Endocrine Research

http://informahealthcare.com/erc
ISSN: 0743-5800 (print), 1532-4206 (electronic)

Endocr Res, 2014; 39(3): 94–98
 DOI: 10.3109/07435800.2013.840652

informa healthcare

ORIGINAL ARTICLE

Metabolic syndrome and C-reactive protein concentration as independent correlates of chronic kidney disease

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Abstract

Inflammation is a common phenotype for cardiometabolic disorders. In this study, we attempted to investigate inter-relationships between metabolic syndrome (MetS), C-reactive protein (an inflammatory biomarker) and chronic kidney disease (CKD). We performed a cross-sectional analysis of data from a representative sample of 4425 Chinese adults in Taiwan. The MetS was defined by a unified criteria set by several major organizations. A CKD event was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2. Additionally, a CRP cutpoint of 3 mg/L was used to differentiate high and low CRP levels. Overall, 1000 participants had MetS, resulting in a prevalence rate of 22.6%. High CRP level was noted in 782 (17.6%) subjects. In addition, a total of 508 (11.5%) persons qualified as having CKD. Subjects with the MetS had 1.55-fold [95% confidence interval (CI), 1.03–2.32] increased odds of CKD compared with their counterparts without the MetS after multiple adjustments. In addition, there was a significantly graded relationship between increasing levels of serum CRP and prevalent CKD (p for trend = 0.001). Participants in the highest category of serum CRP had a significantly elevated odds of CKD as compared with those in the lowest category [odds ratio (OR), 1.60; 95% CI, 1.21–2.12]. However, there was no interaction in excess of additive scale between the presence of MetS and high CRP level ($p = 0.83$). These findings suggest that MetS and high CRP were independently associated with increased prevalence of CKD in Chinese adults.

Keywords

Chronic kidney disease, C-reactive protein, inflammation, metabolic syndrome

History

Received 12 August 2012
Revised 4 November 2012
Accepted 26 August 2013
Published online 23 October 2013

Introduction

Chronic kidney disease (CKD) is becoming a major public health problem worldwide. The progressive nature of chronic kidney failure and the ensuing end-stage renal disease (ESRD) is putting a substantial burden on global health care resources (1). Thus, identifying and treating risk factors for CKD is urgently needed. Hypertension and diabetes mellitus are established risk determinants of CKD (2). These factors also overlap with components that define the metabolic syndrome (MetS), a constellation of metabolic abnormalities of elevated blood pressure, impaired fasting glucose, dyslipidemia [high triglycerides and low high-density lipoprotein cholesterol (HDL-C)] and central obesity (3). Indeed, the MetS has been suggested to be a possible risk factor for CKD (4). In recent years, increasing evidence suggests that chronic, low-grade inflammation may be a common soil involving the pathogenesis of MetS and atherosclerosis (5,6). Further, several studies have reported that inflammation modifies the effects of MetS on atherosclerotic events (7,8). Of note, CKD involves several pathophysiological mechanisms that are analogous to atherosclerosis (9). Therefore, we conducted this cross-sectional study to investigate inter-relationships between the MetS, C-reactive protein (CRP, an inflammatory biomarker) and prevalent CKD in a representative sample of Chinese adults in Taiwan, an area with the greatest incidence of ESRD worldwide (10).

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Methods

Study subjects

Data for this study came from the second wave of the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH-II) that was conducted in 2007. The study design and subject recruitment have been described elsewhere (11). The initial TwSHHH was conducted in 2002 based on a multistage random sample of the civilian, non-institutionalized population in Taiwan.

In total, 10 292 individuals were randomly selected for the TwSHHH. Of these 10 292 subjects, 7578 (73.6%) completed

a questionnaire and 6600 (64.1%) permitted additional blood pressure measurement and blood examination for biomarkers. These 6600 individuals who completed all examinations in the TwSHHH were eligible for the TwSHHH-II. Among them, 242 subjects had died and 581 persons could not be contacted. The remaining 5777 individuals were invited to participate in the TwSHHH-II. Accordingly, a total of 4682 persons were enrolled in the TwSHHH-II, resulting in a response rate of 81.0%. Differences in sex and age distributions were not statistically significant between participants and nonparticipants in the TwSHHH-II. The protocols for the TwSHHH and TwSHHH-II were approved by the Institutional Review Board at the Bureau of Health Promotion, Department of Health, Executive Yuan in Taiwan. Written informed consent was obtained from all participants in the TwSHHH and TwSHHH-II.

