Original Article

Impact of Visceral Adipose Tissue and Subcutaneous Adipose Tissue on Insulin Resistance in Middle-Aged Japanese

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Aim: **The enlargement of visceral adipose tissue (VAT) is considered to mediate the close relationship between obesity and insulin resistance. We aimed to determine whether a stronger association of VAT compared to subcutaneous adipose tissue (SAT) with insulin resistance could be confirmed and generalized in non-diabetic Japanese men and women.**
Methods: **Participants were 912 non-diabetic Japanese (636 men and 276 women, mean age 52.4 ± 7.0 years, and mean BMI 24.9 ± 3.1 kg/m^2). VAT and SAT were measured through the use of computed tomography scanning. Homeostatic model for the assessment of insulin resistance (HOMA-IR) and Matsuda insulin sensitivity index (ISI) were calculated based on results from the oral glucose tolerance test.**
Results: **For both genders, subjects in higher tertiles of SAT as well as VAT showed significantly higher levels of HOMA-IR and lower levels of Matsuda ISI ($p < 0.001$). In multiple regression analyses with VAT and SAT included in the model, only VAT, but not SAT, was independently associated with Matsuda ISI in women ($p < 0.001$), whereas both SAT and VAT were independently associated with HOMA-IR and with Matsuda ISI in men ($p < 0.001$). When VAT and waist circumference were jointly included in the model, only VAT, but not waist circumference, was independently associated with Matsuda ISI in women ($p < 0.001$) but not in men.**
Conclusion: **VAT had a stronger association with insulin resistance than SAT or waist circumference in women but not in men. BMI showed a comparable association with insulin resistance to VAT in this population.**

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Key words; Visceral adipose tissue, Insulin resistance, Obesity

Introduction

Obesity is associated with multiple cardiometabolic risk factors, including type 2 diabetes[1], dyslipidemia[2], and hypertension[3]. The adverse effects of obesity are supposed to be in part mediated by its close relationship with insulin resistance[4, 5]. When assessed by body mass index (BMI), however, not all obese persons are insulin resistant, and insulin resistance is not uncommon in normal-weight persons[6-9]. The inconsistencies in the association between obesity and insulin resistance may be due to the methods of measurement. BMI, or even waist circumference, is an incomplete measure of abdominal fat accumulation, especially visceral fat accumulation. Visceral adipose tissue (VAT) is thought to play a fundamental role in the constellation of metabolic disorders[10] due to its unique position with respect to portal circulation[11] and its secretory function for various bioactive substances[12-14]. Epidemiological studies have demon-

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strated that enlarged VAT increases the risk for type 2 diabetes[15], impaired glucose tolerance (IGT)[16], and risk factor clustering[17] independent of anthropometric indices or subcutaneous adipose tissue (SAT).

To date, several investigators have examined the association of directly measured VAT and SAT with insulin resistance, but their results have been conflicting; some have documented that VAT is more closely associated with insulin resistance as measured by clamp studies than SAT in non-diabetic subjects[18-20], whereas others have demonstrated that SAT, not VAT, is a stronger correlate of insulin resistance[21-23]. These discrepancies among studies can be attributed to the difference in gender, the degree of obesity, and the ethnicities of the included subjects. There have been few studies on relatively lean Japanese people with sufficiently large sample sizes to evaluate the independent contributions of VAT and SAT to insulin resistance.

The aim of this study was to determine whether the stronger association of VAT than SAT with insulin resistance can be confirmed and generalized in non-diabetic Japanese. To this end, we investigated the cross-sectional relationship between computed-tomography (CT)-measured VAT and SAT and indices of insulin resistance derived from the oral glucose tolerance test (OGTT) in a large number of Japanese men and women.

