Original Article

Visceral Obesity in Japanese Patients with Metabolic Syndrome: Reappraisal of Diagnostic Criteria by CT Scan

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To reappraise the cutoff level of abdominal circumference (AC) for diagnosis of visceral obesity in Japanese, we examined the association of visceral fat deposition with other constituents of metabolic syndrome and atherosclerotic cardiovascular disease (ASCD). CT was used for determination of visceral-fat area (VFA), subcutaneous-fat area (SFA) and AC on CT (AC_{CT}) in 420 Japanese patients with (n=180) or without ASCD (n=240). VFA cutoff levels were calculated by receiver operating characteristic (ROC) analysis. AC_{CT} correlated with VFA (r=0.828), SFA (r=0.795), and AC measured with an anthropometric tape (AC_M, r=0.96). The VFA cutoff levels yielding the maximum sensitivity and specificity to predict two or more components of metabolic syndrome were 92 cm^2 in males and 63 cm^2 in females, which correspond to AC_M values of 83 cm and 78 cm, respectively. The male AC_M cutoff level was similar to the AC in current Japanese criteria (85 cm), but the female AC_M cutoff level was considerably smaller than the criteria, and this change in cutoff level increased the prevalence of metabolic syndrome in females three-fold. The cutoff levels of VFA for predicting presence of ASCD were 98 cm^2 in males and 75 cm^2 in females, corresponding to AC_M values of 84 cm and 80 cm, respectively. The present results obtained by CT support the validity of the current Japanese criteria for visceral obesity in males but not in females. AC_M of 78 cm appears to be a cutoff level suitable for diagnosing visceral obesity in Japanese females, though further confirmation is needed. (*Hypertens Res* 2007; 30: 315–323)

***Key Words*: metabolic syndrome, coronary arterial disease, visceral obesity, aging**

Introduction

Clustering of major risk factors (hypertension, diabetes mellitus, and hyper-lipidemia) has been shown to have synergistic effects on the development of atherosclerotic cardiovascular disease (ASCD) (*1*, *2*). The contribution of clustered minor risk factors for ASCD has also received attention recently, and attractive clinical concepts (*3–6*) emerged in the 1980s: metabolic syndrome X, insulin resistance syndrome, visceral fat syndrome, and multiple risk factor syndrome. Currently, the cluster of minor metabolic factors for ASCD is referred to as metabolic syndrome, and consists of visceral obesity, glucose intolerance or insulin resistance, dyslipidemia, and raised blood pressure. However, several definitions of metabolic syndrome, which differ in their required combinations of risk factors and cutoff levels for each factor, have been proposed (*7–9*).

One of the marked differences among the current diagnostic criteria of metabolic syndrome is the method used to assess visceral obesity and its requirement for diagnosis. In the definition of metabolic syndrome by the National Choles-

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Table 1. Clinical Backgrounds in Studied Subjects

	All (n=420)	Male (n=235)	Female (n=185)
Age (years old)	62±15	63±14	61±17
Gender [male/female]	235/185		
Risk factors (n (%))			
Hypertension	275 (66)	163 (69)	112 (61)
Diabetes mellitis	141 (34)	84 (36)	57 (31)
Hyperlipidemia	297 (71)	167 (71)	130 (70)
Hyperuricemia	132 (32)	93 (40)	39 (21)*
Smoking	174 (42)	143 (63)	31 (17)*
Family history	65 (16)	34 (15)	31 (17)
Weight (kg)	60±14	65±14	53±11*
BMI (kg/m^2)	23±4	23±4	22±4*
Systolic blood pressure (mmHg)	134±21	135±20	133±20
Diastolic blood pressure (mmHg)	77±13	77±13	76±13
Major disease (n (%))			
Coronary heart disease	122 (29)	88 (37)	34 (18)
Cardiomyopathy	33 (8)	19 (8)	14 (8)
Valvular disease	40 (10)	15 (6)	25 (14)
Aortic disease	41 (10)	27 (11)	14 (8)
Arrhythmia	61 (15)	38 (16)	23 (12)
Renal disease	56 (13)	27 (11)	29 (16)
Stroke	12 (3)	7 (3)	5 (3)
Others	54 (17)	14 (6)	40 (22)
Medication (n (%))			
Antihypertensive agents	241 (57)	149 (63)	92 (50)*
Antihyperlipidemia agents	112 (26)	49 (21)	63 (34)*
Antidiabetic agents	81 (19)	45 (19)	36 (20)

All the variables are expressed as mean±1 SD. *$p<0.05$ *vs*. male group, respectively.

terol Education Program Adult Treatment Panel III (NCEP ATP III) (*7*), visceral obesity is not a requisite. However, visceral obesity needs to be present in metabolic syndrome as defined by the International Diabetes Federation (IDF 2005) (*8*) and the Examination Committee of Criteria for Metabolic Syndrome in Japan (Japanese criteria) (*9*). In these definitions, visceral obesity is assessed by abdominal (waist) circumference, but its cutoff level is not the same: abdominal circumferences (ACs) are ≥102 cm in males and ≥88 cm in females in the NCEP ATP III criteria, ≥85–94 cm in males and ≥80–90 cm in females, depending on ethnic groups, in the IDF criteria, and ≥85 cm in males or ≥90 cm in females in the Japanese criteria. These differences in diagnostic criteria of visceral obesity derive from different rationales in each subject population.

