

Risk Factors for Metabolic Syndrome Independently Predict Arterial Stiffness and Endothelial Dysfunction in Patients With Chronic Kidney Disease and Minimal Comorbidity

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OBJECTIVE—Metabolic syndrome (MS) is common in patients with chronic kidney disease (CKD), but its contribution to arterial stiffness and endothelial dysfunction in CKD is not well defined. We hypothesized that risk factors for MS would independently predict arterial stiffness and endothelial dysfunction in CKD patients.

RESEARCH DESIGN AND METHODS—Risk factors for MS, carotid-femoral pulse wave velocity (CF-PWV) and flow-mediated dilation (FMD) as measures of arterial stiffness and endothelial dysfunction, respectively, were assessed in 113 minimally comorbid CKD patients and in 23 matched control subjects.

RESULTS—CF-PWV correlated with systolic blood pressure (SBP), waist circumference, and plasma glucose ($r^2 = 0.25, 0.09, \text{ and } 0.09; P < 0.01$ for all). FMD correlated with SBP ($r^2 = 0.09; P < 0.01$) and waist circumference ($r^2 = 0.03; P < 0.05$). CF-PWV increased progressively ($r^2 = 0.07; P < 0.01$) with increasing number of risk factors for MS. In multiple linear regression, SBP and waist circumference were independent determinants of CF-PWV, whereas only SBP predicted FMD.

CONCLUSIONS—The number of MS risk factors is an important determinant of arterial stiffness in CKD patients irrespective of the degree of renal impairment. Although BP remains the major determinant of arterial stiffness and endothelial dysfunction, waist circumference independently predicts arterial stiffness. MS risk factors, particularly abdominal girth, are potential targets for future interventional studies in patients with CKD.

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Chronic kidney disease (CKD) is common and associated with an increased risk of cardiovascular disease (CVD) (1). Conventional (Framingham) CVD risk factors, including high blood pressure (BP), hypercholesterolemia, and diabetes, all of which are common in CKD patients, only partly explain the high cardiovascular risk (2). CKD is now regarded as an independent risk factor for CVD (1,3), and we have recently shown

that renal dysfunction also contributes to arterial stiffness and endothelial dysfunction in a group of minimally comorbid CKD patients (4).

Increased arterial stiffness, as measured by pulse wave velocity (PWV), is a commonly recognized feature of CKD (4), a marker of cardiovascular risk (5,6), and an independent predictor of mortality and survival in dialysis patients (6). The vascular endothelium is an important regulator

of arterial stiffness (7), and endothelial dysfunction is also a common feature of CKD (8) and a predictor of CVD (9).

Metabolic syndrome (MS) is a clustering of metabolic abnormalities and risk factors for CVD and includes abdominal obesity, hyperglycemia, hypertension, hypertriglyceridemia, and reduced HDL cholesterol (10). As MS is associated with increased risks of diabetes and CVD (11,12), its treatment and prevention have become one of the major public health challenges worldwide. The risk factors for MS, either together or individually, are also associated with arterial stiffness and endothelial dysfunction both in health (13,14) and disease (15,16).

MS is widely prevalent in CKD (17) and is itself a risk factor for CKD (18). Although a recent study has suggested that MS and its risk factors contribute to arterial stiffness and endothelial dysfunction in dialysis patients (19), there are no data relating to predialysis CKD. This is clearly important because targeting MS risk factors in early CKD may retard CKD progression, delaying the onset of dialysis and its associated morbidity, as well as reducing the overall risk of CVD.

In this current study, we investigated the relationships of MS and its individual components to arterial stiffness and endothelial dysfunction in CKD patients across a wide range of renal function from early CKD to predialysis. Importantly, we planned to recruit patients without diabetes or cardiovascular comorbidity. We hypothesized that the presence of MS, or its components, would be associated with increased arterial stiffness and endothelial dysfunction and that these relationships would be independent of renal function and other well-established risk factors for CVD.

RESEARCH DESIGN AND METHODS

The rationale and study design have been reported in detail elsewhere (4). In brief, subjects were recruited

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from the renal outpatient clinic at the Royal Infirmary of Edinburgh. They were categorized into the five stages of CKD on the basis of the Kidney Disease Outcome Quality Initiative (K/DOQI) classification (20). Age-matched healthy volunteers were recruited from the community as a control group.

