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High-sensitivity C-reactive protein predicts target organ damage in Chinese patients with metabolic syndrome

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Abstract

Observational studies established high-sensitivity C-reactive protein as a risk factor for cardiovascular events in the general population. The goal of this study was to determine the relationship between target organ damage and high-sensitivity C-reactive protein in a cohort of Chinese patients with metabolic syndrome. A total of 1082 consecutive patients of Chinese origin were screened for the presence of metabolic syndrome according to the National Cholesterol Education Program's Adult Treatment Panel III. High-sensitivity C-reactive protein and target organ damage, including cardiac hypertrophy, carotid intima-media thickness, and renal impairment, were investigated. The median (25th and 75th percentiles) of high-sensitivity C-reactive protein in 619 patients with metabolic syndrome was 2.42 mg/L (0.75 and 3.66 mg/L) compared with 1.13 mg/L (0.51 and 2.46 mg/L) among 463 control subjects ($P < .01$). There was a progressive increase in high-sensitivity C-reactive protein level with the number of components of the metabolic syndrome. Stratification of patients with metabolic syndrome into 3 groups according to their high-sensitivity C-reactive protein concentrations (<1.0, 1.0-3.0, and >3.0 mg/L) showed that the subjects with the elevated high-sensitivity C-reactive protein had a higher percentage of target organ damage than those with lower high-sensitivity C-reactive protein. Stepwise multiple logistic regression confirmed that high-sensitivity C-reactive protein was significantly associated with cardiac hypertrophy, carotid intima-media thickness, and renal impairment. The study shows a strong independent association between inflammation and target organ damage in a large cohort of patients of Chinese origin with metabolic syndrome.
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1. Introduction

High-sensitivity C-reactive protein (CRP) has been used as an acute inflammatory marker for many decades. Recently, epidemiologic studies have shown that high-sensitivity CRP level is elevated in subjects with metabolic syndrome and that persistent subclinical increase of CRP is a strong and independent risk predictor for future cardiovascular morbidity and mortality in this population [1,2]. Observational studies indicated that CRP is associated with cardiovascular morbidity and mortality in the general population and patients with chronic diseases including diabetes mellitus or chronic renal failure.

However, presently, it is unknown whether high-sensitivity CRP in patients with metabolic syndrome indicates the presence of target organ damage. Based upon the established relationship between high-sensitivity CRP, metabolic syndrome [1-3], and cardiovascular disorders [1,4-8], we hypothesized that the higher cardiovascular events seen in previous investigations most likely happened in the presence of target organ damage that developed during metabolic syndrome. We further hypothesized that persistently elevated

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high-sensitivity CRP correlates to target organ damage during metabolic syndrome. To test our hypothesis, we (1) investigated how the proinflammatory biomarker high-sensitivity CRP was related to metabolic syndrome and (2) examined the relationship between high-sensitivity CRP and target organ damage in a cohort of 1082 subjects of Chinese origin from Chongqing area in southwestern China.

2. Methods

2.1. Study population

A total of 1082 subjects were screened for the presence of metabolic syndrome. All subjects were of Chinese origin. Subjects were recruited from among patients who were admitted for minor medical complaints such as skin rash and backache. Participants who previously had cardiovascular disease (clinical or laboratory evidence of heart failure, cerebrovascular disease, valvular defect, secondary hypertension) or major noncardiovascular disease (infection, trauma, surgical operation) were excluded. Each participant gave written informed consent.

2.2. Definition of metabolic syndrome and its measurement

Metabolic syndrome was defined according to the modified National Cholesterol Education Program's Adult Treatment Panel III report [9] as having 3 or more of the following conditions: (1) abdominal obesity: waist circumference >90 cm in men and >80 cm in women; (2) hypertriglyceridemia: >150 mg/dL (1.7 mmol/L); (3) high-density lipoprotein cholesterol: <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women; (4) high blood pressure: systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg; or (5) high fasting blood glucose: >110 mg/dL (>6.1 mmol/L).

Waist circumference was measured at the midpoint between the bottom of the rib cage and above the top of the iliac crest at minimal respiration to the nearest 0.1 cm. Blood pressure was measured by a physician using a mercury sphygmomanometer (first and fifth phases of Korotkoff sounds taken as systolic blood pressure and diastolic blood pressure, respectively) after the subjects had rested for at least 5 minutes in the sitting position. Three measurements were taken at 1-minute intervals, and the average was used to define the clinical systolic and diastolic blood pressure. Plasma triglyceride, high-density lipoprotein cholesterol, and fasting blood glucose were measured with the hospital's routine assays.

