Does Obesity Attenuate the Effect of Metabolic Syndrome on Chronic Kidney Disease in Patients With Coronary Artery Disease? Report From China Heart Survey

Hao Liu, PhD; Jinming Yu, PhD; Fang Chen, MD*; Jinsong Wang, PhD*; Shengbao Chen, MD*; Fang Wang, MD*; Dayi Hu, MD**

**Background:** The present study explored the relationship between metabolic syndrome (MetS) and chronic kidney disease (CKD) in patients with coronary artery disease (CAD) in China.

**Methods and Results:** The prevalence of MetS and CKD were determined in 3,465 participants with CAD from the China Heart Survey, from June 1st to August 31st, 2005. The relationship between MetS and CKD was analyzed. The prevalence of MetS and CKD was 53.0% and 21.1%, respectively. Patients with MetS had a higher prevalence of CKD than those without MetS. All traits of MetS except central obesity were statistically significantly associated with CKD. The multivariate-adjusted odds ratio (OR) of CKD in participants with and without MetS was 1.27 (95% confidence interval (CI) 1.07–1.51). In the multivariate-adjusted model, patients with 3 MetS components, excluding central obesity, had a higher OR for CKD (OR 2.17, 95%CI 1.21–3.88).

**Conclusions:** MetS is a significantly higher risk factor for CKD in patients with CAD. Central obesity might attenuate the effect of MetS on CKD in patients with CKD, regardless of the number of MetS components. (*Circ J* 2010; 74: 462–467)

**Key Words:** Central obesity; Chronic kidney disease; Coronary artery disease; Metabolic syndrome

Metabolic syndrome (MetS) and obesity have causative roles in the development of chronic kidney disease (CKD), which is now widely accepted as a risk factor for cardiovascular disease (CVD) and mortality. MetS and CKD are both recognized as conditions associated with increased prevalence of coronary atherosclerosis. Occurring before these conditions type 2 diabetes and cardiovascular and all-cause mortality. MetS has also been linked to CKD. Obesity is a major determinant of kidney dysfunction, but to our knowledge, most of the latter studies were conducted in general populations and limited information is available for patients with coronary artery disease (CAD). Diabetes and hypertension are the main driving forces for the rising epidemic of CKD and endstage renal disease (ESRD). Components of MetS, such as hypertension, dyslipidemia and abnormal glycemia, are common among subjects with CAD, but the effect of the clustering of these risk factors in the form of MetS on CKD in individuals with CAD remain to be established.

Furthermore, a previous study showed that in China patients with CAD had a high prevalence of CKD. Against this background, we initiated this cross-sectional study, the China Heart Survey, to examine the association of MetS and its components with CKD in patients with CAD.

**Methods**

**Study Population**

The China Heart Survey was a multicenter study involving 52 centers in 7 Chinese cities. Recruitment took place from June 1st to August 31st, 2005. All patients admitted to hospital cardiovascular wards were screened for CAD and all were assessed, investigated and treated at the discretion of their physician-in-charge according to the usual institutional practice. A consecutive cohort of 3,513 patients underwent detailed assessments. Data were collected by means of case record form as previously described.

The study complied with the Declaration of Helsinki. The data collection protocol was approved by the Beijing University Research Ethics Committee and all participants signed informed consent to access their medical records.
### Definition of MetS

According to the new definition of the International Diabetes Federation (IDF),\(^1^3\) for a person to be defined as having MetS central obesity (defined as waist circumference (WC)≥90 cm in males, WC≥80 cm in females for the Chinese population) must be present plus any 2 or more of the following three risk factors: (a) triglycerides (TG)≥1.7 mmol/L, or specific treatment for this lipid abnormality; (b) high-density lipoprotein-cholesterol (HDL-C)<1.03 mmol/L in males or<1.29 mmol/L in females for the Chinese population; (c) systolic blood pressure (BP)≥130 mmHg or diastolic BP≥85 mmHg, or treatment of previously diagnosed hypertension; (d) fasting plasma glucose (FPG)≥5.6 mmol/L or previously diagnosed type 2 diabetes mellitus (DM).