In the present study, we used multi-detector-row CT (MDCT) to reappraise visceral obesity criteria for the diagnosis of metabolic syndrome and screening of ASCD in Japanese subjects. Since visceral fat, but not subcutaneous fat, is primarily responsible for the production of cytokines relevant to the development of metabolic syndrome (*10*, *11*), the amounts of visceral and subcutaneous fat were separately determined by MDCT together with AC. The relationships between the amount of visceral fat and metabolic syndrome or ASCD were analyzed by use of receiver operating characteristic (ROC) curves, and the results suggest that the current Japanese criterion of visceral obesity in males (AC=85 cm) is valid but that the criterion for females needs to be modified possibly to AC of 78 cm.

Methods

Study Subjects

We enrolled 420 consecutive patients who underwent MDCT at Sapporo Medical University Hospital between January 2001 and December 2003 (Table 1). Informed consent for use of their data in scientific research was obtained from all study subjects. Data from each subject were saved in anonymous formats and securely stored in a computer. Information on coronary risk factors, including data on the blood pressure category, serum triglyceride and high-density lipoprotein (HDL) cholesterol levels and presence/absence of ASCD, was obtained by physical and laboratory examinations. Unless otherwise stated, metabolic syndrome was diagnosed in accordance with the current Japanese criteria (*10*), which

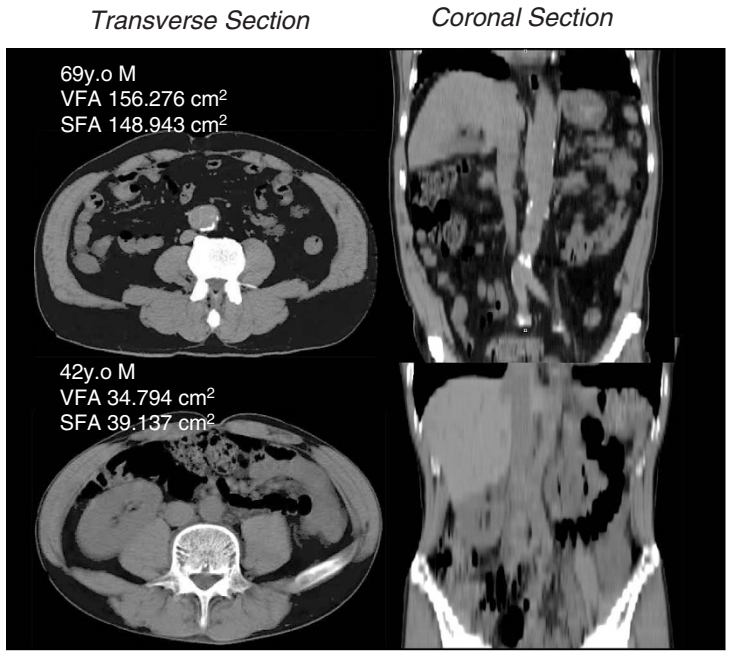

Fig. 1. *Representative MDCT images used for determination of visceral fat area and subcutaneous fat area. CT slices at the level of the umbilicus were used for the determination of areas. VFA, visceral fat area; SFA, subcutaneous fat area. Upper: a case of visceral obesity; Lower: a non-obese case.*

require the presence of visceral obesity (defined as a waist measurement of ≥85 cm in males or ≥90 cm in females) and two or more of the following minor abnormalities: 1) glucose intolerance (fasting blood glucose ≥110 mg/dl) or taking medication for diabetes, 2) serum triglyceride ≥150 mg/dl, 3) HDL cholesterol <40 mg/dl in either males and females, and 4) blood pressure ≥130/85 mmHg. Cases of severe congestive heart failure (NYHA IV), ascites, malignant tumor, thyroidal disease, and the other emaciating disorders were excluded from the study to prevent entry bias. General obesity was determined as body mass index (BMI) ≥25%, following the criteria of the Japanese Society of Obesity (*12*). ASCD in this study included coronary artery disease, cerebrovascular disease, arotic atherosclerotic disease, and atherosclerotic valvular heart disease. The subclinical forms of atherosclerosis, such as thickening of the intima in the carotid artery, were not examined and not included in ASCD in this study.

