METABOLIC SYNDROME AND ITS RELATION TO CHRONIC KIDNEY DISEASE IN A SOUTHEAST ASIAN POPULATION

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Abstract. The metabolic syndrome has been documented to increase the risk of cardiovascular disease and chronic kidney disease (CKD); however, there are few studies of this in developing countries. A total of 15,357 participants of a standardized check-up, included metabolic screening, were enrolled. Metabolic syndrome was defined using criteria modified from the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and the International Diabetes Federation (IDF). CKD was defined as a glomerular filtration rate <60 ml/min per 1.73 m^2. Eighty point four percent of participants were men and 2,228 (14.5%) had CKD. Metabolic syndrome was more prevalent among CKD subjects than non-CKD subjects (modified NCEP-ATP III, 30.1% *vs* 24.4%; $p<0.001$; modified IDF 26.9% *vs* 23.1%; $p<0.001$, respectively). Abdominal obesity, high triglycerides, high blood pressure and impaired fasting glucose were significantly associated with an increased prevalence of CKD. There was also a significant graded relationship between the number of metabolic syndrome components and the prevalence of CKD. Participants with metabolic syndrome according to the modified NCEP-ATP III and modified IDF criteria had a 1.34-fold increase in adjusted odds ratio (95% CI 1.21-1.49) and a 1.20-fold increase in adjusted odds ratio (95% CI 1.08-1.33), respectively, compared to those without metabolic syndrome. Our study demonstrated metabolic syndrome defined with modified NCEP-ATP III and modified IDF criteria was significantly associated with increased prevalence of CKD in a Southeast Asian population.

Keywords: metabolic syndrome, chronic kidney disease, Southeast Asian population

INTRODUCTION

Chronic kidney disease (CKD) is associated with cardiovascular disease, and all cause mortality (Glynn *et al*, 2007). Individuals with CKD often progress to end stage renal disease (ESRD) and its attendant complications. According to data from the Nephrology Society of Thailand for 2006, the overall prevalence and incidence of patients with ESRD starting chronic dialysis treatment were 323 and 155 per million population, respectively (Tungsanga *et al*, 2008). A high prevalence rate of CKD has been seen in Thailand (Ouppatham *et al*, 2008). Although it is

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well established that overt diabetes is a major risk factor for CKD and ESRD, it is unclear whether early metabolic changes in patients without diabetes and hypertension are associated with the development of kidney disease.

The defining components of metabolic syndrome are high waist circumference, triglycerides, blood pressure (BP), elevated fasting glucose, and reduction in high density cholesterol. An increase in the number of subjects with metabolic syndrome worldwide has occurred during the past decade. Using the recommendations for Asian populations detailed in the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), a previous study reported that 23.0% of those aged > 35 years living in Thailand had metabolic syndrome (Boonyavarakul *et al*, 2005).

Metabolic syndrome is an established cardiovascular risk factor in the general population (Lakka *et al*, 2002). CKD shares a clustering of cardiovascular risk factors that overlap with defining factors of metabolic syndrome. Epidemiologic studies have also linked metabolic syndrome with an increased risk of incident CKD (Lucove *et al*, 2008; Ryu *et al*, 2009). Therefore, the issue of whether metabolic syndrome associated with CKD is important. To date, there are few studies about the association between metabolic syndrome and CKD in developing countries where genetic and environmental backgrounds are different from those in Western countries (Kitiyakara *et al*, 2007). The purpose of this study was to examine the relationship between metabolic syndrome and CKD in a Southeast Asian population.

MATERIALS AND METHODS

From January to December 2007, 15,357 participants of a standardized check-up, which included metabolic screening, at the Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand was recruited. The institutional review board of Phramongkutklao Hospital and College of Medicine approved the study protocol. All participants aged 18-60 years old were reviewed to retrieve medical and personal data, including baseline demographic characteristics, and presence of co-morbidities. Blood pressure (BP) was measured according to standard guidelines. Waist circumference, height, and weight were measured according to standard protocols. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood samples were collected in the morning after an overnight fast of at least 12 hours. Plasma levels of total cholesterol, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides, glucose, uric acid, blood urea nitrogen and creatinine were measured by standardized methods. Principles of measurement were the enzymatic colorimetric assay for total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides; the hexokinase enzyme reference method for fasting plasma glucose, and the modified kinetic Jaffe reaction for creatinine.