2.3. High-sensitivity CRP measurement

Fasting blood samples were collected in EDTA and assayed for high-sensitivity CRP by a validated high-sensitivity assay using turbidimetric immunoassay (Orion Diagnostica, Espoo, Finland). Samples were stored frozen at −70°C until measurements of CRP levels. The CRP levels were measured in duplicate, and mean values are reported throughout the article. The intraassay precision was tested. The coefficient of variation for low high-sensitivity CRP levels (mean, 0.62 mg/L), medium high-sensitivity CRP levels (mean, 3.34 mg/L), and high high-sensitivity CRP levels (mean, 8.71 mg/L) was 6.6, 0.3, and 0.8, respectively. The interassay precision was also tested. The coefficient of variation for low high-sensitivity CRP levels (mean, 0.59 mg/L), medium high-sensitivity CRP levels (mean, 5.53 mg/L), and high high-sensitivity CRP levels (mean, 9.12 mg/L) was 11.8, 2.1, and 3.4, respectively. The recovery was tested by adding aliquots of high-sensitivity CRP–containing serum to a serum sample with low high-sensitivity CRP levels. The resultant high-sensitivity CRP levels covered a range from 0.83 mg/L to 7.89 g/L and the recoveries from 93% to 107% (mean, 97%). The recovery for serial dilution of high-sensitivity CRP sample (8.91 mg/L) ranged from 92% to 98%.

2.4. Echocardiography

The M-mode, 2-dimensional, and Doppler echocardiographic examinations were performed using HP Sonic 5500 (Hewlett Packard, Palo Alto, CA) equipped with a 2.25-MHz imaging transducer. End-diastolic and end-systolic left ventricular internal diameter, interventricular septum thickness, and left ventricular posterior wall thickness were calculated from 2-dimensionally guided M-mode tracing and measured during 3 to 5 consecutive cycles [10]. Left ventricular mass index was estimated by the formula of Devereux et al [11] and normalized by body surface area and height.

2.5. Carotid intima-media thickness

Images of the extracranial carotid artery walls (common, bifurcation, internal carotid arteries) were obtained in several projections by a high-resolution linear array 10-MHz probe, with the patient supine and the neck in slight hyperextension. End-diastolic intima-media thickness of the far wall of both common carotid arteries was measured 5, 10, 15, 20, and 25 mm caudal to the bulb using 2-dimensional longitudinal sections of the vessel and the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line [12,13]. Echocardiography and determination of carotid intima thickness were performed by investigators blinded to the assignment of subjects to the different groups to ensure unprejudiced determination of these parameters.

2.6. Microalbuminuria

The 24-hour urinary albumin concentration was measured by nephelometry (detection limit, 0.1 mg/dL).

2.7. Definition of target organ damage

Target organ damage was defined by the presence of left ventricular hypertrophy, increased carotid intima-media thickness, or kidney damage assessed by microalbuminuria.

Table 1
Demographic and clinical characteristics of the study population

Parameter	Sum	No metabolic syndrome	Metabolic syndrome
n	1082	463	619
Age (y)	56.0 ± 13.2	55.2 ± 13.3	56.7 ± 13.1
Sex (male/female)	569/513	275/188	294/325 **
Waist circumference (cm)	87 ± 10	82 ± 9	90 ± 9 **
Male	88 ± 10	83 ± 9	93 ± 9 **
Female	86 ± 9	81 ± 10	88 ± 8 **
Waist-to-hip ratio	0.90 ± 0.09	0.82 ± 0.10	0.97 ± 0.08 **
Male	0.91 ± 0.09	0.84 ± 0.10	0.98 ± 0.08 **
Female	0.88 ± 0.10	0.80 ± 0.09	0.97 ± 0.09 **
Diastolic blood pressure (mm Hg)	86 ± 15	85 ± 16	86 ± 14 **
Total cholesterol (mmol/L)	4.90 ± 1.23	4.76 ± 1.11	5.01 ± 1.32 *
Triglycerides (mmol/L)	1.80 ± 1.49	1.20 ± 0.91	2.27 ± 1.69 **
Low-density lipoprotein cholesterol (mmol/L)	2.84 ± 0.84	2.75 ± 0.75	2.91 ± 0.90
High-density lipoprotein cholesterol (mmol/L)	1.24 ± 0.37	1.42 ± 0.37	1.11 ± 0.30 **
Fasting blood glucose (mmol/L)	8.29 ± 4.08	7.11 ± 3.69	9.24 ± 4.27 **
Left ventricular mass index ($g/m^{2.7}$)	45 ± 15	43 ± 13	48 ± 16 **
Intima-media thickness (mm)	0.87 ± 0.33	0.85 ± 0.27	0.88 ± 0.37 *
Urinary albumin excretion (mg/24 h)	11.4 (5.8-27.3)	9.9 (5.4-20.0)	13.6 (6.3-32.7) *
High-sensitivity CRP (mg/L)	1.68 (0.75-3.66)	1.13 (0.51-2.46)	2.42 (1.15-5.51) **