Measurements

At study entry, participants underwent questionnaire interviews and anthropometric measurements by well-trained nurses under a standardized protocol. Anthropometric measurements, including body weight, height and waist circumference, were taken from each participant. Arterial blood pressure was also taken from each participant using an electric sphygmomanometer (BP3AC1-1, Microlife Cooperation, Berneck, Switzerland). The electric sphygmomanometer has been validated according to the international protocol published by the European Society of Hypertension (12). In the current study, well-trained nurses measured the systolic blood pressure (SBP) and diastolic blood pressure (DBP) two times in the left arm of seated participants according to a standardized protocol. A third blood pressure measurement was made if the first two blood pressure readings differed by >10 mmHg. The average of the two closest readings was calculated to determine the reported blood pressure for each participant.

A blood sample was collected into an EDTA anticoagulant tube for each participant after a 12-h overnight fast. Standard enzymatic methods were used to determine serum cholesterol and triglycerides. Electrophoresis was performed to measure HDL-C and low-density lipoprotein cholesterol (LDL-C). Fasting plasma glucose (FPG) was measured by the hexokinase glucose-6-phosphate dehydrogenase procedure. In addition, CRP levels were assessed by the immunoturbidimetric CRP-latex high-sensitivity assay from Denka Seiken (Tokyo, Japan) performed according to the manufacturer's protocol. This assay has been validated against the Dade Behring method (Deerfield, Ill) (13). Further, serum creatinine was assayed by uncompensated Jaffe method with alkaline picrate kinetic test. The coefficients of variation of these measurements were ~5%. All biochemical tests were performed using automatic analyzers (TBA-200FR, Toshiba Corporation, Tokyo, Japan). All measurements were taken with blinded quality control specimens in the central laboratory.

Definitions

In the present study, the MetS was defined according to the criteria set by a joint statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; Word Heart Federation; International Atherosclerosis Society and International Association for the Study of Obesity (3). Participants with three or more of the following attributes are defined as having the MetS: (1) elevated blood pressure: blood pressure of at least 130/85 mmHg or use of anti-hypertensive medication; (2) elevated triglycerides: serum triglycerides of at least 150 mg/dL or use of drug treatment for elevated triglycerides; (3) reduced HDL-C: HDL-C <40 mg/dL in men and <50 mg/dL in women or use of drug treatment for reduced HDL-C; (4) elevated fasting plasma glucose (FPG): FPG of 100 mg/dL or more or use of drug treatment of elevated glucose and (5) elevated waist circumference: waist circumference $\geq$90 cm in men and $\geq$80 cm in women. Accordingly, participants under medication treatments for hypertension ($n = 666$), elevated triglycerides and/or reduced HDL-C ($n = 203$), and elevated FPG ($n = 270$) were included in the MetS definition. In addition, glomerular filtration rate (GFR) was estimated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation: $186.3 \times (\text{serum creatinine in mg/dL})^{-1.154} \times \text{age}^{-0.203} \times (0.742$ for women) (14). Accordingly, a CKD event was defined as an eGFR <60 mL/min per 1.73 m^2, based on the US National Kidney Fundation Kidney Disease Outcome Quality Initiative Working Group definition (14). With regards to CRP levels, we used currently recommended cutoff points for low (<1.0 mg/L), average (1.0–3.0 mg/L) and high (>3.0 mg/L) (15), with <1.0 mg/L as a reference.

Statistical analysis

For study purposes, participants without data on SBP, DBP, FPG, triglycerides, waist circumference, creatinine and CRP levels ($n = 257$) were excluded from data analysis. The final analytic sample included 4425 participants [mean ($\pm$SD) age, 48.07($\pm$16.19) years; 46.4% males].

Baseline characteristics are presented as the mean $\pm$ SD for continuous variables and as percentages for categorical variables. The statistical significance of differences in these characteristics between MetS cases and non-MetS individuals was examined by means of Student's t test (continous variables) and the Wald χ^2 test (categorical variables). The associations of the MetS as a whole and components of the MetS and CRP categories with prevalent CKD were examined from the logistic regression model, with the calculation of odds ratios (ORs) and their 95% confidence intervals (CIs). Covariates considered in the multivariate model included age, sex, BMI groupings, individual components of the MetS, and CRP categories. All statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC), and all of the statistical tests were 2-tailed with an α level of 0.05.

