Tentative Cut Point of High-Sensitivity C-Reactive Protein for a Component of Metabolic Syndrome in Japanese

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Background: High-sensitivity C-reactive protein (hs-CRP) is an independent risk factor of diabetes and cardiovascular disease, and is proposed as a component of metabolic syndrome (MetS). An optimal cut point of hs-CRP as a component of MetS was previously reported as 0.65 mg/L based on data from a small-sized study.

Methods and Results: Medical check-up data of 1,062 men and 647 women whose plasma levels of hs-CRP were <10 mg/L were examined using a receiver-operating characteristic (ROC) curve for diagnosing MetS, which was defined by revised NCEP criteria for Japanese. An optimal cut point was defined as the point on a ROC curve nearest to the point where both sensitivity and specificity were 1. The area under the ROC curve of hs-CRP was 0.74 (95% confidence interval (CI) 0.70–0.79) in men and 0.73 (95%CI 0.66–0.79) in women. The optimal cut point of hs-CRP and its sensitivity–specificity were, respectively, 0.45 mg/L and 0.67–0.72 in men and 0.25 mg/L and 0.71–0.62 in women.

Conclusions: Among Japanese patients, a tentative cut point of hs-CRP as a component of MetS may be 0.45 mg/L in men and 0.25 mg/L in women. However, standardization of the measurement of hs-CRP is required. (Circ J 2009; 73: 755–759)

Key Words: High-sensitivity C-reactive protein; Inflammation; Metabolic syndrome; Obesity

High-sensitivity C-reactive protein (hs-CRP) has been reported as an independent risk factor of diabetes¹ and cardiovascular disease² and proposed as a component of metabolic syndrome (MetS)². Levels of hs-CRP lower than 1 mg/L, between 1 mg/L and 3 mg/L, and higher than 3 mg/L are considered as low, intermediate and high risk category, respectively, in Western countries³ but hs-CRP levels in Japanese are substantially lower than those in Westerners. Previously, we reported 0.65 mg/L as an optimal cut point of hs-CRP as a component of MetS among Japanese⁴ and it seemed appropriate^{5–9} but the sample size was rather small, so we repeated the study in different subjects using different measurement methods and obtained a lower cut point of hs-CRP as a component of MetS. However, the median hs-CRP was also substantially lower than the previous value.

Methods

Subjects

Between April 1 and August 31 in 2008, 1,076 men and 650 women visited for routine medical check-ups. They were all required to fill out a questionnaire from the Ministry of Health, Labor, and Welfare for the purpose of “Special Health Examination and Instruction”, including questions

about history of cardiovascular disease, smoking status, antihypertensive and hypoglycemic medications, and alcohol consumption. Of this group, 14 men and 3 women were excluded as subjects of the present study because their serum levels of hs-CRP were higher than 10 mg/L. The protocol for the present study was approved by the Ethics Committee of Tachikawa Medical Center and signed informed consent was given by each subject.

Measurements

After an overnight fast, blood samples were taken to measure serum levels of glucose, triglyceride, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), hemoglobin A_{1c} and uric acid, blood cell counts, electrolytes, liver and kidney function tests, including gamma glutamyltransferase, alkaline phosphatase, leucine aminopeptidase, cholinesterase, amylase, and hs-CRP. Biochemical measurements were all performed at BML Nagaoka (Nagaoka, Japan), except for hs-CRP, which was measured at BML General Laboratory (Tokyo, Japan), with nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan). The measurement limit of hs-CRP was 0.02 mg/L and the value of hs-CRP less than the measurement limit was considered as 0.01 mg/L. Body fat percentage was measured by bioelectrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). An average blood pressure was calculated from 2 measurements with the subjects seated after 5 min rest. Body weight was measured with the subjects wearing light clothing provided by the Center and the weight of the clothes was subtracted from the measured body weight. Waist circumference (WC) was measured at the level of the umbilicus. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

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Table 1. Baseline Data

	Men (n=1,062)		Women (n=647)	
	Mean±SD	Median	Mean±SD	Median
Age, years	51.7±9.3	52.0	51.1±10.2	51.0
BMI, kg/m ²	23.2±3.0	23.0	21.6±3.2	21.2
Body fat, %	21.7±5.0	21.5	26.5±5.9	25.9
Waist circumference, cm	83.9±8.3	83.3	78.4±8.8	77.3
Systolic blood pressure, mmHg	121.4±16.8	119.0	111.3±16.1	108.5
Diastolic blood pressure, mmHg	77.1±10.4	76.5	69.5±10.0	68.0
Fasting glucose, mg/dl	95.1±13.4	92.0	89.5±11.3	88.0
Triglyceride, mg/dl	117.8±81.5	97.5	84.1±54.9	72.0
HDL-cholesterol, mg/dl	57.9±14.6	56.0	67.1±14.7	65.0
hs-CRP, mg/L	0.61±1.05	0.28	0.42±0.73	0.20
LDL-cholesterol, mg/dl	119.5±28.9	119.0	119.5±28.8	117.0
Antihypertensives, %	17.9		9.3	
Hypoglycemics, %	3.6		1.7	
Cardiovascular disease, %	6.6		3.4	
Current smoker, %	33.8		7.0	
MetS, %	13.2		7.0	
JMetS, %	11.4		1.7	

BMI, body mass index; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein. Metabolic syndrome (MetS) was defined according to the revised NCEP criteria for Japanese and Japanese metabolic syndrome (JMetS) was defined by the Examination Committee for Criteria of Metabolic Syndrome.