An estimate of the GFR was obtained by the four-variable Modification of Diet in Renal Disease (MDRD) equation: GFR = 186.3 x serum creatinine$^{-1.154}$ x age$^{-0.203}$ x 0.742 if female x 1.21 if black. Irrespective of the presence or absence of proteinuria, CKD was defined as a GFR of less than 60 ml/min per 1.73 m^2. The laboratory services provide laboratory testing for the Thai Army in Bangkok using a single regional laboratory and standardized methods.

Metabolic syndrome was defined using modified-NCEP-ATP III and modified International Diabetes Federation (IDF) criteria. Modified-NCEP-ATP III criteria consider metabolic syndrome present when any three of following five conditions are present (Grundy *et al*, 2005): abdominal obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women according to the 1998 World Health Organization Asian Pacific Guideline (Tan *et al*, 2004), elevated serum triglycerides (≥150 mg/dl after 12 hours fasting), low HDL-cholesterol (<40 mg/dl in men and < 50 mg/dl in women), high BP (systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg) or the use of antihypertensive medications or a self reported history of hypertension), and high fasting plasma glucose (≥ 100 mg/dl or use of antidiabetic agents or a self reported history of diabetes). According to modified-IDF criteria (Alberti *et al*, 2005), metabolic syndrome can be diagnosed if abdominal obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women) is accompanied by any two of the following four conditions: (1) triglycerides levels ≥ 150 mg/dl, (2) an HDL-cholesterol < 40 mg/dl in men and < 50 mg/dl in women, (3) a BP ≥ 130/85 mm Hg or treatment of previously diagnosed hypertension, and (4) a fasting plasma glucose > 100 mmol/l or previously diagnosed type 2 diabetes.

Continuous variables are expressed as mean ± SD and compared using the Student *t*-test, whereas categorical variables are expressed as percentages and compared using the chi-square test. Odds ratio (OR) with 95% confidence intervals (CI) was calculated. Multivariate binary logistic regression was performed to correct for confounders. The included covariates were age, gender, body weight, total cholesterol, and LDL-cholesterol. All analyses were performed using statistical software for Windows (SPSS version 12.0, Chicago, IL). Differences were considered statistically significant at $p < 0.05$.

RESULTS

Of the 15,357 study participants, all were Thai, 80.4% were men and 2,228 (14.5%) had CKD (GFR <60 ml/min per 1.73 m^2). Of the entire study group 8.8% had hypertension and 4.6% had diabetes mellitus as co-morbid diseases. Demographic and biochemical characteristics of subjects classified by CKD status are shown in Table 1. Percentage of males, age, systolic BP, diastolic BP, waist circumference, BMI, fasting plasma glucose, total cholesterol, triglycerides, LDL-cholesterol, serum uric acid, blood urea nitrogen and serum creatinine were higher (p<0.001) in subjects with CKD (Table 1). The estimated GFR and HDL-cholesterol levels were lower in subjects with CKD. There were no differences in body weight.

The prevalence of individual components of metabolic syndrome and metabolic syndrome according to the presence or absence of CKD were examined (Table 2). Abdominal obesity, high triglycerides, high BP and impaired fasting glucose were significantly increased in participants with CKD. Furthermore, there was a significant graded relationship between the number of metabolic syndrome components present and the prevalence of CKD (Fig 1). The overall prevalence of participants with metabolic syndrome was 25.3% (20.9% in women, 26.3% in men) using modified NCEP-ATP III criteria and 23.6% (28.3% in women, 22.5% in men) using modified IDF criteria. Metabolic syndrome was more prevalent in people with CKD than in people without CKD (modified NCEP-ATP III 30.1% *vs* 24.4%; p<0.001; modified IDF 26.9% *vs* 23.1%; p<0.001, respectively).