Results

Overall, 1000 participants had MetS, resulting in a prevalence rate of 22.6% (95% CI, 21.3–23.8%). High CRP level (>3 mg/L) was noted in 782 (17.6%) subjects. In addition, from the 4425 participants that met criteria for our study, a total of 508 (11.5%) qualified as having CKD. Participants' baseline

Table 1. Clinical characteristics of study subjects with and without metabolic syndrome (MetS).

Characteristic	Without MetS [3425 (77.4%)]	With MetS [1000 (22.6%)]
Men (%)	1593 (46.5)	459 (45.9)
Age (years)	45.6 ± 15.7*	56.5 ± 14.9*
Body mass index (kg/m^2)	23.1 ± 3.5*	27.5 ± 4.0*
Systolic blood pressure (mmHg)	117 ± 17*	136 ± 18*
Diastolic blood pressure (mmHg)	74 ± 11*	82 ± 12*
FPG (mg/dL)	87 ± 19*	111 ± 41*
Waist circumference (cm)	80.0 ± 10.0*	92.9 ± 9.3*
Triglyceride (mg/dL)	104 ± 63*	200 ± 139*
HDL cholesterol (mg/dL)	54 ± 11*	46 ± 9*
Estimated GFR (mL/min/1.73 m^2)	88.8 ± 23.1*	81.2 ± 22.6*
C-reactive protein (mg/L)	1.9 ± 6.0*	3.7 ± 7.8*

FPG, fasting plasma glucose; HDL, high-density lipoprotein; GFR, glomerular filtrate rate.
*The difference in the characteristics shown in the table between the two groups was statistically significant at $p < 0.001$.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for chronic kidney disease in relation to the number of metabolic syndrome (MetS) components and the MetS as a whole.

	No. of subjects (%)	No. of CKD cases (%)	Multivariate-adjusted OR (95% CI)
0 component	1348	63 (4.7)	1.00 (reference)
1 component	1171	63 (9.7)	1.30 (0.93–1.83)
2 components	906	147 (16.2)	1.67 (1.32–2.55)
3 components	620	106 (17.1)	1.80 (1.18–2.38)
4 or 5 components	380	78 (20.5)	1.83 (1.23–2.65)
p for trend			0.020
Metabolic syndrome	1000	184 (18.4)	1.55 (1.03–2.32)

Individuals with metabolic syndrome were compared with those without the syndrome. ORs were adjusted for age, gender, body mass index and C-reactive protein concentration.

Table 3. Association between C-reactive protein (CRP) concentration and prevalence of chronic kidney disease (CKD).

	CRP (mg/L)			
	<1.0	1.0–3.0	>3.0	*p* for trend
No. of subjects	2255	1374	782	
CKD, No. (%)	166 (7.36)	185 (13.46)	143 (18.29)	
OR (95% CI)	1.00 (reference)	1.46 (1.14–1.87)	1.60 (1.21–2.12)	0.001

OR, odds ratio; CI, confidence interval. Odds ratios were adjusted for age, gender and individual components of the metabolic syndrome.

characteristics according to MetS status are shown in Table 1. As expected, the mean age, BMI, waist circumference, SBP, DBP, FPG, triglyceride and CRP were significantly higher in subjects with the MetS than in those without ($p < 0.001$). In contrast, participants with the MetS had a significantly lower average value of HDL-C and eGFR ($p < 0.001$).

Table 2 presents the prevalence and OR of CKD by number of components of the MetS. Relative to subjects without any component of the MetS, there was significant, stepwise increase in odds for CKD with each increment. Participants with 1, 2, 3 and ≥4 components of the MetS had increased OR of CKD after multiple adjustments. Overall, subjects with the MetS had 1.55-fold (95% CI, 1.03–2.32) increased odds of CKD compared with their counterparts without the MetS after multiple adjustments.

Table 3 shows the relation of CRP with CKD in the study population. Overall, there was a significantly graded relationship between increasing categories of serum CRP and prevalent CKD (*p* for trend = 0.001). After adjustment for covariates of CKD, participants in the highest category of serum CRP had a significantly elevated odds of CKD as compared with those in the lowest category. Table 4 presents the crude and multivariate-adjusted ORs of CKD associated with individual components of the MetS and serum level of CRP. In a multivariate model, elevated blood pressure and high FPG level were significantly associated with an increased OR of CKD. High CRP level was also found to be independently associated with an increased OR of CKD.

