Comparison between High-Sensitivity C-Reactive Protein (hs-CRP) and White Blood Cell Count (WBC) as an Inflammatory Component of Metabolic Syndrome in Japanese

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Abstract

Objective To compare two systemic inflammatory markers, high-sensitivity C-reactive protein (hs-CRP) and white blood cell count (WBC), as a component of metabolic syndrome (MetS).

Methods Data of hs-CRP and WBC from 2,185 Japanese men and 1,383 Japanese women were examined using receiver operating characteristic (ROC) curve for diagnosing MetS and Spearman's correlation coefficients.

Results The area under ROC curve (AUC) of hs-CRP was 0.71 in men and 0.74 in women. The AUC of WBC was 0.65 in men and 0.69 in women. The optimal cutoff point (sensitivity; specificity) of hs-CRP was 0.40 mg/L (0.69; 0.65) in men and 0.35 mg/L (0.67; 0.72) in women. The optimal cutoff point (sensitivity; specificity) of WBC was 5,600/L⁶ (0.61; 0.61) in men and 5,000/L⁶ (0.65; 0.63) in women. Correlations between obesity parameters, blood pressure, and liver function tests were stronger with hs-CRP than with WBC. But, no correlation between MetS-related risk factors was stronger with WBC than with hs-CRP.

Conclusion Hs-CRP is superior to WBC as an inflammatory component of MetS in Japanese. However, WBC may be useful when hs-CRP is not available because WBC is routinely measured in clinical practice.

Key words: metabolic syndrome, high-sensitivity CRP, white blood cell count, inflammation

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Introduction

Insulin resistance syndrome (syndrome X) (1) or metabolic syndrome (MetS) (2) is a constellation of interrelated metabolic risk factors that appear to directly promote the development of diabetes and cardiovascular disease. Recent studies indicate that MetS is associated with not only diabetes and cardiovascular disease but also fatty liver disease (3), chronic kidney disease (CKD) (4), atrial fibrillation (5), obstructive sleep apnea (6), and restrictive lung disease (7). The predominant underlying mechanisms of MetS appear to be insulin resistance (1), leptin resistance (8), abdominal obesity (9), autonomic dysfunction (8), endothelial dysfunction (10), and inflammation (11, 12). Inflammation may be a core mechanism of both MetS (11-13) and atherosclerotic

cardiovascular disease (14). High-sensitivity C-reactive protein (hs-CRP), a marker of low-grade systemic inflammation, is reported as an independent risk factor of diabetes (15) and cardiovascular disease (16). In Western countries, hs-CRP levels lower than 1 mg/L, between 1 mg/L and 3 mg/L, and higher than 3 mg/L are considered as low risk, intermediate risk, and high risk categories, respectively (17). But, hs-CRP levels in Japanese are substantially lower than those in Westerners. Previously, we reported 0.45 mg/L in men and 0.25 mg/L in women as a tentative cutoff point of hs-CRP as a component of MetS among Japanese (18). White blood cell count (WBC) is also a routinely measured marker of systemic inflammation and, recently, reported to be a risk factor of cardiovascular mortality in Japanese from NIPPON DATA 90 (19).

Methods

Subjects

Between April 1 2008 and March 31 2009, 2,541 men and 1,502 women visited our medical check-up center for general health screening. Visitors were all required to fill out a questionnaire including questions about history of stroke and coronary heart disease, smoking and drinking status, and antihypertensive, hypoglycemic, and antihyperlipidemic medications. Among these persons 25 men and 20 women without signed consent, 18 men and 17 women lacking some laboratory data, and 33 men and 12 women with hs-CRP levels of higher than 10 mg/L were excluded from the subjects resulting in 2,449 men and 1,448 women. Then, 104 men and 23 women with a history of coronary heart disease, 35 men and 16 women with a history of stroke, and 125 men and 26 women with diabetes were further excluded resulting in 2,185 men and 1,383 women. The protocol for the present study was approved by the ethics committee at Tachikawa Medical Center and signed informed consent was obtained from each subject.