Methods and Procedures

Study Sample

Hokuriku Central Hospital has a designated department where public school employees receive routine medical checkups. Among the employees who received a regular checkup between April 2006 and March 2010, 942 individuals voluntarily underwent both CT scanning to evaluate abdominal fat distribution and OGTT. All of the subjects were Japanese men and women aged 30-62 years. After excluding those who had fasting plasma glucose (PG) values ≥126 mg/dL (n=24), those who were taking steroids (n=3), and those who were taking hormone replacement therapy (n=3), the remaining 912 (636 men and 276 women) were ultimately enrolled in this study. Participants were considered smokers if they smoked at least one cigarette per day. Alcohol use was defined by the number of days per week that an alcoholic drink was consumed, regardless of the amount. Women reporting no menses for at least six months were considered menopausal. Individuals who had received hysterectomies were considered postmenopausal if they were over the age of 51, which was the average menopausal age of this sample. All participants signed informed consent forms, and the hospital review board approved the study protocol.

Study Protocol and Assays

All subjects were asked to visit the hospital between 8:00 a.m. and 9:00 a.m. after an overnight fast. BMI was calculated as the weight in kilograms divided by the square of height in meters and waist circumference was measured at the umbilicus by well-trained nurses according to published methods[24]. An OGTT (75 g dextrose monohydrate in 250 mL water) was performed with 0-, 30-, 60-, and 120-min sampling to establish PG and insulin levels. PG was assessed using the glucose oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160; Arkray, Kyoto) at the hospital laboratory. Insulin concentration assays were performed by the chemiluminescence immunoassay method at a commercial laboratory (BML, Inc., Tokyo, Japan).

Measurement of Abdominal Adipose Tissue by CT

Detailed methods have been published previously[24]. Briefly, an axial CT scan at the level of the umbilicus was obtained for each subject using an electron-beam CT scanner (Aquilion Toshiba Medical Systems, Tokyo, Japan). Planimetric measurements at the level of the umbilicus have been reported to correlate well with volumetric quantifications of VAT (r=0.81 in men and r=0.85 in women, p<0.001) and SAT (r=0.95 in men and r=0.92 in women, p<0.001)[25]. The images generated were transferred to a workstation and analyzed using commercial software designed for the quantification of VAT and SAT, Fat Scan version 3.0 (N2 System, Osaka, Japan). The correlation coefficients between two observers analyzing the same image to determine VAT and SAT (n=30) were r=0.98, p<0.001 and r=0.99, p<0.001, respectively.

Assessment of Insulin Resistance

In this study, we assessed insulin resistance using two OGTT-derived indices, the homeostatic model for the assessment of insulin resistance (HOMA-IR) and the Matsuda insulin sensitivity index (ISI). These values were calculated using the following formulas: HOMA-IR = fasting PG (mmol/L) × fasting insulin (mU/L)/22.5[26] and Matsuda ISI = 10000/(fasting PG (mg/dL) × fasting insulin (mU/L) × 2-hour PG (mg/dL) × 2-hour insulin (mU/L))0.5[27].

Statistical Analysis

Data are presented as the mean ± SD, medians with the interquartile ranges for continuous variables

Table 1. Clinical characteristics of study participants

Characteristics	Men (n=636)	Women (n=276)
Age (years)	51.6±7.1	54.2±6.2*
Weight (kg)	73.3±10.2	58.6±8.5*
Body mass index (kg/m²)	25.3±2.9	24.0±3.2*
Waist circumference (cm)	87.9±7.5	83.8±8.6*
VAT (cm²)	140.9±50.7	84.9±38.5*
SAT (cm²)	145.1±56.0	199.2±74.3*
Fasting insulin (mU/L)	3.2/4.4/6.1	3.1/4.4/6.1
HOMA-IR (mU/L, mg/dL)	0.79/1.07/1.51	0.73/1.03/1.42
Matsuda ISI (mU/L, mg/dL)	5.7/8.3/12.7	6.0/9.5/13.7
Impaired fasting glucose (Fasting plasma glucose ≧100 mg/dL)	43.2	25.0*
Impaired glucose tolerance (2-hour plasma glucose ≧140 mg/dL)	26.3	21.4*
Anti-hypertensive medication	16.4	12.7*
Lipids-lowering medication	9.3	10.2
Current cigarette smoker (%)	22.3	1.8*
Alcohol use (%)		
drinking every day	33.8	10.5*
drinking 1-6 days per week	39.6	22.8*
Postmenopausal		74.3

