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Generation and Gender Differences in the Components Contributing to the Diagnosis of the Metabolic Syndrome According to the Japanese Criteria

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Background To clarify whether there are age and gender differences in the components contributing to the diagnosis of metabolic syndrome (MS) in the Japanese population.

Methods and Results A total of 21,870 individuals (ie, 7,329 men aged 68±8.1 years, body mass index (BMI) 23.2±2.9 kg/m^2 and 14,541 women aged 66±9.4 years, BMI 22.8±3.3 kg/m^2) participated in the study. The subjects were obtained from the general population and examinations were conducted in hospitals located in Kanazawa city. MS was diagnosed according to the Japanese criteria. Information regarding medication is lacking in all participating subjects. Overall, the incidence of MS was 18.4% and 5.78% for men and women, respectively. When analyzed according to age group, the incidence of MS in men did not differ significantly, whereas its prevalence was higher in older women than in younger women. Among the indicators of MS, high blood pressure (BP; high systolic BP and/or high diastolic BP) was the most frequent, followed by dyslipidemia (high triglycerides and/or low high-density lipoprotein-cholesterol (HDL-C)), and high fasting plasma glucose was the least frequently occurring in both genders. In contrast to the high frequency of high BP, isolated high diastolic BP was rare across both genders regardless of age group. Similarly, isolated low HDL-C was quite rare.

Conclusions Frequency of the components contributing to the diagnosis of MS differed considerably according to gender and age group in the Japanese population. (*Circ J* 2007; **71:** 1734–1737)

Key Words: Atherosclerosis, Carotid artery; Coronary artery; Triglycerides; Visceral fat

There is accumulating evidence that metabolic syndrome (MS) is highly related to the incidence of type 2 diabetes mellitus and cardiovascular disease![1–5] Insulin resistance or visceral fat accumulation is considered to be an important factor causing MS![6–9] However, the genetic background of subjects with MS appears to be quite heterogeneous. The frequency of MS in the general population has been reported in several populations using several types of modified criteria for the diagnosis of MS![10–16] To our knowledge, there have been few reports on age and gender differences among the components, which include high systolic blood pressure (SBP) and/or high diastolic blood pressure (DBP), high triglycerides (TG), low high-density lipoprotein-cholesterol (HDL-C) and high fasting plasma glucose (FPG), contributing to the diagnosis of MS.

Recently, it has been reported that among 8,144 Japanese subjects who underwent a routine medical checkup, 1,251 individuals were diagnosed with MS according to NCEP-ATPIII, with high blood pressure (BP) being the most common component of MS![14] In 2005, the published Japanese criteria for MS was defined as visceral obesity plus at least 2 of the following metabolic disorders: hyperglycemia (FPG ≥110 mg/dl), high blood pressure (SBP ≥130 and/or DBP ≥85 mmHg), dyslipidemia (high TG (TG ≥1.7 mmol/L) and/or low HDL-C (HDL-C <1.0 mmol/L))![17–19] The overall frequency of MS in the general Japanese population is estimated to be 12.1% in men and 1.7% in women, according to this criteria![13] As mentioned above, each component of MS does not appear to contribute equally to the diagnosis

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Table 1 Clinical Profile of All Study Subjects

	Men (n=7,329)	*Women (n=14,541)*
Age (years)	*68.1±8.1*	*66.1±9.37*
BMI (kg/m^2)	*23.2±2.9*	*22.8±3.29*
Waist circumference (cm)	*82.7±9.6*	*84.5±8.2*
SBP (mmHg)	*131±16.9*	*129±17.4*
DBP (mmHg)	*78.3±10.6*	*76.0±10.3*
FPG (mmo/L)	*5.63±1.44*	*5.21±1.06*
HbA1c (%)	*5.7±0.9*	*5.5±0.7*
TC (mmo/L)	*5.06±0.85*	*5.51±0.83*
HDL-C (mmo/L)	*1.48±0.40*	*1.74±0.42*
TG (mmo/L)	*1.16 (0.85, 1.67)*	*1.04 (0.78, 1.41)*
LDL-C (mmo/L)	*2.94±0.79*	*3.22±0.78*
UA (mmo/L)	*0.35±0.08*	*0.28±0.07*
Creatinine (mmo/L)	*0.07±0.03*	*0.05±0.01*

Values are shown as the mean±SD except for TG, which are shown as the median (1st, 3rd quartile). The survey was conducted from May 1, 2005 through to October 31, 2005.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; Hb, hemoglobin; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; UA, uric acid.

Table 2 Clinical Profile of the Subjects With or Without MS

	MS		*Non-MS*	
	Men (n=1,348)	*Women (n=840)*	*Men (n=5,981)*	*Women (n=13,701)*
Age (years)	68.0±7.92	69.5±8.60**	68.1±8.2	65.9±9.4
BMI (kg/m²)	25.4±2.36**	27.1±3.17**	22.7±2.7	22.5±3.1
Waist circumference (cm)	91.8±5.41**	96.6±5.77**	82.9±7.8	80.9±9.7
SBP (mmHg)	141±13.9**	142±13.2**	129±16.7	128±17.2
DBP (mmHg)	83.2±10.0**	81.9±9.66**	77±10.4	75.6±10.2
FPG (mmo/L)	6.52±1.87**	6.30±1.63**	5.39±1.23	5.12±0.98
HbA1c (%)	6.14±1.16**	6.13±1.07**	5.6±0.8	5.5±0.7
TC (mmo/L)	5.22±0.93**	5.64±0.88**	5.02±0.82	5.5±0.82
HDL-C (mmo/L)	1.27±0.32**	1.46±0.34**	1.53±0.4	1.75±0.41
TG (mmo/L)	1.90 (1.44, 2.44)**	1.84 (1.31, 2.26)**	1.07 (0.8, 1.44)	1.02 (0.77, 1.37)
LDL-C (mmo/L)	2.99±0.85*	3.30±0.82*	2.92±0.78	3.22±0.78
UA (mmo/L)	0.37±0.08**	0.32±0.08**	0.35±0.08	0.28±0.06
Creatinine (mmo/L)	0.07±0.02	0.06±0.02**	0.07±0.02	0.05±0.01

*$p<0.01$, **$p<0.001$ vs non-MS for the same gender.
Values are shown as the mean±SD except for TG, which are shown as the median (1st, 3rd quartile). The survey was conducted from May 1, 2005 through to October 31, 2005.
MS, metabolic syndrome. Other abbreviations see Table 1.

of MS, with high BP being the most common component. It is also unclear how clinical profiles of metabolic parameters differ among each age group and gender in MS subjects.

With all this in mind, in the present study we clarified how the contribution of each component to the diagnosis of MS, according to the Japanese criteria, differed in each gender and age group by analyzing the cross-sectional data from the general population of Kanazawa city, Japan, who underwent a regular medical checkup.

Methods

A total of 21,870 people (7,329 men and 14,541 women) residing in Kanazawa city, Japan, who had an annual health examination from May 1, 2005 through to October 31, 2005, were involved in the study (Table 1). The participating subjects came from the general population and the examinations were conducted in hospitals located in Kanazawa city.

Study subjects were categorized into 5 groups according to age (years); namely, those in their 40s (In 40s: only age 40 and 45 were involved in the study), 50s, 60s, 70s, and 80 and older. When categorized further according to age group and gender, the number of men in those 5 groups were, respectively, 126; 815; 3,360; 2,442; and 586, respectively, and the number of women were 528; 2,844; 6,175; 3,884; and 1,110, respectively. MS was diagnosed based on the following Japanese criteria:[17–19] (1) waist circumference ≥85 cm for men or ≥90 cm for women; and (2) at least 2 of the following 3 components: TG ≥1.7 mmol/L and/or HDL-C <1.0 mmol/L, FPG ≥6.1 mmol/L and SBP ≥130 mmHg and/or DBP ≥85 mmHg.

Subjects fasted overnight before their blood samples were collected. Anthropometric parameters such as BP, body height and weight, and waist circumference were also measured on the same day. Total cholesterol and TG concentrations were measured enzymatically, as were HDL-C and low-density lipoprotein-cholesterol concentrations. Concentrations of FPG were determined using the glucose oxidase–oxygen electrode method. Hemoglobin A1c, excluding unstable fractions, was determined by high-pressure liquid chromatography. Informed consent was obtained from all subjects included in the study. Information regarding medication is lacking for all study subjects.

