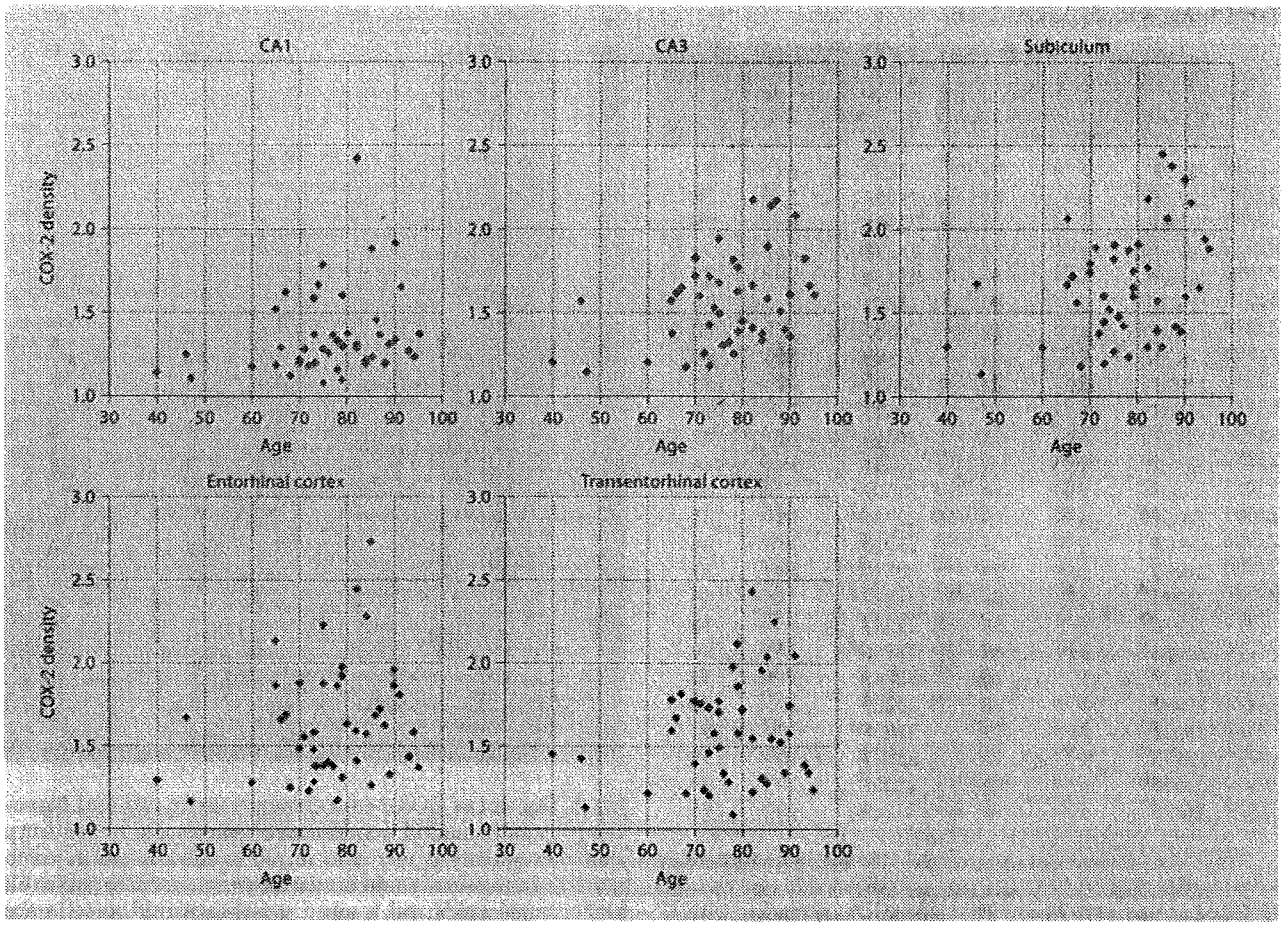

Fig. 3. A significant correlation exists between aging and COX-2 immunoreactivity in CA3 and the subiculum of nondemented subjects. In nondemented subjects, aging correlates with COX-2 immunoreactivity in CA3 and the subiculum (Pearson's correlation coefficient test, r = 0.399, p = 0.007; r = 0.380, p = 0.010, respectively).

sion of the hippocampus and subiculum of nondemented subjects, COX-2 immunoreactivity correlated with age (Pearson's correlation coefficient test, r = 0.399, p = 0.007; r = 0.380, p = 0.010, respectively) and this correlation was not evident in the CA1 subdivision of the hippocampus, entorhinal cortex or transentorhinal cortex (Pearson's correlation coefficient test, r = 0.268, p = 0.078; r = 0.220, p = 0.147; r = 0.194, p = 0.202, respectively).

Study B

Information of Nondemented Subjects and AD Patients

In study B, in order to compare the nondemented subjects with AD patients, we examined 25 nondemented subjects aged 76 years or more from study A and we collected another 25 age- and sex-matched AD autopsy cases derived from Hisayama Town (table 1). All of the AD patients were free of other types of dementia.

COX-2 Immunoreactivity in the Hippocampus

The degrees of COX-2 immunoreactivity in different hippocampal subdivisions of nondemented subjects and AD patients are shown in figure 4. The immunoreactivity in CA1 was increased in AD patients as compared to nondemented subjects with high statistical significance (Mann-Whitney U test, p = 0.001; fig. 2c, e). On the other hand, the differences between the nondemented subjects and AD patients were small in CA3, subiculum, entorhinal cortex and transentorhinal cortex (Mann-Whitney U test, p = 0.171, p = 0.467, p = 0.712, p = 0.621,

Table 1. Subjects of study B

Nondemented subjects			Age- and sex-matched AD patients		
ID	Sex	Age	ID	Sex	Age
22735	F	76	23297	F	77
22907[C]	F	77	21363	F	78
22880	F	78	22598	F	79
22939[C]	M	78	23373	M	79
22739	F	79	23114	F	79
22910[C]	F	79	23392	F	79
22819	M	79	20565	M	80
22803	M	80	23185	M	81
22933	M	82	20189	M	83
22828[C]	F	82	20617	F	82
22892	M	82	20316	M	83
22772[C]	F	84	20461	F	84
23015[C]	F	84	22502	F	84
23061	M	85	20706	M	85
22906	F	85	23018	F	84
22950	F	86	20240	F	87
22795	M	87	21501	M	86
22976[C]	F	88	23334	F	88
22798	M	89	22156	M	90
22767	F	90	20748	F	90
22992	F	90	23289	F	90
23021[C]	M	91	23028	M	92
22955[C]	F	93	23377	F	93
23055[C]	F	94	22661	F	94
22896[C]	F	95	23269	F	95

We studied all subjects aged >76 years of the 45 nondemented subjects of study A. As a comparison, we collected 25 age- and sex-matched AD patients. The subjects whose IDs are marked with 'C' are nondemented subjects with AD pathology (CERAD: moderate or frequent, with Braak and Braak stage 4, 5 or 6) and are the subjects of study C.