Data are the mean±SD, 25/50/75th percentile values, or %. VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; HOMA-IR, homeostatic model assessment of insulin resistance; meosta, Matsuda ISI, Matsuda insulin sensitivity index. *$p<0.05$ between men and women.

or as frequencies for categorical variables. Continuous variables were compared by the t-test or Mann-Whitney test, and categorical values were compared by the χ^2 test between men and women. Correlations between VAT and SAT were assessed using age-adjusted Pearson correlation coefficients. Subjects were subdivided into tertiles of VAT or SAT and age-adjusted mean levels of the indices of insulin resistance were calculated through the analysis of co-variance. Tests for linear trends across tertiles of VAT or SAT were performed by assigning the median value within each category and treating the categories as a continuous variable. Multivariable linear regression analysis was used to assess the associations of VAT and SAT with each of the indices of insulin resistance. Three models were generated in stages: 1) either VAT or SAT was included in the model; 2) VAT and SAT were jointly included in the model to assess the independent associations of these two measures; and 3) VAT and waist circumference were jointly included to address whether the association of VAT with insulin resistance exceeded that of waist circumference. VAT, SAT, and waist circumference were first standardized to a mean of 0 and standard deviation of 1 within a given sex and then were included in the regression models, so that β denotes the average change per 1-SD increase in these measurements of adiposity. All models included the following non-adipose variables as covariates: age, smoking (currently smoking or not), alcohol use (three-level variable: drinking every day/drinking 1-6 days per week/drinking less than 1 day per week), anti-hypertensive medications (yes or no), lipid-lowering medications (yes or no), and menopausal status (women only). The significance of interactions between VAT and SAT was examined using interaction terms (VAT×SAT) in the second model. HOMA-IR and Matsuda ISI were normalized by logarithmic (natural log) transformation because of a skewed distribution before analysis. Receiver operating characteristics (ROC) curve analysis was performed to determine the discriminative ability of each indicator of obesity for elevated insulin resistance. We defined elevated insulin resistance with HOMA-IR above the 75th percentile or with Matsuda ISI below the 25th percentile. The areas under the ROC curves (AUCs) were calculated for each indicator of obesity. $P<0.05$ was considered significant, and all analyses were conducted using SPSS software version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The clinical characteristics of the participants are presented in **Table 1**. The mean age of the study sam-