Statistical Analysis

Values are shown as the mean±SD unless otherwise noted. As serum TG did not distribute normally, data are expressed as the median (1st quartile, 3rd quartile). The frequency distribution of MS and central obesity was compared using the standard chi-squared test. Unpaired Student's t-test was conducted to compare parameters between MS and non-MS subjects. The TG values were logarithmically transformed before statistical analysis. Stat View 5.0 was used for statistical calculation. Probability values <0.05 were considered to be statistically significant.

Results

Overall Frequency of MS in the General Population and Values of Metabolic Parameters Between MS and Non-MS

The overall numbers of subjects with MS were 1,348 (18.4%) and 840 (5.8%) in men and women, respectively, in the studied general population (Table 2). Then, we compared metabolic parameters between MS and non-MS subjects for each gender. Almost all of the parameters, including serum uric acid (UA) levels, differed significantly between MS and non-MS for both genders with the exception that age and serum creatinine did not differ between MS and non-MS in men (Table 2).

Categorized further according to each age group and gender, the frequencies of MS were almost plateau across the various age groups in men, whereas frequencies of MS were higher in older women than in younger women (Fig 1). A similar tendency was observed for individuals with central obesity (waist circumference ≥85 cm for men and ≥90 cm for women) (Fig 2).

Contribution of Each Component to the Diagnosis of MS

We investigated how the metabolic components contributing to the diagnosis of MS differed among each age group for each gender. Across the genders and age groups, high BP was the most frequent contributor to the diagnosis of MS, followed by dyslipidemia, with high FPG being the least frequent contributor (Table 3). In contrast to this finding, isolated high DBP contributed very little to the diagnosis of MS. Similar findings were applied to isolated low HDL-C as a contributor to MS in both genders across the

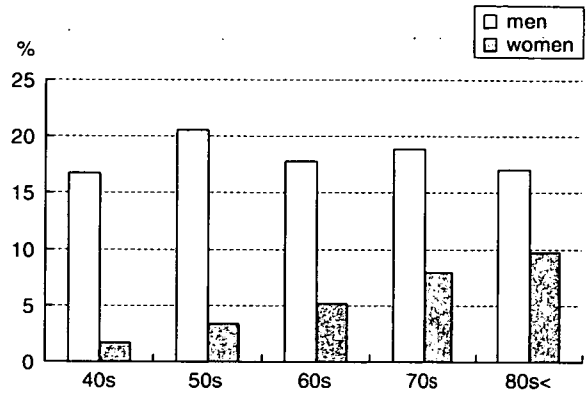

Fig 1. Prevalence of metabolic syndrome by age group in the studied population for each gender. The number of studied subjects was 7,329 men and 14,541 women. The survey was conducted from May 1, 2005 through to October 31, 2005. Age is shown as the median (1st, 3rd quartile). For men, p-values were not statistically significant. For women, p<0.0001 using the standard chi-square test. Men, age 68 (63–75); women, age 66 (60–72).

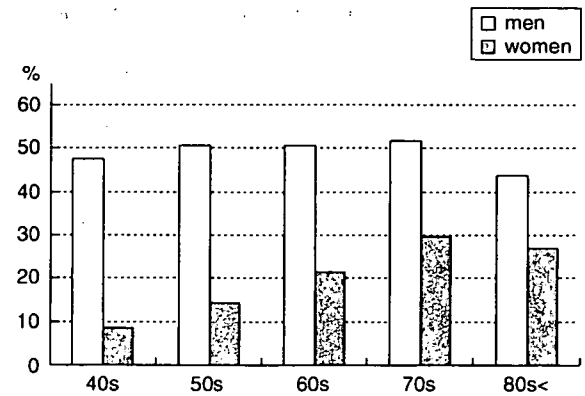

Fig 2. Prevalence of central obesity (waist circumference ≥85 cm in men; ≥90 cm in women) by age group in the studied population for each gender. The number of studied subjects was 7,329 men and 14,541 women. Age is shown as the median (1st, 3rd quartile). The survey was conducted from May 1, 2005 through to October 31, 2005. For men, p-values were not statistically significant. For women, p<0.0001 using the standard chi-square test. Men, age 68 (63–75); women, age 66 (60–72).

Table 3 Combinations of the Components for the Diagnosis of MS by Age Group

Combination	*40&45 years*	*Ratio*	*50s*	*Ratio*	*60s*	*Ratio*	*70s*	*Ratio*	*>80s*	*Ratio*	*Whole*	*Ratio*	*p value*
Men (n=1,348)													
No. by age group		*21*		*167*		*598*		*462*		*100*		*1,348*	
Dyslipidemia contributing to MS	*21*	*100%*	*142*	*85%*	*442*	*74%*	*351*	*76%*	*64*	*64%*	*1,020*	*76%*	*<0.0001*
Isolated high TG	*17*	*81%*	*107*	*64%*	*312*	*52%*	*223*	*48%*	*30*	*30%*	*689*	*51%*	*<0.0001*
Isolated low HDL-C	*2*	*10%*	*7*	*4%*	*45*	*8%*	*45*	*10%*	*20*	*20%*	*119*	*9%*	*0.001*
High BP contributing to MS	*21*	*100%*	*155*	*93%*	*561*	*94%*	*420*	*91%*	*94*	*94%*	*1,251*	*93%*	*<0.05*
Isolated high SBP	*8*	*38%*	*50*	*30%*	*266*	*44%*	*282*	*61%*	*76*	*76%*	*682*	*51%*	*<0.0001*
Isolated high DBP	*1*	*4.8%*	*18*	*11%*	*14*	*2.3%*	*7*	*1.5%*	*1*	*1.0%*	*41*	*3.0%*	*<0.0001*
High FPG contributing to MS	*4*	*19%*	*70*	*42%*	*324*	*54%*	*248*	*54%*	*63*	*63%*	*709*	*53%*	*<0.001*
Women (n=840)													
No. by age group	*9*		*96*		*322*		*305*		*108*		*840*		
Dyslipidemia contributing to MS	*7*	*78%*	*68*	*71%*	*219*	*68%*	*198*	*65%*	*79*	*73%*	*571*	*68%*	*NS*
Isolated high TG	*6*	*67%*	*63*	*66%*	*198*	*61%*	*173*	*57%*	*64*	*59%*	*504*	*60%*	*NS*
Isolated low HDL-C	*1*	*11%*	*3*	*3.1%*	*3*	*0.9%*	*12*	*3.9%*	*10*	*9.3%*	*29*	*3.5%*	*<0.001*
High BP contributing to MS	*8*	*89%*	*92*	*96%*	*307*	*95%*	*300*	*98%*	*96*	*89%*	*803*	*96%*	*<0.01*
Isolated high SBP	*2*	*22%*	*41*	*43%*	*168*	*52%*	*210*	*69%*	*71*	*66%*	*492*	*59%*	*<0.0001*
Isolated high DBP	*1*	*11%*	*7*	*7.3%*	*10*	*3.1%*	*7*	*2.3%*	*1*	*0.9%*	*26*	*3.1%*	*<0.05*
High FPG contributing to MS	*5*	*56%*	*48*	*50%*	*166*	*52%*	*154*	*50%*	*56*	*52%*	*429*	*51%*	*NS*

High TG, TG ≥1.7 mmol/L; low HDL, HDL-C <1.0 mmol/L; BP, blood pressure; high SBP, SBP ≥130 mmHg; high DBP, DBP ≥85 mmHg; high FPG, FPG ≥6.1 mmol/L. Other abbreviations see in Tables 1,2.

The frequency distribution of MS components between each gender was compared using the standard chi-square test.

various age groups. For men with MS, dyslipidemia was a greater contributing factor to MS in younger men than in older men; the opposite was true for high FPG. In women with MS, the contribution of dyslipidemia or high FPG to the diagnosis of MS did not differ with age.

Discussion

In the present study, we clarified the age and gender differences in the components contributing to the diagnosis of MS, according to the Japanese criteria, in the general Japanese population. We also analyzed the differences in clinical parameters in MS among each age group.