Table 2. Median hs-CRP Level According to the Number of MetS Components

Components	Men		Women	
	n	Median hs-CRP (mg/L)	n	Median hs-CRP (mg/L)
0	400	0.21	293	0.13
1	318	0.26	214	0.24
2	204	0.39	95	0.33
3	92	0.67	33	0.42
4, 5	48	0.66	12	0.57

Abbreviations see in Table 1.

Statistical Analysis

MetS was defined according to the revised NCEP criteria¹⁰ as 3 or more of 5 components in which the cut point of WC was modified for Japanese as ≥90 cm in men and ≥80 cm in women according to the recommendation by the International Diabetes Federation (IDF),¹¹ the cut points of the other components were systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg for blood pressure, ≥150 mg/dl for triglyceride, <40 mg/dl in men and <50 mg/dl in women for HDL-C, and ≥100 mg/dl for fasting glucose. Subjects receiving antihypertensive or hypoglycemic medication were considered to have the respective component. Diagnosis of the Japanese MetS (JMetS) proposed by the Examination Committee for Criteria of Metabolic Syndrome¹² was also performed. The median hs-CRP in each category defined by the number of MetS components was calculated. Receiver-operating characteristic (ROC) curve analysis for diagnosing MetS was performed to obtain the area under ROC curve (AUC) and an optimal cut point of hs-CRP for diagnosing MetS using Dr SPSS-2. An optimal cut point was defined as the point on a ROC curve nearest to the point where both sensitivity and specificity were 1.

Results

Baseline data are shown in **Table 1**: 1,062 men aged 52±9 (mean±SD) years and 647 women aged 51±10 (mean±SD) years were the subjects of the present study. The median

hs-CRP was 0.28 mg/L in men and 0.2 mg/L in women. The prevalence of MetS, JMetS, current smokers, and cardiovascular disease was 13.2%, 11.4%, 33.8%, and 6.6%, respectively, in men and 7.0%, 1.7%, 7.0%, and 3.4%, respectively, in women. Median hs-CRP in each category defined by the number of MetS components is presented in **Table 2**. The median hs-CRP in 0, 1, 2, 3, and 4 or 5 MetS components category was 0.21 mg/L, 0.26 mg/L, 0.39 mg/L, 0.67 mg/L, and 0.66 mg/L, respectively, in men and 0.13 mg/L, 0.24 mg/L, 0.33 mg/L, 0.42 mg/L, and 0.57 mg/L, respectively, in women. ROC curves of hs-CRP for diagnosing MetS and JMetS are shown in **Figure**. The AUC of hs-CRP for diagnosing MetS and JMetS and the tentative optimal cut points of hs-CRP as a component of MetS and JMetS are presented in **Table 3**. The AUC of hs-CRP for MetS was 0.74 (95% confidence interval (CI) 0.70–0.79) in men and 0.73 (95%CI 0.66–0.79) in women. The AUC of hs-CRP for JMetS was 0.72 (95%CI 0.67–0.77) in men and 0.75 (95%CI 0.65–0.86) in women. The optimal cut point of hs-CRP as a component of MetS and JMetS was the same: 0.45 mg/L in men and 0.25 mg/L in women. The sensitivity–specificity was 0.67–0.72 for MetS and 0.63–0.71 for JMetS in men, and 0.71–0.62 for MetS and 0.77–0.60 for JMetS in women.

Discussion

For the past several decades, there has been considerable effort made to understand the underlying biology and to

Figure. Receiver operating characteristic curves of high-sensitivity C-reactive protein for revised NCEP metabolic syndrome (MS) and Japanese metabolic syndrome (JMS).

Table 3. AUC and Optimal Cut Points of hs-CRP for MetS and JMetS

	AUC	95%CI	Cut point	Sensitivity	Specificity
Men					
MetS	0.74	0.70–0.79	0.45 mg/L	0.67	0.72
JMetS	0.72	0.67–0.77	0.45 mg/L	0.63	0.71
Women					
MetS	0.73	0.66–0.79	0.25 mg/L	0.71	0.62
JMetS	0.75	0.65–0.86	0.25 mg/L	0.77	0.60

AUC, area under the receiver-operating characteristic curve; CI, confidence interval. Other abbreviations see in Table 1.