Urinary albumin excretion and high-sensitivity CRP are expressed by median and 25th to 75th percentile values (in the parentheses).
* $P < .05$ vs non–metabolic syndrome group.
** $P < .01$ vs non–metabolic syndrome group.

Left ventricular hypertrophy was diagnosed if left ventricular mass index ≥51 $g/m^{2.7}$ in men and ≥47 $g/m^{2.7}$ in women [14]. Increased carotid media thickness was diagnosed if common carotid wall thickness exceeded 0.9 mm [15]. *Microalbuminuria* was defined as a urinary albumin excretion between 30 and 300 mg/d [16].

2.8. Statistical analysis

The Statistical Package for the Social Sciences (SPSS for Windows, version 13.0; SPSS, Chicago, IL) was used for the analyses. Normally distributed data are presented as means ± SD. The differences between 2 groups were analyzed using Student *t* test. The differences within multiple groups were tested using analysis of variance. Skewed data are expressed as median and 25th and 75th percentiles, and the median values are compared using the median test or Kruskal-Wallis test when appropriate. Analysis of categorical data was carried out using the χ^2 test or Fisher exact test when appropriate. The strength of correlation between variables was tested by Spearman correlation or multiple regression analysis when appropriate. Stepwise multivariate logistic regression analyses were used to examine associations between target organ damage and their risk factors and to predict the incidence rate of target organ damage in patients with metabolic syndrome. In stepwise multivariate logistic regression, the dependent variable was left ventricular mass index, intima-media thickness, or urinary albumin excretion rate; and the independent variables were age, sex, systolic blood pressure, diastolic blood pressure, waist circumference, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting plasma glucose. Variables were included into the model, whereas *P* values were less than .05. One-sample Kolmogorov-Smirnov test was used to check normal distribution of data. Two-sided *P* values less than .05 were considered to indicate statistical significance.

3. Results

The demographic and clinical characteristics of the 1082 subjects are shown in Table 1. The cohort is further characterized according to the absence or presence of metabolic syndrome. In patients with metabolic syndrome, an increased waist circumference and systolic and diastolic blood pressure were observed (each $P < .05$). According to the modified National Cholesterol Education Program's

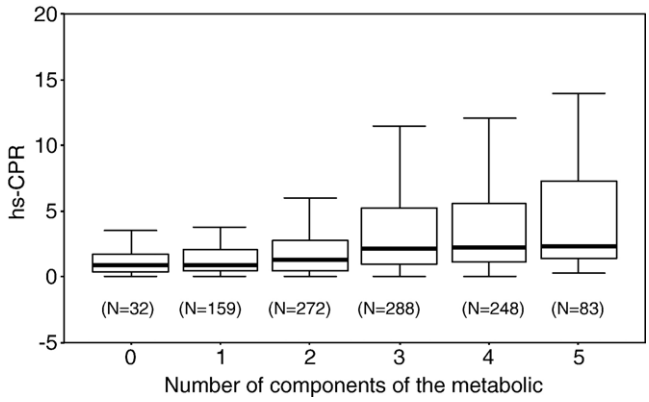

Fig. 1. Distribution of high-sensitivity CRP levels among 1082 participants according to presence of 0, 1, 2, 3, 4, or 5 components of metabolic syndrome. Box plots demonstrate median and 25th and 75th percentile values, and whiskers demonstrate 10th to 90th percentile values for high-sensitivity reactive protein.

