

# Visceral fat accumulation as a predictor of coronary artery calcium as assessed by multislice computed tomography in Japanese patients

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Received 19 January 2008; received in revised form 17 April 2008; accepted 19 April 2008

Available online 24 April 2008

## Abstract

The impact of visceral adiposity on subclinical coronary atherosclerosis is unclear in Japanese patients. We investigated the sex-specific relationship between the amount of visceral fat and coronary artery calcium (CAC) using multislice computed tomography (MSCT). This is a cross-sectional study of 321 consecutive Japanese patients (213 men and 108 women) who underwent MSCT scanning for the examination of coronary heart disease. CAC score, visceral fat area (VFA), subcutaneous fat area (SFA), and waist circumference (WC) were determined by MSCT for all patients. The prevalence of detectable CAC was 73% and 57% in men and women, respectively. Using a multivariable logistic and ordinal regression analyses adjusting for traditional cardiovascular risk factors and adiposity measurements, VFA represented an independent predictor of the presence and extent of CAC (odds ratio (95% confidence interval) per one-unit-standard deviation increase in VFA: 2.48 (1.23–6.05) in logistic regression analysis; 2.05 (1.18–3.98) in ordinal regression analysis). Similar relationships were observed across the gender. We further assessed the sex-specific cut-off levels of VFA and WC to predict the presence of CAC. The results of receiver operator characteristic analysis indicated that the VFA cut-off level in men was 116 cm<sup>2</sup>; and in women, it was 82 cm<sup>2</sup>, corresponding to WC values of 87.7 cm in men and 82.6 cm in women. In conclusion, we found that visceral adiposity measured by MSCT is significantly associated with the presence and extent of CAC as a marker of subclinical atherosclerosis in Japanese patients.

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**Keywords:** Visceral fat; Coronary calcification; Multislice computed tomography

## 1. Introduction

Numerous studies have demonstrated the relationship of obesity with the increased risks of coronary heart disease [1,2]. In the past decades, visceral adiposity has been found to be related to a number of atherogenic conditions [3], and it is considered as a part of ‘metabolic syndrome’. Excessive accumulation of visceral fat is associated with insulin resistance which contributes to the progression of atherosclerosis [4]. Although several studies have suggested that visceral adiposity may be a stronger predictor of coronary heart disease than overall obesity [5,6], epidemiologic

studies of the association among visceral adiposity, overall obesity, and coronary heart disease are still lacking in Japanese populations. Coronary artery calcium (CAC) is considered to be a marker of subclinical atherosclerosis. Many studies using electron-beam tomography have suggested that the presence and extent of CAC strongly correlates with the overall atherosclerotic plaque burden, and with the development of subsequent coronary events [7,8]. Recently, multislice computed tomography (MSCT) has become available, allowing for the reliable detection and quantification of CAC with a high agreement with electron-beam tomography [9,10].

To the best of our knowledge, there has been little research on the relation between visceral adiposity and subclinical atherosclerotic vascular disease in Japanese populations.

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Visceral fat area (VFA) measured by CT which is considered as the gold-standard method for determining the quantity of visceral adipose tissues, is a direct index of visceral adiposity [11]. The purpose of this study was to investigate whether body mass index (BMI) and CT measurements of adiposity including VFA, subcutaneous fat area (SFA) and waist circumference (WC) were related to the presence and extent of CAC as detected by MSCT in a clinical setting. We further analyzed the sex-specific cut-off points of the amount of visceral fat for predicting the presence of CAC.

## 2. Methods

### 2.1. Subjects

Between August 2005 and June 2007, 390 patients aged 36–87 years underwent MSCT scanning for the examination of coronary heart disease at the Hiroshima University Hospital. We selected consecutive 321 patients for this analysis after exclusion of those who had a history of percutaneous coronary intervention ( $n=42$ ) or coronary artery bypass surgery ( $n=27$ ). Two-hundred and thirty nine patients were asymptomatic and came for regular cardiovascular disease evaluation and 82 patients had the test for the examination of chest pain. MSCT measurements of CAC, VFA, SFA, and WC were also determined for each patient. The study protocol was approved by the Ethics committee at Hiroshima University, and written informed consent was obtained from all patients.