The inclusion criteria were as follows: male or female CKD patients, 18–65 years old, and clinic BP \leq 160/100 mmHg, whether or not on antihypertensive medication. We excluded patients with a renal transplant or on dialysis, systemic vasculitis or connective tissue disease, a history of established CVD, peripheral vascular disease, diabetes, respiratory or neurologic disease, and current alcohol abuse or pregnancy and those treated with an organic nitrate or β -agonist. Patients continued their usual medications until the study morning. Smokers and hypercholesterolemic patients were not excluded, but the latter had to be established on statin medication, with good cholesterol control, for at least 3 months before taking part in the study.

Diagnosis of MS

MS was diagnosed according to the criteria from the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel [ATP] III) (10,21). The diagnosis of MS was made when subjects had three or more risk factors for MS. Subjects with zero to one and two risk factors for MS were classified as no MS and risk for developing MS, respectively (Supplementary Table 1).

Measurements

Brachial systolic and diastolic BP (SBP and DBP) were recorded in duplicate, with an appropriately sized cuff, using a validated oscillometric sphygmomanometer (Omron HEM-705CP) (22), and values were presented as an average of two recordings. BMI was calculated as weight (kg)/(height [m])². Waist and hip circumferences (cm) were measured on a subject in a standing position with feet 15 cm apart. Waist circumference was measured at the midpoint between the iliac crest and lowest rib. Hip circumference was measured at the midpoint between the waist and groin. During the measurement, the tape measure was parallel to the ground.

Arterial stiffness was assessed by measuring carotid-femoral PWV (CF-PWV), as previously described (23), using the

SphygmoCor apparatus (SphygmoCor BPAS-1; AtCor Medical, Sydney, Australia). Central augmentation index (cAIx) was estimated using the same system (23). Brachial artery flow-mediated dilation (FMD) was used to assess endothelium-dependent vasomotor function as described elsewhere (24). FMD was quantified as a percentage change from baseline in brachial artery diameter after 5 min of forearm ischemia. Endothelium-independent vasomotor function was assessed using 25 μ g nitroglycerine (NTG) by sublingual administration (25).

Renal function assessment

Creatinine clearance, as an estimate of glomerular filtration rate (eGFR), was calculated according to the Cockcroft and Gault (C&G) equation (26): $(140 - \text{age} [\text{years}] \times \text{weight} [\text{kg}] \times 1.23 \text{ for male or } 1.05 \text{ for female})/\text{serum creatinine} (\mu\text{mol/L})$. The C&G equation was selected to assess renal function in this study because it is more accurate than the Modification of Diet in Renal Disease (MDRD) equation when used to assess mild renal insufficiency (27). It was further corrected by body surface area.

Statistical analyses

Data were statistically analyzed using SPSS program for Windows (SPSS 15.0; SPSS Inc., Chicago, IL). Descriptive data are given as mean \pm SD unless otherwise stated. Means of the categorical data (subjects without MS, subjects with risk of

developing MS, and subjects with MS) were compared by one-way ANOVA. Continuous data (risk factors for MS as zero to five risk factors) were analyzed by correlation coefficients calculated using the Pearson method. Stepwise linear regression was used for multivariate analysis. A significant level was taken as P value <0.05 .

RESULTS—CKD patients ($n = 113$) and age-matched non-CKD control subjects ($n = 23$) were enrolled into the study. Baseline characteristics of the studied subjects are given in Supplementary Table 2. Causes of CKD and medication used by the patients are described in Supplementary Table 3.

Subjects were classified into three categories according to the number of risk factors for MS (see RESEARCH DESIGN AND METHODS). Twenty-six subjects (19%) had MS and 27 (20%) were defined as at risk for developing MS. All three categories were comparable in respect to age and eGFR. As expected, subjects with MS had a higher BMI, waist circumference, SBP, DBP, plasma glucose, and triglycerides and lower HDL cholesterol compared with those without MS or those at risk for developing it (Table 1). With regard to the relationship of the risk factors for MS to renal function, only SBP increased as eGFR declined ($r^2 = 0.11$; $P < 0.01$); waist circumference, DBP, plasma glucose, triglycerides, and HDL cholesterol showed no