Table 2
The corresponding change of high-sensitivity CRP levels according to each component greater than or less than the cutoff of metabolic syndrome

Criteria	n	High-sensitivity CRP	P
Waist circumference (cm)			
<90 (male)	322	1.31 (0.57-3.25)	<.001
≥90 (male)	247	2.18 (1.30-5.43)	
<80 (female)	126	1.41 (0.68-2.76)	<.001
≥80 (female)	387	2.03 (0.38-1.76)	
Systolic blood pressure (mm Hg)			
<130	256	1.45 (0.68-3.21)	.012
≥130	826	1.82 (0.81-3.82)	
Diastolic blood pressure (mm Hg)			
<85	535	1.51 (0.72-3.46)	.018
≥85	547	1.95 (0.84-3.82)	
Fasting plasma glucose (mmol/L)			
<6.1	478	1.37 (0.58-3.24)	<.001
≥6.1	604	2.01 (0.89-4.67)	
Triglycerides (mmol/L)			
<1.7	683	1.53 (0.61-3.45)	.004
≥1.7	399	2.01 (0.95-4.05)	
High-density lipoprotein cholesterol (mmol/L)			
>1.04 (male)	345	1.46 (0.74-3.25)	.001
≤1.04 (male)	224	2.17 (1.06-6.12)	
>1.29 (female)	240	1.35 (0.46-3.08)	<.01
≤1.29 (female)	273	1.94 (0.89-3.82)	
Metabolic syndrome			
No	463	1.13 (0.51-2.46)	<.001
Yes	619	2.42 (1.15-5.51)	

High-sensitivity CRP (in milligrams per liter) is expressed by median and 25th and 75th percentile values (in the parentheses).

Adult Treatment Panel III report [9], we used waist circumference >90 cm in men and >80 cm in women. Hence, patients (both male and female) with metabolic syndrome had increased waist circumference (Table 1). As expected, we also observed a significant correlation between waist circumference and waist-to-hip ratio ($r^2 = 0.754$, $P < .001$). The waist-to-hip ratio was also significantly increased in patients with metabolic syndrome compared with subjects without metabolic syndrome (0.97 ± 0.08 vs 0.82 ± 0.10, $P < .01$). In patients with metabolic syndrome, total cholesterol and serum triglycerides were significantly increased (each $P < .05$).

Fig. 1 displays the distribution of high-sensitivity CRP levels according to their total number of components of the metabolic syndrome. As shown, there was a linear and progressive increase in high-sensitivity CRP levels as the number of components of the metabolic syndrome increased; median and 25th and 75th percentiles of high-sensitivity CRP levels for those with 0, 1, 2, 3, 4, or 5 components of the metabolic syndrome were 0.88 mg/L (0.41 and 1.70 mg/L), 0.89 mg/L (0.49 and 2.12 mg/L), 1.28 mg/L (0.50 and 2.76 mg/L), 2.15 mg/L (1.00 and 5.24 mg/L), 2.34 mg/L (1.17 and 5.55 mg/L), and 2.32 mg/L (1.38 and 7.27 mg/L), respectively ($\chi^2 = 86.77$, $P < .001$).

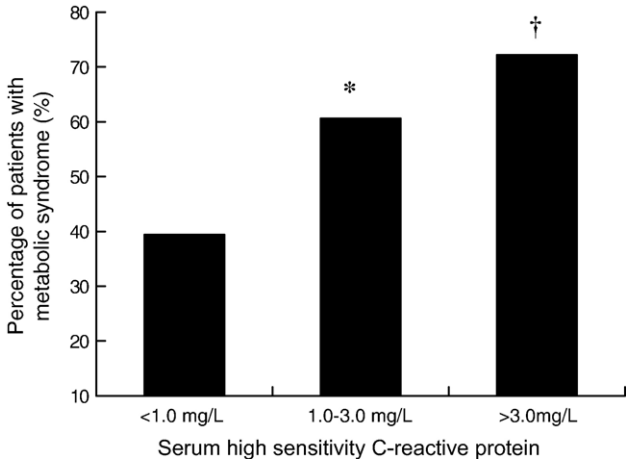

Fig. 2. Percentage of patients with metabolic syndrome in the cohort of 1082 subjects according to high-sensitivity CRP levels <1.0, 1.0 to 3.0, and >3.0 mg/L. *$P < .05$, †$P < .01$ vs 1.0-mg/L group.

