Very Low Levels of High-sensitivity C-reactive Protein are not Bimodally Distributed but are Significantly Related to Other Metabolic Risk Factors in Japanese

Eiji Oda and Ryu Kawai

Abstract

Background High-sensitivity C-reactive protein (hs-CRP) is an independent risk factor of diabetes and cardiovascular disease and it is proposed as a component of metabolic syndrome. Blood levels of hs-CRP are reported to be much lower in Japanese than in Westerners and bimodally distributed in Japanese.

Methods Very low levels of hs-CRP were examined using medical check-up data of 1,360 Japanese men and 821 women whose plasma levels of high-sensitivity C-reactive protein (hs-CRP) were below 10 mg/L.

Results The distribution of hs-CRP levels were skewed but not bimodal in both men and women and very low levels of hs-CRP were significantly related to waist circumference, systolic blood pressure, diastolic blood pressure, fasting glucose, triglycerides, and low-density lipoprotein cholesterol in both men and women. The area under receiver operating characteristic curve of hs-CRP for diagnosing metabolic syndrome and Spearman's correlation coefficients between hs-CRP and components of metabolic syndrome were comparable to those of components of metabolic syndrome in both men and women.

Conclusion Very low levels of hs-CRP were not bimodally distributed but were significantly related to metabolic risk factors in Japanese.

Key words: metabolic syndrome, obesity, inflammation, CRP

(*Inter Med* 48: 953-958, 2009)

(DOI: 10.2169/internalmedicine.48.1890)

Introduction

High-sensitivity C-reactive protein (hs-CRP) is reported as an independent risk factor of diabetes (1) and cardiovascular disease (2) and is proposed as a component of metabolic syndrome (2). Hs-CRP levels lower than 1 mg/L, those between 1 mg/L and 3 mg/L, and those higher than 3 mg/L are considered to be a low risk, an intermediate risk, and a high risk category, respectively in Western countries (3). But, hs-CRP levels and the degree of obesity in Japanese are substantially lower than those in Westerners (4-10). Yamada et al reported that median hs-CRP was 0.16 mg/L in Japanese men and 0.09 mg/L in women and that the distribution of hs-CRP was bimodal in Japanese though the reason for this peculiar distribution was unknown (4). To clarify this peculiar distribution of hs-CRP, we examined very low lev-

els of CRP and their relation with other metabolic risk factors in Japanese.

Methods

Subjects

Between April 1 and September 30, 2008, 1,386 Japanese men and 837 women visited our medical check-up center for "Ningen Dock", one of the medical check-up programs of our center. Visitors were all required to fill out a questionnaire designed by the Ministry of Health, Labor, and Welfare for the purpose of "Special Health Examination and Instruction" including history of cardiovascular disease (stroke, ischemic heart disease, and chronic renal failure), smoking status, antihypertensive and hypoglycemic medication, and alcohol consumption. Among these persons, 7 men

and 8 women without signed consent and 19 men and 8 women with serum levels of high-sensitivity C-reactive protein (hs-CRP) higher than 10 mg/L were excluded. Therefore, the present study was performed among 1,360 male and 821 female subjects. The protocol for the present study was approved by the ethics committee in Tachikawa Medical Center and signed informed consent was obtained from each subject.

Measurements

After an overnight fast, blood samples were withdrawn to measure serum levels of routine medical check-up markers: glucose, triglycerides, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), hemoglobin A1c, uric acid, blood cell counts, electrolytes, liver and kidney function tests including gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), and hs-CRP. Chemical measurements were all performed at BML Nagaoka (Nagaoka, Niigata, 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 % was measured with bioelectrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). An average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from two measurements with the subjects in a sitting position after 5 minutes rest. Body weight was measured with the subjects wearing a lightweight hospital gown provided by our center and the weight of the hospital gown 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 kilogram divided by the square of height in meters.