### 2.2. Risk factor assessment

All patients provided details of their demographics, medical history, and medication usage at the clinical consultation. If a subject was a current smoker, he was considered to have a positive history of cigarette smoking. Patients were classified as hypertensive if their systolic blood pressure was  $\geq 140$  mm Hg, diastolic blood pressure was  $\geq 90$  mm Hg, and/or the subject was on antihypertensive therapy. Prior to CT scan, we obtained fasting blood samples from an antecubital vein. Concentrations of triglycerides and uric acid were measured with standard enzymatic methods. High-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were measured by direct methods. Glycohemoglobin A1c (HbA1c) was measured using high-performance liquid chromatography. Diabetes mellitus was defined by self-report and current use of hypoglycemic agents. Hypercholesterolemia was characterized by a fasting serum LDL cholesterol level  $\geq 140$  mg/dl on direct measurement [12], or when the patient was using lipid-lowering agents. Metabolic syndrome was diagnosed by Japanese criteria, which was reported in 2005 [13]. Height (m) and body weight (kg) were used to calculate the body mass index (BMI).

### 2.3. CAC scoring using MSCT

Total of 321 consecutive patients were imaged using either a 16-slice MSCT scanner (LightSpeed Ultrafast16, GE Healthcare, Waukesha, Wisconsin) between August 2005 and November 2005 (men, 27; women, 17; age  $66 \pm 10$  years) or a 64-slice CT scanner (LightSpeed VCT, GE Healthcare) between December 2005 and June 2007 (men, 186; women, 91; age  $65 \pm 11$  years). Prospective electrocardiogram-triggered scans were performed in mild inspiration from the root of aorta to the apex of the heart with the following parameters (16-slice CT and 64-slice CT): axial scan; gantry rotation times, 500 ms and 350 ms; X-ray exposure times, 333 ms and 233 ms; tube voltage, 120 kV; tube currents, 100 mA and 140 mA; center of imaging window, 75% of R-R. Thirty-five to 40 contiguous images of 2.5-mm thickness were obtained.

The calcium score was determined using a commercially available external workstation (Advantage Windows, version 4.2, GE Healthcare), and using the CAC scoring software (Smartscore, version 3.5, GE Healthcare). CAC score (CACS) was calculated according to the Agatston method as previously described [14]. We defined the regions of interest based on the vessels and slices, and using the threshold option for pixels greater than 130 Hounsfield units (HU) to measure the area and peak density of the plaques. Depending on the peak density of the plaque, an area of at least  $0.52 \text{ mm}^2$  (2 pixels) was multiplied by one of the following cofactors: a factor of one for 130–199 HU, a factor of two for 200–299 HU, a factor of three for 300–399 HU, and a factor of 4 for densities greater than 400 HU. The total coronary artery calcium score was calculated as the sum of the individual lesion scores in all coronary arteries.

### 2.4. Measurement of VFA, SFA, and WC using MSCT

In addition to MSCT heart scans, abdominal scans were performed at the lumbar 4–5 levels in spine position, and single 5-mm slices were taken during suspended respiration after normal expiration. The fat areas and WC in each subject were determined from an image at the level of the umbilicus using a commercially supplied software (Virtual Place, AZE Inc., Tokyo, Japan). Subcutaneous fat was defined as the extraperitoneal fat between the skin and muscles, with attenuation ranging from  $-150$  to  $-50$  HU. The intraperitoneal part with the same density as the subcutaneous fat layer was defined as visceral fat. The VFA and SFA were determined by automatic planimetry. The WC was determined at the umbilicus level using a mobile caliper.