Table 2 presents the effect of each component of metabolic syndrome on high-sensitivity CRP levels. Compared with subjects without metabolic syndrome, high-sensitivity CRP levels were significantly higher in patients with metabolic syndrome in each component of the metabolic syndrome.

As shown in Table 3, in patients with metabolic syndrome, a significant positive correlation between the high-sensitivity CRP and waist circumference, blood pressure, fasting plasma glucose, and serum triglycerides could be observed (each $P < .01$); and a significant negative correlation between high-sensitivity CRP and high-density lipoprotein cholesterol was found ($P < .05$). On the other hand, in healthy control subjects without metabolic syndrome, no significant correlation between CRP levels and systolic blood pressure, diastolic blood pressure, fasting plasma glucose, triglyceride levels, and high-density lipoprotein levels could be observed (each $P > .05$).

Table 3
Correlation between high-sensitivity CRP levels and components of the metabolic syndrome in patients with metabolic syndrome

Variable	Correlation coefficient (r)	P
Waist circumference	0.281	<.001
Systolic blood pressure	0.084	.006
Diastolic blood pressure	0.064	.035
Fasting plasma glucose	0.125	<.001
Triglycerides	0.198	<.001
High-density lipoprotein cholesterol	−0.154	<.001

Table 4
Correlation between high-sensitivity CRP levels and target organ damage of metabolic syndrome in patients with metabolic syndrome

	Correlation coefficient (r)	P
Urinary albumin excretion	0.070	.044
Intima-media thickness	0.082	.035
Left ventricular mass index	0.111	.004

Table 5
Stepwise multiple logistic regression analyses with urinary albumin excretion levels as the dependent variable in patients with metabolic syndrome

	Partial regression coefficient	Standard error	*P*	Odds ratio	95% CI for odds ratio	
					Lower	Upper
High-sensitivity CRP	0.029	0.004	<.001	1.029	1.021	1.037
Fasting plasma glucose	0.095	0.004	<.001	1.099	1.091	1.108
High-density lipoprotein cholesterol	−0.584	0.045	<.001	.558	.511	.609
Waist circumference	0.015	0.002	<.001	1.015	1.012	1.019
Systolic blood pressure	0.016	0.001	<.001	1.016	1.014	1.018

CI indicates confidence interval.

As shown in Fig. 2, the percentage of patients with metabolic syndrome is related to high-sensitivity CRP level. Subjects were stratified according to high-sensitivity CRP levels (<1.0, 1.0-3.0, and >3.0 mg/L). In those subjects with high-sensitivity CRP >3.0 mg/L, a higher percentage of the metabolic syndrome could be observed compared with those subjects with lower high-sensitivity CRP levels.

Table 4 shows the correlation between serum high-sensitivity CRP level and target organ damage in patients with metabolic syndrome. We found a statistically significant positive correlation between high-sensitivity CRP and urinary albumin excretion rate, left ventricular mass index, and intima-media thickness (each $P < .05$).

After adjustment by age and sex, urinary albumin excretion, left ventricular mass index, and intima-media thickness were significantly correlated with serum high-sensitivity CRP by multivariable regression analysis ($P < .001$, Table 5–7).

Fig. 3 shows the correlation between serum high-sensitivity CRP concentration and the percentage of patients with target organ damage. Subjects were stratified according to high-sensitivity CRP levels (<1.0, 1.0-3.0, and >3.0 mg/L). In those subjects with high-sensitivity CRP >3.0 mg/L, a higher percentage of target organ damage could be observed compared with those subjects with lower high-sensitivity CRP levels.

Table 6
Stepwise multiple logistic regression analyses with left ventricular mass index as the dependent variable in patients with metabolic syndrome

	Partial regression coefficient	Standard error	*P*	Odds ratio	95% CI for odds ratio	
					Lower	upper
High-sensitivity CRP	0.115	0.018	<.001	1.121	1.082	1.162
Systolic blood pressure	0.041	0.009	<.001	1.042	1.024	1.061
Waist circumference	0.036	0.005	<.001	1.036	1.027	1.046

Table 7
Stepwise multiple logistic regression analyses with intima-media thickness of common carotid artery as the dependent variable in patients with metabolic syndrome