### Definition of CKD

The estimated glomerular filtration rate (eGFR) was calculated using a new equation developed by tailoring the Modification of Diet in Renal Disease (MDRD) equation to data from Chinese patients with CKD.\(^1^4\) eGFR (ml·min\(^{-1}\)·1.73 m\(^{-2}\))=175×(serum creatinine\(^{-1.214}\)×(age\(^{-0.203}\))\times0.79 (if female). CKD was defined as eGFR<60 ml·min\(^{-1}\)·1.73 m\(^{-2}\).

### Statistical Analysis

SPSS version 12.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) was used for the statistical analysis. Data are presented as the mean±SD for continuous variables and as proportions for categorical variables. Because of an extremely skewed distribution, variables such as TGs were reported as the median (low–upper quartiles). Prevalence and mean values of selected conditions (such as the components of MetS) were compared between participants with and without MetS, by using \(\chi^2\) statistics for categorical variables and Student’s t-test for continuous values. The associations between the different traits of the MetS and CKD were analyzed by univariate logistic regression analysis and multivariate logistic regression analysis. A P-value of <0.05 was considered significant.

### Results

#### General Participant Characteristics

The general characteristics of the 3,465 study participants are presented by MetS status in Table 1; all were Chinese and 66.7% were men. The mean age of participants was 67.1±11.3 years. The mean serum creatinine was similar, but the eGFR was

### Table 1. Baseline Characteristics of the Study Participants With and Without MetS

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Yes (n=1,837)</th>
<th>No (n=1,628)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>67.2±11.2</td>
<td>67.0±11.4</td>
<td>0.670</td>
</tr>
<tr>
<td>Acute admission, n (%)</td>
<td>1,022 (55.6)</td>
<td>1,289 (79.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>25.6±3.2</td>
<td>23.0±3.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>332 (18.1)</td>
<td>353 (21.7)</td>
<td>0.049</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>95.2±8.2</td>
<td>84.2±8.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>137.7±21.9</td>
<td>131.0±22.5</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79.0±12.7</td>
<td>78.9±12.5</td>
<td>0.335</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>5.8 (4.9–7.3)</td>
<td>5.1 (4.6–5.9)</td>
<td>0.000</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.76 (1.22–2.49)</td>
<td>1.24 (0.90–1.74)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

| Data are mean±SD or median (lower-upper quartiles) unless otherwise indicated. eGFR was defined as an eGFR calculated using the modified MDRD equation from Chinese patients with CKD. CKD was defined as eGFR<60 ml·min\(^{-1}\)·1.73 m\(^{-2}\). MetS, metabolic syndrome; BP, blood pressure; FPG, fasting plasma glucose; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CAD, coronary artery disease; MI, myocardial infarction; ACS, acute coronary syndrome; UAP, unstable angina pectoris; STEMI, ST segment elevated MI; NSTEMI, non-ST segment elevated MI. |
lower among participants with MetS compared with those without MetS. Acute coronary syndrome (64.0%) was the most common diagnosis at admission for CAD and unstable angina pectoris (43.6%) was the most common diagnosis in the MetS group. There was a significant difference between the proportions of acute coronary syndrome in patients with and without MetS ($\chi^2=9.02$, $P=0.002$). Participants with MetS had a higher prevalence of stroke, type 2 DM, hypertension and hyperlipidemia than those without MetS.

**Prevalence of MetS and CKD**

The frequency of MetS traits differed significantly by sex (Figure 1). Women had a higher frequency of all MetS traits than men. The overall prevalence of MetS was 53.0% (95% confidence interval (CI) 51.4–54.6%). MetS was more prevalent in women than in men (70.6% vs 44.2%; $P<0.001$).

A total of 728 participants (21.1%, 95%CI 19.6–25.1%) had CKD, with the median eGFR being 79.5 (63.2–97.4) ml·min$^{-1}$·1.73 m$^{-2}$. Figure 2 shows that the prevalence of CKD had a significantly upward trend with increased age. Compared with the prevalence of CKD in participants...
without MetS, its prevalence was higher in participants with MetS (22.7% vs 19.2%; P=0.012) (Table 1).