### 2.5. Statistical analysis

Categorical variables were presented as number of patients (%) and continuous variables were expressed as mean  $\pm$  S.D. Between-group comparisons were performed using Student's *t*-test or the Mann-Whitney *U*-test and the correlation

coefficient was estimated by Pearson correlation. Differences among three groups by CAC category were tested by ANOVA with post hoc analysis. Multivariable logistic regression analysis was performed to assess the independent relationship of metabolic syndrome and adiposity measurements to the presence of CAC. Additionally, we also used ordinal regression analysis to assess the relationship of metabolic syndrome and adiposity measurements with increasing levels of CAC [15]. Confidence intervals (CI) that excluded 1.0 were considered to indicate significant results. Utilization of CAC scores as a continuous variable in standard parametric analyses is extremely challenging due to high frequency of zero scores resulting in a high skewed distribution, CAC scores were therefore dichotomized (i.e., presence or absence of CAC) for use in logistic regression analysis. We also categorized CAC scores into three groups: 0, 1–100 and >100 for use in ordinal regression analysis. For analysis between metabolic syndrome and CAC, we used a set of atherosclerotic risk factors – age, current smoking, LDL cholesterol, uric acid and lipid-lowering agents – as explanatory variables. Two sets of multivariable models were used in a hierarchical fashion to determine the independent association of the adiposity measurements. Model 1 was adjusted for traditional cardiovascular risk factors including hypertension, diabetes, current smoking, triglycerides, HDL cholesterol, LDL cholesterol, uric acid and HbA1c levels, and medication use. Metabolic syndrome was not included in the model because of collinearity. Model 2 was additionally standardized for fat measurements including VFA, BMI, SFA, and WC. A receiver operator characteristic (ROC) analysis was performed to determine the increase in discriminative ability that was afforded by VFA in addition to clinical fat measurements such as BMI and WC. All analyses were performed on the whole population and then stratified by gender. Furthermore, the sex-specific VFA was tested using a ROC curve to detect the presence of CAC. The optimal cut-off point was obtained from the Youden index (maximum (sensitivity + specificity – 1)) [16]. All analyses were performed using the JMP 5.0.1 statistical software (SAS Institute Inc, North Carolina). A  $p$  value < 0.05 was considered statistically significant.

### 3. Results

#### 3.1. Patient characteristics

The study patients consisted of 213 men (mean age, 65 years; range, 36–87 years) and 108 women (mean age, 68 years; range, 44–86 years). Coronary calcium, defined as CAC > 0, was present in 73% men and 57% women. The median (range) CAC in men and women were 138 (0–4370) and 33.5 (0–1998), respectively. The distribution of CAC by sex is shown in Fig. 1a. The characteristics of the study subjects based on CAC status are shown in Table 1. In both sexes, patients with any CAC were significantly older, had a

higher BMI, a larger VFA, SFA, VFA/SFA ratio and WC, and a higher prevalence of hypertension, hypercholesterolemia, diabetes and metabolic syndrome. The percentages of pharmacological treatment for hypertension and diabetes were significantly higher in men with CAC than those without and in hypertensive women with CAC.

#### 3.2. Metabolic syndrome and coronary artery calcium

The prevalence of metabolic syndrome in our study patients was 41.4% (133/321) in all subjects, 49.8% (106/213) in men and 25.0% (27/108) in women. Multivariable logistic regression analysis showed that the odds ratio of the presence of CAC, adjusted for age, sex (for all subjects), current smoking, uric acid, LDL cholesterol and lipid-lowering agents, was 4.28 (95%CI, 2.14–9.02;  $p$  < 0.0001) in all subjects, 3.83 (95%CI, 1.61–9.81;  $p$  = 0.0032) in men and 5.23 (95%CI, 1.65–20.7;  $p$  = 0.0088) in women. Similarly, multivariable ordinal regression analysis revealed that the odds ratio of increasing CAC categories, adjusted for the same explanatory variables as above, was 1.71 (95%CI, 1.31–2.25;  $p$  < 0.0001) in all subjects, 1.66 (95%CI, 1.19–2.33;  $p$  = 0.0030) in men and 1.93 (95%CI, 1.21–3.16;  $p$  = 0.0064) in women. These results demonstrated that metabolic syndrome was an independent predictor of CAC in both sexes.