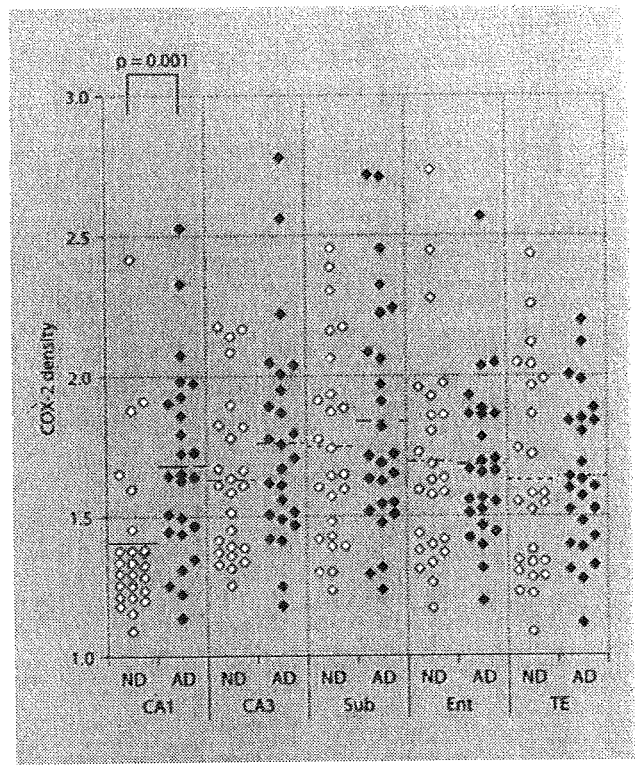

Fig. 4. Degrees of COX-2 immunoreactivity in different hippocampal subdivisions of nondemented subjects and AD patients. Immunoreactivity is increased in AD patients as compared to nondemented subjects, and the increase is observed in almost all hippocampal fields and reached statistical significance in the CA1 field (Mann-Whitney U test, p = 0.001). Bars represent the mean density of neurons in each area.

respectively). From these results, COX-2 immunoreactivity in CA1 has presumably been induced along with the development of AD; therefore, we assessed the influence of AD pathology on neuronal COX-2 expression in CA1.

COX-2 Immunoreactivity in CA1 Correlates with SP and NFT Density in AD Patients

In the CA1 subdivision of the hippocampi of AD patients, COX-2 immunoreactivity correlated with the semiquantification of SPs (Spearman's rank correlation test, $\rho = 0.500$, $p = 0.001$; fig. 5a) and with the number of NFTs (Pearson's correlation coefficient test, $r = 0.536$, $p = 0.003$; fig. 5b). On the other hand, in the CA1 subdivision of the hippocampi of nondemented subjects, COX-2 immunoreactivity did not correlate with either the semiquantification of SPs (Spearman's rank correlation test, $\rho = 0.013$, $p = 0.949$) or the number of NFTs (Pearson's correlation coefficient test, $r = -0.141$, $p = 0.501$).

Study C

In the Hisayama study, we sometimes encountered autopsy cases that were cognitively normal though exhibited severe Alzheimer type pathology in their brains. Therefore, in study C, we compared the immunoreactivity of COX-2 in CA1 of 11 nondemented subjects with AD pathology (CERAD: moderate or frequent, with Braak and Braak stage 4, 5 or 6; table 1) with that of 11 age- and sex-matched AD patients. The immunoreactivity of COX-

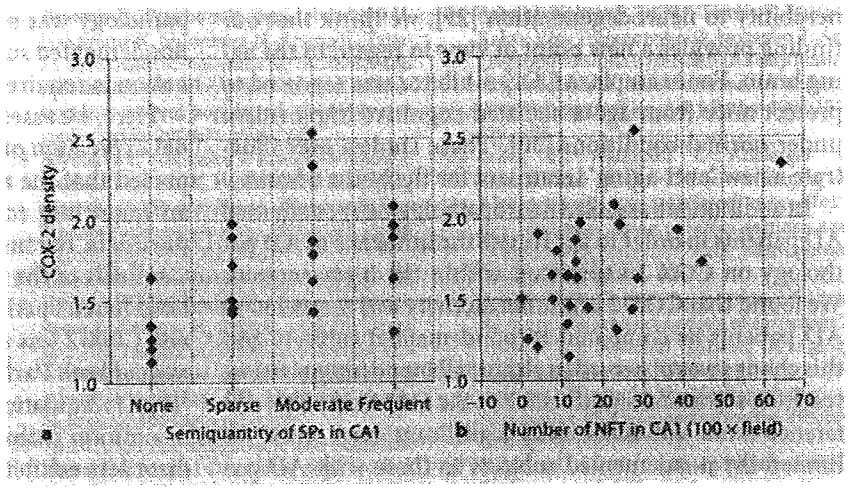

Fig. 5. COX-2 immunoreactivity in CA1 correlates with SP (**a**) and NFT (**b**) density in AD patients. The semiquantitative density of SPs in CA1 was determined using guidelines established by CERAD. In AD patients, a correlation between COX-2 immunoreactivity and the semiquantitative density of SPs in CA1 was statistically significant (Spearman's rank correlation test, $\rho = 0.500$, $p = 0.001$). Also, a correlation between COX-2 immunoreactivity and the density of NFT in CA1 was statistically significant (Pearson's correlation coefficient test, $r = 0.536$, $p = 0.003$).

2 in CA1 of AD patients was obviously stronger than in nondemented subjects with AD pathology (Mann-Whitney U test, $p < 0.001$; fig. 6).

Discussion

To our knowledge, this is the first report that explores the regional distribution of COX-2 immunoreactivity in the hippocampi of nondemented subjects of a general population. We found that among nondemented subjects, COX-2 immunoreactivity in CA3, subiculum, entorhinal cortex and transentorhinal cortex was widespread, suggesting that COX-2 is constitutively expressed in these subdivisions of the hippocampus, whilst weak immunoreactivity was observed in CA1. In addition, in the CA3 subdivision of the hippocampi and subiculum of nondemented subjects, COX-2 immunoreactivity correlated with age, suggesting that the COX-2 expression in this region was augmented with aging in the normal condition.

Strong expression of COX-2 in the CA3 subdivision of the hippocampus and expression of COX-2 in the subiculum was reported previously in the normal rat brain [27]. Also, an immunohistochemical study of the human hippocampus showed more COX-2 positive neurons to be present in the CA3 than in the CA1 or CA2 field, and this difference became clearer when analysis was limited to dense staining [11]. These results are compatible with our data and indicate that our staining and assessment of COX-2 are reasonable and also suggest the constitutive expression of COX-2 in these subdivisions of the hippocampus.

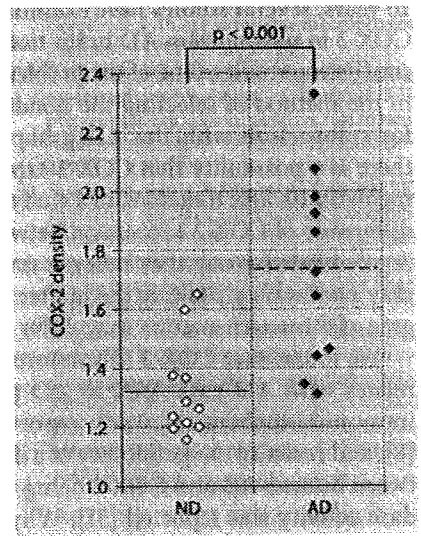

Fig. 6. Degrees of COX-2 immunoreactivity in the CA1 subdivision of the hippocampus of nondemented subjects with AD pathology and AD patients. COX-2 immunoreactivity is increased in AD patients as compared to nondemented subjects (Mann-Whitney U test, $p < 0.001$). Bars represent the mean density of neurons in each area.

The enhanced expression of COX-2 with age was reported in a study examining aged mouse macrophages [28], but little is known about changes in COX-2 expression in the human brain during aging. Now that several inflammatory processes are thought to play a critical role in brain aging and to be associated with an increased vul-

nerability to neurodegeneration [29], we think that our finding provides a new point of view in regard to the aging brain. For example, a COX inhibitor was reported to protect mice from age-associated cognitive impairment under normal conditions [30]. These studies may illustrate a new 'anti-aging' treatment for the human brain.