Table 1—Risk factors for MS, arterial stiffness, and endothelial function

	No MS	Risk for MS	MS
N	83	27	26
Male/female (n)	50/33	18/9	20/6
Smoker/nonsmoker (n)	14/69	2/25	9/17
Age (years)	46 \pm 10	49 \pm 11	50 \pm 8
eGFR (mL/min/1.73 m ²)	73 \pm 34	65 \pm 33	59 \pm 36
BMI (kg/m ²)*	26 \pm 4	28 \pm 5	33 \pm 4
Risk factors for MS			
Waist circumference (cm)*	90 \pm 11	96 \pm 13	111 \pm 12
SBP (mmHg)*	113 \pm 13	124 \pm 15	124 \pm 13
DBP (mmHg)*	72 \pm 10	76 \pm 8	76 \pm 8
Glucose (mmol/L)*	4.8 \pm 0.5	5.1 \pm 0.5	5.4 \pm 0.6
Triglycerides (mmol/L)*	1.1 \pm 0.4	1.4 \pm 0.8	2.4 \pm 1.2
HDL cholesterol (mmol/L)*	1.4 \pm 0.3	1.2 \pm 0.3	0.9 \pm 0.2
Arterial stiffness and endothelial dysfunction			
CF-PWV (m/s)*	6.4 \pm 1.0	7.0 \pm 1.4	7.5 \pm 1.7
cAIx (%)	22 \pm 13	22 \pm 13	25 \pm 11
FMD (%)	4.8 \pm 2.9	3.4 \pm 2.8	3.5 \pm 2.8
NTG (%)	12.4 \pm 5.2	10.6 \pm 4.1	10.2 \pm 4.6

No MS, subjects with zero to one risk factor for MS; risk for MS, subjects with two risk factors for MS; MS, subjects with three or more risk factors for MS. * $P < 0.05$ for one-way ANOVA by MS groups.

relationship to renal function. CF-PWV was higher in the MS group (Table 1 and Fig. 1A and C) whereas cAIx showed no relationship to MS (Table 1). FMD was lower in the MS group and subjects at risk for MS compared with those without MS (Table 1 and Fig. 1B and D) but this did not reach statistical significance. The endothelium-independent response to NTG had no relationship to MS (Table 1).

Relationships and predictors of arterial stiffness

Univariate analysis to assess the relationship of CF-PWV to individual MS risk

factors, the number of MS risk factors, and related parameters that are not included in the National Cholesterol Education Program (NCEP) ATP III criteria (eGFR, age, BMI, and waist-to-hip ratio) was performed. CF-PWV only correlated with eGFR when all subjects were considered together ($r^2 = 0.07$; $P < 0.01$) but not when split into the three groups according to the presence, risk, or absence of MS (Fig. 1A). However, PWV in subjects with MS was significantly higher than in subjects without MS (Fig. 1A and C). With regard to the individual risk factors for MS, CF-PWV increased with waist

circumference, waist-to-hip ratio, SBP, and plasma glucose (Fig. 2A–D). Additionally, CF-PWV correlated with age ($r^2 = 0.25$; $P < 0.01$), BMI ($r^2 = 0.06$; $P < 0.01$), DBP ($r^2 = 0.07$; $P < 0.01$), and plasma triglycerides ($r^2 = 0.05$; $P < 0.05$) but not sex, smoking status, or HDL cholesterol.

In multivariate analysis, when renal function and conventional risk factors were entered into the model, age and sex were independent predictors of arterial stiffness (Table 2, model 1). When either the presence of MS or the number of risk factors for MS that a subject had were