The main findings of the present study are: (1) The overall frequency of MS in the general population is 7,329 (18.4%) in men and 14,541 (5.8%) in women; (2) among the components of MS, high BP is the most frequent, followed by dyslipidemia, with high FPG being the least frequent, and isolated high DBP or low HDL-C being rare across the various age groups and genders.

The frequency of MS in men (18.4%) and women (5.8%) found in the present study is higher in that found in the study by Arai et al[13] This could be partly because the average age of subjects is much older in the present study than in their study. Indeed, in their study, most of the women satisfying the criteria were 50 years old or older. We compared several metabolic parameters between MS and non-MS subjects in each gender separately and found that serum UA levels, which is not a component in the criteria for MS, were significantly higher in MS than in non-MS subjects, in both men and women. Indeed, several studies suggest that UA is likely to be associated with insulin resis-

tance or risk factors of MS[20–22]

Overall, the contributions of each component, such as dyslipidemia, high FPG and high BP, to the diagnosis of MS differ substantially. Our present finding that high BP was the most frequent component to the diagnosis of MS is consistent with a previous report on individuals who underwent regular medical checkups in Tokyo district, Japan[14] although the average age of that study's subjects is younger compared with the present study.

In contrast to the high frequency of high BP contributing to the diagnosis of MS, that of isolated high DBP is quite low. This suggests that physicians need to pay attention to the prevention of high BP, especially from the viewpoint of high SBP. Whether or not the low prevalence of isolated high DBP is a favorable thing remains to be clarified. There is still some controversy about how to deal with high DBP[23] It has been shown that in individuals with coronary heart disease, low DBP may be related to the development of atherosclerosis. Hence, some might argue that the low frequency of isolated high DBP is not a necessarily favorable thing.

The contribution of high FPG or dyslipidemia did not differ across age groups in women with MS. However, in men with MS, the contribution of high FPG to the diagnosis of MS was higher, and that of dyslipidemia was lower, in older men than in younger men. This finding suggests that in middle-aged men, more attention needs to be paid to the development of dyslipidemia, whereas in older men, the development of high FPG should be paid attention to. Overall, frequencies of isolated low HDL-C were found to be very low in both genders and across all age groups.

One of the limitations of the present study is that we do not have medication information among the study subjects for diabetes mellitus, hypertension or hyperlipidemia, which might affect some data to some degree. As a considerable number of subjects involved in the present study may take medications for treatment of these metabolic disorders, we presumably have underestimated the prevalence of MS in this population. On the other hand, the study's extremely large sample size is a strength and helps to confirm our findings.

In conclusion, the present data obtained from 21,870 Japanese individuals (7,329 men and 14,541 women), who underwent a routine medical checkup, indicates that physicians and other medical staff need to pay attention to age group and gender differences in the components contributing to the diagnosis of MS to properly prevent this metabolic disorder.

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Invited critical review

Serum lipoprotein lipase mass: Clinical significance of its measurement

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Abstract

Lipoprotein lipase (LPL) is a lipolytic enzyme involved in catalyzing hydrolysis of triglycerides (TG) in chylomicrons and very low-density lipoprotein (VLDL) particles. Over the last decade, increasing attention has been paid to the clinical significance of measuring serum LPL protein mass without heparin injection to the study subjects. In earlier studies, this marker was utilized to classify LPL deficient subjects, which is an extremely rare metabolic disorder with a frequency of one in one million. Later, researchers paid more attention to the clinical significance of measuring this parameter in more common metabolic disorders. Studies have shown that pre-heparin plasma or serum LPL mass has significant relationships with serum lipids and lipoproteins, visceral fat area, insulin resistance, and even the development of coronary atherosclerosis in cross-sectional studies, although this might be a metabolic surrogate marker with almost no catalytic activities, which does not appear to be involved in catalyzing hydrolysis of TG in TG-rich lipoproteins. Recently, a prospective study has demonstrated that low serum LPL concentration predicts future coronary events.

Taken together, we suggest that pre-heparin LPL mass in plasma or sera provide us with useful and important information on the development of metabolic disorders leading to atherosclerotic disease.

Keywords: Atherosclerosis; Triglycerides; Visceral fat; Carotid artery; Coronary artery

Contents

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1. Introduction

Lipoprotein lipase (LPL) plays a central role in lipoprotein metabolism by catalyzing hydrolysis of triglycerides (TG) in chylomicrons and very low-density lipoprotein (VLDL) particles [1–3]. Since a decade ago, it has been noted that besides its function of catalytic enzyme, LPL functions as a mediator facilitating binding and/or incorporation of series of lipoproteins through either lipoprotein receptors or heparan sulfate proteoglycans [4–8] into several lines of cells. LPL is synthesized and secreted in adipocytes, muscle cells, cardiomyocytes and macrophages [3], which is transferred to heparansulfate on the luminal surface of the endothelial cells in vessels through unknown mechanism [9–11].

In clinical studies, post-heparin plasma (PHP) is usually used as a material for the measurement of LPL mass and activity. From the last decade, however, several groups of researchers [12–19] have shown the clinical significance of measuring LPL protein mass in plasma or sera by an enzyme-linked immunosorbent assay (ELISA) without heparin injection (simply put as serum or plasma LPL mass). In earlier studies, researchers applied the measurement of plasma or serum LPL mass to detailed analysis and characterization of type 1 hyperlipidemia (HLP) [16,17]. In 1989, Auwerx et al. [16] proposed that type 1 HLP be classified into three subtypes according to the amount of LPL mass in pre- and post-heparin plasma. In 1990, Kern et al. [17] conducted detailed analysis of LPL protein in pre- and post-heparin plasma from both normal subjects and type 1 HLP. In recent years, the measurement of plasma or serum LPL mass has been conducted to clarify the pathophysiology of more common metabolic disorders. Tornvall et al. [13,15] have studied the correlation between lipoproteins and plasma LPL mass from men before the age of 45 years with coronary heart disease and from age-matched controls, and found that there was a strong positive correlation between plasma LPL mass and HDL-C levels as well as weak negative relations to VLDL-TG in the patients. The study by Watanabe et al. [14] has shown that serum LPL mass is lower in conditions in which TG catabolism is disturbed, such as hypertriglyceridemia and individuals with increased remnant lipoproteins.

In this review, we focus on recent advances in the research on clinical significance of measuring plasma or serum LPL mass without heparin-injection into study subjects, based on several clinical findings reported in the last decade.

2. Biochemical properties of pre-heparin LPL

It has been shown that LPL activity in plasma increased about as high as 170-fold, whereas LPL mass increased only about 9-fold after heparin injection [13]. Most of the LPL protein in plasma elutes as an early peak from heparin-Sepharose, corresponding to the position for inactive monomeric LPL and is demonstrated to be full-length LPL, which is bound to plasma lipoproteins [12]. Thus, it is unlikely that the measured plasma LPL mass directly contributes to catalyzing hydrolysis of triglycerides in TG-rich lipoproteins in the plasma. Several researchers have shown that this inactive protein may act as a ligand targeting lipoproteins for binding to cell surfaces and receptors [18].

3. Correlation of serum LPL to post-heparin plasma (PHP) LPL mass

It has been reported that serum LPL mass had a positive relation with PHP-LPL mass [14,19,20], although the degree of the relation appeared to differ among the reports. It should be noted that Hirano et al. [20] have shown that the delta LPL concentration was strongly related to the PHP-LPL concentration (r=.965, P</=.0001), but not to the serum LPL mass, suggesting that the weak correlation between serum LPL and PHP-LPL levels was attributable to contamination of PHP by pre-existing LPL.

4. Relationship between plasma LPL mass and intra-abdominal visceral fat

It is generally recognized that individuals with obesity have high prevalence of complications, such as impaired glucose tolerance, hyperlipidemia, and hypertension However, it is also true that the degree of obesity does not necessarily account for the severity of these disorders [21]. Studies have suggested that fat distribution and abdominal fat accumulation are good predictors of the development of coronary heart disease [22–24]. Moreover, intra-abdominal visceral fat accumulation is shown to be associated with insulin resistance [25]. Several clinical studies were conducted for analyzing the relationship of LPL mass, either in pre-heparin plasma (or serum) or PHP, to visceral fat accumulation. We and other groups have reported that intra-abdominal visceral fat area assessed by CT at umbilical level had an inverse relationship to LPL mass and activity in PHP [26–28]. Similar results were obtained on the association between intra-abdominal visceral fat and pre-heparin LPL mass [19] by recruiting a total of 58 subjects comprising 50 hyperlipidemic and 8 normolipidemic subjects.