	Partial regression coefficient	Standard error	*P*	Odds ratio	95% CI for odds ratio	
					Lower	upper
High-sensitivity CRP	0.013	0.003	<.001	1.014	1.007	1.020
Triglycerides	0.019	0.004	<.001	1.019	1.011	1.028
Systolic blood pressure	0.036	0.005	<.001	1.145	1.004	1.306

4. Discussion

Our cross-sectional study confirms and advances the notion that subclinical levels of high-sensitivity CRP is closely related to the level of individual components of metabolic syndrome as well as to the number of total components in a subject. More importantly, our results demonstrate that the high-sensitivity CRP levels are clearly related to the damage of the target organs (ie, heart, kidney, and artery) during metabolic syndrome. In addition, to our knowledge, no investigation has ever been performed to establish the association between metabolic syndrome, target organ damage, and CRP in such a relative large cohort of Chinese population as the present one.

In the present study, the strong correlation of high-sensitivity CRP with metabolic disorder is demonstrated by the following evidence: First, the subjects with metabolic syndrome had significantly higher high-sensitivity CRP level than those without, which is consistent with previous results in other ethnic groups [1,2,17,18]. Second, there was a progressive and linear increase in high-sensitivity CRP levels when the number of components of the metabolic syndrome increased. A similar phenomenon was recently observed in a

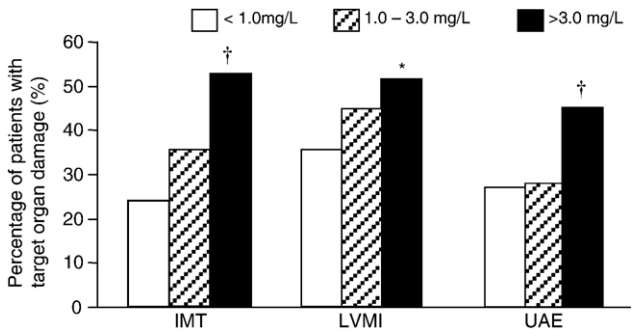

Fig. 3. Percentage of patients with target organ damage in the cohort of 1082 subjects according to high-sensitivity CRP levels <1.0, 1.0 to 3.0, and >3.0 mg/L. *$P < .05$, †$P < .01$ vs 1.0-mg/L group.

few investigations [1,2]. Third, the high-sensitivity CRP level increased when the level of individual component of metabolic syndrome exceeded the cutoff point. Fourth, a significant correlation between high-sensitivity CRP levels and components of the metabolic syndrome could be observed in patients with metabolic syndrome but not in healthy control subjects, thereby strengthening the concept that increased CRP levels are causally associated with the development of the metabolic syndrome.

Numerous mechanistic investigations have documented that metabolic syndrome is a state of chronic low-grade inflammation and that obesity, one of the prominent and frequent components of metabolic syndrome, is the major determinant of the inflammatory marker high-sensitivity CRP in subjects with metabolic syndrome [19-21]. In obesity, proinflammatory cytokines such as interleukins and tumor necrosis factor α are overproduced from the expended adipose tissue [22,23]. In addition, proinflammatory cytokines can also come from monocyte-derived macrophages that reside in adipose tissue [24]. These adipocytokines constitute a stimulant to the liver, therefore causing tonic synthesis and release of high-sensitivity CRP from hepatocytes [22,25].

Epidemic studies have convincingly established high-sensitivity CRP as a predictor for cardiovascular mortality and morbidity. As previously shown in an 8-year follow-up study in American women with metabolic syndrome, the incidence rates of future cardiovascular events was 5.9 per 1000 person-years for those with baseline high-sensitivity CRP >3 mg/L compared with 3.4 per 1000 person-years for those with baseline high-sensitivity CRP <3 mg/L. It is reasonable to hypothesize that the higher cardiovascular events most likely happened in subjects who underwent target organ damage that developed during metabolic syndrome and that such damage is related to elevated high-sensitivity CRP. In the present study, when subjects with metabolic syndrome were stratified into low-, medium-, and high-risk groups according to their high-sensitivity CRP level <1.0, 1.0 to 3.0, and >3.0 mg/L, an unequivocal correlation was found between high-sensitivity CRP levels and the damage of target organs, including carotid artery, heart, and kidney. The fact that nearly half of the subjects with high-sensitivity CRP >3.0 mg/L were at high risk of having target organ damage could add additional diagnostic value in assessing the severity of organ damage caused by metabolic syndrome.