In addition, we assessed neuropathologically confirmed AD patients in order to appreciate the influence of AD pathology on COX-2 expression within the hippocampus. We found that COX-2 immunoreactivity was increased in AD patients as compared to nondemented subjects and this change was observed in almost all hippocampal fields, reaching statistical significance in the CA1 field. This difference remained statistically significant even when we limited the nondemented subjects to those with AD pathology. In other words, the upregulation of COX-2 in the CA1 field in conjunction with AD pathology may be one of the important factors for developing AD. Over the last 10 years, several studies have examined the expression of COX-2 in postmortem AD brain tissues but have yielded conflicting results. One of the problems in these studies is in the method of selecting the nondemented group used for comparison with the AD group. As we mentioned, there is a possibility that COX-2 expression may be augmented with age; therefore, in a study of aged subjects, the difference of COX-2 expression between the AD and the nondemented group may become small and the opposite may also be true. Making the matter complicated, the degree of this augmentation may differ in each area.

We found that COX-2 immunoreactivity in CA1 correlates with AD pathology in AD patients. A previous immunohistochemical study reported a similar result [8], and recently the possibility of a direct interaction between human Aβ and COX-2 being mediated by peroxidase activity was reported [31]. Why the correlation between COX-2 immunoreactivity in the CA1 field and AD pathology was observed only in AD patients and not in nondemented subjects is still unclear and further examination is required.

Here, we assessed the relationship between the neuronal expression of COX-2 and AD. It has recently been reported that the neuronal expression of COX-2 may play an important role in other types of neurodegenerative disorders. For instance, neuronal COX-2 expression in all CA fields of the hippocampus was significantly upregulated in ALS patients as compared to control subjects [13] and COX-2 was upregulated in brain dopaminergic neurons of both Parkinson's disease and MPTP-treated mice [12]. Upregulation of neuronal COX-2 expression may be a common pathway that a variety of neurodegenerative disorders exhibit.

In conclusion, in this study we have explored the regional expression of COX-2 in the hippocampus of the normal brain, and based on this result we have also explored the correlation between AD pathology and COX-2 expression in this region. While COX-2 expression appears to be differently regulated amongst hippocampal subdivisions and its presence may be augmented with age in the cognitively normal brain, COX-2 expression within the CA1 field of AD brains may be associated with the cognitive decline to some extent.

Acknowledgments

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Original Article

Relationship between Visceral Fat and Cardiovascular Disease Risk Factors: The Tanno and Sobetsu Study

Yu CHIBA[1)], Shigeyuki SAITOH[1)], Satoru TAKAGI[1)], Hirofumi OHNISHI[1)], Nobuo KATOH[1)], Junichi OHATA[1)], Motoya NAKAGAWA[1)], and Kazuaki SHIMAMOTO[1)]

We assessed the amount of visceral fat using ultrasonography (US) and studied its relationship to cardiovascular disease risk factors, particularly blood pressure. The subjects in the first study were 45 male and 61 female outpatients. We measured the visceral fat area (VFA) of each subject using abdominal CT and waist circumference (WC), and visceral fat distance (VFD) using US. The subjects in the second study were 353 male and 457 female inhabitants of a rural community, for whom VFD and WC were measured. We divided subjects into tertiles based on VFD and WC, and studied the relationship between each group and individual risk factors. In an analysis of outpatient subjects, the correlation coefficient between VFA and VFD was satisfactory: r=0.660 for men and r=0.643 for women. In the analysis of the rural subjects, the high VFD group had a significantly higher odds ratio than the low VFD group in high blood pressure (HBP) and hypertriglyceridemia (HTG) for men and in HBP, HTG and low high-density lipoprotein cholesterolemia (LHDL) for women. Moreover, adjusting VFD for body mass index revealed that, in comparison to WC, VFD was significantly related to risk factors. VFD was used as an independent variable in multiple regression analysis with blood pressure level as a dependent variable; no significant association between WC and blood pressure was obtained. Visceral fat assessment by US may be useful for epidemiological study and for clinics with no abdominal CT equipment for identifying high-risk individuals, such as those with metabolic syndrome. (*Hypertens Res* 2007; 30: 229–236)

***Key Words*: ultrasonography, visceral obesity, cardiovascular disease risk factors, waist circumference, hypertension**

Introduction

Obesity is often complicated by arteriosclerotic diseases such as hypertension, ischemic heart disease and cerebrovascular disease as well as by their risk factors (*1*, *2*). Since the late 1980s, these complications have been explained by the concept of a multiple risk factor syndrome such as syndrome X (*3*), the deadly quartet (*4*), and visceral fat syndrome (*5*). More recently, the term metabolic syndrome (MS) has been adopted by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) (*6*). Visceral obesity, in which fat markedly accumulates in the peritoneal mesentery and around the greater omentum, is thought to be a fundamental pathology for MS in particular. The incidence of cardiovascular disease is high even in non-obese individuals with a body mass index (BMI) within the normal range who have an accumulation of visceral fat (*7*), and accurate assessment of both body fat distribution and visceral fat accumulation is critical for assessing the risk of arteriosclerotic disease.

Previous studies have shown that waist-to-hip ratio, waist-to-height ratio, waist circumference (WC), and visceral fat

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assessed by abdominal CT are relatively good indicators of the risk of cardiovascular disease (*8–13*). Abdominal CT enables quantification of the visceral fat area (VFA) and therefore serves as the gold standard for visceral fat assessment. On the other hand, WC measurement is recommended as a simpler and easier screening method (*14*). However, abdominal CT has drawbacks, including exposure to radiation, lack of ease and simplicity, and high cost. WC includes subcutaneous fat, and WC measurement therefore has drawbacks such as an inability to account for an individual's height and a low level of reproducibility in the case of marked obesity.

Simple methods for assessing visceral fat accumulation using ultrasonography (US) have been studied in recent years (*15–20*). In addition, previous studies have indicated a relationship between hypertension and visceral fat assessed by abdominal CT and WC, but US was not used in any of those studies (*21–24*). Thus, in the present study, we assessed the usefulness of visceral fat assessment by US in outpatients. Then, based on the results of a cross-sectional study, we assessed the relationships between abdominal obesity determined by US and cardiovascular disease risk factors, particularly blood pressure levels.

Methods

Study 1

The subjects were 45 men and 61 women outpatients (mean ages: 55.4±19.4 years for men and 67.5±10.8 years for women). Individuals with cardiovascular disease, renal disease or a severe debilitating disease were excluded from participation. Height, body weight, WC, VFA and total fat area (TFA) were determined by abdominal CT, and visceral fat distance (VFD) was determined by US. The subcutaneous fat area (SFA) was calculated by subtracting VFA from TFA.

Informed consent was obtained from each outpatient, who completed a form consenting to testing. Height, body weight and visceral fat levels were measured on the same day, and BMI was calculated. Correlations between VFA, SFA, VFD, BMI and WC were investigated.

Measurement of Visceral Fat Levels

CT equipment from Toshiba Medical Systems (Tokyo, Japan) was used for abdominal CT. Imaging was done at the end of expiration at the umbilical level. Tracing in cross-sectional images was done using a trackball; the total cross-sectional area was determined by automatic calculation of portions with a CT number of −200 to 1,000 Hounsfield units (HU) using the method of Grauer *et al.* (*25*). In addition, portions with a CT number of −200 to −10 HU were separated as adipose tissue and their areas were automatically calculated.

