Considerable Disagreement Among Definitions of Metabolic Syndrome for Japanese

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Background The purpose of the present study is to examine the agreement of various existing definitions of metabolic syndrome for Japanese.

Methods and Results One hundred thirty-two apparently healthy men and 147 apparently healthy women underwent testing and diagnosis for metabolic syndrome using 5 different definitions of metabolic syndrome for Japanese, including a newly proposed definition: a modified National Cholesterol Education Program definition replacing abdominal obesity with C-reactive protein. The agreement of these various definitions of metabolic syndrome was studied using an agreement index defined as the number of subjects who met both definitions divided by the number of subjects who met either of the 2 definitions. Agreement indices among these various definitions of metabolic syndrome for Japanese were between 0.19 and 0.6 in men and between 0.31 and 0.89 in women. The average agreement index was 0.41 in men and 0.51 in women, and the overall agreement index was 0.15 in men and 0.21 in women.

Conclusions There was considerable disagreement among various definitions of metabolic syndrome for Japanese. Therefore, diagnosis with this syndrome should not be made until a truly consensual definition of metabolic syndrome can be established. (Circ J 2007; 71: 1239–1243)

Key Words: Diagnosis; Inflammation; Metabolic syndrome; Obesity; Risk factors

Since the proposal of syndrome X by Reaven, metabolic syndrome or insulin resistance syndrome has been highlighted as a clustering of risk factors for diabetes and cardiovascular disease.^{1–3} There are many definitions of metabolic syndrome and the International Diabetes Federation (IDF) recently proposed a new worldwide definition of metabolic syndrome, which was criticized as the most dangerous definition by Reaven.^{4,5} The American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) jointly stated that the National Cholesterol Education Program (NCEP) definition is superior to IDF definition, and the American Diabetes Association and the European Association for the Study of Diabetes (ADA/EASD) jointly stated that no existing definition of metabolic syndrome meets criteria as a syndrome and that one should not label people with it.^{6,7} Meanwhile, obesity has been considered as an endocrine and inflammatory disorder intimately related to insulin resistance rather than merely an anthropometric disfiguration and high-sensitivity C-reactive protein (CRP) was established as an independent risk factor for both diabetes and cardiovascular disease.^{8–10} Therefore, a new criteria was proposed to replace ethnic and gender-specific controversial cut points of waist circumference (WC) by CRP as a component of metabolic syndrome.^{11–13} In the present study, we tried to diagnose apparently normal subjects with metabolic syndrome using

various definitions of metabolic syndrome for Japanese, including the newly proposed definition, and studied the agreement among these various definitions of metabolic syndrome for Japanese.

Methods

One hundred thirty-six apparently healthy men and 148 apparently healthy women who visited our hospital for a routine medical check-up between May 2006 and December 2006, and gave us written informed consent, were the subjects of the present study. Four men and 1 woman were excluded from the study because their CRP values were higher than 20 mg/L. WC was measured according to NCEP

Table 1 Basal Data

	Male (n=132)	Female (n=147)
Age (years)	55.3±9.5	56.4±8.5
BMI (kg/m ²)	23.8±2.9	22.7±3.2
WC (cm)	83.2±8.7	79.5±10.1
Systolic BP (mm/Hg)	124.2±14.9	122.0±16.3
Diastolic BP (mm/Hg)	76.0±9.0	73.3±9.6
FBG (mg/dl)	103.8±18.7	98.1±16.0
TG (mg/dl)	145.8±104.0 (114.5)	93.4±46.2 (85.0)
HDL-C (mg/dl)	60.3±16.1	73.5±18.2
CRP (mg/L)	0.77±1.01 (0.5)	0.68±0.94 (0.4)

Data are n, means±SD, (median).

BMI, body mass index; WC, waist circumference; BP, blood pressure; FBG, fasting blood glucose; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; CRP, C-reactive protein.