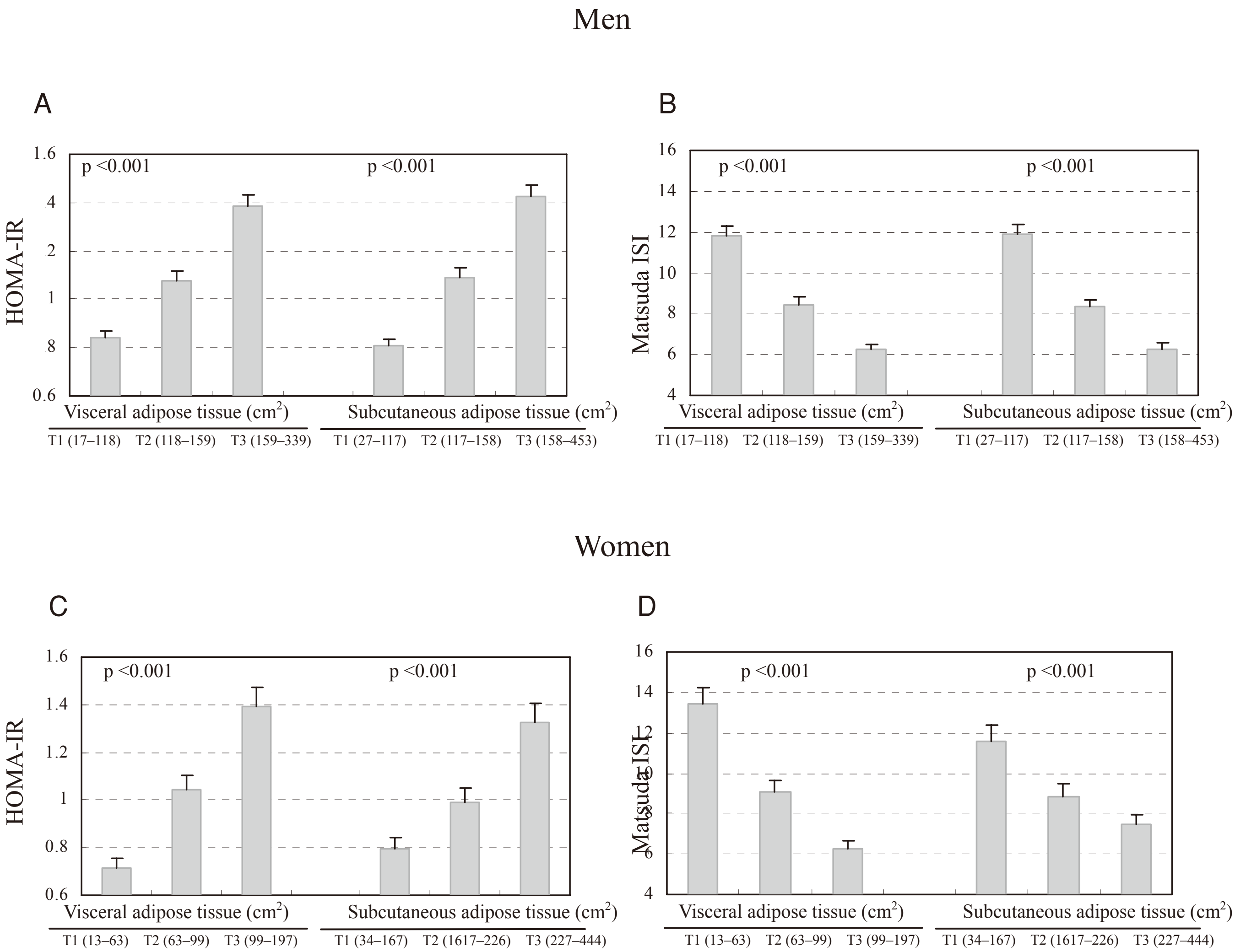

Fig. 1. Age-adjusted mean levels of HOMA-IR (A and C) and Matsuda ISI (B and D) by tertiles of visceral adipose tissue and subcutaneous adipose tissue. Data were log-transformed before analysis and calculated values were untransformed after analysis. Brackets represent 1 standard error for each group.

ple was 52 yr for men and 54 yr for women. The mean BMI was approximately 25 kg/m^2 in both genders. Men had approximately equal amounts of SAT and VAT on average, whereas women had twice as much SAT or more than VAT on average. The levels of HOMA-IR and Matsuda ISI were not significantly different between men and women. Although diabetic participants were excluded as described above, some subjects were taking medications for hypertension and/or dyslipidemia. In addition, 74.3% of the women were postmenopausal. VAT was positively correlated with age in men ($r=0.13$, $p<0.001$) and in women ($r=0.21$, $p<0.001$) and SAT was inversely associated with age in men ($r=-0.19$, $p<0.001$). The mean VAT was significantly larger in postmenopausal women than in premenopausal women (89.2±38.3 cm^2 vs. 72.7±36.8 cm^2, $p=0.002$).