Statistical analysis

Diabetes was defined as fasting glucose levels equal to or higher than 126 mg/dL or receiving hypoglycemic medication. Metabolic syndrome (MS) was defined by the revised National Cholesterol Education Program (NCEP) criteria (10) as three or more of five components in which the cut-off point of WC was modified for Japanese as 90 cm in men and 80 cm in women according to the recommendation by International Diabetes Federation (11), the cut-off points of the other components were SBP of ≥ 130 mmHg and/or DBP of ≥ 85 mmHg for blood pressure, ≥ 150 mg/dL for triglycerides, <40 mg/dL in men and <50 mg/dL in women for HDLc, and ≥ 100 mg/dL for fasting glucose. Subjects receiving antihypertensive or hypoglycemic medication were considered to have the respective component. Japanese metabolic syndrome (JMS) was defined by the Examination Committee for Criteria of Metabolic Syndrome (12). The criteria of JMS is visceral adipose tissue area ≥ 100 cm² or WC ≥ 85 in men and ≥ 90 in women, and 2 or more of the following 3 components; SBP ≥ 130 mmHg and/or DBP $\geq$

85 mmHg for blood pressure, triglycerides ≥ 150 mg/dL and/or HDLc <40 mg/dL, and fasting glucose ≥ 110 mg/dL. Distribution of hs-CRP levels was plotted by gender. Means (SD) of components of MS, hs-CRP, GGT, ALT, LDLc and uric acid were calculated by quintiles of hs-CRP. Receiver operating characteristic (ROC) curve analyses for diagnosing MS and JMS were performed to obtain area under ROC curve (AUC) of components of MS, hs-CRP, GGT, ALT, LDLc and uric acid. Spearman's correlation coefficients among components of MS, hs-CRP, GGT, ALT, LDLc and uric acid were calculated. Statistical analyses were conducted with Dr SPSS-2. *p* values of less than 0.05 were considered to be statistically significant.

Results

One thousand and three hundred sixty men aged [mean (SD)] 51.6 (9.3) years and 821 women aged 51.1 (10.1) were the subjects of the present study. Means (SD) and medians of basal laboratory data and prevalence of smoking, MS, JMS, diabetes, and cardiovascular disease are presented in Table 1. Prevalence of smoking, MS, JMS, diabetes, and cardiovascular disease were 34.3%, 13.5%, 12.1%, 4.7%, and 6.3%, respectively in men and 6.0%, 6.8%, 2.1%, 1.7%, and 3.4%, respectively in women. Figure 1 shows the distribution of hs-CRP by gender. The distribution of hs-CRP was skewed but not bimodal in both Japanese men and women, as shown in Fig. 1. Means (SD) of WC, SBP, DBP, fasting glucose, triglycerides, HDLc, hs-CRP, GGT, ALT, LDLc and uric acid were presented by quintile of hs-CRP by gender in Tables 2 and 3. WC, SBP, DBP, triglycerides, LDLc, and uric acid in quintile 2 (hs-CRP; 0.14-0.23 mg/L) were significantly higher than those in quintile 1 (hs-CRP; 0.02-0.13 mg/L), HDLc in quintile 2 was significantly lower than that in quintile 1, GGT and ALT in quintile 3 (hs-CRP; 0.24-0.37 mg/L) were significantly higher than those in quintile 1, and fasting glucose in quintile 4 (hs-CRP; 0.38-0.72) was significantly higher than that in quintile 1 among men (Table 2). WC, SBP, DBP, fasting glucose, triglycerides, and LDLc in quintile 2 (hs-CRP; 0.09-0.16 mg/L) were significantly higher than those in quintile 1 (hs-CRP; 0.01-0.08 mg/L), GGT, ALT, and uric acid in quintile 3 (hs-CRP; 0.17-0.26 mg/L) were significantly higher than those in quintile 1, and HDLc in quintile 3 was significantly lower than that in quintile 1 among women (Table 3). AUC of metabolic risk factors for diagnosing MS and JMS are presented in Table 4. The AUC (95% confidence interval) of hs-CRP for diagnosing MS and JMS were 0.74 (0.70, 0.77) and 0.72 (0.68, 0.76), respectively in men and 0.72 (0.66, 0.78) and 0.76 (0.67, 0.84), respectively in women and these values were comparable to those of components of MS and other metabolic risk factors in both men and women. Table 5 presents Spearman's correlation coefficients among WC, SBP, DBP, fasting glucose, triglycerides, HDLc, hs-CRP, GGT, ALT, LDLc, and uric acid. Correlations between hs-CRP and components of MS were comparable to those