WC was measured with non-stretchable measuring tape while subjects bared the circumference of the abdomen. The umbilical circumference was measured in increments of 0.1 cm during expiration while standing (*14*).

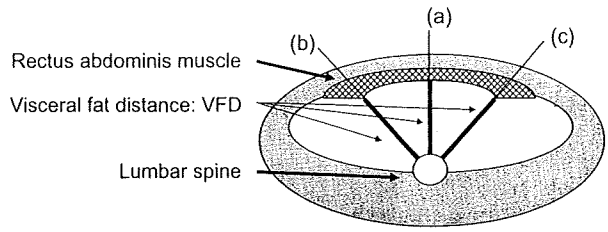

Fig. 1. *VFD was measured between the peritoneum and the lumbar spine, and which was taken as the average value. VFD = (a + b + c)/3. Each subject assumed a supine position, and at the end of expiration the distance from the peritoneum to the front of the vertebral body was measured perpendicularly three times with a 3.5 MHz linear probe while making the slightest contact possible, and the average value was used as the VFD.*

VFD was measured using VF-750XT portable ultrasonography equipment (Fukuda Electrical, Tokyo, Japan) by the method of Stolk *et al.* (*18, 19*). That is, each subject assumed a supine position, and at the end of expiration the distance from the peritoneum to the front of the vertebral body was measured perpendicularly three times with a 3.5 MHz linear probe while making the least possible amount of contact, and the average value was used as the VFD (Fig. 1). All measurements were performed by the same investigator.

Study 2

The subjects were 353 men and 457 women (mean ages: 62.8±12.2 years for men and 57.8±12.6 years for women) out of 1,455 individuals who underwent screening for local residents of a rural community; individuals being treated for hypertension, diabetes or hyperlipidemia were excluded. The study was approved by the Ethics Committee of Sapporo Medical University, and written informed consent was obtained from each subject.

For all subjects, height and body weight were measured after fasting for 8 h or longer since their last meal, blood pressure levels were measured and blood samples were taken. The blood samples were used to measure high-density lipoprotein (HDL)–cholesterol levels (HDL-c), triglyceride levels (TG), fasting plasma glucose levels (FPG) and serum insulin levels. Afterwards, WC and VFD were measured. Height and body weight were measured at intervals of 0.1 cm and 0.1 kg, respectively, with subjects lightly dressed and shoes removed. Blood pressure was measured twice consecutively on the upper arm using an automated sphygmomanometer (HEM-907, Omron Instruments, Tokyo, Japan) with subjects in a seated resting position, and the average was used for systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Table 1. Characteristics of the Subjects for Study 1

	Men (n=45)	Women (n=61)	p-value
Age (years)	55.4±19.4	67.5±10.8	<0.001
Body weight (kg)	67.1±11.8	56.4±8.8	<0.001
BMI (kg/m^2)	24.2±3.2	24.7±3.9	0.462
Lean: BMI<22	11/45 (24%)	14/61 (23%)	
Overweight: 22≤BMI<25	17/45 (38%)	23/61 (38%)	
Obese: 25≤BMI	17/45 (38%)	24/61 (39%)	
WC (cm)	84.9±8.8	85.6±10.1	0.787
VFD (cm)	5.2±1.2	4.9±1.43	0.459
SFA (cm^2)	147.0±63.8	221.2±132.4	<0.001
VFA (cm^2)	137.0±62.6	128.9±51.8	0.606

All values are mean±SD. BMI, body mass index; WC, waist circumference; VFD, visceral fat distance; SFA, subcutaneous fat area; VFA, visceral fat area.

Table 2. Correlation between Adipose Tissue Measured by CT and Other Anthropometric Parameters

	Adipose tissue measured by CT	
	SFA	VFA
Men (n=45)		
BMI	0.763*	0.565*
WC	0.861*	0.646*
VFD	0.237	0.660*
Women (n=61)		
BMI	0.591*	0.571*
WC	0.595*	0.499*
VFD	0.289**	0.643*

Values are Pearson's correlation coefficients. *p<0.001, **p<0.05. SFA, subcutaneous fat area; VFA, visceral fat area; BMI, body mass index; WC, waist circumference; VFD, visceral fat distance.

Measurement Methods

HDL-c was measured by the enzymatic method (homogenous), TG was measured by the enzymatic colorimetric method (free glycerol elimination), FPG was measured by the GOD immobilized oxygen electrode maximum reaction acceleration method, and serum insulin level was measured by the enzyme immunoassay method. In addition, homeostasis model assessment index (HOMA-IR) was calculated on the basis of FPG and serum insulin levels (*26*).

Diagnostic Criteria for Cardiovascular Disease Risk Factors

Diagnostic criteria for cardiovascular disease risk factors followed the NCEP ATPIII criteria for MS (*6*). High blood pressure (HBP) was defined as SBP ≥130 mmHg and/or DBP ≥85 mmHg or higher, hypertriglyceridemia (HTG) was defined as TG ≥150 mg/dl, low HDL cholesterolemia (LHDL) was defined as HDL-c <40 mg/dl for men and <50 mg/dl for women, and high fasting plasma glucose (HFPG) was defined as FPG ≥110 mg/dl.

Statistical Analysis

Statistical analysis was done using Windows SPSS version 11.5J. Numerical values are shown as means (mean)±SD. The correlation between two variables was evaluated using Pearson's correlation coefficient. Comparison between two groups was done with an unpaired t-test. For logistic regression analysis, subjects were divided into tertiles based on VFD and WC, adjusted for age (model 1) and then adjusted for age and BMI (model 2); with the low VFD and low WC groups as a reference, odds ratios (OR) and individual cardiovascular disease risk factors were examined. Comparison of three groups was done by multiple comparisons after one-way ANOVA. For multiple regression analysis, blood pressure level served as a dependent variable, and the relationships between cardiovascular disease risk factors with VFD and WC were studied. In all instances, the level of significance was p<0.05.

Results

Study 1

Table 1 shows characteristics of the 45 male and 61 female outpatient subjects whose visceral fat levels were measured by abdominal CT. No significant difference between the male and female subjects was found in BMI, WC, VFD or VFA. SFA was significantly larger for women than for men.

The correlations between SFA and VFA determined by abdominal CT and BMI, VFD and WC are shown in Table 2. The correlation coefficients between VFA and VFD were r=0.660 (p<0.001) for men and r=0.643 (p<0.001) for women. In addition, VFA had a stronger correlation to VFD than to BMI or WC. Moreover, BMI and WC had stronger

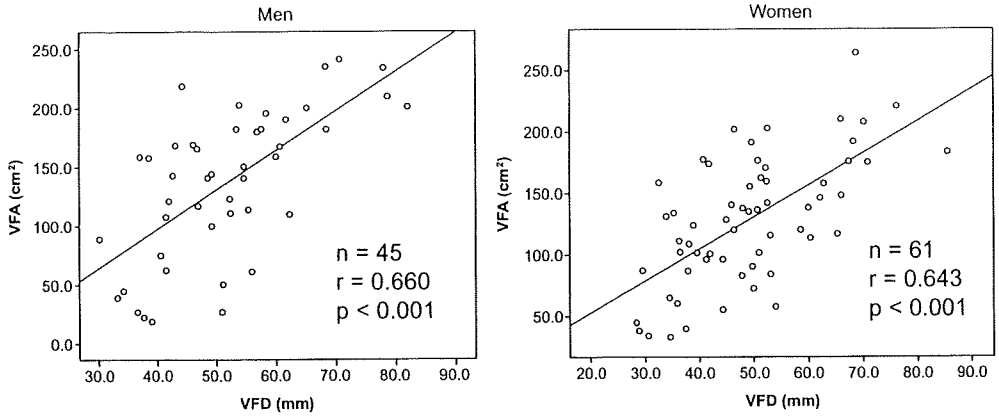

Fig. 2. *Scattergrams of relationship between VFD and VFA for men and women. VFD, visceral fat distance assessed by ultrasonography; VFA, visceral fat area assessed by CT. There were significant positive correlations between VFD and VFA in both men and women.*