VAT and SAT were significantly and positively correlated in men ($r=0.55$, $p<0.001$) and in women ($r=0.62$, $p<0.001$) after adjustment for age. When participants were subdivided into tertiles of VAT or SAT, there were clear relationships between increasing levels of adiposity and indices of insulin resistance (**Fig. 1**). Subjects in higher tertiles of VAT and SAT showed significantly higher levels of HOMA-IR and lower levels of Matsuda ISI in both men and women even after these values were adjusted for age ($p<$ 0.001).

The results of multiple linear regression analyses for indices of insulin resistance with VAT and SAT are

Table 2. Multivariable-adjusted regression analyses for indices of insulin resistance with VAT and SAT

	Multivariable model* with VAT or SAT			Multivariable model* with VAT and SAT			
	β	t-statistic	p value	β	t-statistic	p value	p value for VAT × SAT
Men							
Log HOMA-IR							
VAT	0.24 ± 0.02	11.44	< 0.001	0.14 ± 0.02	5.81	< 0.001	0.773
SAT	0.26 ± 0.02	12.88	< 0.001	0.18 ± 0.02	8.02	< 0.001	
Log Matsuda ISI							
VAT	− 0.29 ± 0.02	− 12.38	< 0.001	− 0.18 ± 0.03	− 6.83	< 0.001	0.380
SAT	− 0.29 ± 0.02	− 12.86	< 0.001	− 0.20 ± 0.03	− 7.56	< 0.001	
Women							
Log HOMA-IR							
VAT	0.30 ± 0.03	8.99	< 0.001	0.22 ± 0.04	5.27	< 0.001	0.102
SAT	0.25 ± 0.03	7.68	< 0.001	0.12 ± 0.04	3.07	0.002	
Log Matsuda ISI							
VAT	− 0.32 ± 0.04	− 9.08	< 0.001	− 0.29 ± 0.05	− 6.43	< 0.001	0.042
SAT	− 0.23 ± 0.04	− 6.08	< 0.001	− 0.05 ± 0.04	− 1.16	0.596	

*Multivariable model is adjusted for age, alcohol intake, smoking, antihypertensive medications, lipids-lowering medications, and menopause (women only). VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue. VAT and SAT were standardized to a mean of 0 and standard deviation of 1 and then were included in the models.

shown in **Table 2**. After adjusting for age, smoking status, alcohol use, anti-hypertensive medications, lipid-lowering medications, and menopausal status (women only), both VAT and SAT were positively associated with HOMA-IR and inversely with Matsuda ISI ($p < 0.001$). When VAT and SAT were simultaneously included in the regression model, the β for VAT and that for SAT were attenuated but both values remained statistically significant for HOMA-IR and Matsuda ISI in men ($p < 0.001$). In women, the associations of VAT were maintained ($p < 0.001$) but that of SAT was lost for Matsuda ISI ($p = 0.596$). The interaction between VAT and SAT in determining indices of insulin resistance was not significant, except for the interaction between VAT and SAT for Matsuda ISI in women ($p = 0.042$), whereas the reduction of Matsuda ISI associated with higher levels of VAT was attenuated at higher levels of SAT.

When VAT and waist circumference were simultaneously included in the model (**Table 3**), the association of VAT with indices of insulin resistance was independent of waist circumference in both men and women. The association of waist circumference was not significant for Matsuda ISI in women but was significant for HOMA-IR and Matsuda ISI in men. Similar results were obtained when the association of VAT was adjusted for BMI in place of waist circumference (data not shown).

The AUCs of the ROC analyses are shown in **Table 4**. All of the AUCs were between 0.5 and 1.0, indicating that each indicator of obesity had a given discriminative ability for insulin resistance. In men, AUC values for different obesity indices were all in a similar range. In women, for identification of low Matsuda ISI (below the 25th percentile), the AUC of VAT was largest but its difference did not reach statistical significance compared to that of SAT or waist circumference. The AUC of VAT was not significantly different from that of BMI in both men and women.