**Association Between MetS and CKD**

Figure 3 shows a clear trend in the association between MetS and CKD, upwards and to the right; however, the MetS components, excluding central obesity, were fitter to a trend of a straight line than when all components were included.

When investigating the relationship between CKD and MetS or its components by regression model, we found age-, sex- and multivariate-adjusted odds ratios (OR) of CKD associated with MetS (OR 1.27, 95%CI 1.07–1.51). In addition, the age-, sex- and multivariate-adjusted model showed that all traits of MetS, except central obesity, were statistically significantly associated with CKD. To evaluate the effect of the MetS components on CKD, we calculated ORs according to the presence or absence of central obesity; the data showed that the association between all components and CKD become significant only when 4 or 5 components were present. However, the association between all components excluding central obesity and CKD become significant when just 3 components were present. Meanwhile, the OR was higher than 3 components without excluding central obesity and the MetS definition by the IDF (Table 2).
Other Findings

Because patients with MetS had a higher prevalence of stroke, univariate and multivariate models were fitted to explore the association between MetS and stroke. The univariate model showed that MetS increased the risk of stroke (OR 1.33, 95% CI 1.06–1.67), but the multivariate model did not find this association. Meanwhile, we found that CKD significantly increased the risk of typical ECG changes (OR 1.28, 95% CI 1.04–1.57) after adjustment for known factors, but did not increase the risk of main branch stenosis (data not shown). The prevalence of MetS as defined by ATP III was 44.2% and was also significantly associated with increased risk of CKD. Furthermore, the degree of the association was stronger than with MetS as defined by the IDF (Table 2).

Discussion

In our study of Chinese patients with CAD, MetS, as newly defined by the IDF, was found to be associated with CKD. The risk of CKD increased progressively with a higher number of components of MetS. This association was independent of age, sex, and other possible risk factors for CKD.

MetS and CKD are becoming common in the Chinese general population. In a study of a large professional population in Beijing, the prevalence of the MetS was 13.2%. In a nationally representative sample of 15,540 Chinese adults aged 35–74 years in 2000–2001, the age-standardized prevalence of the MetS, defined according to NCEP guidelines, was 9.8% in men and 17.8% in women. Although the prevalence of CKD in China is relatively low, the population absolute burden is substantial. The age-specific prevalence of CKD is 0.71%, 1.69%, 3.91%, and 8.14% among persons aged 35–44, 45–54, 55–64, and 65–74 years, respectively, in China. We previously reported that the prevalence of CKD was 24.8% in Chinese adults with CAD.

The relation between MetS and the early stages of kidney malfunction was first recognized in the United States, with more recent reports from China, Japan, and other Asian countries documenting the same relationship. In this context, Luk et al examined risk of MetS with new onset of CKD in 5,829 Chinese patients with type 2 DM and found that MetS independently predicted the development of CKD. However, to our knowledge, most other studies have been either cross-sectional in nature or conducted in general populations. MetS and CKD are both recognized as conditions associated with increased prevalence of coronary atherosclerosis. The extent to which the prevalence of MetS incrementally affects the prevalence of CKD in Chinese patients with CAD is not known.

We used the new IDF definition of MetS, which uses ethnic-specific values for WC to define central obesity. There is a general consensus that WC as a surrogate of visceral adiposity, which is more strongly correlated with adverse metabolic risks including high blood pressure, dyslipidemia, and increased insulin resistance. Furthermore, the MDRD equation is a rapid method of assessing GFR in patients CKD. Nevertheless, 2 recent evaluations of the MDRD equation reported conflicting results for Asian populations. Therefore, we calculated eGFR using an equation more suitable to a Chinese population, which underestimated the GFR in stage 1 to stage 2 CKD significantly less than did previous equations. Apart from MetS, the established CVD risk factors are associated with the development of new-onset CKD.