Determination of Visceral and Subcutaneous Fat Areas by MDCT

All of the MDCT images were obtained either by Aquillion 4DAS (Toshiba Inc., Tokyo, Japan) or Light Speed Ultra 8DAS (General Electrics Japan Co., Tokyo, Japan) with a minimal slice width of 5–7 mm. Data were stored on visual servers and retrospectively analyzed using commercially supplied software without information regarding patients' cardiovascular and biochemical parameters. The fat areas in each subject were determined from an image at the level of the umbilicus (Fig. 1) with Virtual Place (AZE Inc., Tokyo, Japan). Subcutaneous fat was defined as the extraperitoneal fat between skin and muscle, with attenuation ranging from −150 to −50 Hounsfield units. The intraperitoneal part with the same density as the subcutaneous fat layer was defined as visceral fat. The visceral fat area (VFA) and subcutaneous fat area (SFA) were determined by automatic planimetry.

Determination of AC

AC on CT (AC_{CT}) was determined in all subjects from CT images at the umbilical level using a mobile caliper. In 80 randomly selected subjects (37 males and 43 females), abdominal circumference (AC_M) was also measured with an anthropometric tape to confirm its correlation with AC_{CT}.

Statistical Analysis

All numeric variables are expressed as the means±SD. Differences in the incidences between groups were tested by the χ^2 test. Comparison of group mean data was performed by one-way analysis of variance (ANOVA) and Bonferroni's post hoc test. The correlation between two values was evaluated by linear and exponential regression analyses. Difference between regression lines was examined by analysis of covariance. Values of $p<0.05$ were considered statistically significant. ROC analysis was performed to determine cutoff

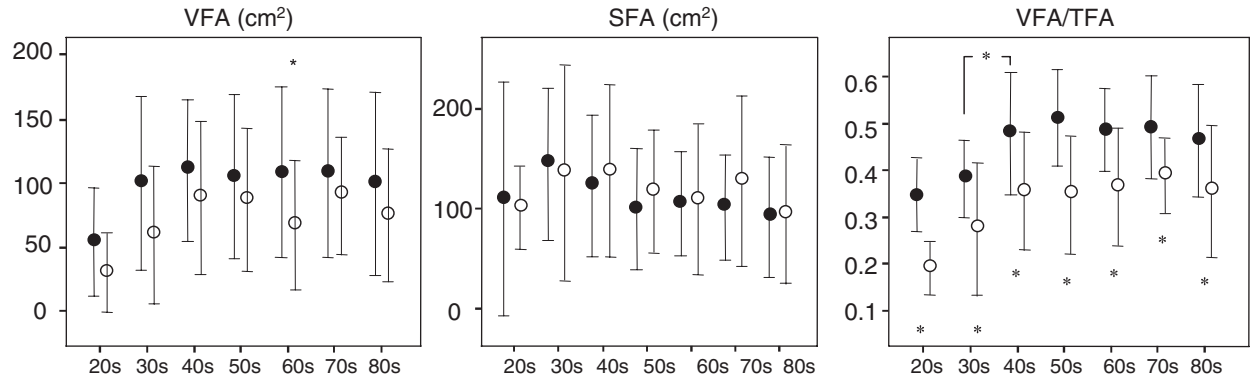

Fig. 2. *Age-related difference in the levels of visceral and subcutaneous fat accumulation. VFA, visceral fat area; SFA, subcutaneous fat area; VFA/TFA, ratio of VFA to total fat areas (VFA+SFA). Closed circles and open circles indicate the data for males and females, respectively.* *$p < 0.05$ vs. *males.*