Table 1. Basal Data

	men		women		p*
	mean (SD)	median	mean (SD)	median	
age years	51.6 (9.3)	52.0	51.1 (10.1)	51.0	0.2
body mass index kg/m ²	23.2 (2.9)	23.1	21.6 (3.0)	21.2	<0.001
body fat %	21.8 (4.9)	21.5	26.5 (5.7)	25.9	<0.001
waist circumference cm	84.0 (8.0)	83.6	78.5 (8.6)	77.6	<0.001
systolic blood pressure mmHg	121.9 (17.0)	119.5	111.7 (16.4)	108.5	<0.001
diastolic blood pressure mmHg	77.5 (10.5)	76.5	69.7 (10.1)	68.5	<0.001
fasting glucose mg/dL	95.1 (13.3)	92.0	89.2 (10.7)	87.0	<0.001
triglyceride mg/dL	119.4 (81.6)	99.0	83.3 (51.6)	72.0	<0.001
HDL cholesterol mg/dL	57.7 (14.4)	56.0	66.8 (14.4)	65.0	<0.001
gamma glutamyltransferase U/L	47.3 (42.8)	34.0	22.4 (19.6)	17.0	<0.001
alanine aminotransferase U/L	25.4 (15.3)	21.0	17.0 (9.4)	15.0	<0.001
LDL cholesterol mg/dL	120.0 (29.4)	120.0	120.9 (28.9)	119.0	0.5
uric acid mg/dL	6.2 (1.3)	6.2	4.5 (0.9)	4.4	<0.001
hemoglobin A1c %	5.1 (0.5)	5.0	5.0 (0.4)	5.0	0.02
high-sensitivity CRP mg/L	0.61 (1.03)	0.29	0.39 (0.57)	0.20	<0.001
	n	%	n	%	
antihypertensive medication	245	18.0	71	8.6	<0.001
current smoker	466	34.3	49	6.0	<0.001
MS	184	13.5	56	6.8	<0.001
JMS	165	12.1	17	2.1	<0.001
diabetes	64	4.7	14	1.7	<0.001
cardiovascular disease	86	6.3	28	3.4	0.003

HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein;

MS, metabolic syndrome defined by revised NCEP definition; JMS, Japanese metabolic syndrome defined by the Examination Committee for Criteria of Metabolic Syndrome

*2 sided t-tests for means and chi-square tests for %

Figure 1. Distribution of blood levels of high-sensitivity C-reactive protein in Japanese by gender. n: number of subjects, CRP: high-sensitivity C-reactive protein (mg/L)