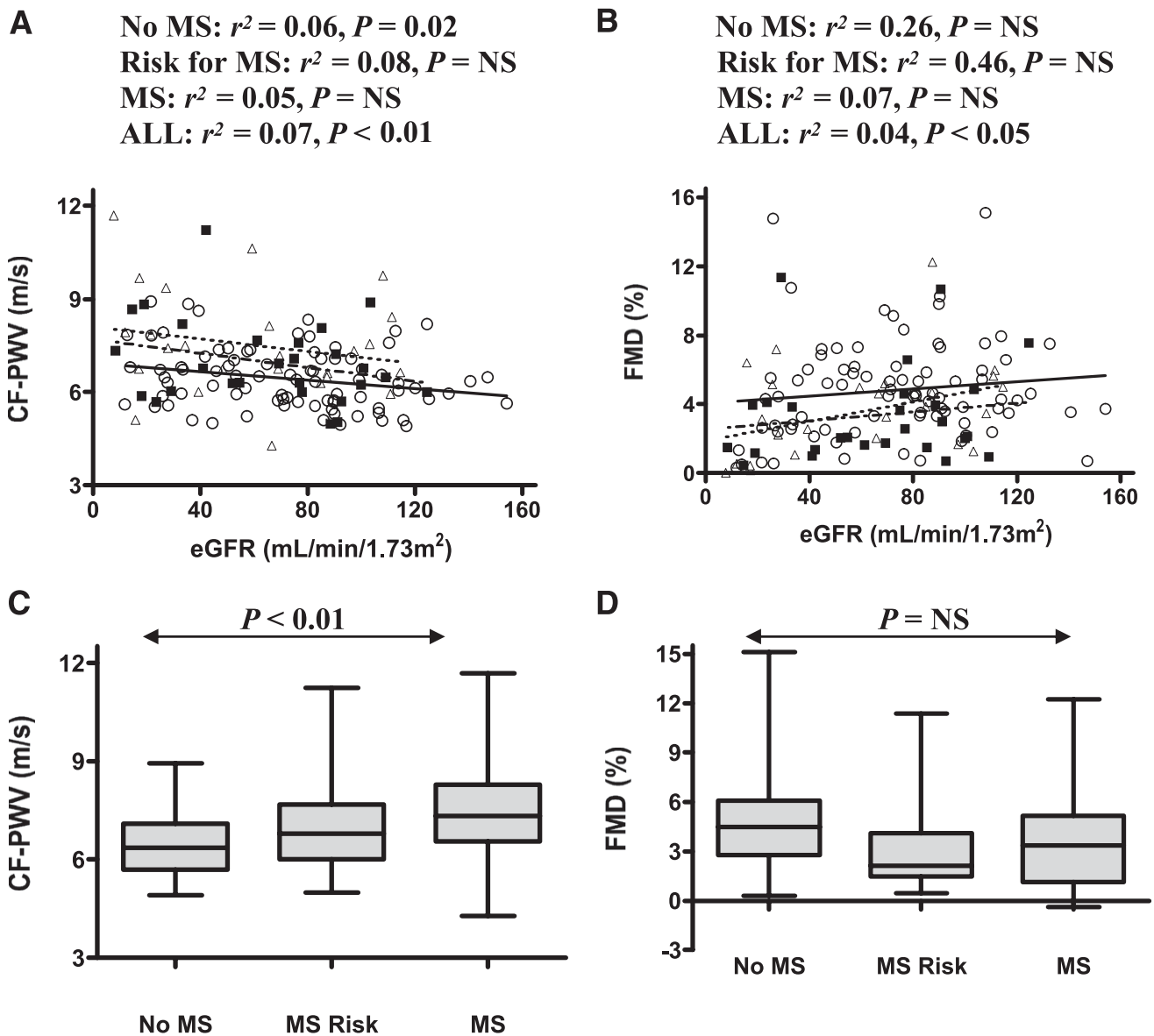


Figure 1—Scatter and box plots showing associations between the number of the MS risk factors and CF-PWV (A and C) and FMD (B and D). No MS (O, solid fitted line), subjects without MS (zero to one risk factor); risk for MS (■, long-dashed fitted line), subjects at risk for developing MS (two risk factors); MS (△, short-dashed fitted line), subjects with MS (three or more risk factors). P values are for one-way ANOVA (C and D).