Table 3. Characteristics of the Study Subjects of Residents of a Rural Community

	Men (n=353)	Women (n=457)	p-value
Age (years)	62.8±12.2	57.8±12.6	<0.001
Body weight (kg)	63.9±10.1	53.7±7.6	<0.001
BMI (kg/m²)	23.7±3.2	23.0±3.2	0.002
Lean: BMI<22	107/353 (30%)	177/457 (39%)	
Overweight: 22≤BMI<25	143/353 (41%)	171/457 (37%)	
Obese: 25≤BMI	103/353 (29%)	109/457 (24%)	
WC (cm)	84.7±9.1	82.6±9.9	0.002
VFD (cm)	5.5±1.7	4.7±1.3	<0.001
SBP (mmHg)	131.9±20.1	127.0±21.2	0.001
DBP (mmHg)	75.5±11.6	71.9±10.6	<0.001
HDL-c (mg/dl)	51.3±11.7	59.3±14.5	<0.001
TG (mg/dl)	115.1±75.2	88.3±49.2	<0.001
FPG (mg/dl)	96.8±15.7	94.4±17.7	0.041
Serum insulin levels (μU/ml)	4.5±4.7	4.4±2.9	n.s.
HOMA-IR	1.13±1.38	1.04±0.72	n.s.

All values are mean±SD. BMI, body mass index; WC, waist circumference; VFD, visceral fat distance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein-cholesterol; TG, triglyceride; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment index; n.s., not significant.

correlations to SFA than to VFA (Table 2).

Figure 2 shows scattergrams of the relationships between VFD and VFA for men and women. There were significant positive correlations between VFD and VFA in both sexes.

Study 2

Table 3 shows the characteristics of the subjects in Study 2. Average VFDs were 5.5±1.7 cm for men and 4.7±1.3 cm for women, and average WCs were 84.7±9.1 cm for men and 82.6±9.9 cm for women.

The subjects were divided into tertiles based on VFD and WC; OR for cardiovascular disease risk factors with individual low-tertile groups as a reference are shown in Table 4. Adjusted only for age (model 1), OR increased significantly for the male VFD group in comparison to that for the low VFD group in HBP (OR: 3.45 [95% CI: 1.83–5.77]; p<0.001) and HTG (OR: 3.74 [1.72–8.12]; p<0.05), and it increased significantly for the female group in HBP (OR: 2.31 [1.37–3.92]; p<0.05), HTG (OR: 13.3 [3.02–58.5]; p<0.05) and LHDL (OR: 4.62 [2.47–8.62]; p<0.001). Similarly, OR increased significantly for the male WC group in comparison to that for the low WC group in HBP (OR: 2.00 [1.15–3.45]; p<0.05), HTG (OR: 3.09 [1.41–6.75]; p<0.05) and LHDL (OR: 8.82 [1.98–39.3]; p<0.05), and it increased significantly for the female group in HBP (OR: 1.95 [1.18–3.23];

Table 4. Odds Ratios and 95% CIs of CAD Risk Factors by Tertile of VFD and WC

	HBP	HTG	HFPG	LHDL
Men (n=353)				
Model 1				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.79 (1.04–3.09)*	2.31 (1.04–5.16)*	1.04 (0.4–2.44)	1.95 (0.83–4.59)
Upper tertile	3.45 (1.83–5.77)†	3.74 (1.72–8.12)*	0.80 (0.32–2.00)	2.02 (0.85–4.77)
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	2.10 (1.22–3.59)*	3.41 (1.56–7.44)*	0.79 (0.32–1.99)	16.4 (3.79–71.1)†
Upper tertile	2.00 (1.15–3.45)*	3.09 (1.41–6.75)*	1.26 (0.54–2.96)	8.82 (1.98–39.3)*
Model 2				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.67 (0.95–2.95)	2.21 (0.97–5.04)	0.88 (0.36–2.13)	1.71 (0.71–4.14)
Upper tertile	2.75 (1.37–5.50)*	3.35 (1.35–8.32)*	0.52 (0.17–1.62)	1.44 (0.52–4.04)
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.60 (0.86–2.96)	3.09 (1.31–7.31)*	0.71 (0.25–1.96)	17.6 (3.77–82.2)†
Upper tertile	1.15 (0.51–2.59)	2.54 (0.87–7.41)	1.00 (0.29–3.46)	10.1 (1.75–58.1)*
Women (n=457)				
Model 1				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.76 (1.04–2.98)*	6.28 (1.38–28.6)*	0.52 (0.16–1.72)	2.32 (1.23–4.38)*
Upper tertile	2.31 (1.37–3.92)*	13.3 (3.02–58.5)*	1.82 (0.71–4.69)	4.62 (2.47–8.62)†
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.05 (0.63–1.76)	3.79 (1.21–11.8)*	1.10 (0.43–2.82)	2.72 (1.52–4.86)*
Upper tertile	1.95 (1.18–3.23)*	5.79 (1.93–17.4)*	0.93 (0.37–2.34)	2.46 (1.36–4.43)*
Model 2				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.27 (0.73–2.22)	4.59 (0.99–21.3)	0.56 (0.16–1.92)	1.91 (0.99–3.70)
Upper tertile	1.06 (0.55–2.04)	6.36 (1.30–31.3)*	2.16 (0.67–6.92)	2.94 (1.40–6.17)*
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	0.65 (0.37–1.15)	2.37 (0.73–7.73)	0.90 (0.32–2.47)	1.78 (0.95–3.33)
Upper tertile	0.74 (0.37–1.45)	2.06 (0.56–7.57)	0.60 (0.17–2.05)	0.97 (0.45–2.09)

Model 1: adjusted for age; Model 2: adjusted for age and BMI. Significantly different from the Lower tertile: *p<0.05, †p<0.001. CI, confidence interval; CAD, cardiovascular disease; HBP, high blood pressure; HTG, hypertriglyceridemia; HFPG, high fasting plasma glucose; LHDL, low high-density lipoprotein cholesterolemia; VFD, visceral fat distance; WC, waist circumference.

p<0.05), HTG (OR: 5.79 [1.93–17.4]; p<0.05) and LHDL (OR: 2.46 [1.36–4.43]; p<0.05).

When additionally adjusted for BMI (model 2), OR increased significantly for the male VFD group in comparison to that for the low VFD group in HBP (OR: 2.75 [1.37–5.50]; p<0.05) and HTG (OR: 3.35 [1.35–8.32]; p<0.05). However, no significant association was found between WC and HBP or between WC and HTG. In addition, OR increased significantly for the female high VFD group in comparison to that for the low VFD group in HTG (OR: 6.36 [1.30–31.3]; p<0.05) and LHDL (OR: 2.94 [1.40–6.17]; p<0.05). However, no significant association was found between WC and any of the factors.

Table 5 shows the results of multiple regression analysis with SBP and DBP as dependent variables. For men, VFD was selected as a significant independent variable for both SBP and DBP. However, there was no significant association between WC and SBP or between WC and DBP.