Table 2. Means (SD) of Metabolic Risk Factors by Quintile of Hs-CRP in Men

hs-CRP quintiles	quintile 1		quintile 2		quintile 3		quintile 4		quintile 5
hs-CRP range mg/L	0.02-0.13		0.14-0.23		0.24-0.37		0.38-0.72		0.73-9.71
n	269		266		274		278		273
metabolic risk factors	mean (SD)	mean (SD)	p*	mean (SD)	p*	mean (SD)	p*	mean (SD)	
hs-CRP mg/L	0.09 (0.03)	0.18 (0.03)	<0.001	0.29 (0.04)	<0.001	0.52 (0.10)	<0.001	1.95 (1.71)	
age years	50.3 (9.9)	50.5 (8.6)	0.8	52.8 (9.4)	0.003	52.0 (8.8)	0.03	52.1 (9.6)	
body mass index kg/m ²	21.6 (2.3)	22.9 (2.4)	<0.001	23.0 (2.3)	<0.001	24.0 (3.0)	<0.001	24.7 (3.3)	
body fat %	18.7 (4.1)	21.1 (4.1)	<0.001	21.4 (4.2)	<0.001	23.1 (4.7)	<0.001	24.4 (5.5)	
waist circumference cm	79.1 (7.0)	82.9 (6.7)	<0.001	83.7 (6.7)	<0.001	86.1 (7.8)	<0.001	88.2 (8.8)	
systolic blood pressure mmHg	116.7 (16.0)	120.6 (16.8)	0.006	120.1 (15.7)	0.004	124.8 (16.6)	<0.001	126.6 (18.2)	
diastolic blood pressure mmHg	74.2 (10.2)	77.2 (10.4)	0.001	76.7 (9.8)	0.004	79.2 (9.8)	<0.001	79.9 (11.4)	
fasting glucose mg/dL	92.6 (11.8)	94.7 (12.9)	0.05	93.8 (11.0)	0.2	96.8 (13.3)	<0.001	97.7 (16.3)	
triglycerides mg/dL	92.6 (60.9)	106.1 (52.0)	0.006	116.7 (66.7)	<0.001	134.9 (91.7)	<0.001	145.4 (110.3)	
HDL cholesterol mg/dL	64.8 (14.5)	59.2 (14.1)	<0.001	57.7 (14.1)	<0.001	55.2 (12.9)	<0.001	51.9 (13.2)	
gamma glutamyl transferase U/L	37.2 (34.3)	42.3 (41.2)	0.1	46.7 (39.1)	0.003	51.7 (41.6)	<0.001	58.1 (52.7)	
alanine aminotransferase U/L	21.8 (12.3)	23.9 (12.9)	0.06	23.9 (10.9)	0.04	26.6 (14.6)	<0.001	30.8 (21.7)	
LDL cholesterol mg/dL	112.1 (27.1)	117.5 (30.1)	0.03	121.2 (28.3)	<0.001	122.8 (29.1)	<0.001	126.0 (30.3)	
uric acid mg/dL	5.8 (1.2)	6.0 (1.2)	0.02	6.1 (1.2)	0.007	6.4 (1.3)	<0.001	6.5 (1.4)	