In that study, plasma LPL mass had an inverse relationship to intra-abdominal visceral fat area, but did not show any statistically significant correlation to subcutaneous fat area. Multiple regression analysis performed with plasma LPL mass as a dependent variable, and visceral fat area and BMI as independent variables revealed that the visceral fat area had an inverse relation to plasma LPL mass, independent of BMI.

We have conducted the receiver operator characteristic (ROC) analysis for LPL concentration to predict the presence of intra-abdominal visceral fat area >100 cm^2 (Fig. 1). This finding suggests that the optimal cut off point of serum LPL

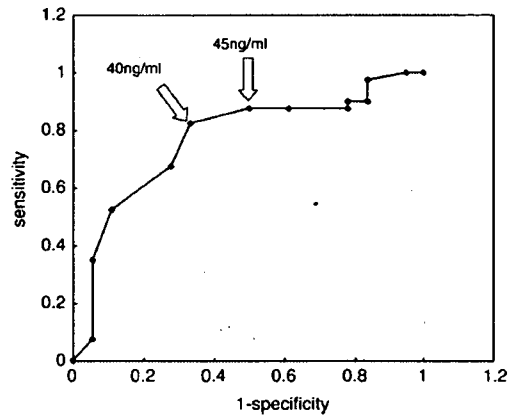

Fig. 1. The receiver operator characteristic (ROC) analysis for serum lipoprotein lipase mass to predict the presence of intra-abdominal visceral fat area ≧ 100 cm^2.

mass for predicting visceral fat accumulation could be around 40 ng/ml. Furthermore, we also subdivided the whole subjects into each gender and found that the optimalcut off point of LPL mass for men might be 35 ng/ml rather than 40 ng/ml (Fig. 2).

5. Relationship of serum LPL concentration with lipoproteins and apolipoproteins

We have shown that plasma LPL mass correlated positively with serum HDL-C level and inversely with serum TG level, but did not significantly correlate with low-density lipoprotein (LDL)-C [19]. Other group in Japan has reported similar results for 377 Japanese individuals who underwent annual health examinations [14].

The study by Tornvall et al. [13] has shown this association existed in 61 men who had suffered myocardial infarction before the age of 45 years. For the association with serum apolipoproteins, plasma LPL mass had a positive correlation with serum apolipoprotein (apo) A-I, but not apo B or E. Furthermore, it has been shown that serum LPL correlated inversely with TG, remnants, and insulin resistance and positively with HDL cholesterol and LDL size in164 Japanese hyperlipidemic subjects [20]. This finding has been confirmed by the recent report [29] showing a strong positive correlation between serum LPL concentration vs. LDL and HDL sizes measured by nuclear magnetic resonance. These observations support the association of a high serum LPL concentration with a beneficial lipid profile.

6. Serum LPL mass in type 2 diabetes mellitus

A study has shown that serum LPL concentration was considerably lower in type 2 diabetic patients (n=40) than in non-diabetic healthy controls, and had an inverse relation to HbA1c in diabetic individuals [30]. For 15 subjects among them, they investigated the effect of insulin treatment on serum LPL mass and plasma glucose levels, and found that serum LPL mass increased significantly at week 4 on insulin treatment, with concomitant reduction in fasting blood glucose level. We analyzed gender difference in plasma LPL mass and other metabolic parameters from Japanese type 2 diabetic subjects after adjusting for age, BMI, and HbA1c [31]. The men group showed a higher serum TG and lower HDL-C levels along with lower plasma LPL mass than did women. Troglitazone, an insulin sensitizer and now out of market in Japan, was reported to cause an increase in pre-heparin LPL mass [32], which is consistent with our study showing this agents increased LPL mass in PHP [33].

7. Serum LPL mass in acute inflammation

We had a diabetic woman with severe foot gangrene, who had a markedly low HDL-C and serum LPL mass [34]. Serum LPL mass and serum HDL-C returned to almost normal level during treatment of her diabetes and gangrene with insulin and anti-biotics. Serum C-reactive protein levels had an inverse relationship to serum LPL mass, suggesting that in acute inflammation, the production of LPL in adipocytes or muscle

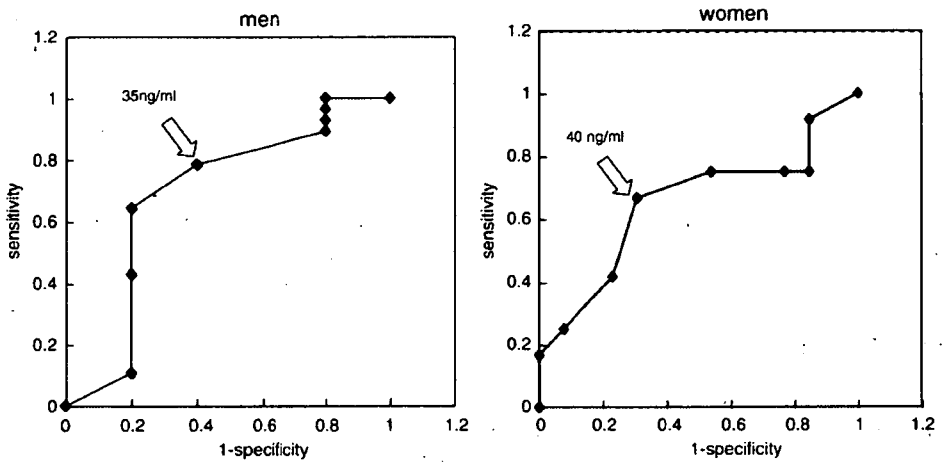

Fig. 2. The receiver operator characteristic (ROC) analysis for serum lipoprotein lipase mass to predict the presence of intra-abdominal visceral fat area ≧ 100 cm^2 in men (n=33) and women (n=25), separately.

tissue is highly inhibited. Serum C-reactive protein levels also showed an inverse relation to plasma glucose levels, although to a lesser degree.

8. Serum LPL concentration and insulin resistance

The recent report by Hanyu et al. [35] has indicated that serum LPL mass correlated significantly with insulin sensitivity analyzed by minimal model, which is applied to all of the subjects they studied regardless of whether the subjects had normal glucose tolerance, impaired glucose tolerance, and diabetes. Also, serum LPL mass correlated negatively with HOMA-R and fasting IRI.

9. Serum LPL concentration and serum adiponectin levels

Recently, it has been shown that LPL activities in post-heparin plasma were positively associated with serum adiponectin levels [36–38]. More recently, Saiki et al [39] have reported that in 362 Japanese subjects with metabolic syndrome, the correlation coefficient between serum LPL mass and plasma adiponectin was high (r=0.562). They also have shown that both serum LPL mass and adiponectin correlated positively with HDL-C and inversely with body weight and TG. Also, serum LPL mass and plasma adiponectin decreased with an increase in severity of the metabolic syndrome with/without obesity and with/without diabetes.

10. The association of pre-heparin LPL mass and the incidence of coronary artery disease (CAD)

Hitsumoto et al. [40,41] compared pre-heparin LPL mass in men with angiographically determined coronary atherosclerosis vs. that in men with normal coronary or healthy men. They found that men with coronary atherosclerosis had significantly lower pre-heparin LPL mass than did men without coronary atherosclerosis or healthy men.

They suggest that serum LPL mass is an independent determinant of incidence [40] or severity [41] of coronary artery disease even after adjustments of a number of metabolic parameters, including serum triglycerides and HDL-C.