When stratified according to the MetS status, we further compared the prevalence rate of CKD between subjects with high CRP level (>3 mg/L) and those without. As shown in Figure 1, the prevalence rate of CKD was significantly higher in subjects with high CRP level than in those without among participants with the MetS and among those without the MetS.

To evaluate the joint effect of MetS and CRP levels on the odds of CKD, we classified the study subjects into 4 groups on the basis of the presence or absence of the MetS and on the basis of CRP levels less than or greater than 3.0 mg/L. Compared with the without MetS/low CRP group, the multivariate-adjusted ORs for CKD of the without MetS/high CRP group and the with MetS/low CRP group were 1.41 (95% CI, 1.03–1.93) and 1.21 (95% CI, 1.01–1.58), respectively. Participants with conjoint MetS and high CRP level had a 1.66-fold (95% CI, 1.20–2.28) increase in OR for CKD (Table 5). However, there was no interaction in excess

Table 4. Odds ratios (ORs) for chronic kidney disease associated with individual components of metabolic syndrome and C-reactive protein (CRP) concentration.

	No. of subjects (%)	No. of CKD cases (%)	Crude OR (95% CI)	Multivariate- adjusted OR (95% CI)
Elevated blood pressure	1682	330 (19.6)	3.52 (2.90–4.27)	1.55 (1.25–1.92)
Elevated triglycerides	1148	168 (14.6)	1.48 (1.21–1.81)	1.19 (0.96–1.47)
Reduced HDL-C	1096	139 (12.7)	1.17 (0.95–1.44)	1.04 (0.82–1.31)
Elevated FPG	743	157 (21.1)	2.54 (2.07–3.13)	1.37 (1.09–1.72)
Elevated WC	1784	270 (15.1)	1.80 (1.50–2.17)	1.17 (0.96–1.44)
High CRP (>3 mg/L)	782	143 (18.3)	2.09 (1.69–2.58)	1.44 (1.14–1.81)

HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; WC, waist circumference; CI, confidence interval. The definitions for elevated blood pressure, elevated triglyceride, reduced HDL-C, elevated FPG and elevated WC were documented in the text. ORs were adjusted for age, gender, body mass index, components of the metabolic syndrome and levels of C-reactive protein.

of additive scale between the presence of MetS and high CRP level ($p = 0.83$).

Discussion

In this study, there was a significantly graded relationship between the number of MetS components present and the corresponding prevalence of CKD. In addition, a significant stepwise increase in the odds of CKD across the gradient of CRP level was also observed. Findings of the present study show for the first time in a representative sample of the Chinese population in Taiwan that the MetS and elevated CRP levels were independent risk factors for prevalent CKD.

Recently, a systematic review and meta-analysis of longitudinal studies found that the presence of MetS was significantly associated with the development of CKD, and the risk estimate increased as the number of MetS components increased (4). The relationship between MetS and CKD is biologically plausible. Hypertension and diabetes mellitus are both addressed by the definition of MetS and are the leading cause of CKD (2,16), as observed in the present study. In addition, Obesity is related to hypertension, hyperinsulinemia, and hyperlipidemia (17), and obesity-related glomerulopathy is an increasingly prevalent condition (18). The MetS has been associated with an increased risk for mortality from cardiovascular disease and all causes (19,20). Therefore, the MetS may be a common phenotype that increases the risk of CKD and mortality from cardiovascular disease in those with CKD.

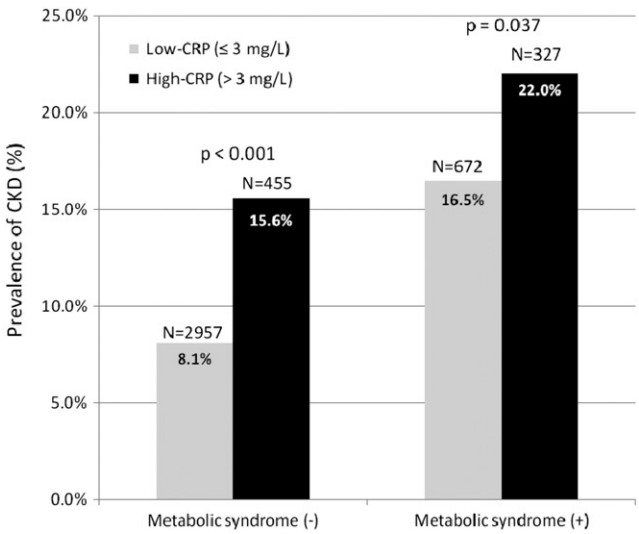

Figure 1. Prevalence of chronic kidney disease (CKD) according to the presence or absence of metabolic syndrome and C-reactive protein (CRP) levels.