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Table 2 Various Definitions of Metabolic Syndrome for Japanese

Criteria	Definition
IDF	WC $\geq$ 90 cm in men and 80 cm in women and 2 or more of following 4 components: BP $\geq$ 130/85 mmHg, TG $\geq$ 150 mg/dl, HDL-C $\geq$ 40 mg/dl in men and 50 cm in women, FBG $\geq$ 100 mg/dl
Japanese	WC $\geq$ 85 cm in men and 90 cm in women and 2 or more of following 3 components: BP $\geq$ 130/85 mmHg, TG $\geq$ 150 mg/dl or HDL-C $\geq$ 40 mg/dl, FBG $\geq$ 110 mg/dl
NCEP	Three or more of following 5 components: WC $\geq$ 90 cm in men and 80 cm in women, BP $\geq$ 130/85 mmHg, TG $\geq$ 150 mg/dl, HDL-C $\geq$ 40 mg/dl in men and 50 cm in women, FBG $\geq$ 100 mg/dl
Hisayama	WC $\geq$ 90 cm in men and 80 cm in women and 2 or more of following 3 components: BP $\geq$ 130/85 mmHg, TG $\geq$ 150 mg/dl or HDL-C $\geq$ 40 mg/dl, FBG $\geq$ 110 mg/dl
CRP	Three or more of following 5 components: CRP $\geq$ 0.65 mg/L, BP $\geq$ 130/85 mmHg, TG $\geq$ 150 mg/dl, HDL-C $\geq$ 40 mg/dl in men and 50 cm in women, FBG $\geq$ 100 mg/dl

The IDF method was defined by IDF criteria;⁴ Japanese method was defined by the Japanese Committee criteria;¹³ the NCEP method was defined by the revised NCEP criteria⁶ using Asian cut-off points of WC;⁴ the Hisayama method was a modified Japanese criteria replacing IDF WC cut-off points;¹⁴ CRP method was a modified NCEP criteria replacing WC with CRP.

IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program. Other Abbreviations see in Table 1.

Table 3 Prevalence of Metabolic Syndrome According to Method Used

	Male	Female
IDF (%)	11.4	11.6
Japanese (%)	14.4	4.8
NCEP (%)	18.9	12.9
Hisayama (%)	6.1	6.8
CRP (%)	22.7	6.8
One or more (%)	29.6	12.9
All (%)	4.5	2.7

IDF was defined by the IDF criteria;⁴ Japanese was defined by the Japanese Committee criteria;¹⁴ NCEP was diagnosed with the revised NCEP criteria⁶ using Asian cut points of WC;⁴ Hisayama was the modified Japanese criteria replacing IDF WC cut-off points;¹⁵ CRP was the modified NCEP criteria replacing WC with CRP, with the cut-off point of 0.65 mg/L.⁶ One or more were subjects who met 1 or more of the above 5 criteria, and All were subjects who met all the above 5 criteria.

Abbreviations see in Tables 1,2.

method and blood pressure (BP) was defined as an average of 2 measurements in sitting position⁶ After an overnight fast, blood samples were withdrawn to measure serum levels of glucose, triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C) and CRP. CRP was measured using CRP-Latex X2 (Denka Seiken, Tokyo, Japan) and values lower than the measurement limit (0.1 mg/L) were considered to be 0.05 mg/L. Metabolic syndrome was defined according to 5 different definitions:

- IDF definition—that is, a combination of WC $\geq$ 90 cm in men and $\geq$ 80 cm in women and 2 or more of the following 4 components: systolic BP $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg; TG $\geq$ 150 mg/dl; HDL-C $\geq$ 40 mg/dl in men and $\geq$ 50 mg/dl in women; fasting blood glucose (FBG) $\geq$ 100 mg/dl⁴
- Japanese committee definition—that is, a combination of WC $\geq$ 85 cm in men and $\geq$ 90 cm in women, and 2 or more of the following 3 components: systolic BP $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg; TG $\geq$ 150 mg/dl and/or HDL-C $\geq$ 40 mg/dl; FBG $\geq$ 110 mg/dl¹⁴
- Revised NCEP definition—that is, a combination of 3 or more of the following 5 components: WC $\geq$ 90 cm in men and $\geq$ 80 cm in women; systolic BP $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg; TG $\geq$ 150 mg/dl; HDL-C $\geq$ 40 mg/dl in men and $\geq$ 50 mg/dl in women; FBG $\geq$ 100 mg/dl^{4,6}
- The modified Japanese definition proposed by Kiyohara et al, in which cut points of WC were replaced as 90 cm