Table 5. Results of Multiple-Regression Analysis Related to SBP and DBP

	Independent	Dependent			
		SBP		DBP	
		β	p-value	β	p-value
Men (n=353)	VFD	2.093	0.015	1.049	0.047
	WC	0.287	0.226	0.163	0.265
Women (n=457)	VFD	1.422	0.118	0.739	0.154
	WC	0.110	0.425	−0.057	0.466

Dependent variables: systolic blood pressure (SBP) or diastolic blood pressure (DBP). Independent variables: visceral fat distance (VFD) or waist circumference (WC) and additionally adjusted for age, triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), fasting plasma glucose (FPG), body mass index (BMI). β: standardized regression coefficient.

Although the data are not shown, when VFD was divided into tertiles, HOMA-IR increased significantly in the higher tertiles. Moreover, in multiple regression analysis using HOMA-IR as a dependent variable and using age, SBP, TG and VFD as independent variables, VFD was found to be a significant independent variable of HOMA-IR for both men and women.

Discussion

The significance of visceral obesity has been noted in recent years, and the accumulation of visceral fat must be accurately assessed. However, abdominal CT is not a simple technique, and WC also has the drawback of leading to an assessment that includes subcutaneous fat. In contrast, US involves no radiation exposure, the technique can be quickly learned, it is typically completed in less than 5 min, and it has been reported to have a good level of reproducibility (*15–20*). In the present study we therefore investigated whether US can be used as an easy screening method for the accurate estimation of the accumulation of visceral fat in Japanese as well.

When the correlations between VFA, SFA, BMI, VFD and WC were examined, VFD was found to have a stronger positive correlation with VFA than with SFA for both men and women. Additionally, BMI and WC each had a stronger positive correlation with SFA than with VFA. This is because measurements of BMI and WC are assessment methods that include elements of subcutaneous fat. The present study indicated that VFD measurement is a simple method for assessing visceral fat that does not include elements of subcutaneous fat and that VFD measurement is a useful means of assessing visceral fat in a large number of subjects.

The relationships between visceral fat and cardiovascular disease risk factors were then assessed in a study using US performed on inhabitants of a rural community who were not being treated for hypertension, diabetes or hyperlipidemia. The data presented in Table 4, obtained after adjustment for age and BMI (model 2), showed that VFD was significantly correlated with HBP, HTG and LHDL in men and with HTG and LHDL in women. On the other hand, WC was correlated with LHDL in men but showed only weak correlations with risk factors in women.

What eliminated the relationship between WC and cardiovascular disease risk factors in women subjects in particular was the effect of subcutaneous fat. Subcutaneous fat has less of an effect on arteriosclerosis than visceral fat and instead has antiarteriosclerotic action (*27*). In general, visceral obesity, a condition in which visceral fat readily accumulates, affects men more than women; women are affected by female sex hormones and exhibit body types that feature subcutaneous obesity (*28*, *29*). Thus, in assessment by BMI and WC, the effects of subcutaneous fat are more intensely reflected in women than in men. This fact is supported by the stronger correlation of BMI and WC to SFA than to VFA in the study of outpatient cases (Study 1).

We could not find a significant association between FPG and a rise in VFD or WC for either men or women. The reasons are threefold. First, individuals on medication for type 2 diabetes were excluded in this study and, second, the study was conducted in a homogenous population with a relatively low FPG. Third, we could not find participants with impaired glucose tolerance (IGT) because we did not conduct oral glucose tolerance test (OGTT) in this study. Thus, there was a small number of participants with high FPG and there was no significant relationship between FPG and VFD for either men or women.

The results of multiple regression analysis showed that VFD was an independent explanatory variable of blood pressure in men. No significant relationship was found between WC and blood pressure in men or women. VFD may be a good indicator of blood pressure in men. Moreover, VFD may also be a useful index for the management of blood pressure in men with metabolic syndrome.

In a state of visceral fat accumulation, it is thought that free fatty acid produced by the decomposition of TG flows into the liver and induces insulin resistance. Moreover, substances that induce insulin resistance such as tumor necrosis factor (TNF)-α are produced from visceral fat. Studies have indicated the possibility that elevation of blood pressure is induced in a state of insulin resistance by various mechanisms *via* adipocytokines (*30*). It has also been reported that compensatory hyperinsulinemia, which occurs in a state of insulin

resistance, plays a role in blood pressure elevation *via* renal mechanisms (*31*).

In multiple regression analysis, no relationship was found between VFD and blood pressure in women. Possible reasons for this are the influence of an autocorrelation due to the addition of BMI to the adjusted items and both the small mean value and the low distribution of VFD in female subjects.

WC measurement is a very useful screening method for assessing visceral fat because it is simple and cheap. It does, however, have drawbacks, such as an inability to assess tall individuals differently than short ones and a low level of reproducibility in the case of marked obesity, since WC includes subcutaneous fat. Therefore, the Japanese criteria of MS recommend assessing real visceral fat accumulation by CT when we find individuals with WC ≥85 cm in men and ≥90 cm in women. Although abdominal CT is the gold standard for visceral fat assessment, it entails exposure to radiation, lack of ease and simplicity, and high cost. General practitioners may have a good deal of opportunity to assess individuals with MS, but very few physicians have CT equipment in their clinics. Assessment by US is a simpler technique than abdominal CT and allows general practitioners to assess visceral fat accumulation in their clinics. When we find high-risk individuals with an accumulation of risk factors and without abdominal obesity (WC <85 cm in men, WC <90 cm in women), it is important to confirm their fat distribution by other methods than WC. In such cases, the US method may be useful simply assessing the accumulation of visceral fat.

One limitation of the present study is that all of the subjects were Japanese; thus the results may not apply to Westerners or individuals of certain ethnic groups. The female body type in particular differs between Westerners and Japanese. Nevertheless, diagnostic criteria for WC that take into account ethnicity have been incorporated in the International Diabetes Federation (IDF)'s diagnostic criteria for MS. While there are differences in extent, the relationship between visceral fat accumulation and cardiovascular disease risk factors is universal (*32*, *33*).

No statistical analysis was performed to evaluate the differences in the measured parameters between premenopausal and postmenopausal women in our study group. In general, postmenopausal women tend toward obesity more than premenopausal women, and their blood pressure levels and visceral fat levels are known to increase (*34*, *35*). A study taking this into account is needed in the future. Additionally, the present study involved cross-sectional studies, and additional prospective studies on the relationship between abdominal obesity and elevated blood pressure are needed.

In conclusion, US is a simpler technique than abdominal CT, and its usefulness in visceral fat assessment was demonstrated in the screening of residents of a rural community. VFD is thought to be a good index for assessing not only visceral fat accumulation but also cardiovascular risk factors. Moreover, in men VFD showed a significant correlation with blood pressure. Visceral fat assessment by US may be useful for epidemiological studies and for clinics with no abdominal CT equipment to identify high-risk individuals such as those with metabolic syndrome.