Table 4. Differences in Median or Geometric Mean hs-CRP Levels Among Different Studies of Japanese

	Men				Women			
	hs-CRP (mg/L)	n	Age	BMI	hs-CRP (mg/L)	n	Age	BMI
Yamada et al ²⁴	0.16 (A)	2,275	55.8	22.8	0.09 (A)	3,832	55.3	22.8
Doi et al ¹	0.49 (A)	694	58	22.9	0.36 (A)	1,065	57	23.0
Nakanishi et al ⁵	0.53 (A)	715	56.1	23.6	0.32 (A)	988	55.8	22.0
Oda et al ⁴	0.60 (A)	179	52.0	23.8	0.30 (A)	166	53.5	22.7
Present study	0.28 (A)	1,062	51.7	23.2	0.20 (A)	647	51.1	21.6
Saito et al ²⁵	0.10 (B)	398	69.0	23.2	0.08 (B)	655	67.6	23.8
Nasermoaddeli et al ²⁶	0.42 (B)	899			0.24 (B)	780		
Matsushita et al ⁷	0.42 (B)	2,523	48	23				

Age and BMI presented as mean; hs-CRP is presented as median (A) or geometric mean (B). Abbreviations see in Table 1.

identify the risk factors of cardiovascular disease. As risk factors were identified, it became apparent that they tended to cluster in the same individual. Thus, the concept of insulin resistance syndrome (syndrome X)¹³ or MetS¹⁴ emerged. MetS is a constellation of interrelated metabolic risk factors that appear to directly promote the development of diabetes and cardiovascular disease. The predominant underlying mechanisms of MetS appear to be insulin resistance, abdominal obesity, and inflammation.¹⁵ However, in 2005, the American Diabetes Association and the European Association for the Study of Diabetes jointly stated that no existing definition of MetS met the criteria of a syndrome¹⁶ and there

have been endless debates on the pros and cons of diagnosing this syndrome in individuals.^{17–20} We thought MetS might develop through adipose tissue disease,²¹ different from obesity, and therefore should be diagnosed with inflammatory, endocrine, metabolic, and histological tests. Criteria that regard anthropometry as an inevitable component of MetS have a serious pitfall, because there are a substantial number of metabolically obese normal weight individuals²² and only approximately one-third of the most insulin-resistant individuals are actually obese.¹⁹ In contrast, hs-CRP is an independent risk factor of cardiovascular disease and has been proposed as a component of MetS?

In our previous study based on data from 179 men and 166 women, we reported 0.65 mg/L as an optimal cut point of hs-CRP for a component of MetS in both Japanese men and women⁴ and this cut point seemed appropriate not only for diagnosing MetS^{5,6} but also for assessing cardiovascular risk⁷, predicting coronary spasm⁸, and differentiating nonalcoholic steatohepatitis from simple fatty liver⁹. In the present study based on the data from 1,062 men and 647 women, we obtained 0.45 mg/L in men and 0.25 mg/L in women as the tentative optimal cut points as a component of MetS in Japanese. Although the measurement limit of hs-CRP was 0.1 mg/L and the median hs-CRP was 0.6 mg/L in men and 0.3 mg/L in women in our previous study⁴, the measurement limit of hs-CRP was 0.02 mg/L and the median hs-CRP was 0.28 in men and 0.2 in women in the present study, though age, BMI and other basal data of the subjects were comparable between the 2 studies. **Table 4** presents the medians or geometric means of the hs-CRP levels among Japanese reported in different studies. There are substantial differences among these reports despite similar ages and BMI of the study subjects. Therefore, the difference in the cut points of hs-CRP seemed to be mainly derived from differences in the measurement methods. Standardization of hs-CRP measurement may be mandatory to establish an optimal cut point of hs-CRP as a component of MetS among Japanese. Though both the previous and the present hs-CRP cut points are very low compared with the standard in Western societies³, where obesity prevails, women with hs-CRP values equal to or higher than 0.5 mg/L have a higher risk of cardiovascular disease than women with hs-CRP values lower than 0.5 mg/L, even in the United States²³.

As for gender differences in hs-CRP, Saltevo et al reported that the levels are significantly higher in women with MetS than in men with MetS, but in subjects without MetS, there are no gender differences in the level of hs-CRP²⁷. Lakoski et al reported that women had substantially higher median hs-CRP levels compared with men.²⁸ However, in Japan, hs-CRP levels among women without MetS are lower than the levels among men, but in subjects with MetS, the gender difference in the level of CRP might be obscured.^{4–6} Thus, clustering of metabolic risk factors and weight gain may have stronger effects on the hs-CRP level in women than in men.⁵

Study Limitations

The present study was a cross-sectional study and the subjects were not a general population, but visitors to a medical check-up center that is in a central city of a rural region in Japan. These conditions may have influenced the low serum levels of hs-CRP and the low prevalence of MetS and JMetS in these subjects. However, both the level of hs-CRP in the general population and the prevalence of obesity are very low in Japan. Therefore, the present data may not represent a peculiar population and the conclusions may be relevant to other regions and populations in Japan. As for the cut points of WC among Japanese, these are quite controversial.²⁹ When we examined JMetS using the WC cut point of 85 cm in men and 90 cm in women, as recommended by Japan Society for the Study of Obesity,^{30,31} the results were essentially the same. Standardization of hs-CRP measurement may be mandatory to determine an optimal cut point of hs-CRP as a component of MetS and longitudinal studies are required to establish hs-CRP as a risk factor of diabetes and cardiovascular disease in Japanese.

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