

Metabolic syndrome and its components associated with endothelial dysfunction in chronic kidney disease patients

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Background: Cardiovascular disease is more common in patients with chronic kidney disease (CKD) than in the general population. Endothelial dysfunction is an early predictor of cardiovascular events.

Objective: We conducted a cross-sectional study in CKD patients to explore the association of metabolic syndrome (MetS) components with endothelial cell function.

Methods: We evaluated clinical and laboratory data in 161 CKD patients from stage 1 to stage 5. Endothelial function was estimated by flow-mediated dilatation (FMD) of the brachial artery and expressed as percentage change relative to baseline diameter. MetS was defined according to the National Cholesterol Education Program-Adult Treatment Panel III criteria.

Results: Patients were grouped into two groups according to whether or not they had MetS. FMD was significantly lower in the MetS group than in the group without MetS ($P = 0.012$). In a Pearson's correlation analysis, FMD was significantly negatively correlated with waist circumference in women ($r = -0.223$, $P = 0.03$) and fasting blood glucose ($r = -0.186$, $P = 0.001$). Multiple linear regression analysis showed that fasting blood glucose was an independently associated factor for FMD.

Conclusion: MetS and some components of MetS (waist circumference in women and fasting blood glucose) are closely associated with a decreased FMD in CKD patients.

Keywords: metabolic syndrome, endothelial dysfunction, flow-mediated dilatation, chronic kidney disease

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including visceral obesity, high blood pressure, hyperglycemia, and dyslipidemia,¹⁻⁴ which are associated with increased cardiovascular risk in various clinical conditions.^{5,6} The mechanisms through which this syndrome increases cardiovascular risk are only partially understood. Recently, research has found that several of the individual components of MetS, including high blood pressure,⁷ hyperglycemia,⁸ and abdominal obesity,^{9,10} have been related to increased endothelial dysfunction in the general population.

Endothelial dysfunction, detected noninvasively as a decreased flow-mediated dilatation (FMD) of the brachial artery,^{11,12} is an early and potentially reversible functional disturbance in the development of vascular lesion and disease.¹³ It is also common in subjects with MetS, and it is believed to reflect the metabolic derangements present in this condition.¹⁴

In CKD, endothelial dysfunction also appears to predict cardiovascular disease (CVD) and outcome.¹⁵ Johnson et al¹⁶ have shown that MetS is exceedingly common

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in CKD, and it is thus also a plausible cause of high morbidity and mortality. To date, the relationship of MetS to endothelial dysfunction has been evaluated mostly in the general population but is not clearly elucidated in the CKD population. In the present study, we aimed to investigate the possible link of metabolic components of MetS of patients with CKD with endothelial function assessed by FMD.

Subjects and methods

Subjects and collection of data

This study was approved by the Ethics Committee of Peking University Third Hospital, Beijing, People's Republic of China, and all patients gave written informed consent to all the procedures.

All patients visiting our CKD outpatient clinics from December 1, 2008 to June 30, 2010 were eligible to participate in this study except for those with (1) clinical or laboratory evidence of heart failure (New York Heart Association classes III–IV); (2) peripheral arterial disease; (3) pre-existent chronic inflammatory disease; (4) cancer; (5) active arteriovenous fistula, which may interfere with the results of FMD; and (6) primary or secondary nephrotic syndrome. A total of 161 individuals (78 men and 83 women; age range 20–88 years; mean 65.58 ± 14.57 years) were studied. All patients' clinical data and laboratory test data were collected. A dedicated physician and nurse were responsible for all blood pressure, weight, and waist circumference measurements and performed measurements under strict instructions without any knowledge of the study protocol or objectives. The waist circumference measurement point in this study was the umbilical level. The mercury sphygmomanometer was calibrated regularly. The patients were allowed to take regular antihypertensive medications before each visit. The antihypertensive medications prescribed during the previous days were recorded in detail to calculate the defined daily dose.¹⁷ Moreover, every drug agent, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), β - or α -receptor blockers, calcium antagonists, statins, or aspirin, was recorded. Pre-existing CVD was evaluated. CVD in our study included coronary artery disease (angina pectoris and myocardial infarction), arrhythmia, congestive heart failure, and cerebrovascular disease.