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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

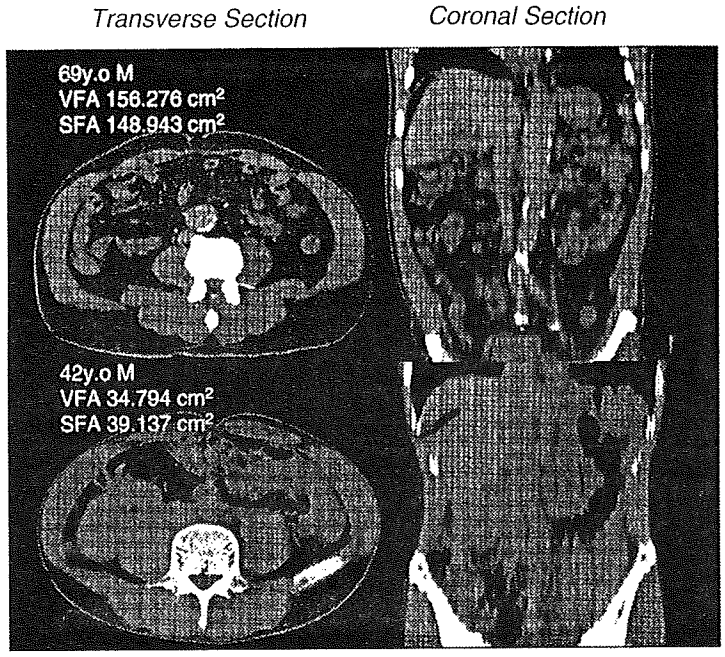

Fig. 1. *Representative MDCT images used for determination of visceral fat area and subcutaneous fat area. CT slices at the level of the umbilicus were used for the determination of areas. VFA, visceral fat area; SFA, subcutaneous fat area. Upper: a case of visceral obesity; Lower: a non-obese case.*

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

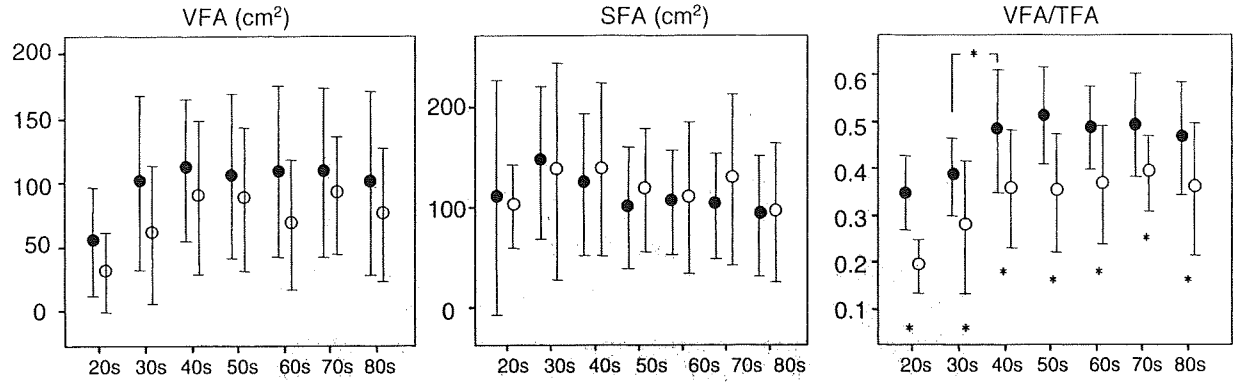

Fig. 2. *Age-related difference in the levels of visceral and subcutaneous fat accumulation. VFA, visceral fat area; SFA, subcutaneous fat area; VFA/TFA, ratio of VFA to total fat areas (VFA+SFA). Closed circles and open circles indicate the data for males and females, respectively.* $*p < 0.05$ *vs.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

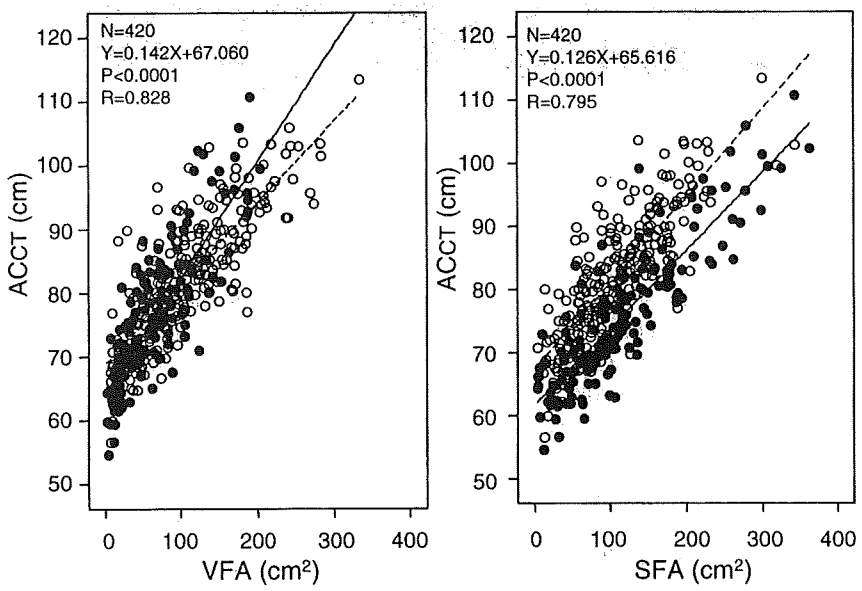

Fig. 3. *Correlation between abdominal circumference (AC_{CT}) and accumulation of visceral (VFA) and subcutaneous fat (SFA). Open circles and closed circles indicate the data for males and females, respectively. There was no significant difference in the regression lines for the AC_{CT}-VFA relationships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

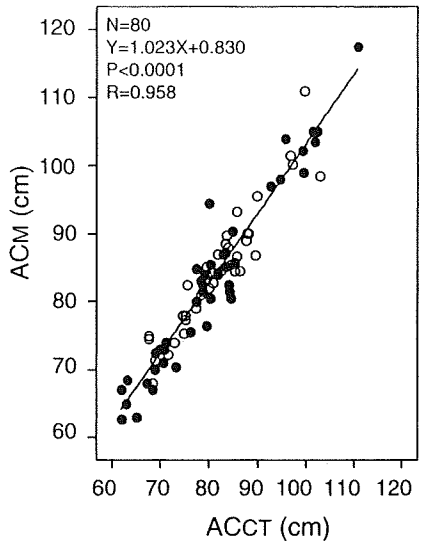

Fig. 4. *Correlation between MDCT-determined abdominal circumference (AC_{CT}) and abdominal circumference measured by anthropometric tapes (AC_M). Open circles and closed circles indicate the data for males and females, respectively.*

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.