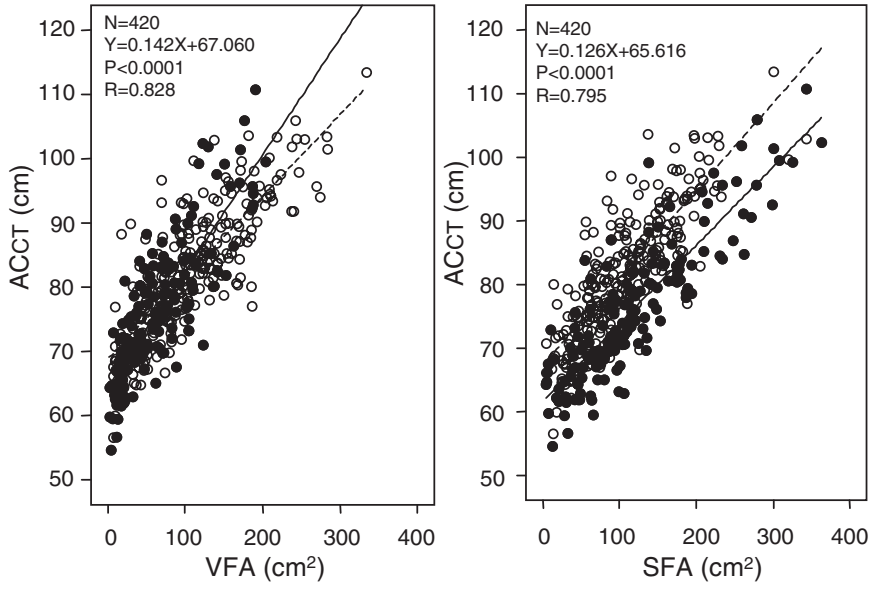

Fig. 3. *Correlation between abdominal circumference (AC_{CT}) and accumulation of visceral (VFA) and subcutaneous fat (SFA). Open circles and closed circles indicate the data for males and females, respectively. There was no significant difference in the regression lines for the AC_{CT}-VFA relationships between males (broken line) and females (solid line). However, the regression line for the AC_{CT}-SFA relationship was shifted upwards in females compared with males.*

points of VFA yielding the maximum sensitivity and specificity for predicting metabolic syndrome and ASCD.

Results

Characteristics of Subjects

As shown in Table 1, we enrolled 420 patients aged 62±15 years old (age range, 14–92 years). The age and incidences of risk factors, except for hyperuricemia and smoking, were comparable in the male and female subjects. Of the 420 patients, 180 (42.9%) had ASCD, and the incidence of coronary artery disease tended to be higher in males than in females, though the difference was not statistically significant. The percentages of subjects on pharmacological treatments for hypertension, hyperlipidemia and diabetes were 57%, 26% and 19%, respectively.

Visceral and Subcutaneous Fat Deposition in Age Subgroups

Figure 2 shows the levels of VFA and SFA and ratio of VFA to total fat area (TFA; TFA=VFA+SFA) in each age group. There was a trend for lower VFA and higher SFA in subjects

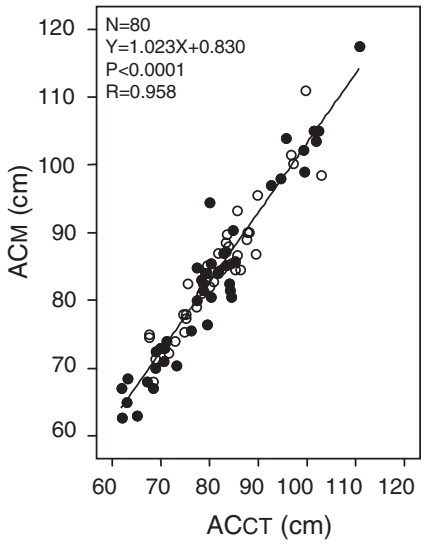

Fig. 4. *Correlation between MDCT-determined abdominal circumference (AC_{CT}) and abdominal circumference measured by anthropometric tapes (AC_M). Open circles and closed circles indicate the data for males and females, respectively.*

in their 20s. The VFA-to-TFA ratio was lower in subjects in their 20s and 30s, and this ratio was consistently lower in females than in males regardless of age. These findings suggest that an increase in visceral fat deposition occurs in the 40s and that the preference of fat deposition for the visceral compartment is more predominant in males than in females.

Relationship between Fat Deposition and AC

Both VFA and SFA correlated with AC_{CT} in both male and female subjects (Fig. 3): $AC_{CT} = 0.142 \times VFA + 67.060$, $r=0.828$, $p<0.0001$, $AC_{CT} = 0.126 \times SFA + 65.616$, $r=0.795$, $p<0.0001$. The regression line for the relationship between VFA and AC_{CT} did not differ between males and females ($Y = 0.128X + 68.517$ *vs*. $Y = 0.182X + 64.536$). As expected, TFA was strongly correlated with AC_{CT} ($r=0.815$ in males and 0.919 in females), whereas there was no significant correlation between AC_{CT} and VFA-to-SFA ratio in either gender. However, the regression line for the SFA-AC_{CT} relationship was significantly shifted upwards in females compared with that in males ($Y = 0.139X + 67.076$ *vs*. $Y = 0.123X + 61.594$, $p<0.05$ by analysis of co-variance), indicating a larger contribution of SFA to AC_{CT} in females. Since directly measured AC_M is currently used for diagnosis of visceral obesity in the criteria of metabolic syndrome, we examined the relationship between AC_{CT} and AC_M in 80 randomly selected subjects. There was a tight correlation between AC_{CT} and AC_M, as shown in Fig. 4. The regression equation for the AC_M-AC_{CT} relationship ($Y = 1.023X + 0.830$) suggests that the difference between AC_{CT} and AC_M is only a few percent on average.