11. Prospective associations between serum LPL concentration and risk for future CAD

To demonstrate whether or not low LPL mass is the result or the cause of coronary heart disease, it is essential to conduct a prospective study on the association of these two markers. Recently, Rip et al. [29] determined serum LPL concentrations from men and women in the EPIC-Norfork population cohort who developed fatal or nonfatal CAD during 7 years of follow-up. Subjects with highest LPL concentration quartile had a 34% lower risk for future CAD compared with those in the lowest quartile. This effect remained significant after adjustment for blood pressure, diabetes, smoking, body mass index, and LDL-C but not significant after additional adjustment for TG or HDL-C. Their results suggest that high LPL concentrations may be athero-protective through associations with decreased TG levels and increased HDL-C levels. In this regard, their study did not appear to be consistent with the above-mentioned cross-sectional study by Japanese investigators suggesting that serum LPL mass could be risk factor for CAD, independent of TG and HDL-C. In addition to the relation of serum LPL mass to the incidence of coronary heart disease, we have recently found that in Japanese hyperlipidemic subjects, serum LPL mass showed an inverse association with average intima-media thickness of right and left common carotid arteries assessed with ultrasonography following previously reported method [42], independent of age, gender, body mass index, LDL-C, HDL-C and TG in a multiple regression analysis, (Table 1). This finding suggests that serum LPL mass predict the development of atherosclerosis in carotid artery as well as in coronary artery.

12. Effects of several lipid-lowering agents on serum LPL mass

It has been shown that bezafibrate, a lipid lowering compound known to cause a reduction in serum TG level with increase in HDL-C levels [43], has produced a considerable increase in serum LPL mass in hypertriglyceridemic patients [44]. This observation has been in line with the previous reports on the effects of this compound on LPL activity in PHP [45,46]. Recently, it has been reported that series of statins, such as pravastatins, atorvastatins and pitavastatins may produce a significant increase in serum LPL mass after the treatment [47,48]. An in vitro study has shown that that pitavastatins increase the expression of LPL mRNA from cultured 3T3 L1 cells [47]. Their study appeared to be somehow incompatible with our study showing atorvastatin did not produce an increase in pre-heparin LPL mass in hyperlipidemic subjects, despite causing a substantial reduction in serum TG level [49]. This might be partly associated with the different clinical profile of the study subjects with their study subjects being type 2 diabetes having lower serum HDL-C levels at baseline compared with ours.

We have suggested that the main mechanisms by which atorvastatins produced considerable TG reductions may be due

Table 1
A multiple regression analysis with intima-media thickness of common carotid artery assessed with ultrasonography, with age, gender, body mass index, LDL-C, HDL-C and TG as independent variables

	S.E.	β	t	p
Ln LPL	.142	−.461	−2.209	.0352
Age	.004	.409	2.467	.0198
Gender	.092	.093	.519	.6079
Body mass index	.020	−.091	−.497	.6228
LDL-C	.001	.296	1.608	.1187
HDL-C	.003	.046	.224	.8245
TG	3.765E^{-4}	.215	.896	.3776

The measurement of intima-media thickness in the common carotid artery was made along a 10 mm long section just proximal to the carotid bulb. The means of three separately analyzed images was used and average IMT was calculated from right and left intima-media thickness of common carotid arteries.

to their inhibition of the production and secretion of VLDL from the liver.

13. Concluding remarks

According to considerable number of evidence above mentioned, measuring pre-heparin LPL mass in plasma or sera provides us with useful information on understanding the pathophysiology of several metabolic disorders, such as visceral fat accumulation, diabetes mellitus and insulin resistance, which are highly associated with the incidence of coronary heart disease, despite its simplicity from a practical point of view in daily clinical practice.

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Clinical research

Reassessment of the cutoff values of waist circumference and visceral fat area for identifying Japanese subjects at risk for the metabolic syndrome

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ABSTRACT

In the new world-wide criteria for metabolic syndrome (MetS) by the International Diabetes Federation (IDF) in 2006, the Japanese is the only ethnicity in which the recommended waist circumference (WC) cutoff value is higher in women (≧90 cm) than in men (≧85 cm), and its validity appears to be controversial. We investigated the optimal cutoff points for the diagnosis of central obesity in Japanese men and women, using the receiver operating characteristic (ROC) curve analysis for both of WC and visceral fat area (VFA) in 1870 middle-aged Japanese. VFA was superior to WC and Body mass index (BMI) for discriminating the subjects with two or more nonadipose components of MetS. The optimal cutoff points of VFA and WC were 132.6 cm^2 and 89.8 cm for men and 91.5 cm^2 and 82.3 cm for women. The stratifications of MetS components more than 1.0 in average occurred more steeply by the accumulation of VFA in women than in men.

In conclusion, setting the cutoff points of WC and VFA lower values in women than in men for the definition of central obesity is needed to identify the subjects with MetS in Japanese, as in other Asian populations.

1. Introduction

The number of subjects with metabolic syndrome (MetS) has markedly increased in Japan as well as in Western countries [1–3]. Because subjects with MetS are at increased risk for type 2 diabetes [4] and cardiovascular disease (CVD) [5], there is an urgent need to establish an appropriate and sensitive screening system to identify these high risk individuals and to prevent an epidemic of this syndrome.

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In 2006, the International Diabetes Federation (IDF) announced a new world-wide definition of MetS that is expected to be used in clinical practice in any country, including Japan [6]. For MetS diagnosis, special emphasis has been placed on the central obesity, as assessed by waist circumference (WC) cutoff values specific for ethnicity and gender. Accumulating evidence argues that lower cutoff points for WC should be used for Asians than for Europeans, as the former is prone to obesity-related morbidity and mortality at lower BMI and/or shorter WC than the latter [7–11]. Thus, the report of the joint WHO/IASO/IOTF committee proposed WC values of 90 cm for men and 80 cm for women as Asian-specific cutoff points for central adiposity [12]. These values have been adopted as the criteria for South Asians and Chinese in the IDF consensus [6].

Among the Japanese in particular, cutoff values of WC ≧85 cm for men and ≧90 cm for women have been adopted [6,13]. This is the only ethnic group in which the recommended WC cutoff point is higher in women than in men [6] and its validity appears to be controversial. It seems to be based on the 2002 report from the Examination Committee of Criteria for 'Obesity Disease' in Japan, which stated that the optimal cutoff value for identifying individuals at risk for obesity-related disorders was a visceral fat area (VFA) of 100 cm^2 measured by computed tomography (CT) in a study that combined both sexes [14]. The WC corresponding to 100 cm^2 of VFA was then identified as 85 cm in men and 90 cm in women [14]. Indeed, in the recent declaration of the criteria, the IDF added the annotation that Asian values (male 90 cm; female 80 cm) should be used for Japanese populations as well until more data are available [6].

There is only a little information to ascertain what would be appropriate cutoff points for indicators of central obesity in Japanese men and women. Much shorter cutoff points of WC in women by Hara et al. [15] and smaller cutoff points of VFA in women by Miyawaki et al. [16] have been proposed as more appropriate to predict the presence of multiple risk factors than the currently accepted values. Comparable results have also been shown by other studies in Japanese-Brazilian [17] and in Korean [18].

To address this controversial point, in this study we attempted to reassess the cutoff points for the diagnosis of central obesity in Japanese men and women, using the receiver operating characteristic (ROC) curve analysis for both of WC and VFA. To the best of our knowledge, this is the largest study analyzing both of these indicators for central adiposity in relation to the presence of components of MetS.

2. Materials and methods

2.1. Study population

Hokuriku Central Hospital has a special department, as a health service sponsored by their mutual aid association, where employees at public schools can receive routine medical checkups. Among subjects who enrolled in a regular medical checkup in 2006, 1893 persons were included in this study. Of these subjects, 93% were teachers, 5% were retired teachers, and 2% were secretaries at schools. All subjects voluntarily chose to be examined by CT for VFA values. After exclusion of 23 participants for missing answers on questionnaires regarding their medical histories, complete data were obtained for 1870 Japanese adults (1061 men and 809 women), whose age and body mass index (BMI) were 50.9 ± 7.6 years and 24.3 ± 2.9 kg/m^2, respectively. Signed informed consent was obtained from all subjects and the hospital review board approved the study protocol.

2.2. Anthropometric measurements and laboratory assays

All evaluations were performed at the health check department of Hokuriku Central Hospital. Anthropometric measurements of individuals wearing light clothing and without shoes were conducted by well-trained nurses. BMI was calculated by dividing weight (kg) by height squared (m^2). WC was taken at the end of normal expiration, measuring the minimum circumference at the level of umbilicus to the nearest 0.5 cm. Single CT scans (Aquilion, Toshiba Medical Systems, Tokyo, Japan) were obtained in the supine position at the end of inspiration. VFA was determined using commercial software, Fat Scan version 3.0 (N2 System, Osaka, Japan). Blood pressure (BP) was measured by automatic device (Colin Model BP-203RVII, Colin, Tokyo, Japan) after at least 5 min of rest in the sitting position.