Table 4 Agreement Indices Between 2 Definitions of Metabolic Syndrome

	IDF	Japanese	NCEP	Hisayama	CRP
IDF		0.41	0.89	0.59	0.4
Japanese	0.31		0.37	0.6	0.31
NCEP	0.6	0.52		0.53	0.53
Hisayama	0.53	0.42	0.32		0.43
CRP	0.23	0.4	0.53	0.19	

Agreement index=(the number of persons who met both of the 2 definitions)/(the number of persons who met either of the 2 definitions). The IDF method was defined by IDF criteria;⁴ Japanese method was defined by the Japanese Committee criteria;¹³ the NCEP method was defined by the revised NCEP criteria⁶ using Asian cut-off points of WC;⁴ the Hisayama method was a modified Japanese criteria replacing IDF WC cut-off points;¹⁴ CRP method was a modified NCEP criteria replacing waist circumference with CRP. Abbreviations see in Table 1,2.

in men and 80 cm in women.¹⁵

- Then WC in the revised NCEP definition was replaced by CRP and 0.65 mg/L was used as the cut-off point of CRP.⁶

The agreement index was defined as the number of subjects diagnosed with metabolic syndrome according to both definitions divided by the number of subjects diagnosed with metabolic syndrome according to either of the 2 definitions, and the overall agreement index was defined as the number of subjects who met all these 5 definitions divided by the number of subjects who met 1 or more of these 5 definitions. The study was approved by the ethics committee of our hospital.

Results

Basal data were presented in Table 1 and various definitions of metabolic syndrome for Japanese were summarized in Table 2. The prevalence of metabolic syndrome was shown in Table 3. Among 132 apparently healthy men and 147 apparently healthy women, 11.4% men and 11.6% women were diagnosed with metabolic syndrome according to the IDF criteria using Asian cut-off points for abdominal obesity;⁴ 14.4% men and 4.8% women were diagnosed with metabolic syndrome according to the Japanese committee criteria;¹³ 18.9% men and 12.9% women were diagnosed with metabolic syndrome according to the revised NCEP criteria using Asian cut-off points for abdominal obesity;⁶

6.1% men and 6.8% women were diagnosed with metabolic syndrome according to the modified Japanese criteria recommended by Kiyohara et al;¹⁵ and 22.7% men 6.8% women were diagnosed as metabolic syndrome replacing WC by CRP in the revised NCEP criteria, using the CRP cut-off point of 0.65 mg/L.^{11–13,16} Only 4.5% men and 2.7% women met all the above 5 criteria. Agreement indices among these various definitions of metabolic syndrome for Japanese were between 0.19 and 0.6 in men and between 0.31 and 0.89 in women as presented in Table 4. The average agreement index calculated from Table 4 was 0.41 in men and 0.51 in women, and the overall agreement index calculated from Table 3 was 0.15 in men and 0.21 in women.