Glomerular filtration rate was estimated (eGFR) by the simplified Modified Diet in Renal Disease (MDRD) formula.

MetS definition

MetS was defined according to the National Cholesterol Education Program-Adult Treatment Panel III^{18–20} when

patients had at least three of the following five criteria: (1) waist circumference >90 cm or 80 cm for men and women, respectively; (2) systolic blood pressure >130 mmHg and/or diastolic blood pressure >85 mmHg; (3) serum triglyceride (TG) levels >1.69 mmol/L (150 mg/dL); (4) serum high-density lipoprotein (HDL) cholesterol <1.04 mmol/L (40 mg/dL) in men and <1.30 mmol/L (50 mg/dL) in women; and (5) fasting plasma glucose >5.6 mmol/L (100 mg/dL).

Laboratory methods

Blood samples were obtained in the early morning after the subjects had fasted for at least 8 hours. Biochemical indices, such as fasting glucose, total cholesterol, TG, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, blood urea nitrogen, serum creatinine, calcium, and phosphate, were determined using standard methods with the Olympus AU5400 chemistry immunoanalyzer (Olympus, Tokyo, Japan).

Flow-mediated dilatation

Noninvasive endothelium-dependent FMD was measured in each subject after they took a 10-minute rest in a supine position with an empty abdomen. The right brachial artery image was recorded in a longitudinal section 15 cm above the antecubital fossa using a 7 MHz linear array transducer and a standard Acuson 128XP/10 system (Siemens, Erlangen, Germany). Baseline brachial artery diameter was measured using an automated wall tracking system (Sonoline G50, Siemens), which utilizes movement in the radiofrequency amplitude peaks over the cardiac cycle to identify the arterial walls.^{11,21} A pneumatic cuff was then inflated to 50 mmHg above systolic blood pressure on the forearm for 5 minutes to induce a reactive hyperemia. Cuff deflation resulted in increased flow through the brachial artery, stimulating endothelial-dependent dilatation. The percentage of the change in brachial artery diameter 1 minute after cuff release to baseline diameter was recorded as FMD. Our coefficient of variation of FMD measurement in our study was $1.1\% \pm 0.2\%$ intra-assay and $4.5\% \pm 1.0\%$ interassay.

Statistical analysis

Statistical analysis was performed using SPSS software (v 16.0; SPSS Inc, Chicago, IL). Continuous variables are expressed as means \pm standard deviation, and categorical variables are expressed as percentages. Independent sample Student's *t*-test or one-way analysis of variance were used to compare two groups

or multiple groups of normally distributed continuous variables, and the Mann–Whitney *U* test was used for non-normally distributed variables. For comparison of categorical variables in two groups, such as the proportion of gender distribution, the χ^2 test was employed. Pearson's correlation analysis was performed to explore the possible relationship between FMD and other continuous variables (Spearman's correlation analysis was performed if they were abnormal distributed variables). Multiple linear regression analysis was performed among those significant variables in Pearson's correlation analysis. A value of $P < 0.05$ was taken as statistically significant.

Results

Patients' clinical characteristics

Demographic data of the study population are listed in Table 1. Of the 161 patients, 78 were male and 83 were female. Mean age was 65.58 ± 14.57 years. The etiologies of CKD were glomerulonephritis (29.2%), diabetes mellitus (13.7%), hypertension (20.5%), and others (21.7%).