Measurements

After an overnight fast, blood samples were obtained to measure blood levels of routine medical check-up tests: glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, hemoglobin A1c, uric acid, blood cell counts, electrolytes, liver and kidney function tests, and hs-CRP. Simple qualitative urinalyses were performed with test papers. Chemical measurements were all performed at BML Nagaoka (Nagaoka, Japan) with routine laboratory methods 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. LDL cholesterol was measured with a direct surfactant method using Choletest-LDL (Sekisui Medical Inc, Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated as $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ in men, and $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ in women according to the recommendation from the Japanese Society of Nephrology. Body fat percentage was measured with bio-electrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). An average systolic blood pressure (SBP) and diastolic blood pressure (DBP) was calculated from two measurements with the subjects in a sitting position after a 5 minutes rest period. Heart rate was automatically recorded with electrocardiography. Body weight was measured with the subjects wearing lightweight clothes provided by our center and the weight of the clothing was subtracted from the measured body weight. Waist circumference 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.

Definitions

We adopted the revised National Cholesterol Education Program (NCEP) definition (20) for MetS because the Japanese definition of MetS (21) which includes obesity as an inevitable component was already revealed to be inappropriate by recent large longitudinal epidemiological studies (22-25). The revised NCEP criteria of MetS (20) was defined as three or more of five components where the cutoff point of waist circumference was modified for Japanese as ≥ 90 cm in men and ≥ 80 cm in women according to the recommendation by International Diabetes Federation (IDF) (9). The cutoff points of other components were SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg for blood pressure, ≥ 150 mg/dL for triglycerides, < 40 mg/dL in men and < 50 mg/dL in women for HDL cholesterol, and ≥ 100 mg/dL for fasting glucose. Subjects receiving antihypertensive or hypoglycemic medication were considered to have the respective component. Diabetes was defined as fasting glucose ≥ 126 mg/dL and/or hypoglycemic medication. Chronic kidney disease (CKD) was defined as eGFR < 60 mL/min/1.73 m² and/or proteinuria.

Statistical analysis

Medians of hs-CRP and means of WBC in each category defined by the number of MetS components were calculated. Receiver operating characteristic (ROC) curve analysis for diagnosing MetS was performed to obtain area under ROC curve (AUC) and optimal cutoff points of hs-CRP and WBC for diagnosing MetS. Hs-CRP was transformed to logarithm because it was skewed. An optimal cutoff point was defined as a point on a ROC curve nearest to the point where both sensitivity and specificity were one. Spearman's correlation coefficients were calculated between hs-CRP and MetS-related risk factors and between WBC and MetS-related risk factors, and these calculations were repeated excluding current smokers. Statistical analyses were performed using Dr SPSS-2 (SPSS Japan Inc., Tokyo, Japan). Means were compared with two-sided t-tests, ratios were compared with chi-square tests, and correlation coefficients were compared with Fisher's z-transformations. P values of lower than 0.05 were considered to be statistically significant.

Results

Basal data are shown in Table 1. The frequency of MetS was 12.4% in men and 7.6% in women and the frequency of CKD was 7.7% in men and 7.5% in women. Medians of hs-CRP and means of WBC in each category defined by the number of MetS components are presented in Table 2. The median of hs-CRP in 0, 1, 2, 3, and 4 or 5 MetS component category was 0.22 mg/L, 0.29 mg/L, 0.41 mg/L, 0.53 mg/L, and 0.62 mg/L, respectively in men and 0.15 mg/L, 0.27 mg/L, 0.30 mg/L, 0.50 mg/L, and 0.75 mg/L, respectively in

Table 1. Basal Data

	men	women	
n	n = 2185	n = 1383	p
age (years)	51.2 ± 9.4	51.2 ± 9.7	ns
BMI (kg/m ²)	23.0 ± 2.9	21.7 ± 3.0	<0.0001
body fat percentage (%)	22.1 ± 5.0	26.6 ± 5.9	<0.0001
waist circumference (cm)	83.8 ± 8.0	78.9 ± 8.5	<0.0001
SBP (mmHg)	121.5 ± 17.3	112.1 ± 17.0	<0.0001
DBP (mmHg)	77.2 ± 10.7	70.1 ± 10.3	<0.0001
fasting glucose (mg/dL)	93.4 ± 8.8	88.8 ± 8.3	<0.0001
triglycerides (mg/dL)	120.6 ± 74.3 (101)	83.1 ± 47.3 (71)	<0.0001
HDL cholesterol (mg/dL)	58.0 ± 14.5	67.3 ± 14.6	<0.0001
hs-CRP (mg/L)	0.60 ± 0.95 (0.30)	0.46 ± 0.78 (0.22)	<0.0001
GGT (U/L)	51.3 ± 53.8 (35)	23.5 ± 20.4 (17)	<0.0001
ALT (U/L)	26.6 ± 18.8 (22)	18.0 ± 13.6 (15)	<0.0001
WBC (/L ⁻⁶)	5536 ± 1470	4864 ± 1281	<0.0001
uric acid (mg/dL)	6.1 ± 1.3	4.4 ± 1.0	<0.0001
LDL cholesterol (mg/dL)	121.5 ± 29.7	120.7 ± 29.6	ns
hemoglobin A1c (%)	5.0 ± 0.3	5.0 ± 0.3	ns
MetS	12.4	6.9	<0.0001
chronic kidney disease	7.7	7.5	ns
antihypertensives	14.8	8.7	<0.0001
antihyperlipidemics	6.7	9.3	<0.01
current smokers	34.4	7.8	<0.0001
everyday drinkers	51.3	15.5	<0.0001