Discussion

In this study, we cross-sectionally examined the associations of VAT and SAT with indices of insulin resistance in middle-aged, non-diabetic Japanese men and women. A stronger association of VAT with insulin resistance was confirmed, as assessed by Matsuda ISI, compared to SAT or waist circumference in women but not in men in this population. Although it is commonly thought that the adverse effects of obesity as related to insulin action and to glucose and lipid metabolism are associated with fat accumulation as VAT, these results suggest that fat accumulation as measured by VAT, SAT, and waist circumference may

Table 3. Multivariable-adjusted regression analyses for indices of insulin resistance with VAT and waist circumference

	β	*t*-statistic	*p* value
Men			
Log HOMA-IR			
VAT	0.09 ± 0.03	3.44	0.001
Waist circumference	0.21 ± 0.03	7.87	< 0.001
Log Matsuda ISI			
VAT	− 0.17 ± 0.03	− 5.55	< 0.001
Waist circumference	− 0.17 ± 0.03	− 5.49	< 0.001
Women			
Log HOMA-IR			
VAT	0.23 ± 0.04	5.26	< 0.001
Waist circumference	0.96 ± 0.04	2.26	0.025
Log Matsuda ISI			
VAT	− 0.28 ± 0.05	− 5.79	< 0.001
Waist circumference	− 0.07 ± 0.05	− 1.51	0.133

*Multivariable model is the same as in Table 2. VAT, visceral adipose tissue. VAT and waist circumference were standardized to a mean of 0 and standard deviation of 1 and then were included in the models.

Table 4. Areas under the ROC curves (AUCs) for indices of obesity to identify insulin resistance

	VAT		SAT		VAT + SAT		waist circumference		BMI	
	AUC	95%CI	AUC	95%CI	AUC	95%CI	AUC	95%CI	AUC	95%CI
Men										
high HOMA-IR	0.72	0.67-0.76	0.77	0.72-0.81	0.78	0.74-0.82	0.75	0.71-0.79	0.77	0.73-0.81
low Matsuda ISI	0.74	0.70-0.79	0.74	0.69-0.78	0.78	0.74-0.82	0.73	0.69-0.77	0.75	0.70-0.79
Women										
high HOMA-IR	0.73	0.66-0.80	0.68	0.61-0.75	0.73	0.66-0.80	0.66	0.59-0.73	0.74	0.67-0.80
low Matsuda ISI	0.77	0.71-0.83	0.68	0.61-0.75	0.75	0.68-0.81	0.70	0.61-0.75	0.74	0.67-0.80

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index. The 75th percentile was used for the cut point for high HOMA-IR and the 25th percentile for low matsuda ISI.

have comparable relevance to insulin resistance in men.

In women, we confirmed that only VAT but not SAT showed an independent association with insulin resistance as assessed by Matsuda ISI, in agreement with prior studies based on euglycemic clamp studies[18-20]. When assessed by HOMA-IR, the data also revealed an independent association of SAT with insulin resistance. In a study in non-diabetic Germans, the association between insulin resistance and VAT was more pronounced when assessed by Matsuda ISI rather than by fasting insulin levels[28]. Matsuda ISI mainly reflects peripheral insulin sensitivity and has a better correlation with directly measured insulin resistance as measured by euglycemic clamp than the indices derived from fasting measurements including HOMA-IR[29, 30]. The independent association between VAT and Matsuda ISI in this study suggests that VAT has a stronger impact on peripheral insulin resistance than SAT in women. Although the reason why this finding was confirmed only in women is unknown, it is in line with the evidence from epidemiological studies that the association of VAT with incident diabetes was more pronounced in women than in men[31, 32].