Comparison of clinical and laboratory data of patients with and without MetS

Thirty-seven percent of the patients displayed MetS according to the National Cholesterol Education Program-Adult Treatment Panel III. As there was no significant difference in MetS and non-MetS between male and female patients, patients were grouped into two groups according to whether or not they had MetS. As is shown in Table 2, patients in the first group (those with MetS) had an expected higher weight and waist circumference than patients in the second group (both $P = 0.000$). Also, primary renal diagnosis of diabetic nephropathy was more frequent ($P = 0.008$), TG ($P = 0.000$) and glucose ($P = 0.000$) were higher, and HDL cholesterol ($P = 0.001$) differed among the two groups, being lower in the MetS group compared with in the non-MetS group. There were no significant differences between the two groups with regard to blood pressure, MDRD stage, total cholesterol, calcium, phosphate, LDL, blood urea nitrogen, and serum creatinine. Notably, FMD was significantly lower in the group of patients with MetS than in the group without MetS ($7.65\% \pm 3.93\%$ vs $9.99\% \pm 5.54\%$, $z = -2.46$, $P = 0.014$). We found a higher total defined daily dose of anti-hypertensive medication in patients with MetS than in patients without MetS, but without significant difference.

Association between FMD and other variables

Pearson's correlation analysis between FMD and other variables is shown in Table 3. A significant negative correlation

Table 1 Demographic characteristics of the study population

	N \pm SD or number and percentage
Patients (number)	161
Male/female (ratio)	78/83
Age (mean \pm SD), years	65.58 ± 14.57
Weight (mean \pm SD), kg	65.56 ± 11.99
Waist circumference (mean \pm SD), cm	82.44 ± 11.90
Primary diagnosis (%)	
Chronic glomerulonephritis	29.2
Diabetes mellitus	13.7
Interstitial nephritis	14.9
Hypertension	20.5
Others	21.7
Systolic BP (mean \pm SD), mmHg	117.75 ± 22.83
Diastolic BP (mean \pm SD), mmHg	70.36 ± 14.17
MDRD stage, %	
CKD stage I	1.9
CKD stage II	11.8
CKD stage III	47.8
CKD stage IV	28.0
CKD stage V	10.6
Pre-existing cardiovascular disease (%)	14
Total DDD of antihypertensive drug	1.45 ± 1.22
ACEI DDD	0.27 ± 0.71
ARB DDD	0.32 ± 0.57
Calcium antagonist DDD	0.56 ± 0.74
β -receptor blocker	0.08 ± 0.185
A-receptor blocker	0.05 ± 0.149

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; DDD, defined daily dose; MDRD, Modified Diet in Renal Disease; SD, standard deviation.

was found between FMD and waist circumference in women ($r = -0.223$, $P = 0.03$) but not in men ($r = -0.055$, $P = 0.625$); moreover, FMD was inversely associated with fasting glucose ($r = -0.254$, $P = 0.001$) (Table 3) and 24-hour urine protein excretion (Spearman correlation analysis $r = -0.204$, $P = 0.011$), and FMD was also weakly correlated with serum calcium. FMD was higher in nondiabetic patients than in diabetic CKD patients ($10.07\% \pm 5.48\%$ vs $7.12\% \pm 3.60\%$, $P = 0.000$) and was also higher ($10.07\% \pm 5.48\%$ vs $6.97\% \pm 3.95\%$, $P = 0.009$) in nondiabetic patients than in high-fasting glucose patients without diabetes (fasting glucose >6.1 mmol/L but <7.0 mmol/L), but there was no significant difference in FMD between diabetic and high-fasting glucose patients. There was no significant difference in patients' FMD between those with pre-existing CVD and those without CVD. No correlation was observed between FMD and age, blood pressure, serum cholesterol, TG, phosphate, uric acid, HDL cholesterol, LDL cholesterol, serum creatinine, and blood urea nitrogen (Table 3). We did not find an effect of drug agents such as ACEIs/ARBs,

Table 2 Clinical and laboratory data of patients with and without metabolic syndrome