Although our study was not designed to distinguish whether the relationship between high-sensitivity CRP and target organ damage is correlational or causal, some other investigations have provided increasing evidence for the involvement of high-sensitivity CRP in the onset, development, and evolution of the damage during metabolic syndrome [26,27]. For example, first, high-sensitivity CRP can cause nitric oxide deficiency. In 2000, it was found that elevated high-sensitivity CRP levels in human subjects are inversely correlated with endothelial-dependent vasodilator response to acetylcholine and endothelial-dependent vasoconstrictor response to NG-monomethyl-L-arginine monoacetate (L-NMMA) [28,29], suggesting a relationship between elevated high-sensitivity CRP and nitric oxide deficiency. This was later interpreted as causal because high-sensitivity CRP could directly cause nitric oxide deficiency by down-regulating endothelial nitric oxide synthase transcription and destabilizing endothelial nitric oxide synthase messenger RNA (mRNA) in vitro, which in turn decreases both basal and stimulated production of nitric oxide, a key vasodilator and vasoprotective molecule [30,31]. By degradation of Iκ-B-κ, high-sensitivity CRP was also found to up-regulate nuclear factor–κ, a transcription factor that is known to mediate inflammatory response and lesion formation in endothelium [32]. Persistent endothelial dysfunction and nitric oxide deficiency appear to play an important role in mediating vascular damage in these target organs [33]. Second, high-sensitivity CRP can lead to proatherosclerotic vascular injury. Incubation of endothelial cells from human umbilical vein with high-sensitivity CRP induced increased expression of adhesion molecules, for example, intercellular adhesion molecule and vascular cell adhesion molecule [34], which cause mononuclear cells to adhere to the endothelium and then penetrate into the arterial wall, a crucial step for early atherosclerotic lesion and fatty streak. Third, high-sensitivity CRP can facilitate the pathogenic actions of angiotensin II. High-sensitivity CRP at concentrations known to predict cardiovascular events can up-regulate the expression of angiotensin II type 1 receptor mRNA and protein and increase the angiotensin II type 1 receptor number on vascular smooth muscle cells [35], therefore facilitating reactive oxygen species production and promoting vascular smooth muscle cells migration and proliferation and vascular remodeling. Those are just a few examples to illustrate the roles of high-sensitivity CRP in the pathogenesis of target organs [36], and a recent study actually showed that incubation of vascular endothelial cells with high-sensitivity CRP changed mRNA expression in as many as 17 genes (11 increased and 6 decreased) [37]. Both hemodynamic and neurohumoral actions of angiotensin II can lead to the development of target organ damage.

In the present study, the relations between metabolic syndrome and high-sensitivity CRP could be observed in a large population of subjects of Chinese origin. Recently, Maple-Brown et al [38] showed that components of the metabolic syndrome contribute significantly to premature atherogenesis in other genetic background, that is, Indigenous Australians. That report underscores our present findings that elevated high-sensitivity CRP is a likely candidate to explain the higher cardiovascular disease prevalence in these subjects. Thus, all of these new research progresses in recent years have provided increasingly stronger evidence for high-sensitivity CRP being not just a marker but also a mediator of and contributor to the target organ damage of metabolic syndrome.

Taking this and previous investigations together, we conclude that high-sensitivity CRP levels can provide prognostic estimation for future cardiovascular morbidity and mortality and diagnostic estimation for target organ damage in subjects with metabolic syndrome.

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References

[1] Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.

[2] Rutter MK, Meigs JB, Sullivan LM, D'Agostino Sr RB, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004;110:380-5.

[3] Ford ES, Ajani UA, Mokdad AH. The metabolic syndrome and concentrations of C-reactive protein among US youth. Diabetes Care 2005;28:878-81.

[4] Executive summary of 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 III). JAMA 2001;285:2486-97.

[5] Trevisan M, Liu J, Bahsas FB, Menotti A. Syndrome X and mortality: a population-based study. Risk factor and life expectancy research group. Am J Epidemiol 1998;148:958-66.

[6] Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, et al. The metabolic syndrome and chronic kidney disease in US adults. Ann Intern Med 2004;140:167-74.

[7] Blake GJ, Rifai N, Buring JE, Ridker PM. Blood pressure, C-reactive protein, and risk of future cardiovascular events. Circulation 2003;108:2993-9.