Table 1
Baseline characteristics of study participants with and without CKD.

Characteristics	CKD (*n*=2,228)	No. CKD (*n*=13,129)	*p*-value
Demographics			
Male *n* (%)	2,010 (90.2)	10,338 (78.7)	<0.001
Age (yrs)	50.77 ± 5.50	45.27 ± 6.03	<0.001
Clinical features			
Systolic BP (mmHg)	137.05 ± 18.08	131.45 ± 16.75	<0.001
Diastolic BP (mmHg)	85.61 ± 12.45	82.38 ± 11.75	<0.001
Body weight (kg)	66.89 ± 10.23	66.67 ± 10.26	0.337
Waist circumference (cm)	83.97 ± 8.61	82.03 ± 8.67	<0.001
Body mass index (kg/m^2)	25.06 ± 3.29	23.98 ± 3.11	<0.001
Biochemical			
Fasting plasma glucose (mg/dl)	102.24 ± 31.32	100.24 ± 30.90	0.005
Total cholesterol (mg/dl)	227.53 ± 44.79	221.04 ± 42.12	<0.001
Triglycerides (mg/dl)	163.74 ± 102.97	154.34 ± 106.58	<0.001
HDL-cholesterol (mg/dl)	54.16 ± 12.49	55.84 ± 13.68	<0.001
LDL-cholesterol (mg/dl)	140.73 ± 42.17	134.67 ± 39.51	<0.001
Serum uric acid (mg/dl)	7.20 ± 1.67	6.24 ± 1.51	<0.001
Blood urea nitrogen (mg/dl)	15.03 ± 4.21	12.59 ± 3.05	<0.001
Serum creatinine (mg/dl)	1.25 ± 3.05	0.99 ± 0.15	<0.001
Estimated GFR (ml/min per 1.73 m^2)	53.90 ± 5.89	76.69 ± 10.97	<0.001

All values are expressed as mean ± SD
GFR, glomerular filtration rate

Table 2
Prevalence of individual components of metabolic syndrome and metabolic syndrome in participants with and without CKD.

Variable	CKD (*n*=2,228)	No CKD (*n*=13,129)	*p*-value
Metabolic syndrome component			
Abdominal obesity	631 (28.3)	3,373 (25.7)	0.009
High triglycerides	951 (42.7)	4,922 (37.5)	<0.001
Low HDL-cholesterol	258 (11.6)	1,637 (12.5)	0.238
High BP	1,553 (69.7)	7,459 (56.8)	<0.001
Impair fasting glucose	798 (35.8)	3,864 (29.4)	<0.001
Metabolic syndrome			
Modified NCEP-ATP III	670 (30.1)	3,208 (24.4)	<0.001
Modified IDF	599 (26.9)	3,032 (23.1)	<0.001

All values are expressed as *n* (%)

Table 3
Binary logistic regression analysis of association between metabolic syndrome and CKD.

Variable	Crude OR (95% CI)	*p*-value	Adjusted[a] OR (95% CI)	*p*-value
Number of components				
0 component	1.00		1.00	
1 component	1.34 (1.16-1.54)	<0.001	1.32 (1.15-1.53)	<0.001
2 components	1.76 (1.53-2.03)	<0.001	1.76 (1.53-2.03)	<0.001
3 components	1.76 (1.51-2.05)	<0.001	1.78 (1.52-2.09)	<0.001
4-5 components	1.98 (1.66-2.37)	<0.001	2.07 (1.72-2.48)	<0.001
Metabolic syndrome				
Modified NCEP-ATP III	1.33 (1.20-1.45)	<0.001	1.34 (1.21-1.49)	<0.001
Modified IDF	1.22 (1.11-1.36)	<0.001	1.20 (1.08-1.33)	<0.001

[a]Adjusted for age, gender, body weight, total cholesterol and LDL-cholesterol

Table 4
Binary logistic regression analysis of association between metabolic syndrome and CKD.