	Metabolic syndrome (n = 59)	No metabolic syndrome (n = 102)	P value
Age, years	66.34 ± 15.08	61.99 ± 15.20	0.068
Male/female	26/33	52/50	0.398
Weight (kg)	72.41 ± 11.30	61.60 ± 10.54	0.000
Waist circumference (cm)	91.01 ± 8.34	77.48 ± 10.58	0.000
Systolic BP (mmHg)	117.54 ± 24.41	117.87 ± 21.99	0.907
Diastolic BP (mmHg)	71.02 ± 15.36	69.98 ± 13.50	0.694
Primary diagnosis (n) (%)			
Chronic glomerulonephritis	14 (23.7)	33 (32.4)	0.283
Diabetes mellitus	14 (23.7)	8 (7.8)	0.008
Interstitial nephritis	10 (16.9)	14 (13.7)	0.648
Hypertension	13 (22.0)	20 (19.6)	0.840
MDRD stage (n) (%)			
CKD stage I	0 (0)	3 (2.9)	0.299
CKD stage II	7 (11.9)	12 (11.8)	1.000
CKD stage III	30 (50.8)	47 (46.1)	0.624
CKD stage IV	18 (30.5)	27 (26.5)	0.590
CKD stage V	4 (6.8)	13 (12.7)	0.294
Total cholesterol (mmol/L)	5.43 ± 1.47	5.14 ± 1.13	0.132
Triglycerides (mmol/L)	2.96 ± 1.95	1.66 ± 0.84	0.000
Calcium (mmol/L)	2.26 ± 0.11	2.25 ± 0.22	0.652
Phosphate (mmol/L)	1.29 ± 0.28	1.34 ± 0.24	0.232
HDL cholesterol (mmol/L)	1.32 ± 0.80	1.43 ± 0.40	0.001
LDL cholesterol (mmol/L)	3.29 ± 1.13	3.04 ± 0.96	0.350
Fasting glucose (mmol/L)	6.34 ± 1.58	5.50 ± 1.13	0.000
Uric acid (μmol/L)	412.99 ± 116.09	349.91 ± 112.81	0.334
Serum creatinine (μmol/L)	175.32 ± 70.82	200.56 ± 124.49	0.987
Blood urea nitrogen (mmol/L)	10.24 ± 3.61	11.78 ± 6.66	0.593
24-hour urine proteinuria excretion (g/day)	1.24 ± 1.84	0.94 ± 1.20	0.393
Pre-existing cardiovascular disease (%)	16.7	11.0	0.404
Total DDD of antihypertensive drug	1.78 ± 1.36	1.25 ± 1.1	0.969
FMD (%)	7.65 ± 3.93	9.99 ± 5.54	0.012

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; DDD, defined daily dose; FMD, flow-mediated dilatation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MDRD, Modified Diet in Renal Disease.

β- or α-blockers, Ca antagonists, statins, or aspirin on FMD determination (data not shown).

Multiple linear regression analysis

Multiple linear regression analysis showed that only fasting blood glucose was an independently associated factor for FMD (Table 4).

Discussion

More than half of the mortality for CKD patients is attributable to CVD. The true impact of CVD on outcomes for dialysis patients is better illustrated by the rate of death from CVD, which is 10–20 times higher than in the general population.²² Epidemiologic studies have shown an increased risk of cardiovascular mortality in the general population with MetS.^{23,24} The MetS is thought to be an important contributor to CVD among these patients and has become a major public health challenge around the world.^{25,26} How MetS increases

Table 3 Correlation analysis between flow-mediated dilatation and other variables

Variables	Correlation coefficient	P value
Age	−0.086	0.227
Systolic BP	0.005	0.953
Diastolic BP	0.058	0.469
UA	0.033	0.674
24-hour urine protein excretion	−0.204	0.011*
Cr	0.124	0.177
BUN	0.118	0.137
eGFR	−0.002	0.984
Fasting glucose	−0.254	0.001*
Triglycerides	−0.105	0.186
Total cholesterol	0.030	0.708
HDL-C	−0.041	0.602
LDL-C	0.061	0.441
Calcium	0.173	0.049*
Phosphate	0.042	0.594

Note: *Significant at $P < 0.05$.

Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid.

Table 4 Coefficients of multiple regression analysis (dependent variable flow-mediated dilatation [%])

	Unstandardized coefficients	SE	Standardized coefficients	t	P value	95% CI
Constant	11.56	1.29		8.95	0.000	9.01 to 14.11
Fasting glucose	-0.44	0.20	-0.18	-2.17	0.03	-0.8 to -0.04
Waist circumference	-0.10			-1.17	0.24	
Serum calcium	-0.03			-0.33	0.74	

Abbreviations: CI, confidence interval; SE, standard error.

the risk of CVD is not completely understood. Previous studies suggest that abnormal metabolism, associated with end-stage renal disease per se or with a pre-existing MetS, could also be an important driver of endothelial dysfunction and CVD.