* compared with quintile 1 by 2 sided t-tests

Table 3. Means (SD) of Metabolic Risk Factors by Quintile of Hs-CRP in Women

hs-CRP quintiles	quintile 1	quintile 2	quintile 3		quintile 4		quintile 5	
hs-CRP range mg/L	0.01-0.08	0.09-0.16	0.17-0.26		0.27-0.52		0.53-5.18	
n	167	167	161		162		164	
metabolic risk factors	mean (SD)	mean (SD)	p*	mean (SD)	p*	mean (SD)	p*	mean (SD)
hs-CRP mg/L	0.05 (0.02)	0.12 (0.02)	<0.001	0.21 (0.03)	<0.001	0.36 (0.07)	<0.001	1.23 (0.85)
age years	48.6 (9.1)	49.7 (10.0)	0.3	51.7 (10.2)	0.004	52.9 (10.0)	<0.001	52.6 (10.4)
body mass index kg/m ²	20.1 (2.3)	20.9 (2.4)	0.002	21.7 (2.6)	<0.001	22.3 (3.1)	<0.001	23.2 (3.7)
body fat %	23.0 (4.2)	24.8 (4.6)	<0.001	26.8 (4.8)	<0.001	28.0 (5.6)	<0.001	29.9 (6.4)
waist circumference cm	73.6 (6.7)	76.4 (7.2)	<0.001	79.5 (7.8)	<0.001	80.5 (7.9)	<0.001	82.5 (10.0)
systolic blood pressure mmHg	106.3 (13.5)	110.7 (14.9)	0.005	111.2 (14.4)	0.002	113.8 (18.4)	<0.001	116.6 (18.7)
diastolic blood pressure mmHg	66.7 (8.8)	69.9 (9.7)	0.002	68.8 (8.7)	0.03	70.6 (10.9)	<0.001	72.5 (11.2)
fasting glucose mg/dL	86.8 (8.1)	88.9 (8.7)	0.02	88.7 (9.8)	0.05	89.4 (8.7)	0.005	92.3 (15.9)
triglycerides mg/dL	65.0 (24.1)	75.1 (30.0)	<0.001	82.1 (39.2)	<0.001	94.0 (75.8)	<0.001	101.1 (62.0)
HDL cholesterol mg/dL	71.4 (15.2)	70.1 (13.5)	0.4	65.6 (13.6)	<0.001	65.9 (14.0)	<0.001	61.0 (13.4)
gamma glutamyl transferase U/L	16.7 (7.7)	18.3 (10.2)	0.1	22.3 (17.9)	<0.001	25.5 (22.4)	<0.001	29.3 (29.1)
alanine aminotransferase U/L	14.8 (5.1)	14.9 (5.3)	0.9	18.0 (10.3)	<0.001	18.3 (12.7)	0.001	19.1 (10.5)
LDL cholesterol mg/dL	111.4 (26.1)	119.3 (26.5)	0.007	118.4 (25.3)	0.01	126.7 (32.3)	<0.001	128.7 (30.5)
uric acid mg/dL	4.2 (0.8)	4.3 (0.9)	0.1	4.4 (0.9)	0.005	4.7 (1.0)	<0.001	4.9 (1.0)

* compared with quintile 1 by 2 sided t-tests

Table 4. Area Under ROC Curve (AUC) of Metabolic Risk Factors for Diagnosing MS (JMS)

	men		women	
	AUC	95% CI	AUC	95% CI
waist circumference	0.90 (0.88)	0.88, 0.92 (0.86, 0.90)	0.86 (0.97)	0.82, 0.91 (0.96, 0.99)
systolic blood pressure	0.74 (0.79)	0.70, 0.78 (0.75, 0.82)	0.79 (0.88)	0.72, 0.85 (0.80, 0.97)
diastolic blood pressure	0.72 (0.77)	0.68, 0.76 (0.73, 0.80)	0.78 (0.83)	0.71, 0.84 (0.73, 0.94)
fasting glucose	0.78 (0.72)	0.74, 0.82 (0.68, 0.77)	0.83 (0.85)	0.77, 0.89 (0.78, 0.92)
triglyceride	0.83 (0.83)	0.80, 0.87 (0.80, 0.87)	0.80 (0.81)	0.73, 0.86 (0.70, 0.92)
- HDL cholesterol	0.78 (0.76)	0.74, 0.82 (0.72, 0.79)	0.81 (0.84)	0.74, 0.87 (0.76, 0.93)
high-sensitivity CRP	0.74 (0.72)	0.70, 0.77 (0.68, 0.76)	0.72 (0.76)	0.66, 0.78 (0.67, 0.84)
gamma glutamyltransferase	0.69 (0.70)	0.66, 0.73 (0.66, 0.74)	0.74 (0.71)	0.67, 0.80 (0.59, 0.83)
alanine aminotransferase	0.71 (0.70)	0.67, 0.75 (0.66, 0.74)	0.72 (0.80)	0.65, 0.79 (0.70, 0.91)
uric acid	0.63 (0.62)	0.58, 0.67 (0.57, 0.67)	0.73 (0.71)	0.65, 0.81 (0.56, 0.86)
LDL cholesterol	0.57 (0.58)	0.52, 0.61 (0.53, 0.63)	0.67 (0.73)	0.60, 0.74 (0.62, 0.84)

ROC, receiver operating characteristic; CI, confidence interval; HDL, high-density lipoprotein;

CRP, C-reactive protein; LDL, low-density lipoprotein;

MS, metabolic syndrome defined by revised NCEP definition;

JMS, Japanese metabolic syndrome defined by the Examination Committee for Criteria of Metabolic Syndrome

Data for JMS are presented in parentheses.

among components of MS.