Cutoff Points of VFA and AC_M for Prediction of Metabolic Syndrome and ASCD

Since VFA is a more direct measure of visceral obesity than AC_M, we used ROC analysis to detect VFA cutoff points to predict the presence of two or more components of metabolic syndrome (Fig. 5A). Although the areas under the curves (AUC) were not large, indicating that the results had limited accuracy, the VFA values of 92 cm^2 in males and 63 cm^2 in females predicted the presence of metabolic syndrome with sensitivities of 0.612 and 0.673 and specificities of 0.507 and 0.608, respectively. The exclusion of subjects on antidiabetic medications ($n=81$) from the ROC analysis did not markedly change the VFA cutoffs for predicting two or more metabolic syndrome components (97 cm^2 in males and 55 cm^2 in females).

As another method to assess the clustering of components of metabolic syndrome with increase in VFA, we also calculated the odds ratio for the presence of two or more metabolic syndrome components (except for visceral obesity) at each level of VFA. As shown in Fig. 6, the VFA cutoff giving the highest odds ratio of metabolic syndrome was 94 cm^2 in males and 74 cm^2 in females, which was consistent with the results of ROC analysis (Fig. 5). Figure 5B shows the results of ROC analysis for prediction of ASCD by VFA. At a VFA cutoff of 97.5 cm^2 in males, the sensitivity and the specificity were 0.612 and 0.504, respectively, and at a VFA cutoff of 74.6 cm^2 in females, the sensitivity and specificity were 0.602 and 0.526, respectively. These VFA cutoff values correspond to AC_M values of 84 cm in males and 80 cm in females.

We also performed ROC analysis using SFA and TFA to predict two or more components of metabolic syndrome. However, the AUC was smaller in the ROC using SFA or TFA than in the ROC using VFA (data not shown), supporting the notion that VFA is better than SFA or TFA as an index for diagnosis of metabolic syndrome.

Discussion

In the present study, we first characterized VFA, a direct index of visceral obesity, and its relationship with an indirect but easily used index of visceral obesity, AC_M. Using VFA as a basic tool, we reassessed the cutoff level of AC_M for diagnosis of visceral obesity relevant to metabolic syndrome in Japanese. The results of ROC analysis indicate cutoff levels of 92 cm^2 in males and 63 cm^2 in females, which correspond to AC_M values of 83 cm in males and 78 cm in females. This male AC_M cutoff is almost the same as the current cutoff level (85 cm), but the female AC_M cutoff was considerably smaller than the current Japanese criterion (90 cm). The validity of the new AC_M cutoff level for females needs to be further examined using larger numbers of subjects.

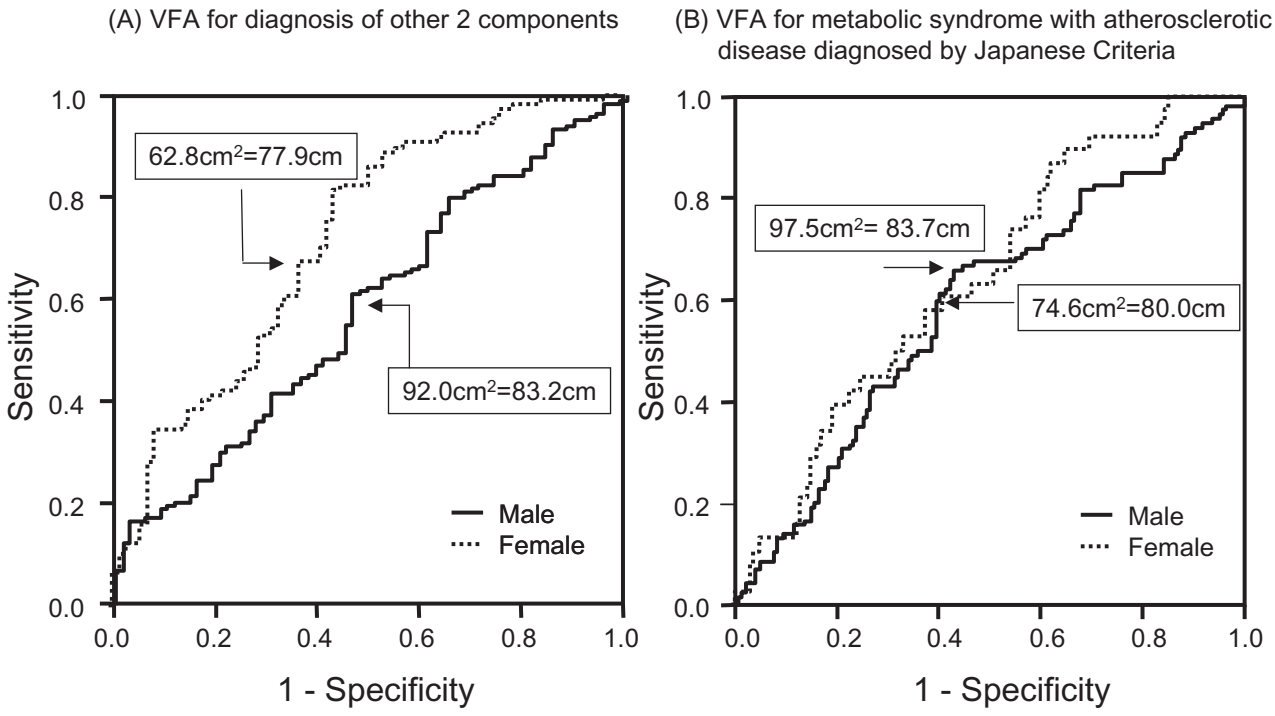

Fig. 5. *Receiver operating characteristic (ROC) analysis of VFA to predict the presence of two or more components of metabolic syndrome and ASCD. Solid lines and broken lines depict the ROC curves for males and females, respectively.*