After an overnight 12 h fast, blood samples were drawn to measure the levels of plasma glucose (PG), triglyceride, and HDL cholesterol. PG was determined by the glucose oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160, Arkray, Kyoto) and triglyceride and HDL cholesterol by enzymatic analytical chemistry (Autoanalyzer BioMajesty JCA-BM1650, JEOL Ltd., Tokyo, Japan).

2.3. Definition of metabolic syndrome

The nonadipose components of MetS were defined using the criteria of Japanese Society of Internal Medicine (JIM) [13] as the presence of two or more of the following: (1) TG ≧150 mg/dL (1.7 mmol/L) and/or HDL cholesterol <40mg/dL (<1.03 mmol/L) for both of men and women, or taking lipid-lowering medications (2) systolic BP ≧130 mmHg, diastolic BP ≧85 mmHg, or receiving antihypertensive medications; and (3) fasting PG ≧110 mg/dL (6.1 mol/L) or treatment with oral hypoglycemic medications or insulin.

2.4. Statistical analysis

Statistical analyses were conducted using SPSS version 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviations, and discrete variables were expressed as proportions. The ROC curve analyses were performed to determine the appropriate cut points for VFA, WC, and BMI in identifying subjects with two or more nonadipose components of MetS. Comparison of the diagnostic abilities of the tests was performed using the areas under the curves (AUC) and the significance of the difference between two areas was assessed by the method described by Hanley and McNeil [19]. The values of VFA, BMI, and WC that resulted in maximizing the Youden index (sensitivity + specificity − 1) were defined as optimal. Youden index is an integrative indicator of sensitivity and specificity [20,21].

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3. Results

3.1. Subject characteristics

Subject characteristics and the prevalence of metabolic risk factors are shown in Table 1. We found 392 (36.9%) of 1061 men and 106 (13.1%) of 809 women had two or more nonadipose components of MetS according to the criteria of JIM. Both men and women with two or more components of MetS had higher VFA, WC, and BMI than those without MetS.

3.2. ROC curve analyses

Fig. 1 shows ROC curves of VFA, WC, and BMI in men (A) and in women (B) which were used to identify subjects with two or more nonadipose components of MetS. All three curves lay above the diagonal line. Table 2 presents AUC values used to distinguish subjects with two or more nonadipose components of MetS or subjects with each component. In both men and women, VFA showed greater AUC values than WC and BMI, suggesting that VFA was superior to WC and BMI for discrimination of the subjects. Values in men were 0.675 for VFA (0.642–0.708), 0.641 for WC (0.607–0.675), and 0.642 for BMI (0.607–0.676). Similarly, in women, values were 0.759 for VFA (0.711–0.806), 0.686 for WC (0.636–0.735), and 0.727 for BMI (0.677–0.776).

Table 3 shows sensitivity, specificity, positive and negative predictive values, and the Youden index for VFA, WC, and BMI to detect subjects with two or more components of MetS according to the JIM criteria. In men, optimal cutoff points were 132.6 cm^2 for VFA, 89.8 cm for WC, and 24.1 kg/m^2 for BMI. In women, optimal cutoff points were 91.5 cm^2 for VFA, 82.3 cm for WC, and 23.1 kg/m^2 for BMI.

3.3. The number of MetS components by VFA level

The mean number of MetS components increased in proportion to the increase in VFA. The average value exceeded 1.0 at 90 and 110 cm^2 in men and women, respectively, but it exceeded 1.5 at lower VFA levels in women (140 cm^2) than in men (150 cm^2) (Fig. 2).

3.4. The prevalence of MetS according to the cutoff points obtained from this study.

According to the criteria by IDF and JIM, 25.8% of men and 4.2% of women in our sample were classified as MetS. If we adopted the criteria obtained from ROC analysis in this study, WC ≧89.8 cm in men and WC ≧82.3 cm in women, the revised prevalence of MetS in our population was 16.5% in men and 9.4% in women.

4. Discussion

These cross-sectional data comprising 1870 middle-aged Japanese subjects demonstrated that the cutoff points of 132.6 cm^2 VFA, 89.8 cm WC, and 24.1 kg/m^2 BMI for men and

Table 1 – Characteristics of study subjects according to metabolic syndrome status in Japanese men and women

	Men			Women		
	Total	Two or more nonadipose components of the JIM criteria other than waist circumference		Total	Two or more nonadipose components of the JIM criteria other than waist circumference	
		Absent	Present		Absent	Present
n	1061	669	392	809	703	106
Age (years)	50.6 ± 7.8	50.2 ± 8.2	51.4 ± 7.2	51.2 ± 7.2	50.7 ± 7.4	53.9 ± 5.2
BMI (kg/m^2)	24.9 ± 2.7	24.4 ± 2.4	25.7 ± 2.8	23.5 ± 3.1	23.2 ± 2.9	25.7 ± 3.4
Waist circumference (cm)	86.9 ± 7.1	85.5 ± 6.7	89.2 ± 7.2	81.9 ± 8.2	81.2 ± 8.1	86.6 ± 7.5
VFA (cm^2)	128 [97, 159]	117 [90, 149]	148 [115, 178]	69 [48, 98]	66 [45.5, 92]	105 [73, 135]
Type 2 diabetes or fasting PG ≧110 mg/dl (%)	17.3	3.4	41.1	5.8	1.0	37.7
Taking oral hypoglycemic medication or insulin (%)	4.0	1.0	8.9	0.7	0.0	5.7
High blood pressure (%)[a]	60.4	40.4	94.6	42.5	34.0	99.1
Taking antihypertensive medications (%)	13.6	7.2	24.5	11.9	8.4	34.9
HDL cholesterol (mg/dl)	54.1 ± 12.4	55.8 ± 12.2	51.1 ± 12.3	64.2 ± 14.3	65.4 ± 13.9	56.6 ± 14.8
Low HDL cholesterol (%)[b]	9.3	5.2	16.3	1.9	0.6	10.4
Triglycerides (mg/dl)	122 [87, 172]	104 [75, 134]	172 [128,227]	85 [61, 118]	80 [59, 106]	153 [106, 182]
Hypertriglyceridemia (%)	35.2	15.7	68.6	11.2	4.7	54.7
Taking lipid-lowering medication (%)	7.4	1.9	16.6	6.9	3.8	27.4

Data are mean ± S.D., median [interquartile range], or %. JIM, Japanese Society of Internal Medicine; PG, plasma glucose; WC, waist circumference.

[a] High blood pressure was diagnosed if systolic blood pressure was ≧130 mmHg, diastolic blood pressure was ≧85 mmHg, or the subject was receiving antihypertensive medications.

[b] Low HDL cholesterol was diagnosed if HDL cholesterol was <40 mg/dl in men and women.

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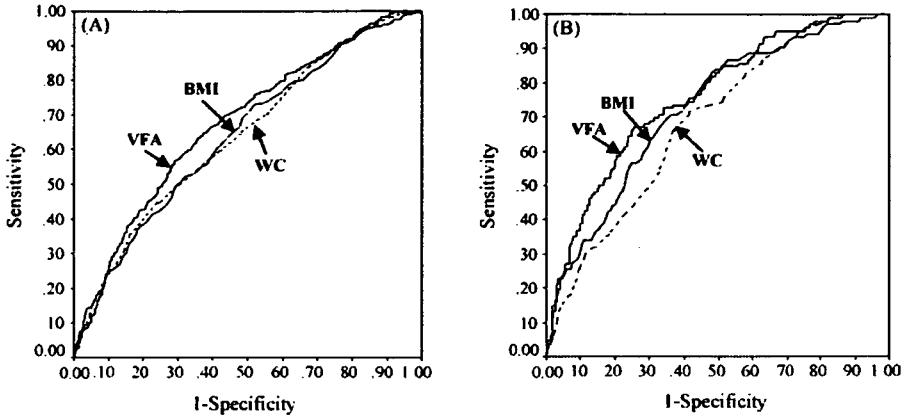

Fig. 1 – The ROC curves for visceral fat area (VFA), waist circumference (WC) and body mass index (BMI) to predict the presence of two or more components of MetS, as defined by the criteria by Japanese Society of Internal Medicine (JIM), in men (A) and in women (B).