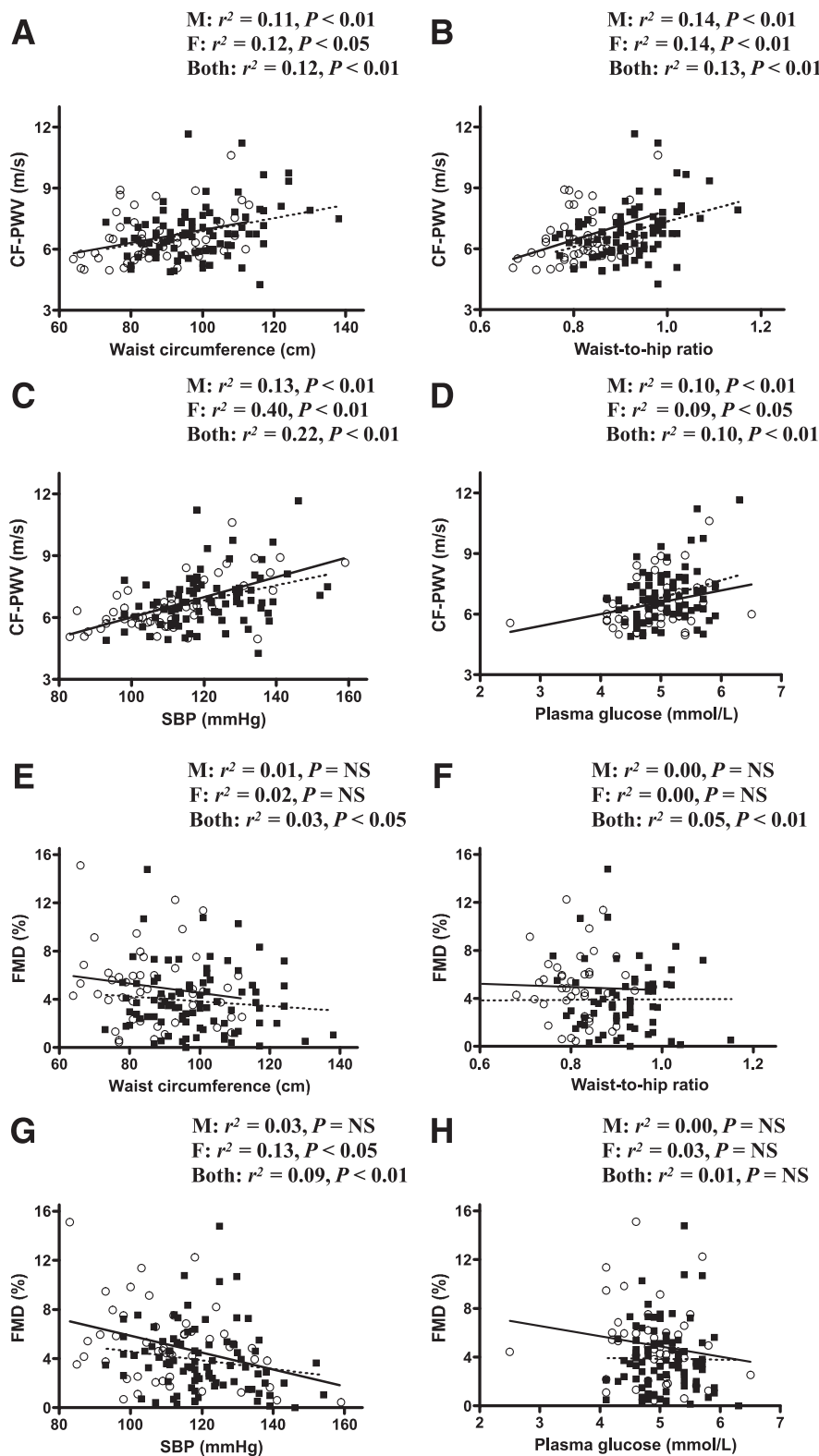


Figure 2—Scatter plots showing correlations between CF-PWV and waist circumference (A), waist-to-hip ratio (B), SBP (C), and plasma glucose (D). Scatter plots showing correlations between FMD and waist circumference (E), waist-to-hip ratio (F), SBP (G), and plasma glucose (H). Male: ■, dashed line; female: ○, solid line.

considered, both of them, together with age and sex, independently predicted CF-PWV (Table 2, models 2 and 3). When the individual risk factors for MS were considered, sex was replaced by waist circumference, SBP, and DBP as independent predictors of CF-PWV (Table 2, model 4).

Relationship and predictors of endothelial dysfunction

In univariate analysis, FMD correlated with eGFR when all subjects were considered together ($r^2 = 0.04; P < 0.05$) but not when subjects were divided into the three MS groups. FMD did not change according to the presence, risk, or absence of MS (Fig. 1B and D). FMD correlated with waist circumference, waist-to-hip ratio, and SBP but not plasma glucose (Fig. 2E–H). Additionally FMD did not correlate with age, BMI, DBP, plasma triglycerides, HDL cholesterol, or smoking status.

In multivariate analysis assessing renal function and conventional risk factors, eGFR was an independent predictor of FMD (Table 2, model 1). Although the presence or absence of MS did not predict endothelial dysfunction, the number of MS risk factors did (Table 2, models 2 and 3). When the risk factors for MS were considered individually in the model, SBP and DBP alone were independent predictors of FMD (Table 2, model 4).