[8] Cankurtaran M, Halil M, Yavuz BB, Dagli N, Oyan B, Ariogul S. Prevalence and correlates of metabolic syndrome (MS) in older adults. Arch Gerontol Geriatr 2006;42:35-45.

[9] Scott M, Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart Lung, and Blood Institute scientific statement. Circulation 2005;112:2735-52.

[10] Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55:613-8.

[11] Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-8.

[12] Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399-406.

[13] Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high-resolution B-mode ultrasonography: inter- and intra-observer variability. Ultrasound Med Biol 1991;17:225-30.

[14] de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 1995;25:1056-62.

[15] 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011-53.

[16] Asselbergs FW, Diercks GFH, Hillege HL, Boven AJ, Janssen WMT, Voors AA, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004;110: 2809-16.

[17] LaMonte MJ, Ainsworth BE, Durstine JL. Influence of cardiorespiratory fitness on the association between C-reactive protein and metabolic syndrome prevalence in racially diverse women. J Womens Health (Larchmt) 2005;14:233-9.

[18] Piche ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor–alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. Am J Cardiol 2005;96:92-7.

[19] Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westendorp IC, et al. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. Arterioscler Thromb Vasc Biol 1999;19:1986-91.

[20] Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA 1999;282:2131-5.

[21] Aronson D, Goldberg A, Roguin A, Petcherski S, Rimer D, Gruberg L, et al. Effect of obesity on the relationship between plasma C-reactive protein and coronary artery stenosis in patients with stable angina. Atherosclerosis 2005.

[22] Trayhurn P. Endocrine and signalling role of adipose tissue: new perspectives on fat. Acta Physiol Scand 2005;184:285-93.

[23] Wang B, Jenkins JR, Trayhurn P. Expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture: integrated response to TNF-alpha. Am J Physiol Endocrinol Metab 2005;288:E731-40.

[24] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796-808.

[25] Libby P, Ridker PM. Novel inflammatory markers of coronary risk: theory versus practice. Circulation 1999;100:1148-50.

[26] Jialal I, Devaraj S, Venugopal SK. C-reactive protein: risk marker or mediator in atherothrombosis? Hypertension 2004;44:6-11.

[27] Yeh ET. CRP as a mediator of disease. Circulation 2004;109:II11-4.

[28] Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmeler S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. Circulation 2000;102:1000-6.

[29] Cleland SJ, Sattar N, Petrie JR, Forouhi NG, Elliott HL, Connell JM. Endothelial dysfunction as a possible link between C-reactive protein levels and cardiovascular disease. Clin Sci (Lond) 2000;98:531-5.

[30] Verma S, Wang CH, Li SH, Dumont AS, Fedak PW, Badiwala MV, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation 2002;106: 913-9.

[31] Verma S, Kuliszewski MA, Li SH, Szmitko PE, Zucco L, Wang CH, et al. C-reactive protein attenuates endothelial progenitor cell survival, differentiation, and function: further evidence of a mechanistic link between C-reactive protein and cardiovascular disease. Circulation 2004;109:2058-67.

[32] Verma S, Badiwala MV, Weisel RD, Li SH, Wang CH, Fedak PW, et al. C-reactive protein activates the nuclear factor–kappaB signal transduction pathway in saphenous vein endothelial cells: implications for

atherosclerosis and restenosis. J Thorac Cardiovasc Surg 2003;126: 1886-91.

[33] Augustyniak RA, Thomas GD, Victor RG, Zhang W. Nitric oxide pathway as new drug targets for refractory hypertension. Curr Pharm Des 2005;11:3307-15.

[34] Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 2000;102: 2165-8.

[35] Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation 2003;107:1783-90.

[36] Verma S, Yeh ET. C-reactive protein and atherothrombosis—beyond a biomarker: an actual partaker of lesion formation. Am J Physiol Regul Integr Comp Physiol 2003;285:R1253-6.

[37] Wang Q, Zhu X, Xu Q, Ding X, Chen YE, Song Q. Effect of C-reactive protein on gene expression in vascular endothelial cells. Am J Physiol Heart Circ Physiol 2005;288:H1539-45.

[38] Maple-Brown L, Cunningham J, Celermajer DS, O'Dea K. Increased carotid intima-media thickness in remote and urban Indigenous Australians: impact of diabetes and components of the metabolic syndrome. Clin Endocrinol (Oxf) 2007;66:419-25.