In this study, both SAT and VAT were independently associated with insulin resistance in men. Prior studies found that SAT had an equal[33-35] or even stronger[21-23] positive association with insulin resistance than VAT in men. Frederksen *et al.* reported that SAT, but not VAT, was associated with higher levels of HOMA-IR in 783 European young men using magnetic resonance imaging[22]. A recent study in Japanese men demonstrated that the change in BMI but not in waist circumference was an independent factor associated with the improvement of HOMA-IR over a one-year period[36]. Because BMI reflects the combination of VAT and SAT[24], their and our results collectively indicate that the adverse effects of SAT on insulin sensitivity cannot be overlooked in men.

In both men and women, the association of VAT with indices of insulin resistance was independent of waist circumference. The association of VAT with Matsuda ISI indeed exceeded that of waist circumference in women; however, in men again, waist circumference was independently associated with insulin resistance with a comparable strength of association, as shown by t-statistics. These results suggest that VAT has a stronger association with insulin resistance than waist circumference in women but not in men.

Using ROC analysis to compare the discriminative ability for insulin resistance, we could not observe any significant difference among the AUCs for VAT, SAT, VAT + SAT, waist circumference, and BMI in both genders. These results suggest that, in the general population, they are equivalent in their ability to identify subjects with elevated insulin resistance. Also, using ROC analysis to predict the future incidence of diabetes in the Diabetes Prevention Program (DPP)[37], it was reported that the predictive ability of VAT measured at the L2-3 level or at the L4-5 level was not significantly different with that of waist circumference or BMI in men, although in women, VAT measured at the L2-3 level was a significantly better predictor than anthropometric indices. A very recent study of Japanese-Americans also demonstrated that VAT was not a better predictor of obesity-related mortality than BMI[38]. Further study is needed to clarify to what extent VAT would improve the risk assessment of obesity-related morbidity and mortality beyond BMI in the general population.

Recently, a protective effect of SAT against insulin resistance was demonstrated in overweight/moderately obese Americans with a mean BMI of 30 kg/m^2[39]. In this study, the adverse association between VAT and Matsuda ISI was slightly attenuated with higher levels of SAT in women, but no beneficial association between SAT and Matsuda ISI was observed. Studies from the Framingham Heart Study have reported a potential beneficial effect of SAT in relation to lipid concentrations and the prevalence of metabolic syndrome[40] but not in relation to the prevalence of IFG or indices of insulin resistance[41]. The direction of the association of SAT appears to be identical to that of VAT or is at most neutral with regard to insulin resistance or glucose metabolism.

Several limitations of this study should be considered. First, the cross-sectional design is unable to examine the causal or temporal sequence between adiposity and indices of insulin resistance. Second, insulin resistance was not measured by the glucose-clamp technique, which is the gold standard for evaluating insulin resistance/sensitivity; however, it has been demonstrated that Matsuda ISI and HOMA-IR correlated well with directly measured insulin resistance and with metabolic abnormalities in non-diabetic subjects[29, 30, 42]. Third, the mean BMI of the study subjects appears higher than that of the general Japanese population. Our subjects comprised those who requested an evaluation of abdominal fat distribution by CT scan at health check-ups, which may have resulted in a selection bias toward obese subjects. Indeed, the mean BMI of the subjects who received health check-ups in this study period but did not undergo a CT scan was significantly lower than that of the study subjects (23.8 ± 3.1 kg/m^2 vs. 25.3 ± 2.9 kg/m^2 in men and 22.0 ± 3.0 kg/m^2 vs. 24.0 ± 3.2 kg/m^2 in women, $p < 0.001$). Finally, our female study subjects included more postmenopausal women (74.3%). Since the accumulation of VAT has been considered to be affected by menopause, the generalizability of our results should also be examined in premenopausal women,

In conclusion, VAT had a stronger association with insulin resistance than SAT or waist circumference in women but not in men. In men, excess fat as measured by VAT, SAT, and waist circumference had comparable relevance to insulin resistance in this population.

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Disclosure

The authors declare no conflicts of interest.

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