CONCLUSIONS—In a cohort of subjects with minimal comorbidity and an eGFR ranging from 8 to 154 mL/min/1.73 m², we have previously shown that renal function is related to an increase in arterial stiffness and endothelial dysfunction, as measured by CF-PWV and FMD, respectively (4). We now show that subjects in this cohort with MS have increased arterial stiffness compared with those without MS. Importantly, this is independent of the level of renal function (eGFR). Both the presence of MS and the number of MS risk factors are independent predictors of arterial stiffness in this cohort. Furthermore, when risk factors for MS were considered individually, waist circumference and blood pressure were determinants of arterial stiffness, independent of renal function, age, sex, and smoking status.

Our study cohort was carefully selected to have low comorbidity. Thus, the prevalence of MS in this CKD population is lower than previously reported in dialysis (19,28), hypertensive (15), and diabetic patients (16) but is comparable to healthy subjects (18 vs. 10–19%) (14). Interestingly, despite this selection bias against MS and its risk factors, we have

Table 2—Multivariate analysis of renal function, conventional cardiovascular risk factors, and risk factors for MS, as independent predictors for CF-PWV and FMD

Predictors	CF-PWV			
	Model 1	Model 2	Model 3	Model 4
eGFR	−0.11	−0.11	−0.12	−0.11
Age	0.52*	0.49*	0.47*	0.39*
Sex (male/female)	0.18†	0.15†	0.16†	0.01
Smoking status (yes/no)	−0.09	−0.14	−0.10	−0.03
Presence of MS (yes/no)	—	0.20*	—	—
Number of MS risk factors (0–5)	—	—	0.23*	—
Waist circumference	—	—	—	0.24*
SBP	—	—	—	0.53*
DBP	—	—	—	−0.27*
Plasma glucose	—	—	—	0.03
Triglycerides	—	—	—	0.06
HDL cholesterol	—	—	—	−0.09
r ²	0.28*	0.31*	0.32*	0.48*

Predictors	FMD			
	Model 1	Model 2	Model 3	Model 4
eGFR	0.02†	0.02†	0.18†	0.10
Age	−0.10	−0.10	−0.07	−0.05
Sex (male/female)	−0.11	−0.11	−0.11	−0.06
Smoking status (yes/no)	−0.02	−0.02	−0.01	−0.02
Presence of MS (yes/no)	—	−0.10	—	—
Number of MS risk factors (0–5)	—	—	−0.18†	—
Waist circumference	—	—	—	−0.14
SBP	—	—	—	−0.50*
DBP	—	—	—	0.28†
Plasma glucose	—	—	—	−0.02
Triglycerides	—	—	—	−0.05
HDL cholesterol	—	—	—	0.08
r ²	0.04†	0.04†	0.07†	0.12*

The table gives standard regression coefficients (β values). * $P < 0.01$. † $P < 0.05$.

shown that, irrespective of renal function, there is an increase in arterial stiffness in our subjects with MS or risk factors for MS, and that these independently predict arterial stiffness when considered alongside conventional risk factors. This finding is in keeping with previous data from healthy subjects (13,14,29,30), hypertensive patients (15), and patients with diabetes (16).

Our data also show that waist circumference is a predictor of arterial stiffness in this population and this is independent of renal function, age, BP, and sex. Our analysis considered the whole cohort of 113 CKD patients and 23 age-matched, non-CKD control subjects, but waist circumference remains an independent predictor of arterial stiffness when the CKD patients are considered alone. This has previously only been shown in hypertensive patients (15). Obesity is associated both with increased arterial stiffness (31)

and an increased risk of CVD (32). Our data suggest that, in patients with CKD, waist circumference, a marker of central obesity, may be a better surrogate for arterial stiffness than BMI or cholesterol subtypes such as HDL cholesterol and triglycerides.

In the current study, subjects with MS did not have significantly impaired endothelial function compared with those without MS, regardless of renal function. This is similar to data from studies in healthy subjects (33,34), those at risk for developing diabetes (35,36), and those with peripheral vascular disease (37). However, in a study of ~1,000 elderly subjects, including those with CVD and diabetes, where endothelial function was assessed using both an invasive forearm technique and FMD (38), the former showed significantly impaired endothelial function in the MS group. The invasive forearm technique is considered to

assess vascular function of the resistance arteries, whereas FMD is a measure of conduit artery function. Thus, it is possible that MS is associated with a predominant dysfunction of the resistance vessels and, hence, by using FMD, we did not detect significant endothelial dysfunction in our study cohort. We also observed no association between the number of risk factors for MS and FMD. This is in contrast to a previous study in subjects at risk for developing diabetes (36), but this may in part be explained by genetic influences in diabetes (and insulin resistance states) not currently considered to be of importance in the majority of CKD patients.