Discussion

For the past several decades, there was considerable effort to understand the underlying biology and to identify the risk factors of cardiovascular disease. As risk factors were identi-

fied, it became apparent that they tended to cluster in the same individual. Thus, the concept of insulin resistance syndrome (syndrome X) (13) or metabolic syndrome (14) emerged. Metabolic syndrome 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 metabolic syndrome

Table 5. Spearman's Correlation Coefficients among Metabolic Risk Factors*

	WC	SBP	DBP	FG	TG	HDLc	GGT	ALT	LDLc	UA	hs-CRP
WC		0.341	0.326	0.260	0.270	-0.266	0.288	0.264	0.297	0.239	0.365
SBP	0.327		0.908	0.300	0.238	-0.062	0.203	0.253	0.268	0.184	0.221
DBP	0.300	0.926		0.296	0.228	-0.031	0.187	0.227	0.247	0.188	0.199
FG	0.275	0.238	0.226		0.179	-0.130	0.232	0.200	0.139	0.094	0.173
TG	0.388	0.213	0.224	0.165		-0.407	0.302	0.232	0.331	0.212	0.259
HDLc	-0.394	-0.027	-0.017	-0.093	-0.507		-0.069	-0.065	-0.158	-0.071	-0.243
GGT	0.333	0.302	0.317	0.257	0.382	-0.042		0.513	0.190	0.305	0.323
ALT	0.392	0.210	0.183	0.214	0.330	-0.210	0.533		0.189	0.273	0.199
LDLc	0.218	-0.005	-0.007	0.070	0.260	-0.208	0.082	0.153		0.155	0.203
UA	0.234	0.166	0.182	0.039	0.240	-0.121	0.242	0.206	0.125		0.245
hs-CRP	0.369	0.207	0.184	0.134	0.268	-0.304	0.254	0.207	0.150	0.208	

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; TG, triglycerides;

HDLc, high-density lipoprotein cholesterol; GGT, gamma glutamyltransferase; ALT, alanine aminotransferase;

LDLc, Low-density lipoprotein cholesterol; UA, uric acid; hs-CRP, high-sensitivity C-reactive protein

* Male data are in the lower left triangle (n = 1360) and female data are in the upper right triangle (n = 821).

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 metabolic syndrome meets criteria as a syndrome (16) and there have been endless debates on pros and cons of diagnosing with this syndrome for individuals (17-20). We thought that metabolic syndrome might develop through adipose tissue disease (21) different from obesity and to be diagnosed with inflammatory, endocrine, metabolic, and histological tests. Criteria that regard obesity as an inevitable component of metabolic syndrome have a serious drawback because there is a substantial number of metabolically obese normal weight individuals (22) and only about one-third of the most insulin resistant individuals are actually obese (19). On the contrary, hs-CRP, a marker of inflammation, is an independent risk factor of cardiovascular disease and proposed as a component of metabolic syndrome (2). Studies with transgenic or diet-induced obesity animals indicate that the infiltration of activated macrophages into adipose tissue and accompanied inflammation, but not increased adipose tissue mass, increased adipocyte size, or increased visceral adipose tissue mass *per se*, are crucial for the metabolic consequences of obesity including insulin resistance (21). Thus, we prefer the concept of adipose tissue disease or adipopathy to the concept of obesity or adiposity (21).