Values are presented as mean ± SD or %. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, GGT: gamma glutamyltransferase, ALT: alanine aminotransferase, WBC: white blood cell count, LDL: low-density lipoprotein, MetS: metabolic syndrome.

Table 2. Hs-CRP and WBC by the Number of MetS Components

MetS components	men			women		
	n	hs-CRP (mg/L)	WBC (/L ⁻⁶)	n	hs-CRP (mg/L)	WBC (/L ⁻⁶)
0	833	0.22 (0.12, 0.41)	5232 ± 1367	612	0.15 (0.07, 0.27)	4670 ± 1272
1	673	0.29 (0.16, 0.54)	5454 ± 1468	464	0.27 (0.15, 0.51)	4864 ± 1209
2	409	0.41 (0.24, 0.75)	5864 ± 1478	202	0.30 (0.16, 0.62)	5077 ± 1358
3	195	0.53 (0.30, 1.18)	6063 ± 1431	83	0.50 (0.25, 0.83)	5416 ± 1163
4 or 5	75	0.62 (0.44, 1.27)	6497 ± 1561	22	0.75 (0.54, 1.60)	6205 ± 1066

Values are presented as median (25 percentile, 75 percentile) or mean ± SD. Abbreviations are the same as Table 1.

women. The means of WBC in 0, 1, 2, 3, and 4 or 5 MetS component category was 5,232/L⁻⁶, 5,454/L⁻⁶, 5,864/L⁻⁶, 6,063/L⁻⁶, and 6,497/L⁻⁶, respectively in men and 4,670/L⁻⁶, 4,864/L⁻⁶, 5,077/L⁻⁶, 5,416/L⁻⁶, and 6,205/L⁻⁶, respectively in women. ROC curves of hs-CRP and WBC for diagnosing MetS are shown in Fig. 1. AUC of hs-CRP and WBC for diagnosing MetS and optimal cutoff points of hs-CRP and WBC as a component of MetS are presented in Table 3. The AUC and its 95% confidence interval (CI) of hs-CRP were 0.71 and 0.68-0.75 in men and 0.74 and 0.70-0.79 in women. The AUC and its 95% CI of WBC were 0.65 and 0.62-0.69 in men and 0.69 and 0.64-0.74 in women. The optimal cutoff point (sensitivity; specificity) of hs-CRP was 0.40 mg/L (0.69 ; 0.65) in men and 0.35 mg/L (0.67 ; 0.72) in women. The optimal cutoff point (sensitivity; specificity)

of WBC was 5,600/L⁻⁶ (0.61 ; 0.61) in men and 5,000/L⁻⁶ (0.65 ; 0.63) in women. Spearman's correlation coefficients between hs-CRP or WBC and MetS-related risk factors are shown in Table 4. The Spearman's correlation coefficients between BMI, body fat %, waist circumference, SBP, DBP, GGT, and uric acid were significantly stronger with hs-CRP than with WBC in men and those between BMI, body fat %, waist circumference, DBP, GGT, ALT, LDL cholesterol, uric acid, and hemoglobin A1c were significantly stronger with hs-CRP than with WBC in women. There was no significantly stronger correlation between WBC and other MS-related risk factors than those between hs-CRP and other MS-related risk factors. Table 5 shows similar correlation coefficients in subjects excluding current smokers. The correlation coefficients were essentially the same except for the

Figure 1. Receiver operating characteristic curves of high-sensitivity C-reactive protein (CRP) and white blood cell count (WBC) for diagnosing metabolic syndrome.