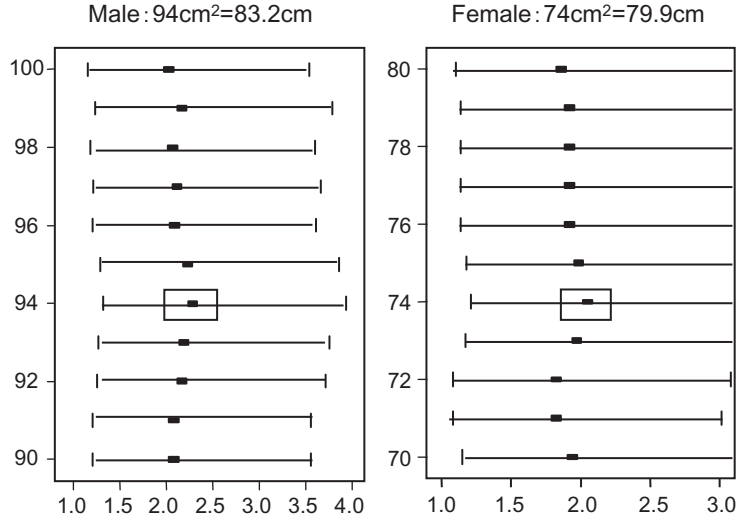

Fig. 6. *Odds ratio for the presence of two or more components of metabolic syndrome at each level of VFA. An odds ratio was calculated for every cm² of VFA and is presented along with the confidential interval. The highest odds ratio was given by a VFA of 94 cm² in males and by a VFA of 74 cm² in females.*

Definition of Visceral Obesity as a Component of Metabolic Syndrome in Japanese

In both the latest criteria by IDF (*8*) and the Japanese criteria (*9*), visceral obesity is a requisite factor in metabolic syndrome. The cutoff levels of AC_M in the Japanese criteria (*i.e.*, 85 cm in males and 90 cm in females) were defined as the values that correspond to VFA of 100 cm² in abdominal CT in each gender. The rationale for this level of VFA was the association of VFA larger than 100 cm² with more than one obesity-related disease (*i.e.*, hyperglycemia, dyslipidemia and hypertension) in the pooled data from both males and