Discussion

Since the proposal of syndrome X by Reaven, metabolic syndrome has been highlighted as a clustering of risk factors for diabetes and cardiovascular disease in the modern civilized world with its excess food and a sedentary lifestyle.^{1,2} There are many definitions of metabolic syndrome and the IDF recently proposed a new worldwide definition of metabolic syndrome, criticized as the most dangerous definition by Reaven, which made abdominal obesity the essential component of metabolic syndrome.^{4,5} The Japanese definition of metabolic syndrome also made abdominal obesity the essential component of metabolic syndrome, though the definition of abdominal obesity was quite different from IDF definition.¹⁴ The AHA/NHLBI jointly stated that the NCEP definition is superior to the IDF definition and the ADA/EASD jointly stated that no existing definition of metabolic syndrome meets criteria as a syndrome and that people should not be labeled with this syndrome.^{6,7} Reaven endorsed this ADA/EASD statement and stated that it is possible to create an almost infinite number of scenarios in which persons who do not meet the diagnostic criteria for metabolic syndrome would be at greater risk of cardiovascular disease than would those who do.⁵ Meanwhile, high-sensitivity CRP has been established as an independent risk factor for both diabetes and cardiovascular disease.^{9,10} Festa et al suggested CRP as part of insulin resistance syndrome, and the IDF and AHA/NHLBI listed CRP as an optional component of metabolic syndrome.^{4,6,17} A role for inflammation has been well established in every step of the atherosclerotic disease process and as part of the insulin resistance syndrome over the past decades, and CRP is recommended as the most suitable inflammatory marker in clinical and public health practice.^{17,18} In a previous study, we determined 0.65 mg/L as the optimal cut-off point for CRP as a component of metabolic syndrome for Japanese.¹⁶ Saijo et al reported that adjusted geometric mean concentrations of CRP in men with 0, 1, 2, 3 or more components of metabolic syndrome were 0.36, 0.49, 0.59 and 0.76 mg/L, respectively (p for trend <0.001), and adjusted geometric mean concentrations of CRP in women with 0, 1, 2, 3 or more components of metabolic syndrome were 0.23, 0.3, 0.57 and 0.77 mg/L, respectively (p for trend <0.001) among Japanese.¹⁹ Nakanishi et al also reported that adjusted geometric mean concentrations of CRP in men with 0, 1, 2, 3, 4 or more components of metabolic syndrome were 0.36, 0.47, 0.62, 0.68 and 0.82 mg/L, respectively (p for trend <0.001) and adjusted geometric mean concentrations of CRP in women with 0, 1, 2, 3, 4 or more components of metabolic syndrome were 0.28, 0.31, 0.49, 0.75 and 0.9 mg/L,

Table 5 Controversial Cut Points of WC for Abdominal Obesity

Ethnic group	Male	Female
European (IDF)	94 cm	80 cm
European (NCEP)	102 cm	88 cm
Asian (IDF)	90 cm	80 cm
Korean (KSSO)	90 cm	85 cm
Japanese (IDF)	90 cm	80 cm
Japanese (Hisayama)	90 cm	80 cm
Japanese (JASSO)	85 cm	90 cm
Japanese (Tokyo)	85 cm	78 cm
Japanese (Washington)	90 cm	84 cm

Parentheses indicate organizations or groups by which these cut points are recommended.

KSSO, Korean Society for the Study of Obesity³⁶; Hisayama, Hisayama Study Group¹⁵; JASSO, Japanese Society for the Study of Obesity²⁶; Tokyo, Tokyo University Group³⁷; Washington, Washington University Group³³. Other abbreviations see in Tables 1,3.