Variable	Crude OR(95% CI)	*p*-value	Adjusted[a] OR (95% CI)	*p*-value
Abdominal obesity	1.14 (1.03-1.26)	0.009	0.97 (0.88-1.08)	0.610
High triglycerides	1.24 (1.13-1.36)	<0.001	1.23 (1.10-1.37)	<0.001
Low HDL-cholesterol	0.92 (0.80-1.06)	0.238	0.87 (0.75-1.01)	0.069
High BP	1.75 (1.59-1.93)	<0.001	1.67 (1.51-1.84)	<0.001
Impaired fasting glucose	1.34 (1.22-1.47)	<0.001	1.21 (1.09-1.33)	<0.001

[a]Adjusted for age, gender, body weight, total cholesterol and LDL-cholesterol

The association between those with CKD and the presence or absence of metabolic syndrome and the number of metabolic syndrome components is shown in Table 3. Participants with metabolic syndrome defined by the modified NCEP-ATP III criteria and modified IDF criteria had a 1.33-fold higher OR (95% CI 1.20-1.47) and a 1.22-fold higher OR (95% CI 1.11-1.36), respectively, compared to those without metabolic syndrome. After adjusting for age, gender, body weight, total cholesterol, and LDL-cholesterol, CKD was associated with the presence of metabolic syndrome defined by modified-NCEP-ATP III criteria (OR 1.34; 95% CI 1.21-1.49) and modified IDF criteria (OR 1.20; 95% CI 1.08-1.33). Compared to participants with no components of metabolic syndrome, both the unadjusted and adjusted OR for CKD in subjects with ≥1 components was significant ($p<0.001$).

The association between each of the components of metabolic syndrome and CKD was examined (Table 4). CKD was associated with abdominal obesity, high triglycerides, high BP, and impaired fasting glucose. After adjustments were made

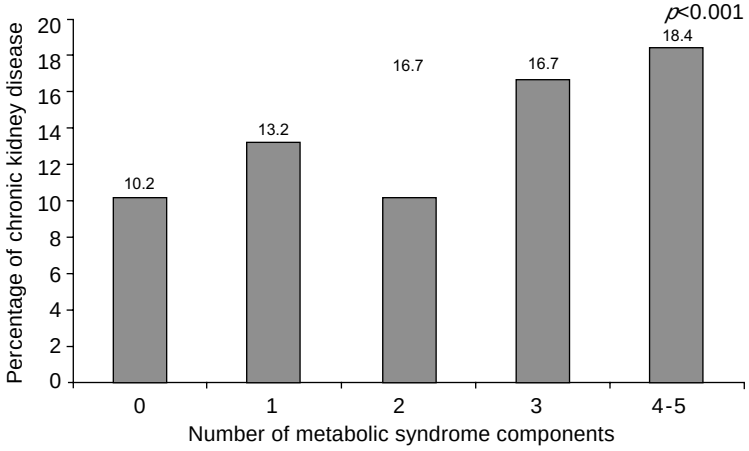

Fig 1–Prevalence of CKD by number of metabolic syndrome components.

for age, gender, body weight, total cholesterol and LDL-cholesterol; high triglycerides (OR 1.23; 95% CI 1.10-1.37), high BP (OR 1.67; 95% CI 1.51-1.84), and impaired fasting glucose (OR 1.21; 95% CI 1.09-1.33) were independently associated with CKD.

DISCUSSION

The present study demonstrated metabolic syndrome and components of metabolic syndrome are independently associated with increased prevalence of CKD in of 15,357 subjects in Bangkok, Thailand. These findings provide additional evidence metabolic syndrome defined by modified NCEP-ATP III and modified IDF criteria, is associated with an increased prevalence of CKD, independent of well-described risk factors for developing CKD, such as diabetes, hypertension, dyslipidemia, obesity and aging. Few epidemiologic studies have quantified the link between metabolic syndrome and kidney disease in Thailand.