91.5 cm^2 VFA, 82.3 cm WC, and 23.1 kg/m^2 BMI for women were optimal to yield maximal sensitivity plus specificity for predicting two or more nonadipose components of MetS. VFA was superior to WC and BMI in identifying subjects with multiple risk factors both in men and women. Given our findings, WC cutoff values for the Japanese population recommended by the IDF [6] and JIM [13] should be reevaluated, especially in women.

To date, there have been a few studies supporting a lower WC cutoff point than that currently accepted for Japanese women. Hara et al. analyzed data from a community-based cohort of 692 Japanese subjects and proposed 85 cm in men and 78 cm in women as optimal to identify subjects with multiple risk factors of MetS defined by National Cholesterol Education Program-Adult Treatment Panel (NCEP) III [15]. In another study, in terms of predicting the insulin resistance,

Table 2 – Areas under the ROC curve of WC, BMI, and VFA to identify the presence of components of MetS

	Men (n = 1061)		Women (n = 809)	
	ROC curve area (95% CI)	P value compared with WC[a]	ROC curve area (95% CI)	P value compared with WC[a]
Two or more nonadipose components of the JIM criteria other than waist circumference				
VFA	0.675 (0.642–0.708)	0.164	0.759 (0.711–0.806)	0.046
WC	0.641 (0.607–0.675)		0.686 (0.636–0.735)	
BMI	0.642 (0.607–0.676)	0.971	0.727 (0.677–0.776)	0.175
Fasting plasma glucose ≥110 mg/dl or type 2 diabetes				
VFA	0.612 (0.566–0.658)	0.072	0.760 (0.695–0.824)	0.352
WC	0.553 (0.508–0.598)		0.712 (0.634–0.790)	
BMI	0.549 (0.502–0.595)	0.951	0.740 (0.668–0.812)	0.604
High blood pressure[b]				
VFA	0.641 (0.607–0.676)	0.751	0.686 (0.649–0.723)	0.236
WC	0.634 (0.600–0.668)		0.654 (0.616–0.692)	
BMI	0.637 (0.603–0.671)	0.882	0.683 (0.646–0.720)	0.285
Hypertriglyceridemia				
VFA	0.664 (0.631–0.697)	0.192	0.748 (0.700–0.797)	0.026
WC	0.632 (0.597–0.666)		0.664 (0.609–0.720)	
BMI	0.637 (0.602–0.671)	0.855	0.663 (0.603–0.723)	0.967
Low HDL cholesterol[c]				
VFA	0.614 (0.557–0.670)	0.880	0.645 (0.571–0.718)	0.148
WC	0.625 (0.567–0.682)		0.570 (0.502–0.638)	
BMI	0.618 (0.561–0.674)	0.804	0.593 (0.526–0.661)	0.655

JIM, Japanese Society of Internal Medicine; WC, waist circumference; VFA, visceral fat area.

[a] P value compared with waist circumference by the method of Hanley and MnNeil.

[b] High blood pressure was diagnosed if systolic blood pressure was ≥130 mmHg, diastolic blood pressure was ≥85 mmHg, or the subject was receiving antihypertensive medications.

[c] Low HDL cholesterol was diagnosed if HDL cholesterol was <40 mg/dl in men and women.

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Table 3 – Sensitivity and specificity of VFA, WC, and BMI to detect subjects with two or more nonadipose components of the JIM criteria

	Cut point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	J value[a]
Men (n = 1061)						
VFA (cm^2)						
Optimal cutoff point[b]	132.6	63.3	64.3	51.0	74.9	0.28
JIM cutoff point for Japanese	100	83.4	34.8	42.8	78.2	0.18
Waist circumference (cm)						
Optimal cutoff point[b]	89.8	44.6	76.1	52.2	70.1	0.21
JIM cutoff point for Japanese	85	69.9	45.1	42.7	71.9	0.15
IDF cutoff point for South Asians and Chinese	90	44.6	76.1	52.2	70.1	0.21
IDF cutoff point for Europids	94	26.0	88.3	56.6	67.1	0.14
BMI (kg/m^2)						
Optimal cutoff point[b]	24.1	73.0	48.0	45.1	75.2	0.21
Overweight	25	56.1	61.3	45.9	70.4	0.17
Obesity	30	7.7	97.8	67.2	64.4	0.05
Women (n = 809)						
VFA (cm^2)						
Optimal cutoff point[b]	91.5	67.0	74.4	28.3	93.7	0.41
JIM cutoff point for Japanese	100	51.9	81.4	29.6	91.8	0.33
Waist circumference (cm)						
Optimal cutoff point[b]	82.3	71.7	58.5	20.7	93.2	0.30
JIM cutoff point for Japanese	90	32.1	86.2	26.0	89.4	0.18
IDF cutoff point for South Asians, Chinese, and Europids	80	82.1	42.5	33.4	87.1	0.25
BMI (kg/m^2)						
Optimal cutoff point[b]	23.1	83.0	52.2	20.7	95.3	0.35
Overweight	25.0	50.0	77.2	24.8	91.1	0.27
Obesity	30.0	14.2	98.2	54.3	88.4	0.12

PPV, positive predictive value; NPV, negative predictive value; JIM, Japanese Society of Internal Medicine.

[a] J = sensitivity + specificity − 1.

[b] The optimal cut point was obtained from Youden index as [maximun (J = sensitivity + specificity − 1)].

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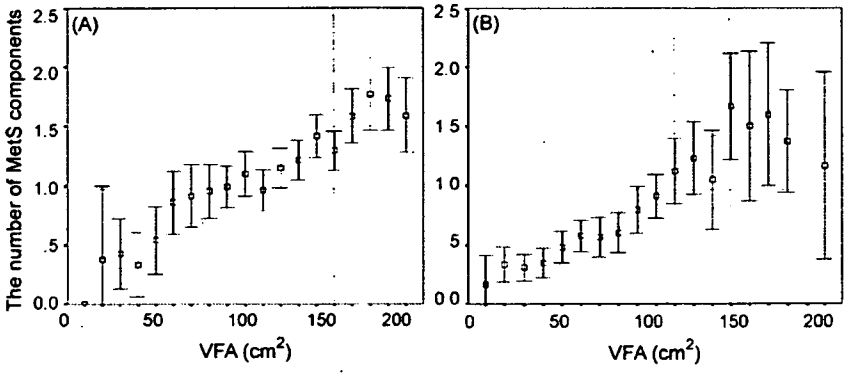

Fig. 2 – The mean number of nonadipose components of MetS by visceral fat area (VFA) in men (A) and in women (B). The dotted lines represent the levels at which an average number of components exceeded 1.0 and 1.5, respectively. The VFA value represents the level of VFA divided by each 10 cm².

the WC cutoff level was proposed to be 83 cm in men and 75 cm in women [22]. In these studies, they employed ROC curve analyses to identify cutoff points using Youden index (maximum [sensitivity + specificity − 1]), which was also employed in our study.

A recent study investigated the optimal cutoff points for both WC and VFA in 639 Japanese-Americans [23]. Consistent with our findings, they demonstrated that VFA was better than WC and BMI for identification of subjects with at least two nonadipose components of MetS and that the optimal cutoff points of VFA as well as WC were lower in women than in men: 96 cm² VFA and 90 cm WC for men, and 75 cm² VFA and 84 cm WC for women. Their WC cutoff values were comparable to those found in our data, but VFA cutoff points were larger in our study than theirs. It is not clear whether it was due to methodological differences in VFA measurement or to possible differences in the composition of body fat of Japanese-Americans from that of native Japanese. The percentage of subjects receiving treatment of diabetes was much higher in Japanese-Americans than in our population (45.8% of men and 44.9% of women vs. 4.0% of men and 0.7% of women). Differences in life-style may affect the cutoff points between these two populations who share a genetic background.

The prevalence of MetS according to the cutoff points obtained from this study would be a better reflection of the true prevalence of MetS because it is consistent with the mortality from coronary heart disease (35.7 male vs. 17.5 female, per 100,000) and cerebrovascular disease (60.5 male vs. 38.4 female, per 100,000) in Japan [24,25].