Table 3. AUC and Optimal Cut Points of Hs-CRP and WBC for Diagnosing Metabolic Syndrome

		AUC	95% CI of AUC		optimal cutoff point	sensitivity	specificity
men	hs-CRP	0.71	0.68	0.75	0.40 mg/L	0.69	0.65
	WBC	0.65	0.62	0.69	5600 /L ⁻⁶	0.61	0.61
women	hs-CRP	0.74	0.70	0.79	0.35 mg/L	0.67	0.72
	WBC	0.69	0.64	0.74	5000 /L ⁻⁶	0.65	0.63

AUC: area under receiver operating characteristic curve, CI: confidence interval. Other abbreviations are the same as Table 1.

Table 4. Spearman's Correlation Coefficients of Hs-CRP and WBC with Other Metabolic Risk Factors

n	men 2185		women 1383	
	hs-CRP	WBC	hs-CRP	WBC
BMI	0.376	0.223 [#]	0.357	0.184 [#]
body fat %	0.343	0.191 ^{**}	0.358	0.199 [*]
waist circumference	0.344	0.223 [#]	0.331	0.138 ^{#,†}
systolic blood pressure	0.201	0.091 ^{***}	0.216	0.162 [†]
diastolic blood pressure	0.174	0.081 ^{**}	0.206	0.118 [*]
fasting glucose	0.118	0.071	0.163	0.091
triglycerides	0.293	0.302	0.281	0.211 ^{††}
HDL cholesterol	-0.308	-0.284	-0.255	-0.192 ^{††}
GGT	0.252	0.170 ^{**}	0.314 [†]	0.121 [#]
ALT	0.214	0.158	0.213	0.033 ^{#,†††}
LDL cholesterol	0.143	0.139	0.186	0.032 ^{#,††}
uric acid	0.215	0.126 ^{**}	0.274	0.159 ^{**}
hemoglobin A1c	0.175	0.125	0.200	0.063 ^{***}

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, # $p < 0.0001$ compared with hs-CRP. † $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ compared with men. Abbreviations are the same as Table 1.

slightly stronger correlations between WBC and obesity indices or blood pressures in men compared with Table 4.

Discussion

In the past several decades, there has been considerable effort to understand the underlying biology and to identify the risk factors of cardiovascular diseases. 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) (1) or MetS (2) emerged.

However, in 2005, the American Diabetes Association and the European Association for the Study of Diabetes jointly stated that no existing definition of MetS meets criteria as a syndrome (26) and there have been endless debates on the pros and cons of diagnosing this syndrome for individuals (27-30). Criteria that regard obesity as an inevitable component of MetS have a serious pit hole because there are a substantial number of metabolically obese normal weight individuals (31) and only about one third of the most insulin resistant individuals are actually obese (29). An essential drawback of Japanese MetS (visceral fat syn-

Table 5. Spearman's Correlation Coefficients of Hs-CRP and WBC with Other Metabolic Risk Factors Excluding Current Smokers

n	men 1434		women 1275	
	CRP	WBC	CRP	WBC
BMI	0.372	0.265**	0.352	0.168 ^{#,††}
body fat %	0.389	0.269***	0.400	0.195 ^{#,†}
waist circumference	0.372	0.255***	0.378	0.167 ^{#,†}
systolic blood pressure	0.208	0.151	0.223	0.152
diastolic blood pressure	0.188	0.141	0.207	0.105**
fasting glucose	0.104	0.091	0.159	0.067*
triglycerides	0.264	0.307	0.276	0.199 ^{*,††}
HDL cholesterol	-0.277	-0.257	-0.260	-0.173 ^{*,†}
GGT	0.260	0.170 [†]	0.307	0.094 ^{#,†}
ALT	0.239	0.191	0.202	0.020 ^{#,‡}
LDL cholesterol	0.151	0.146	0.185	0.031 ^{#,††}
uric acid	0.214	0.153	0.259	0.147**
hemoglobin A1c	0.160	0.132	0.203	0.064***

* p < 0.05, ** p < 0.01, *** p < 0.001, [#] p < 0.0001 compared with hs-CRP. [†] p < 0.05, ^{††} p < 0.01, ^{†††} p < 0.001,

[‡] p < 0.0001 compared with men. Abbreviations are the same as Table 1.