There are several mechanisms underlying the effect of MetS on renal function and proteinuria. Obesity is a major determinant of kidney dysfunction. Insulin resistance and related cardiovascular risk factors clustering into MetS (among which, obesity is the keystone) have been reported as associated with kidney dysfunction. However, in our study, central obesity did not result as a significant predictor of CKD in patients with CAD. Dyslipidemia is also an important risk factor for developing renal dysfunction. TG-rich apolipoprotein B-containing lipoproteins clearly promote the progression of human renal insufficiency. High TG levels are a risk factor for developing proteinuria. Our results showed that elevated TG was positively associated with CKD, and reduced HDL-C was also associated with CKD. Early detection of MetS or high TG levels might be beneficial if accompanied by an early intervention such as statin therapy to lower TG levels and suppress the pathways of renal injury.

The salient features in the genesis of microalbuminuria and loss of GFR in patients with MetS are hypertension and insulin resistance/abnormal glycemia. In the study by Franciosi et al, post-load glycemia and insulin resistance as evaluated by the homeostasis model of insulin resistance were powerful predictors of the risk for microalbuminuria in concert with hypertension and age. The results of our study of Chinese patients with CAD are consistent with those findings, suggesting that even mildly elevated BP (≥130/85 mmHg) or mildly increased FPG level (≥5.6 mmol/L) is associated with an increased risk for CKD.

Despite the evidence relating the individual components of MetS to CKD, the association between MetS components and CKD became significant only when 4 or 5 components were present in our study, which suggests that only when there is a high burden of risk factors are signs of kidney damage observed. Early detection and appropriate management of CKD would be helpful in CAD patients with MetS. However, the OR of CKD associated with 3 components excluding central obesity was 2.17, which was higher than that of the strict IDF definition, which suggests that obesity might attenuate the effect of MetS on CKD in patients with CAD. The reasons for this paradox may be explained as follows: (1) WC might not be applicable for evaluation of MetS among Asian population; (2) body composition analysis techniques to accurately diagnose obesity in patients with CAD might be necessary, because of missing more than 50% of CAD patients with a true excess in body adiposity; or (3) the contribution of obesity may be diluted within the other MetS-related factors (eg, lipids). In addition, we found that MetS patients had a higher prevalence of stroke and patients with CKD had a 1.3-fold risk of developing typical ECG changes compared with no CKD, which agrees with other studies.

Study Limitations

Firstly, the cross-sectional design makes it difficult to infer causality between MetS and the risk of CKD. Another limitation could be that we used an equation developed by tailoring the MDRD equation to data for Chinese patients with CKD. However, a recent study by Rule et al showed that equations developed for assessing eGFR in nephrology referral samples were limited in their usefulness as CKD screening tools for the general population. Furthermore, in the present study only one-third of all patients (1,193) underwent a urine protein test. Thus, we were not able to use further analysis involving microalbuminuria or proteinuria.

Despite these limitations, our study is important because
it shows that the link noted between MetS and CKD in general populations is also observed in Chinese patients with CAD. The findings of our study point to the urgent necessity for further research into the mechanisms of kidney damage in MetS and for clinical trials assessing the impact of treatment for MetS on CKD incidence and disease progression in China. In addition, MetS can be treated at low cost if detected early. Furthermore, both MetS and CKD increase the risk of CVD.\textsuperscript{2,3}\textsuperscript{3} China and other economically developing countries have experienced a cardiovascular epidemic in recent decades, with cardiovascular morbidity and mortality predicted to increase yet further in China.\textsuperscript{4}

In conclusion, MetS is a significantly higher risk factor for CKD in Chinese patients with CAD. Early identification of MetS might be beneficial in preventing CKD and ESRD. However, central obesity might dilute the association between MetS and CKD. These findings suggest that obesity might not be a pivotal factor for MetS-related CKD in Chinese patients with CAD. Further studies are required to explore this phenomenon.

\section*{Acknowledgments}

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\section*{Disclosure}

Conflict of interest: none declared.

\section*{References}