Previous studies determined metabolic syndrome increased the risk of microalbuminuria and CKD in non-diabetic patients (Chen *et al*, 2004). A study from the United States found patients with metabolic syndrome had a 2.60-fold higher OR for CKD suggesting metabolic syndrome may be an important factor in causing CKD (Chen *et al*, 2004). The studies conducted in Asian populations also showed a significant association with CKD (OR 1.54; 95% 1.28-1.85 in Japanese adults; OR 1.64; 95% 1.16-2.32 in Chinese adults) (Tanaka *et al*, 2006; Chen *et al*, 2007). Further cohort studies support metabolic syndrome contributes to the development of CKD (Lucove *et al*, 2008; Ryu *et al*, 2009). The results of the present study suggest in the Thai population, the metabolic syndrome defined by modified-NCEP-ATP III and modified IDF criteria, had a 1.34-fold higher adjusted OR and a 1.20-fold higher adjusted OR, respectively, compared to those without metabolic syndrome. However, some differences in the OR for CKD and metabolic syndrome may be partly due to differences in the definitions used for metabolic syndrome and CKD.

Hypertension, diabetes and high triglycerides are well-described risk factors for developing proteinuria and kidney disease (Haroun *et al*, 2003). Even high normal BP levels, fasting plasma glucose levels and triglycerides, that are individual components of metabolic syndrome were also significant risk factors for increasing serum creatinine and developing CKD in a previous study (Lee *et al*, 2007). A recent study showed the pathological kidney findings in patients with components of metabolic syndrome had a greater preva-

lence of tubular atrophy, interstitial fibrosis and arterial sclerosis, suggesting microvascular injury in these patients (Alexander *et al*, 2009). Our finding that individual components of metabolic syndrome were associated with a significantly increased risk for CKD agrees with previous findings and the risk for CKD being increased progressively with greater numbers of components of metabolic syndrome.

The present study used the modified NCEP-ATP III and modified IDF criteria for metabolic syndrome, which uses ethnic-specific values for waist circumference to define abdominal obesity. Our study revealed a relationship between the waist circumference, BMI and the prevalence of CKD. These findings are consistent with recent studies of CKD and central obesity (Kwan *et al*, 2007; Chou *et al*, 2008). In seeking an explanation for the strong association between metabolic syndrome and renal damage, obesity related glomerulopathy is very likely to play a role. The mechanisms by which central obesity increase the risk for CKD have yet to be elucidated. Abdominal obesity and insulin resistance are prominent features of metabolic syndrome, and both have been associated with secretion of inflammatory mediators, such as leptin, IL-6, TNF-alpha and adiponectin (Satirapoj and Supasyndh, 2007). Many of these cytokines produced by adipose tissue have a role in renal damage in patients with metabolic syndrome and have a pathogenetic role in the development of CKD by mechanisms such as activation of sympathetic nervous activity, worsening renal hemodynamics, increased oxidative stress and inflammatory states (Iseki, 2008).

This study has several strengths. The data were carefully collected, and ethnically homogenous. The study population included a large sample of participants with CKD and all plasma creatinine assays were carried out at one laboratory with one method that was calibrated to be traceable to isotope dilution mass spectrometry. Limitations of the study were several: first, the cross-sectional study design is limited in its ability to estimate causal relationships between metabolic syndrome and CKD; second, data regarding proteinuria, hematuria and imaging of the kidney were unavailable, as a result, participants with a GFR ≥60 ml/min per 1.73 m^2 and non-GFR based evidence of kidney damage were classified into the non-CKD group on analysis; third, a selection bias of subjects might exist, since our subjects were mainly the Thai army and their relatives. This may be one reason why more men than women participated.

In conclusion, our study showed metabolic syndrome, defined using modified NCEP-ATP III and modified IDF criteria was significantly associated with increased prevalence of CKD in a Southeast Asian population.

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