Many previous studies had shown that FMD may reflect endothelial function. Endothelial dysfunction is both an early marker of vascular disease and a facilitative process in the development of atherosclerosis in the general population and patients with CKD. The Northern Manhattan Study (NOMAS)²⁷ has shown that hazard ratios for cardiovascular events were 43% greater in those with MetS and 24% greater in those with endothelial dysfunction than in those with neither, respectively, but there was no significant difference in patients' FMD whether or not they had pre-existing CVD in our current study. It might be because the role of pre-existing CVD in endothelial dysfunction of CKD patients was less than with MetS or its components.

All the components of MetS can individually impair endothelial function. Several studies have shown that both hypertension²⁸ and diabetes type 2 are associated with endothelial dysfunction in the general population.²⁹ Experimental glucose loading also impairs endothelial function,³⁰ and abdominal obesity is associated with endothelial dysfunction.³¹ Impaired endothelial function was also reported in patients with low levels of HDL cholesterol.³² Reduced endothelium-dependent vasodilation (EDV) was also reported in patients with elevated TG levels.³³

Regarding the contribution of each MetS component in the pathogenesis of endothelial dysfunction in patients with MetS, a large study (n = 1016) by Lind reported that TG levels, waist circumference, and diastolic BP independently predicted EDV.³⁴ Waist circumference was more strongly related to endothelial dysfunction followed by TG levels and diastolic blood pressure.³⁴ In other reports, only HDL cholesterol levels³⁵ were independently associated with reduced FMD in patients with MetS.

In our study, FMD was significantly lower in the group of patients with MetS than in the group of patients without MetS, indicating that MetS might be associated with

endothelial dysfunction in patients with CKD. Moreover, patients with components of MetS, such as hyperglycemia (higher fasting blood glucose) and abdominal obesity in female CKD patients, correlated negatively with FMD, whereas other components, such as blood pressure, HDL cholesterol, and TG levels, did not correlate with FMD. Fasting blood glucose level was the only independently associated factor with endothelial dysfunction, but only 13.7% of patients in our study were diabetic. The most common cause of CKD in China is glomerulonephritis, and many diabetic patients were followed up by an endocrine doctor. Only those patients with severe renal dysfunction were referred to a nephrologist.

We did not find the effect of blood pressure on FMD in our current study. This might have resulted from the patients' blood pressure being controlled (mean systolic blood pressure was 117.75 ± 22 mmHg), and most of them received ACEIs/ARBs or calcium antagonist combinations with ACEIs/ARBs, so it is difficult to judge the effect of the antihypertensive drug category on endothelial dysfunction.

Some reports showed that serum uric acid levels are raised in MetS.³⁶ Elevated serum uric acid levels appear to be associated with endothelial dysfunction and may play a role in the increased vascular risk of patients with MetS in the general population.³⁶ In contrast to these results, we did not find that serum uric acid levels were associated with FMD, neither did we find that serum uric acid levels were significantly raised in CKD patients with MetS compared with those without MetS.

Our results did not show that there was any difference in patients with a different number of MetS components (data not shown).

Our results showed that FMD had no relationship with eGFR, indicating that endothelial dysfunction exists in early CKD stages, which may be a marker predicting CVD events in later stages of CKD. On the other hand, the eGFR by MDRD formula is not precisely for all stages of CKD. As previous reported,³⁷ we also found that proteinuria was inversely associated with FMD.

A few limitations remain in our study. The cross-sectional character of the present study cannot provide proof of direct causality between MetS components and FMD. Currently, we are performing a prospective, controlled, interventional study to explore the impact of management of the components of MetS (such as weight loss, control of blood glucose) on FMD in patients with CKD.

In summary, we showed that MetS and some components of MetS (fasting blood glucose and waist circumference in women) are closely associated with decreased FMD in CKD patients.

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Disclosures

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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