respectively (p for trend <0.001) among Japanese.²⁰ Although one laboratory reported exceptionally low levels of CRP among a general Japanese population, their measurement method was unique and their median CRP levels were 43% lower at the 5-year follow-up measurement than those of baseline and the distribution of CRP levels were different between the baseline and follow-up.^{21–23} Therefore, a CRP cut-off point of 0.65 mg/L may be suitable as a component of metabolic syndrome for Japanese. The CRP levels are considered to be <1.0 mg/L as low risk, 1.0 to 3.0 mg/L as intermediate risk and >3.0 mg/L as high risk factors for cardiovascular disease in Western society.²⁴ The very low cut-off point for CRP for Japanese may be related to the low prevalence of obesity and cardiovascular disease in Japan, and may in part result from the low fat, high fiber Japanese diet rich in fish and processed seaweed and vegetables.²⁵ The criteria for the clinical diagnosis of metabolic syndrome are still controversial and 1 reason of the controversy may be ethnic- and gender-specific controversial cut-off points for WC, as shown in Table 5. At first, the IDF adopted the cut-off points for Japanese reported by the Japanese Society for the Study of Obesity (JASSO) in their table of ethnic-specific WC cut-off points.^{26,27} However, they changed their attitude and recommended a cut-off point of 90 cm in men and 80 cm in women for Japanese.^{4,28,29} There may be substantial differences in values of WC according to the level of the body used for measuring WC adopted for the different definitions. Kiyohara et al reported that metabolic syndrome was not a significant risk factor for cardiovascular disease among Japanese men when abdominal obesity was defined as WC ≥ 85 cm, according to the JASSO criteria, but was a significant risk factor among Japanese men when abdominal obesity was defined as WC ≥ 90 cm, as recently recommended for Japanese men by IDF.^{4,15,26} While metabolic syndrome was a significant risk factor for cardiovascular disease among Japanese women when abdominal obesity was defined as a WC of either ≥ 90 cm (relative risk=2.0) according to the JASSO criteria or ≥ 80 cm (relative risk=2.4) as recommended for Japanese women by IDF, the sensitivity of metabolic syndrome for detecting future cardiovascular events is greater when abdominal obesity was defined as a WC ≥ 80 cm—that is, among 260 subjects who were diagnosed with metabolic syndrome when abdominal obesity was defined as a WC ≥ 80 cm, 147 subjects (57%) were excluded from metabolic syndrome and classified as low-risk subjects when abdomi-

nal obesity was defined as WC ≥ 90 cm.^{4,15,26} Responding to the Letter by 1 of the authors of the present study, Sone et al reported that metabolic syndrome was not a significant risk factor for cardiovascular disease when abdominal obesity was defined as WC ≥ 90 cm, according to JASSO criteria, but was a significant risk factor for cardiovascular disease when abdominal obesity was defined as a WC ≥ 80 cm according to IDF recommendation among Japanese diabetic women.^{26,30,31} Recently Hayashi et al criticized the inconsistent method of analysis used by JASSO, as we previously criticized and reported that the optimal cut-off point of visceral fat area was 96 cm² for men and 75 cm² for women and the optimal cut-off point of WC was 90 cm for men and 84 cm for women among Japanese.^{30,32,33} Meanwhile, obesity has been considered as an endocrine and inflammatory disorder intimately related to insulin resistance rather than merely an anthropometric disfiguration, and only about one-third of the most insulin-resistant individuals are actually obese.^{5,8} In contrast, CRP is significantly positively correlates with plasma leptin levels and significantly negatively relates with plasma adiponectin levels, even in people with a normal body mass index (BMI).^{34,35} Therefore, it was proposed to replace WC with CRP as a component of metabolic syndrome, not for diagnosing individual persons as metabolic syndrome at present, but for the study of this syndrome and recommended WC, BMI, WC to height ratios or other anthropometric markers of obesity as convenient tools for screening of more proximal risk factors for diabetes and cardiovascular disease.^{11–13} However, whether this new definition is useful for the prediction of risks for diabetes and cardiovascular disease or not should be evaluated using longitudinal epidemiological studies. In the present study, we examined the agreement of various definitions of metabolic syndrome for Japanese, and agreement indices among these various definitions of metabolic syndrome for Japanese were between 0.19 and 0.6 in men and between 0.31 and 0.89 in women. The agreement index between IDF definition and the Japanese committee definition, which was intended to coordinate with IDF definition, was 0.31 in men and 0.41 in women. The average agreement index was 0.41 in men and 0.51 in women, and the overall agreement index was 0.15 in men and 0.21 in women, revealing that there were considerable disagreements among various definitions of metabolic syndrome for Japanese. We may only diagnose people with metabolic syndrome tentatively, using 1 of various existing definitions of metabolic syndrome, only if there is no considerable disagreement among various definitions of metabolic syndrome. The diagnostic criteria of metabolic syndrome should be decided only by following up the incidence and mortality of cardiovascular events using prospective studies, such as population-based cohort studies. Therefore, we should not clinically label people with metabolic syndrome, as the ADA and EASD jointly stated, until a truly consensual definition of metabolic syndrome for Japanese is established.⁷

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