We already reported that an optimal cut-off point of hs-CRP as a component of MS may be 0.45 mg/L in men and 0.25 mg/L in women among Japanese (23). In the present study, we examined very low levels (0.02-0.72 mg/L in men and 0.01-0.52 mg/L in women) of hs-CRP among Japanese. The distribution of hs-CRP levels were skewed but not bimodal in both men and women contrary to the previously reported data (4) and very low levels of hs-CRP were significantly related with WC, SBP, DBP, fasting glucose, triglycerides, HDLc, GGT, ALT, LDLc, and uric acid in both men and women. The AUC of hs-CRP for diagnosing metabolic syndrome was comparable to those of components of MS and Spearman's correlation coefficients between hs-CRP and components of MS were comparable to those among components of MS in both men and women.

Yamada et al reported that the distribution of hs-CRP was bimodal in Japanese though the reason for this peculiar distribution was unknown (4). Later, they reported that the distribution pattern of hs-CRP was different between the baseline data and the data after five years and median hs-CRP values were lower by 43% after five years than the baseline values in contrast to the changes in other risk factors (24). Therefore, it is possible that some measurement error might be involved in their data. There are substantial differences in median or geometric mean levels of hs-CRP among different studies (4-10) in Japanese and the differences mainly seem to result from different measuring methods because age and BMI among these study subjects were similar. Standardization of hs-CRP measuring methods may be mandatory to evaluate hs-CRP quantitatively among Japanese. As for gender differences in hs-CRP, Saltevo et al reported that the levels of hs-CRP were significantly higher in women with metabolic syndrome than in men with metabolic syndrome and, in subjects without metabolic syndrome, no gender differences in the levels of hs-CRP were found (25). Lakoski et al reported that women had substantially higher median hs-CRP levels compared with men (26). However, in Japanese, hs-CRP levels among women without metabolic syndrome were lower than those levels among men but, in subjects with metabolic syndrome, the gender difference in the levels of CRP might be obscured (5, 6). Thus, clustering of metabolic risk factors and weight gain may have stronger effects on hs-CRP in women than in men (5). Sekikawa et al reported that Japanese men had less subclinical atherosclerosis compared with the White counterparts, though the Japanese had a less favorable profile regarding many risk factors (27). However, in their study, BMI, WC, CRP, fibrinogen, and insulin were significantly lower and HDLc was significantly higher in Japanese men than in White men. Thus, the degree of obesity-related metabolic risk clustering through adipose tissue disease (21) may be substantially lower in Japanese than in White. Though hs-CRP levels are very low in Japanese compared with the standard in Western societies (3) where obesity prevails, women with hs-CRP values equal to or higher than 0.5 mg/L had a higher risk for cardiovascular disease than women with hs-CRP values lower

than 0.5 mg/L even in the United States (28). Hs-CRP may reflect adipose tissue disease and relate to the clustering of metabolic risk factors even through very low levels as shown in the present study among Japanese.

Limitations

The present study was a cross-sectional study and the subjects were not a general population but visitors to our medical check-up center which is in a central city of a rural region in Japan. These conditions may influence the low serum levels of hs-CRP and the low prevalence of metabolic syndrome in our subjects. However, both the levels of hs-

CRP in general populations and the prevalence of obesity are very low in Japan. Therefore, the present data may not represent a quite peculiar population in Japan and the conclusions may be relevant in other regions and populations in Japan.

Acknowledgement

We thank Dr. Shinzo Tachikawa, Dr. Shinpei Yoshii, and Dr. Masaaki Okabe at Tachikawa Medical Center for their effort to construct study environments and their review of the manuscript. Authors have no conflict of interest to declare.