drome) (21) is that it regards subcutaneous adipose tissue as a protective factor against the morbid effect of visceral adipose tissue (VAT) and ignores the risk contribution of abdominal subcutaneous adipose tissue (SAT). In 2007, comparing correlations of VAT volume and SAT volume with metabolic risk factors, inflammatory markers, markers of oxidative stress, and markers of endothelial dysfunction in Framingham Heart Study, it was clearly shown that the risk contribution of SAT cannot be ignored (32, 33). Furthermore, standardized odds ratios of VAT area, SAT area, BMI, and waist circumference for coronary calcification detected by electron beam CT, which is considered as an early manifestation of coronary artery disease, are 1.9, 2.0, 2.2, and 1.9, respectively in men and 1.8, 1.9, 1.9, and 2.0, respectively in women (34). Thus, VAT area is not superior to SAT area, BMI, or waist circumference as a risk factor of coronary artery disease though the superiority of VAT area as a risk factor of coronary artery disease is the original reason of the proposition of visceral fat syndrome (35). As for insulin resistance, Reaven reviewed world literature comparing VAT area and SAT area regarding insulin resistance and concluded that the correlations of VAT area and SAT area with insulin sensitivity are not statistically different (29). Koutsari and Jensen showed that free fatty acid (FFA) released by VAT contributes only a small percentage of systemic FFA delivery and upper-body SAT is the dominant contributor to circulating FFAs, and that SAT could be more important than VAT as a cause of peripheral insulin resistance (36). A detailed criticism against visceral fat syndrome was discussed in a review (12). Japanese MetS or IDF MetS where obesity is an inevitable component of MetS was already revealed to be inferior to revised NCEP MetS as a predictor of cardiovascular disease in Japanese (24, 25). Therefore, in the present study, revised NCEP criteria where

obesity is not an inevitable component was adopted as the definition of MetS.

Inflammation is a link between obesity and insulin resistance (13) and is thought to be a fundamental mechanism of MetS (11, 12). Hs-CRP is an independent risk factor of diabetes (15) and cardiovascular disease (16) and it is proposed as a component of MetS (16). Previously, we studied the cutoff point of hs-CRP as a component of MetS with a small-sized data (179 men and 166 women) and with a relatively rough hs-CRP measurement method (the measurement limit was 0.1 mg/L) and reported 0.65 mg/L as an optimal cutoff point of hs-CRP in Japanese for both men and women (37). Later, we restudied with data from 1,062 men and 647 women and with a more sensitive hs-CRP measurement method (the measurement limit was 0.02 mg/L) and reported 0.45 mg/L in men and 0.25 mg/L in women as a cutoff point of hs-CRP for a component of MetS in Japanese (18). Nagasawa et al studied the association between WBC and MetS in Japanese men, not in women, using BMI instead of waist circumference (38) and Ishizaka et al also studied the association between WBC and Japanese MetS defined by the Examination Committee for Criteria of Metabolic Syndrome (21) in Japanese men, not in women (39). Tamakoshi et al reported that elevated WBC was nearly significantly associated with a high risk of cardiovascular disease mortality in Japanese (19).

In the present study, we compared hs-CRP and WBC as an inflammatory component of MetS. The AUC of hs-CRP was 0.71 in men and 0.74 in women. The AUC of WBC was 0.65 in men and 0.69 in women. The optimal cutoff point (sensitivity; specificity) of hs-CRP was 0.40 mg/L (0.69 ; 0.65) in men and 0.35 mg/L (0.67 ; 0.72) in women. The optimal cutoff point (sensitivity; specificity) of WBC was 5,600/L⁻⁶ (0.61 ; 0.61) in men and 5,000/L⁻⁶ (0.65 ;

0.63) in women. Correlations between obesity parameters, blood pressure, and liver function tests were stronger with hs-CRP than with WBC. But, no correlation between MetS-related risk factors was stronger with WBC than with hs-CRP. Therefore, hs-CRP was thought to be superior to WBC as an inflammatory component of MetS in Japanese.