VFA was superior to WC and BMI in identifying subjects with two or more nonadipose components of MetS, as shown by the larger AUC of VFA. Indeed, it has been reported that insulin resistance is associated more strongly with VFA directly measured by CT than with waist-to-hip ratio or WC [26–28]. This would also apply to the presence of MetS components. Although WC is an inexpensive and practical screening tool for diagnosing central obesity and serves as a surrogate indicator for visceral fat, its inclusion of subcutaneous fat or skeletal muscle mass is problematic [29].

A VFA value of 100 cm² has been noted as the gold standard in defining the central obesity in Japanese men and women [13,14]. It is based on the report that the average number of obesity-related disorders exceeded 1.0 at the VFA value of 100 cm² in a study sample that combined both sexes [14]. As Hayashi et al. noted [23], this approach did not consider the possibility that the associations between the components of MetS and VFA might vary by sex, which was evident in our study as well as the MONK study [16] and a recent study in Japanese-Americans [23]. Moreover, according to the values of sensitivity and specificity for detecting subjects with multiple risk factors reported in that landmark study [14], Youden indexes were comparable at VFA values from 90 to 110 cm². Our process of assessing cut points for central obesity is more refined than that of the classical study [14] in two points; (1) the optimal cut points for VFA were analyzed in men and women separately. (2) Using ROC analysis, the balance of specificity and sensitivity for identifying subjects at risk for MetS was better than theirs. The optimal cutoff point for VFA in men that we proposed in the present study appears to be much higher than 100 cm². This might be due to the fact that our study sample was limited to the middle-aged Japanese men. Indeed, Hayashi et al. have reported that the cut points for VFA were different by generation [23]. So, further investigation is needed to broaden to apply this cut points to other generations.

A novel finding of our study is that the average number of MetS components exceeded 1.0 at smaller VFA values in men than in women but exceeded 1.5 at smaller VFA values in women than in men. This indicates that the stratification of MetS components in the range from 1.0 to 1.5 occurs more drastically by visceral fat accumulation in women than in men. On average, men had twice as much visceral fat as women and high prevalence of MetS. However, the accumulation of visceral fat may be more detrimental in women than in men. This is in line with other studies showing that relative risk of death from CVD is increased eight times in women with the highest waist-to-hip ratio [30] but only two times in men [31]. These gender differences suggest that it may be important to assess the relationships between VFA and risk factors in women separately from men.

There are several limitations to our study. First, the subjects were not randomly selected but limited to employees

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of public schools. However, the metabolic and anthropometric profiles of subjects in this study were largely in agreement with results from other studies [15,16], suggesting that this sample is representative of the working middle-aged population in Japan. Second, the cutoff points were investigated for all ages combined. The optimal cutoff points may differ by age-group [32,33] or BMI [34]. This relationship may also be more complex in postmenopausal women, who are predisposed to selective fat storage in the visceral region [35]. Finally, our analysis of this cross-sectional data cannot provide causal explanations. Further studies are needed to prospectively relate the accumulation of visceral fat to the presence of risk factors, or to the incidence of CVD.

In conclusion, our data indicate that the optimal cutoff points of VFA as well as WC for identifying subjects at risk for MetS differ between men and women. Setting the cutoff points of WC and VFA lower values in women than in men for the definition of central obesity should be more useful to identify the subjects with MetS in Japanese, as in other Asian populations.

Conflicts of interest

All authors do not have any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work, all within 3 years of beginning the work submitted. None to declare.

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Letter to the Editor

The distribution of fasting and non-fasting serum triglyceride levels in Japanese population

Dear editor,

In recent years, accumulating evidence shows that non-fasting serum triglycerides (TG) are important marker for assessing the risk of cardiovascular disease [1–4]. Several clinical studies have shown that delayed elimination of postprandial TG-rich lipoprotein as well as higher TG levels is associated with coronary artery disease (CAD) [5,6]. It has been reported that the presence of CAD is associated with higher postprandial TG concentrations in plasma compared with healthy controls, even after correction for higher levels of fasting TG in CAD group [6–8]. To date, much of the knowledge about the relationship between lipid and lipoprotein metabolism and the development of atherosclerosis and cardiovascular disease is based on measurements in the fasting state. However, human spends their majority of time in a non-fasting state.

In the guideline proposed by the Japanese Atherosclerosis Society [9], the decision point of serum TG is simply put as <1.69 mmol/l in fasting state across all series of subjects no matter what the degree of risks individuals have. In addition, it is known that serum TG levels change considerably before and after meals. In this circumstance, we investigated how TG values in fasting and non-fasting distributed in Japanese individuals who received annual medical checkup consisting of 8223 men and 16,154 women, among whom 12,990 (M/F 4676/8314) and 11387 (3547/7840) subjects were analyzed for fasting and non-fasting TG levels, respectively. Subjects who fasted for at least 12 h after the last meal were defined as fasting. In non-fasting individuals, the distribution time since last meal was 5.1% <1 h, 25.4% for <2 h, 35.6% for <3 h, 21.2% for <4 h, and 12.8% >4 h. Serum TG values for individuals in these 5 categories were 1.38±0.83, 1.45±0.91, 1.48±0.98, 1.44±1.00 and 1.39±0.90 (mean±S.D. in mmol/l), respectively. The study subjects were given questionnaire on their habit whether or not they had a regular habit of drinking and/or smoking to fill in. In fasting and non-fasting TG subjects, 37% and 39% men, respectively, were smokers, whereas 6.3% and 5.7% women, respectively, were smokers. In fasting and non-fasting TG subjects, 66% and 66% men, respectively, were drinkers whereas 18% and 18% women, respectively were drinkers. Statistical evaluation was performed with StatView 5.0. Results were shown as mean±S.D. Pearson's correlation coefficients analysis was carried out. Statement of institutional approval of the study in accordance with the Declaration of Helsinki and informed consent were obtained from all of the participants in this study. A $p<0.05$ were considered significant. In individuals analyzed for fasting TG, age, body mass index (BMI), plasma glucose (PG), HbA1c, total cholesterol (TC), TG and high-density lipoprotein-cholesterol (HDL-C) were 57±13 years, 22.9±3.2 kg/m^2, 5.38±1.05 mmol/l, 5.3±0.9% (n=6132), 5.26±0.91, 1.19±0.79 and 1.61±

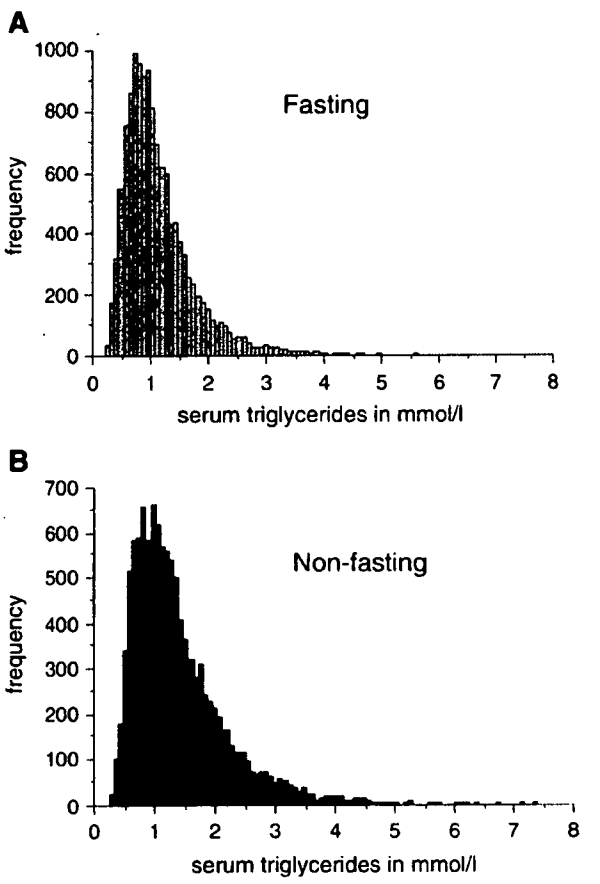

Fig. 1. Distribution of number of subjects for fasting (n=12,990) (A) and non-fasting (n=11,387) (B) serum TG levels in the study population. The median, the 1st and the 3rd quartiles of fasting TG levels were 1.01, 0.73 and 1.41 mmol/l, respectively. With regards to non-fasting TG levels, the median, the 1st and the 3rd quartile of them were 1.22, 0.86 and 1.75 mmol/l, respectively.

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