References

- Doi Y, Kiyohara Y, Kubo M, et al. Elevated C-reactive protein is a predictor of diabetes in a general Japanese population: the Hisayama study. *Diabetes Care* **28**: 2497-2500, 2005.
- Ridker PM, Wilson PWF, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation* **109**: 2818-2825, 2004.
- Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* **107**: 499-511, 2003.
- Yamada S, Gotoh T, Nakashima Y, et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. *Am J Epidemiol* **153**: 1183-1190, 2001.
- Nakanishi N, Shiraishi T, Wada M. C-reactive protein concentration is more strongly related to metabolic syndrome in women than in men: the Minoh study. *Circ J* **69**: 386-391, 2005.
- Oda E, Oohara K, Abe A, et al. The optimal cut-off point of C-reactive protein as an optional component of metabolic syndrome in Japan. *Circ J* **70**: 384-388, 2006.
- Saito I, Yonemasu K, Imai F. Association of body mass index, body fat and weight gain with inflammation markers among rural residents in Japan. *Circ J* **67**: 323-329, 2003.
- Nasermoaddeli A, Sekine M, Kagamimori S. Intra-individual variability of high-sensitivity C-reactive protein. Age-related variation over time in Japanese subjects. *Circ J* **70**: 559-563, 2006.
- Matsushita K, Yatsuya H, Tamakoshi K, et al. High-sensitivity C-reactive protein is quite low in Japanese men at high coronary risk. *Circ J* **71**: 820-825, 2007.
- Grundy SM, Cleeman JJ, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* **112**: 2735-2752, 2005 (Erratum in: *Circulation* **112**: e297-e298, 2005).
- Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* **23**: 469-480, 2006.
- The Examination Committee for Criteria of Metabolic Syndrome. Definition and criteria of metabolic syndrome. *J Jpn Soc Intern Med* **94**: 794-809, 2005 (in Japanese).
- Reaven GM. Role of insulin resistance in human disease. *Diabetes* **37**: 1595-1607, 1988.
- World Health Organization. Definition, diagnosis, and classification of diabetes mellitus and its complications: report of a WHO Consultation. World Health Org, Geneva, 1999.
- Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* **111**: 1448-1454, 2005.
- Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **28**: 2289-2304, 2005.
- Grundy SM. Does the metabolic syndrome exist? *Diabetes Care* **29**: 1689-1692, 2006.
- Kahn R. The metabolic syndrome (emperor) wears no clothes. *Diabetes Care* **29**: 1693-1696, 2006.
- Reaven GM. The metabolic syndrome: is this diagnosis necessary? *Am J Clin Nutr* **83**: 1237-1247, 2006.
- Sattar N. Why metabolic syndrome criteria have not made prime time: a view from the clinic. *Int J Obes* **32** (S2): S30-S34, 2008.
- Oda E. The metabolic syndrome as a concept of adipose tissue disease. *Hypertens Res* **31**: 1285-1293, 2008.
- Ruderman NB, Schneider SH, Berchtold P. The “metabolically-obese,” normal-weight individual. *Am J Clin Nutr* **34**: 1617-1621, 1981.
- Oda E, Kawai R. Tentative cut point of high-sensitivity C-reactive protein for a component of metabolic syndrome in Japanese. *Circ J* **73**: 755-759, 2009.
- Kayaba K, Ishikawa S, Gotoh T, Nago N, Kajii E, Nakamura Y. Five-year intra-individual variability in C-reactive protein in a Japanese population-based study. The Jichi Medical School Cohort Study at Yamato, 1993-1998. *Jpn Circ J* **64**: 303-308, 2000.
- Saltevo J, Vanhala M, Kautiainen H, Kumpusalo E, Laakso M. Gender differences in C-reactive protein, interleukin-1 receptor antagonist and adiponectin levels in the metabolic syndrome: a population-based study. *Diabet Med* **25**: 747-750, 2008.
- Lakoski SG, Cushman M, Criqui M, et al. Gender and C-reactive protein: Data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *Am Heart J* **152**: 593-598, 2006.
- Sekikawa A, Ueshima H, Kadowaki T, et al. Less subclinical atherosclerosis in Japanese men in Japan than in White men in the United States in the post-World War II birth cohort. *Am J Epidemiol* **165**: 617-624, 2007.
- Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham risk scores. *Circulation* **109**: 1955-1959, 2004.