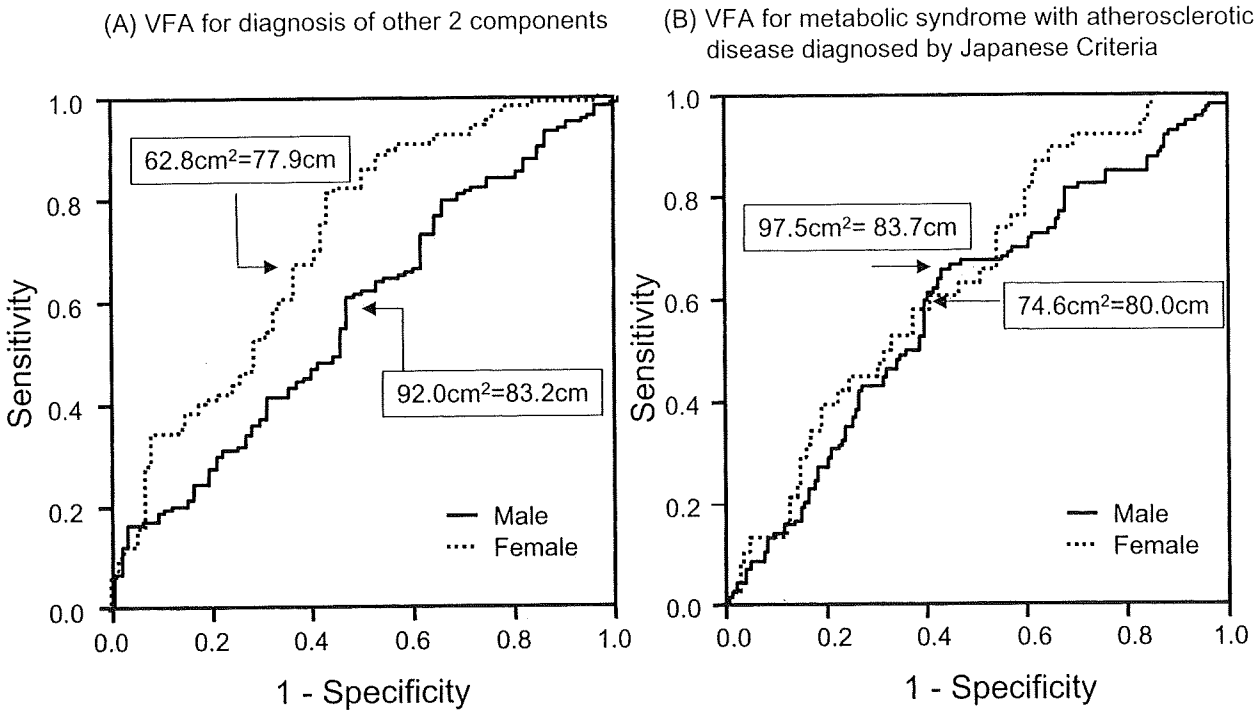

Fig. 5. *Receiver operating characteristic (ROC) analysis of VFA to predict the presence of two or more components of metabolic syndrome and ASCD. Solid lines and broken lines depict the ROC curves for males and females, respectively.*

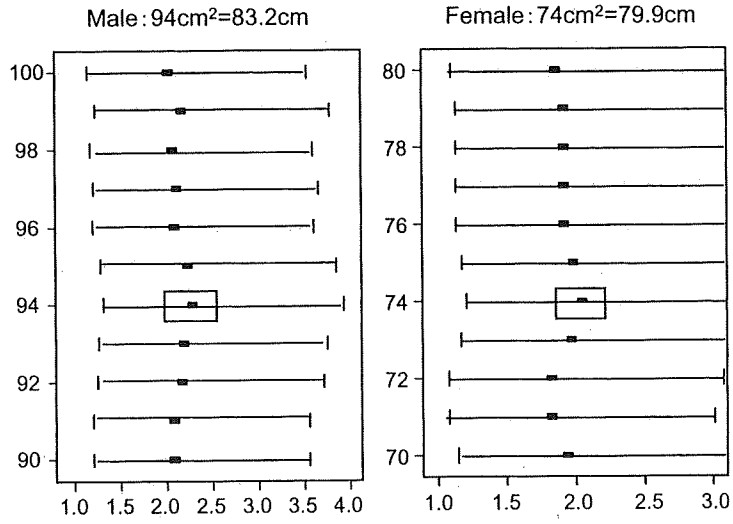

Fig. 6. *Odds ratio for the presence of two or more components of metabolic syndrome at each level of VFA. An odds ratio was calculated for every cm² of VFA and is presented along with the confidential interval. The highest odds ratio was given by a VFA of 94 cm² in males and by a VFA of 74 cm² in females.*

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

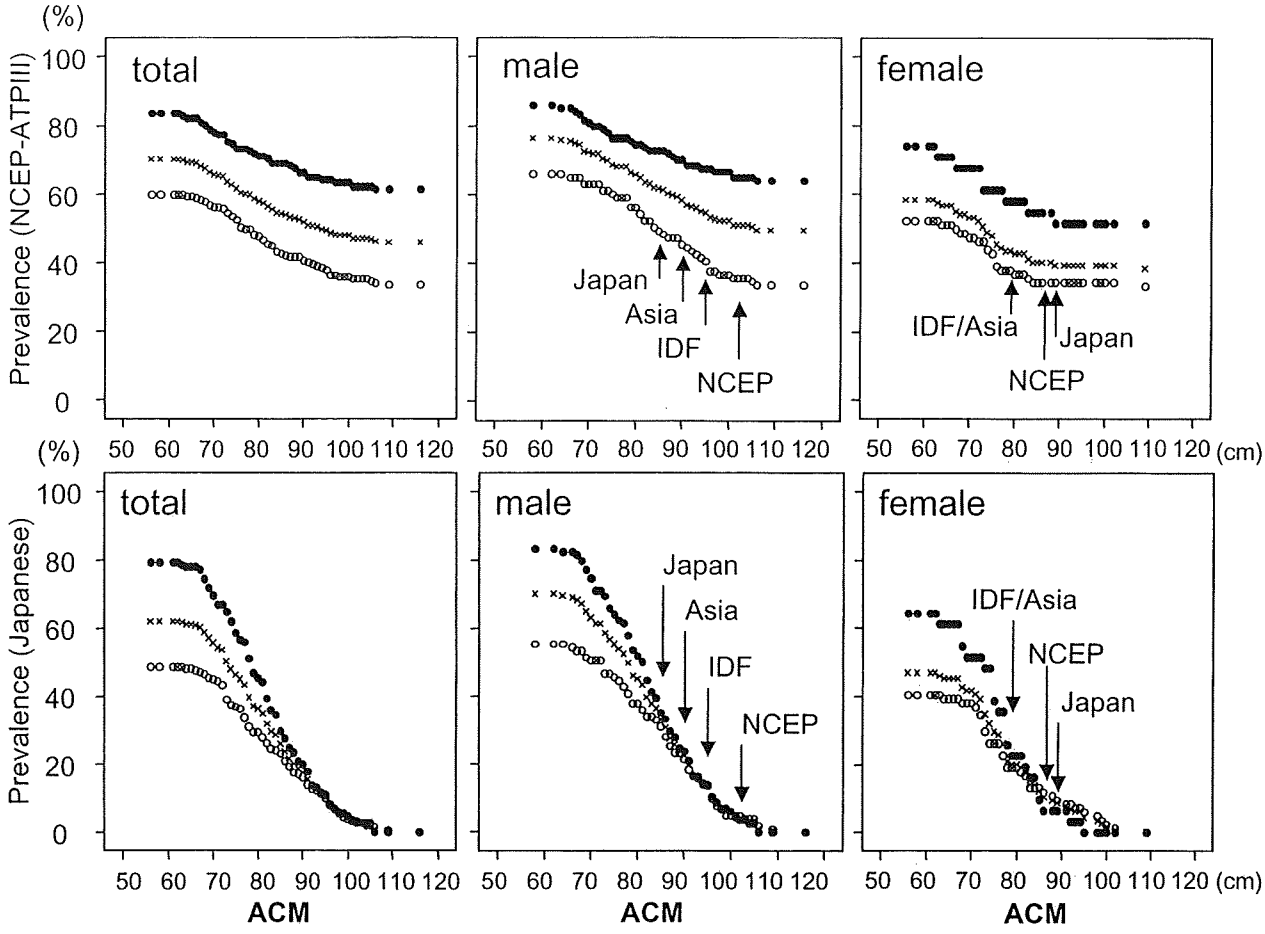

Fig. 7. *Relationship between the cutoff level of abdominal circumference and prevalence of metabolic syndrome. Upper: NCEP-ATP III–defined metabolic syndrome; Lower: metabolic syndrome defined by the current Japanese criteria. Open circles, closed circles and cross symbols represent relationships in 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,