#### 3.3. Adiposity measurements and coronary artery calcium

Adiposity measurements were all significantly correlated with each other, as shown in Table 2. VFA was strongly correlated with WC ( $r$  = 0.79) and moderately correlated with BMI ( $r$  = 0.51) and SFA ( $r$  = 0.44). Fig. 1b shows the mean adiposity measurements (VFA, BMI and SFA) according to the CAC category in both sexes. In men, VFA and BMI were significantly different between the CAC: 0 and CAC: >400 groups ( $p$  < 0.0001 and  $p$  = 0.001), whereas SFA was significantly lower in the CAC: >400 group compared with the CAC: 101–400 group ( $p$  = 0.04). In women, VFA, BMI and SFA were all significantly different between the CAC: 0 and CAC: >400 groups ( $p$  < 0.0001,  $p$  < 0.0001,  $p$  = 0.0012).

Table 3 describes the association of adiposity measurements with CAC using multivariable logistic and ordinal regression analysis. As for all subjects, in Model 1 adjusting for age and traditional risk factors, the odds ratio (95%CI) of the presence of CAC for one-unit-standard deviation increase in VFA (69.8 cm<sup>2</sup>), BMI (3.1 kg/m<sup>2</sup>) and WC (9.5 cm) were 2.01 (1.32–3.27), 1.41 (1.01–1.98) and 1.61 (1.10–1.98), respectively. Similarly, the association of VFA, BMI and WC with increasing CAC categories in the ordinal regression analysis was also statistically significant. On the other hand, both SFA and VFA/SFA ratio (data not shown) were not significantly associated with CAC. In Model 2, which additionally standardized for VFA, BMI, SFA and WC, only VFA persisted to show a significant relationship with CAC in both

