation in elderly persons without chronic kidney disease: The Health, Aging, and Body Composition Study. *Kidney Int* 71: 239–244, 2007
20. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG: Using serum creatinine to estimate glomerular filtration rate: Accuracy in good health and in chronic kidney disease. *Ann Intern Med* 141: 929–937, 2004
21. Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, Seliger SL, Kestenbaum B, Psaty B, Tracy RP, Siscovick DS: Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med* 145: 237–246, 2006
22. Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, Kuller LH, Newman AB: Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 41: 1364–1372, 2003
23. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 99: 2434–2439, 1999
24. Shoji T, Emoto M, Shinohara K, Kakiya R, Tsujimoto Y, Kishimoto H, Ishimura E, Tabata T, Nishizawa Y: Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol* 12: 2117–2124, 2001
25. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A: Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 37: 1236–1241, 2001
26. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J: Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 113: 664–670, 2006
27. Safar ME, London GM, Plante GE: Arterial stiffness and kidney function. *Hypertension* 43: 163–168, 2004
28. Kielstein JT, Boger RH, Bode-Boger SM, Frolich JC, Haller H, Ritz E, Fliser D: Marked increase of asymmetric dimethylarginine in patients with incipient primary chronic renal disease. *J Am Soc Nephrol* 13: 170–176, 2002
29. Chauveau P, Chadefaux B, Coude M, Aupetit J, Hannedouche T, Kamoun P, Jungers P: Hyperhomocys-

teinemia, a risk factor for atherosclerosis in chronic uremic patients. *Kidney Int Suppl* 41: S72–S77, 1993
30. Feletou M, Vanhoutte PM: Endothelial dysfunction: A multifaceted disorder (The Wiggers Award Lecture). *Am J Physiol Heart Circ Physiol* 291: H985–H1002, 2006
31. McEniery CM, Wallace S, Mackenzie IS, McDonnell B, Yasmin, Newby DE, Cockcroft JR, Wilkinson IB: Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension* 48: 602–608, 2006
32. Zocalli C: Traditional and emerging cardiovascular and renal risk factors: An epidemiologic perspective. *Kidney Int* 70: 26–33, 2006
33. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K, Thomas F, Pannier B, Asmar R, Zureik M, Safar M, Guize L: Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation* 105: 1202–1207, 2002
34. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM: Stiffness of capacitive and conduit arteries: Prognostic significance for end-stage renal disease patients. *Hypertension* 45: 592–596, 2005
35. Zieman SJ, Melenovsky V, Kass DA: Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 25: 932–943, 2005
36. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR: Risk factors for renal dysfunction in type 2 diabetes: UK Prospective Diabetes Study 74. *Diabetes* 55: 1832–1839, 2006