Of all the risk factors studied here, conventional and MS related, only BP is an independent predictor of endothelial dysfunction (Table 2, model 4). This result both confirms and contradicts those of previous studies. Similar to our findings, Scuteri et al. (35) found BP (both SBP and DBP) to be an independent predictor of endothelial dysfunction in normoglycemic first-degree relatives of patients with diabetes. However, Kovaite et al. (29) found this not to be the case when studying 186 “asymptomatic subjects without overt cardiovascular disease.” Notably, one-third of subjects studied fulfilled criteria for MS. A study in CKD has shown that, similar to the current data, renal function is a predictor of endothelial dysfunction (39). However, this study was performed in CKD patients with diabetes and this may act as a significant confounder. Furthermore, in that study, an invasive forearm technique measured endothelial function in a different vascular bed compared with the technique of FMD used in the current study.

Interestingly, we found an inverse association between DBP and CF-PWV (Table 2) and a positive association between DBP and FMD (Table 2). However, these may be explained by an effect of pulse pressure, which is positively associated with CF-PWV and inversely related to FMD, since both SBP and DBP were entered into the analysis.

We recognize some limitations to the current study. There are several criteria for the diagnosis of MS (14). As our patients were not diabetic, we cannot use the criteria proposed by the World Health Organization and, therefore, the evaluation of an effect of insulin resistance to arterial stiffness and endothelial dysfunction is limited and does not allow data comparison with other studies using World Health Organization criteria. Also, an increased girth

has the potential to artifactually increase the measurement entered for the distance traveled by the pulse wave (compared with the actual distance) in calculating PWV. Thus, the reported PWV will be higher than the "true" value. It is possible that this is responsible, in part, for the higher PWV in the MS group in this study. However, our subjects were chosen because of low comorbidity and are not typical of "general" CKD patients (including patients with diabetes) particularly in their body habitus. Median BMI was 26.9 kg/m², and the patient with the highest BMI did not have MS by ATP III criteria. Additionally, the 54 patients whose waist measurement was above the defining level for a risk factor for MS were spread throughout the three groups: 16 patients were in the "no MS" group, 17 in the "risk of MS" group, and 21 in the "MS" group. Some of the medications taken by our patients, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, and statins, may have had effects on both CF-PWV and FMD. However, all patients were stabilized on their therapies and did not receive their medications on the study day until after measurements were made. The low number of smokers in this study may be responsible for the lack of expected relationships between smoking status and both arterial stiffness and endothelial dysfunction; although when only the CKD patients are considered in the multivariate analysis, smoking is an independent predictor of PWV in models 2 and 3. Finally, as this was a cross-sectional study, we cannot fully define the causal relationships behind the associations described, though they do have a sound mechanistic basis.

In summary, the current study shows that, in the absence of CVD and diabetes and irrespective of renal function, age, smoking status, and sex, CKD patients with MS have increased arterial stiffness compared with those without MS but no difference in endothelial function. Although BP remains the strongest determinant of both arterial stiffness and endothelial dysfunction, the presence of MS or its risk factors is also an important determinant of arterial stiffness in this CKD cohort. Importantly, waist circumference is an independent predictor of arterial stiffness in this cohort; hence, education on lifestyle changes and weight management interventions offer a different therapeutic perspective, complementary to drug management of traditional cardiovascular risk factors, such as hypertension and hypercholesterolemia, that should not be overlooked in patient

care. Given these currently noncomorbid patients in this cohort only had modest increases in BMI, the early and aggressive control of weight should be a focus for intervention. As this is not related to renal function, it provides an additional target for therapies aimed at improving cardiovascular outcomes at all stages of CKD.

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P.L. designed and performed the study and prepared the manuscript. N.D. designed the study and revised and edited the manuscript. V.M. and D.K. performed the study. D.J.W. and J.G. designed and supervised the study and revised and edited the manuscript. J.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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