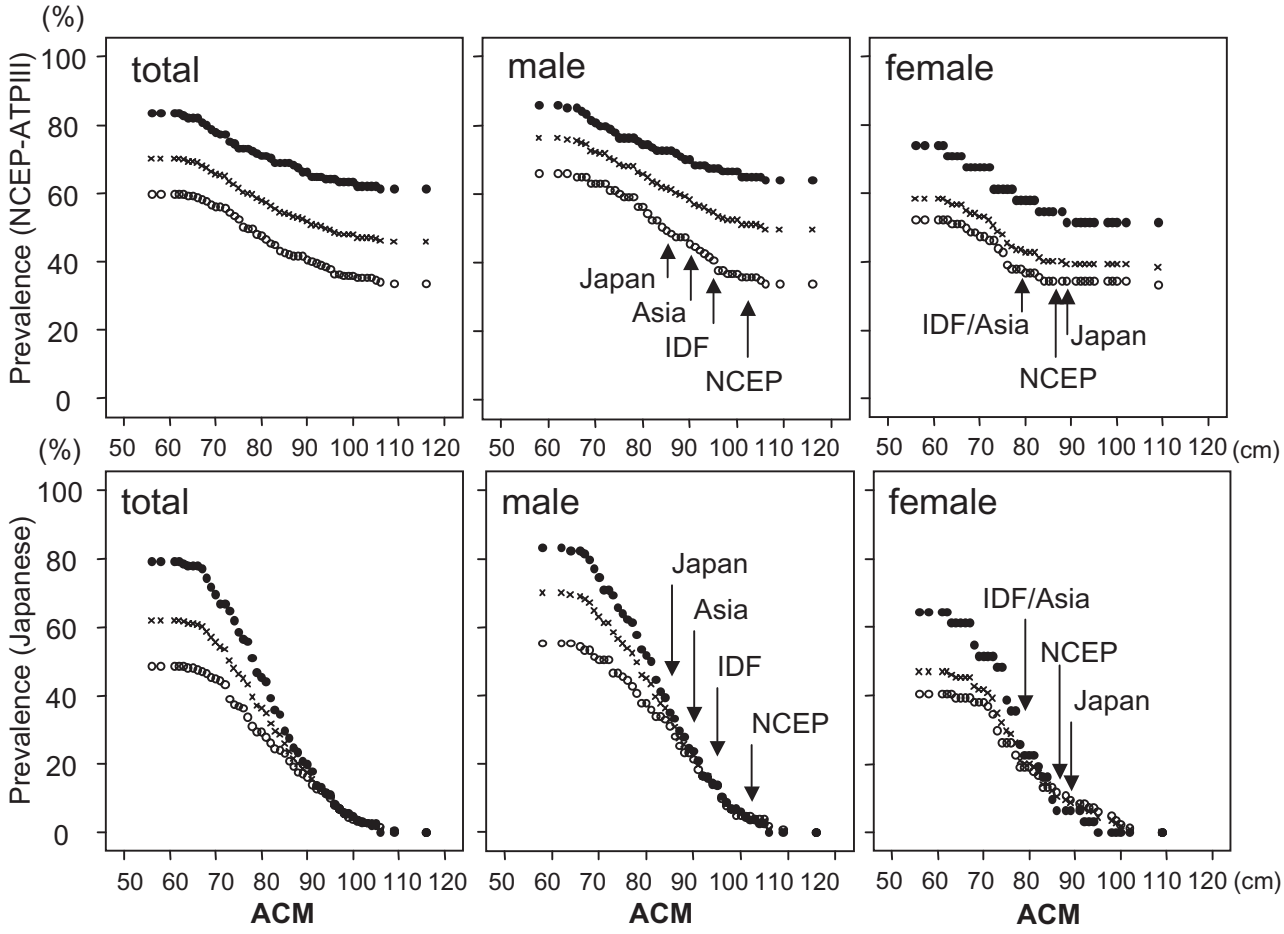

Fig. 7. *Relationship between the cutoff level of abdominal circumference and prevalence of metabolic syndrome. Upper: NCEP-ATP III–defined metabolic syndrome; Lower: metabolic syndrome defined by the current Japanese criteria. Open circles, closed circles and cross symbols represent relationships in subjects without ASCD, those with ASCD and all subjects, respectively.*

females. However, it has not been confirmed that the relationship between the level of VFA and the number of associated obesity-related diseases is quantitatively the same in both genders. Actually, a gender difference in the association of visceral fat accumulation with the other components of metabolic syndrome was recently reported by Miyawaki *et al*. (*13*) and was confirmed in the present study as well (Fig. 5). Miyawaki *et al*. (*13*) analyzed data from 3,574 Japanese subjects aged 40–59 years obtained during health examinations. The sensitivity and the specificity of VFA cutoff to predict metabolic syndrome were 0.72 and 0.55 at 95 cm^2 and 0.67 and 0.60 at 100 cm^2 in males, and the values in females were 0.73 and 0.70 at 65 cm^2 and 0.66 and 0.74 at 70 cm^2. These gender-dependent VFA cutoff levels are similar to those obtained in the present study (Fig. 5), indicating the need to define a VFA cutoff for each gender.

AC_M is a less accurate measure of visceral obesity than is VFA, but it is easier to use for screening of metabolic syndrome. Based on the VFA cutoff level for predicting metabolic syndrome in each gender and the regression equation for the VFA-AC_M relationship (Fig. 3), the AC_M cutoff levels for males and females were calculated in the present study to be 83 cm and 78 cm, respectively. Miyawaki *et al*. (*13*) calculated AC_M cutoff levels for males and females of 86 cm and 77 cm, respectively, based on their VFA cutoff levels of 100 cm^2 in males and 65 cm^2 in females. Although VFA was not determined in their study, Hara *et al*. (*14*) recently applied the waist circumference data for 692 subjects (age: 30–80 years) who had undergone annual health examinations to ROC analysis to determine the AC_M cutoff for diagnosis of metabolic syndrome. They found that the cutoff levels of AC_M yielding maximum sensitivity and specificity were 85 cm for males and 78 cm for females. The difference was partly due to the fact that they measured waist circumference at the mid-level between the lowest rib and the iliac crest, and that measurement in females is a few centimeters longer than AC_M (at the umbilicus level). Thus, Hara *et al*. (*14*) also estimated AC_M cutoff levels for males and females of ~85 cm and ~80 cm,

respectively. Taken together, the results of these two recent studies (*13*, *14*) and the results of the present study on Japanese subjects support the notion that the appropriate AC_M cutoff level for diagnosis of metabolic syndrome in Japanese females is 78–80 cm.