Results from the current study are in compatible with findings from multiple cross-sectional studies that document an association between CRP and impaired kidney function (21–23). It has been known that elevated CRP is associated with endothelial injury and impaired vasodilation, both of which may lead to glomerular damage and progressive loss of kidney function (24). Yet, another theory suggests that CRP and CKD are related through shared risk factors. It is currently recognized that hypertension, diabetes and obesity are all strongly related to both systemic inflammation and renal dysfunction (25). In contrast to these theories, Shankar et al. (26) documented that CRP levels were positively associated with prevalent CKD, as observed in the present study, but were not associated with incident CKD. Thus, elevated CRP may be a marker of heightened inflammatory processes known to be activated secondary to kidney disease.

Several epidemiological studies have reported an interrelationship between MetS, CRP and cardiometabolic events. Two prospective studies have shown that MetS and inflammation have additive effects on atherosclerotic events (7,27). In addition, Beddhu and colleagues reported that MetS had a cross-sectional association with CRP level in patients with renal impairment (28). However, other reports insisted that combining MetS and CRP data added little to cardiovascular disease and stroke risk prediction (8,29). Moreover, Lee and his colleagues found that MetS and elevated CRP levels were independent factors for prevalent CKD (30). The present study showed that MetS and CRP together do not significantly enhanced the OR of CKD beyond their individual effect on prevalent CKD (Table 5). This study also showed that the analysis combining MetS and CRP showed a significant diffenence in CKD prevalence between high and low CRP levels regardless of the presence of MetS (Figure 1). These results suggest that MetS and inflammation may contribute independently to the presence of CKD.

The present study has several limitations. Admittedly, the cross-sectional study design made it difficult to establish a cause-effect relationship of MetS and CRP with CKD. In addition, only one fasting blood sample was collected to measure CRP levels in the present study. However, previous work found that CRP levels are stable over long periods and have no diurnal variation (31,32). Furthermore, GFRs estimated using the abbreviated MDRD study equation [14] were used to define CKD. The MDRD-equation was developed primarily in Caucasian populations in the US (33). However, it has been noted that utilization of the this MDRD

Table 5. Joint effect of the presence of the metabolic syndrome (MetS) and high C-reactive protein (CRP) level on chronic kidney disease.

	No. of subjects (%)	No. of CKD cases (%)	Crude OR (95% CI)	Multivariate- adjusted OR (95% CI)
Without MetS/low CRP	2957	240 (8.1)	1.00 (reference)	1.00 (reference)
Without MetS/high CRP	455	71 (15.6)	2.09 (1.57–2.79)	1.41 (1.03–1.93)
With MetS/low CRP	672	111 (16.5)	2.24 (1.76–2.86)	1.21 (1.01–1.58)
With MetS/high CRP	327	72 (22.0)	3.20 (2.39–4.29)	1.66 (1.20–2.28)

Low and high CRP levels were classified on the basis of CRP levels less than or greater than 3.0 mg/L. OR, odds ratio; CI, confidence interval. Odds ratios were adjusted for age, gender and body mass index.

study equation in the Chinese population in Taiwan yielded sufficiently robust results to identify the group requiring early clinical intervention (34,35).

In conclusion, findings of this study indicate that the presence of MetS and elevated CRP levels were significant correlates for prevalent CKD. There was no interaction in excess of additive properties between both of them. This study result suggests that MetS and inflammation may contribute independently to the presence of CKD.

Acknowledgements

The authors thank the Bureau of Health Promotion, Department of Health for administrative support and nurses at study areas for data collection.

Declaration of interest

This study was supported by a grant from the Bureau of Health Promotion, Department of Health (DOH95-HP-2103), Executive Yuan, Taiwan, Republic of China. The authors declare no conflict of interest.

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