In the present study, the optimal cutoff point of hs-CRP was 0.40 mg/L (0.69 ; 0.65) in men and 0.35 mg/L (0.67 ; 0.72) in women. We excluded subjects with diabetes or with a history of stroke or coronary heart disease in the present study. In contrast, these subjects were included in previous studies (18, 37). Thus, 0.40 mg/L in men and 0.35 mg/L in women may be better than 0.45 mg/L in men and 0.25 mg/L in women (18) as a cutoff point of hs-CRP for a MetS component in Japanese. The median hs-CRP in subjects with no MetS component was 0.22 mg/L in men and 0.15 mg/L in women but the median hs-CRP in subjects with 4 or 5 MetS components was 0.62 mg/L in men and 0.75 mg/L in women. Saltevo et al reported that blood levels of hs-CRP 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-CRP (40). Lakoski et al reported that women have substantially higher median hs-CRP levels compared with men (41). However, in Japanese, hs-CRP levels in women without MetS are lower than the levels in men, but in subjects with MetS, the gender difference in the level of CRP may be obscured. Thus, clustering of MetS components exerts a stronger influence on hs-CRP in women than in men as already reported by Nakanishi et al (42). The reason for this gender difference is unknown, but the association of LDL cholesterol with MetS is also stronger in Japanese women than in men (43). These stronger associations between MetS and other cardiovascular risk factors may cause a greater risk of cardiovascular mortality associated with MetS in women than in men (44). These cutoff points of hs-CRP are very low compared with the standard in Western societies where obesity prevails (17). However, we reported that very low levels of hs-CRP are significantly related with other metabolic risk factors in Japanese (45). Doi et al reported that men with hs-CRP of 0.29-0.77 mg/L have an age-adjusted odds ratio (95% confidence interval) for incident diabetes of 2.67 (1.28-5.56) compared with men with hs-CRP of 0.05-0.28 mg/L and that women with hs-CRP of 0.25-0.57 mg/L have an age-adjusted odds ratio (95% confidence interval) for incident diabetes of 2.12 (0.98-4.58) compared with women with hs-CRP of 0.05-0.24 mg/L in Japanese (15). Women with hs-CRP values ≥ 0.5 mg/L had a higher risk for cardiovascular disease than women with hs-CRP values < 0.5 mg/L even in the United States (46) where hs-CRP values are very high compared with those in Japan.

Tamakoshi et al studied WBC as a predictor of cardiovascular mortality with data from NIPPON DATA 90 and reported that subjects with WBC of 9,000-10,000/L⁻⁶ had a relative risk of 1.79 (95% confidence interval; 0.97-3.71) compared with subjects with WBC of 4,000-4,900/L⁻⁶ (19).

They excluded subjects with WBC lower than 4,000/L⁻⁶ regarding them as in a pathological state of leucopenia both in men and in women. In the present study, 11 % of men and 26 % of women had WBC of lower than 4,000/L⁻⁶. Therefore, it might be possible that the cardiovascular mortality risk of WBC became higher if subjects with WBC lower than 4,000/L⁻⁶ were included in the reference groups. Margolis et al reported that, compared with women in the first quartile of WBC (2,500-4,700/L⁻⁶), women in the fourth quartile (6,700- 5,000/L⁻⁶) had over a 2-fold elevated risk for CHD death (hazard ratio, 2.36; 95% confidence interval, 1.51-3.68) after multivariable adjustment for age, race, diabetes, hypertension, smoking, hypercholesterolemia, BMI, alcohol intake, diet, physical activity, aspirin use, and hormone use; women in the upper quartile of the WBC also had a 40% higher risk for nonfatal myocardial infarction, a 46% higher risk for stroke, and a 50% higher risk for total mortality (47). Further, in multivariable models adjusting for hs-CRP, the WBC was an independent predictor of cardiovascular disease and they concluded that WBC, a stable, well-standardized, widely available and inexpensive measure of systemic inflammation, is an independent predictor of cardiovascular disease events and all-cause mortality in postmenopausal women (47). Thus, WBC may be a useful marker of cardiovascular disease risk.

As for the gender differences in the correlations between hs-CRP or WBC and other metabolic risk factors, the higher frequency of current smokers in men might have some effects on the differences because cigarette smoking increases WBC (48) and triglycerides (49) but decreases HDL cholesterol (49) and blood pressure (50). However, the correlation coefficients after the exclusion of current smokers were essentially the same as before the exclusion except for the slightly stronger correlations between WBC and obesity indices or blood pressures in men after exclusion. Thus, there may be other unknown causes for the gender differences in the correlations between hs-CRP or WBC and other metabolic risk factors.

Conclusions and limitations

Hs-CRP may be superior to WBC as an inflammatory component of MetS in Japanese. However, WBC may be useful as an alternative inflammatory component of MetS when hs-CRP is not available because WBC is routinely measured as a systemic marker of inflammation in clinical practice. The present study was a cross-sectional study and the subjects were not a general population but visitors to a medical check-up center which is in a central city of a rural region in Japan. Longitudinal studies are required to establish hs-CRP and WBC as risk factors of cardiovascular disease in Japanese.

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