Prevalence of Metabolic Syndrome and Cutoff Level for Diagnosis of Visceral Obesity

To illustrate the effect of change in the cutoff level of visceral obesity on the prevalence of metabolic syndrome, we plotted the calculated prevalence of metabolic syndrome in the subjects for a range of AC_M cutoff levels (Fig. 7). The prevalence of NCEP-ATP III–defined metabolic syndrome was less sensitive to change in the AC_M cutoff level than was the prevalence of metabolic syndrome defined by the Japanese criteria, since visceral obesity is not a requisite in the former criteria. As shown in Fig. 7, the prevalences of NCEP-ATP III–defined metabolic syndrome in males were 51.0%, 59.2% and 62.0% for AC_M cutoff levels of 102 cm (NCEP-ATP III), 90 cm (IDF for Asians), and 85 cm (Japanese criteria). The prevalences were reduced to 35.9%, 47.6% and 50.5% when they were calculated for subjects without ASCD. The prevalences in females were 40.5%, 43.9% and 39.6% for AC_M cutoff levels of 88 cm (NCEP-ATP III), 80 cm (IDF for Asians) and 90 cm (Japanese criteria), respectively, and these values were reduced to 34.4%, 38.0% and 34.4%, respectively, when calculated for subjects without ASCD. In contrast, the prevalence of metabolic syndrome defined by the Japanese criteria is strongly dependent on AC_M cutoff levels: male AC_M cutoff levels of 102, 94, 90, and 85 cm give prevalences of metabolic syndrome of 4.6%, 16.0%, 23.8%, and 36.2%, and female AC_M cutoff levels of 88, 80, 90 and 78 cm give prevalences of 10.3%, 19.8%, 8.6% and 25.8%, respectively. Thus, the use of an AC_M cutoff level of 78 cm, which is suggested by the present results, triples the prevalence of metabolic syndrome in the present subjects.

In the recent Tanno-Soubetsu Study (*15*), the prevalence of metabolic syndrome as defined by the modified NECP-ATP III criteria (AC_M cutoff=85 cm) was 25.3% in 808 males undergoing health examinations, and their incidence of cardiovascular events was almost two-fold higher than that in subjects without metabolic syndrome (11.7% *vs*. 6.7%) during a 6-year follow up. The prevalence of metabolic syndrome in the present male subjects was approximately two-fold higher than that in the male subjects in the Tanno-Sobetsu Study, but this is likely to be due to selection bias in the present study. First, the subjects in the present study were older by 3 years (63±14 years old *vs*. 60±12 years old) and preferred in-hospital examination for ASCD and/or known coronary risks. Second, the proportion of subjects with ASCD was higher in this study than in the epidemiological studies. Nevertheless, the present study suggested that the prevalence of metabolic syndrome is lower in females than in males even when an AC_M cutoff of 78–80 cm was used for females. Whether metabolic syndrome in females has the impact on the cardiovascular events that it has in males will need to be investigated in large cohort studies.

Cutoff Level for Visceral Obesity and ASCD

Recent studies have shown that metabolic syndrome is associated with endothelial dysfunction (*16*), a hallmark of early atherosclerotic change, calcification of the coronary artery (*17*, *18*), and subclinical atherosclerosis of the carotid artery (*19*, *20*). On the other hand, obesity *per se* is an established risk factor of ASCD. Thus, we postulated that the AC_M cutoff to predict ASCD might be larger than that to predict metabolic syndrome, which consists of clustered minor risk factors. However, the AC_M cutoff level to predict metabolic syndrome and that to predict ASCD were very similar (Fig. 5B) in the present study. These results may suggest that the level of visceral obesity does not need to be higher than the level of obesity in metabolic syndrome in order for patients to develop ASCD. Nevertheless, the AC_M cutoff levels for diagnosis of metabolic syndrome appear to also be useful for selecting patients who should be screened for ASCD.

Limitations in the Present Study

There were several limitations in the present study. First, data collection was formed in a single institute by use of a retrospective and non-randomized method, which could have resulted in selection bias. Second, since this study is cross-sectional, a sequential relationship between visceral obesity and development of ASCD cannot be established. Third, a substantial number of the subjects were receiving treatment, including lifestyle modification and medications. Although the presence of diabetes mellitus does not preclude diagnosis of metabolic syndrome (*7*–*9*), it has profound effects on the metabolic profiles in patients. Furthermore, a recent Treating to New Targets (TNT) study (*21*) suggested that diabetes mellitus increases the incidence of cardiovascular events in patients with metabolic syndrome. Thus, it may be problematic to determine the VFA cutoff level for diagnosis of visceral obesity by use of mixed data from diabetic and non-diabetic populations. Fourth, we did not perform age-adjustment when calculating the AC_M cutoff, though there was a trend of age-dependent changes in VFA. Therefore, a further investigation using a large population with age-adjustment needs to be performed for obtaining a precise estimation of AC_M cutoff for diagnosis of metabolic syndrome in Japanese.

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