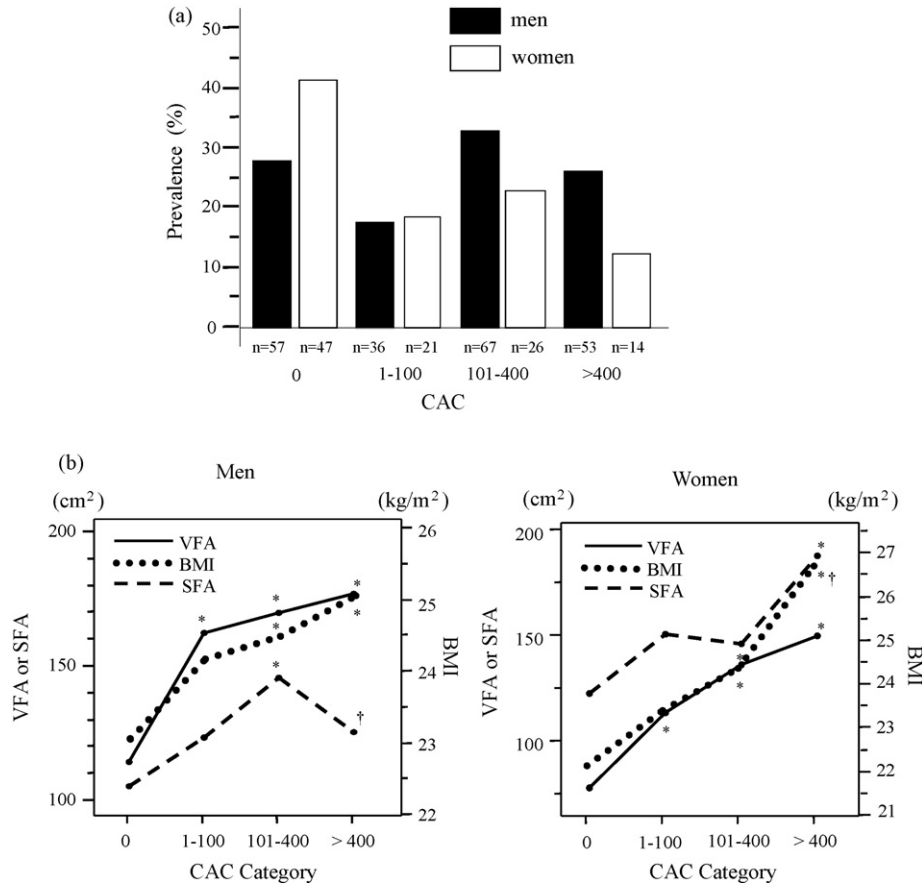


Fig. 1. (a) Distribution of multislice computed tomography (MSCT)-derived coronary artery calcium score by sex. Solid bars and open bars represent men and women, respectively. (b) Mean fat measurements according to the coronary artery calcium (CAC) category in men and women. Solid lines, dotted lines, and broken lines denote visceral fat area (VFA), body mass index (BMI) and subcutaneous fat area (SFA), respectively. Mean values of fat measurements for CAC category: 0, 1–100, 101–400, >400 are 115, 162, 170, 177 cm<sup>2</sup> for VFA, 23.1, 24.1, 24.4, 24.9 kg/m<sup>2</sup> for BMI and 106, 124, 146, 125 cm<sup>2</sup> for SFA in men and 80, 115, 138, 152 cm<sup>2</sup> for VFA, 22.3, 23.5, 24.4, 26.6 kg/m<sup>2</sup> for BMI and 124, 153, 148, 189 cm<sup>2</sup> for SFA in women, respectively. \* *p* < 0.01 versus CAC: 0, † *p* < 0.05 versus CAC: 101–400.

logistic and ordinal regression analyses and was regarded as an independent determinant of CAC. Similar relationships were observed across the gender except that BMI was not associated with CAC in men.

On ROC analysis in all subjects, the area under the curve (AUC) for clinical variables including BMI and WC for presence of CAC > 0 and significant CAC > 100 were 0.740 and 0.698, respectively. When VFA was added in the model, AUC improved to 0.785 and 0.726, respectively. Similar results were obtained for men and women.

### 3.4. Sex-specific cut-off levels of VFA and WC to predict the presence of CAC

From the ROC curve analysis, the optimal cut-off value of VFA to predict the presence of CAC was identified as 116 cm<sup>2</sup> in men, and 82 cm<sup>2</sup> in women. These values provided sensitivities of 79% and 84%, and specificities of 63% and 72% for men and women, respectively (Fig. 2A). Fig. 2B shows the sex-specific correlation between the measured values of VFA and WC using MSCT. According to the regression equations,

the VFA cut-off values corresponded with WC of 87.7 cm and 82.6 cm in men and women, respectively.

## 4. Discussion

To the best of our knowledge, this is the first study to investigate the sex-specific relationship between visceral adiposity measured by MSCT and the presence and extent of CAC in Japanese patients. VFA, a direct index of visceral adiposity, was found to be an independent predictor of the presence and quantity of CAC even after adjustment for BMI, SFA, WC, age, and traditional cardiovascular risk factors in both sexes. These results are consistent with the accumulating evidence that measurements of visceral adiposity are more strongly related to cardiovascular disease compared with BMI [5,6]. We further assessed the sex-specific cut-off levels of VFA and WC to predict the presence of CAC. The results of the ROC analysis indicated that the VFA cut-off levels were 116 and 82 cm<sup>2</sup> in men and women, respectively, which corresponded to WC

Table 1  
Patient characteristics according to CAC status

	All subjects (n = 321)		Men (n = 213)		Women (n = 108)	
	No CAC (n = 104)	Any CAC (n = 217)	No CAC (n = 57)	Any CAC (n = 156)	No CAC (n = 47)	Any CAC (n = 61)
Age (yrs)	62 ± 12	68 ± 9**	60 ± 13	67 ± 9**	65 ± 9	71 ± 7**
BMI (kg/m <sup>2</sup> )	22.7 ± 3.1	24.5 ± 2.9**	23.1 ± 2.9	24.5 ± 2.8**	22.3 ± 3.4	24.6 ± 3.1**
Hypertension, n (%)	34 (33)	139 (64)**	19 (33)	99 (64)**	15 (32)	40 (66)**
Hypercholesterolemia, n (%)	35 (34)	133 (61)**	18 (32)	93 (60)**	17 (36)	40 (66)**
Diabetes mellitus, n (%)	34 (33)	122 (56)**	16 (28)	85 (55)**	18 (38)	37 (61)*
Current Smoking, n (%)	29 (28)	94 (43)**	23 (40)	84 (54)*	6 (13)	10 (16)
Metabolic syndrome, n (%)	19 (18)	114 (53)**	15 (26)	91 (58)**	4 (9)	23 (38)**
Triglyceride (mg/dl)	128 ± 65.5	163 ± 84.7**	132 ± 71.1	164 ± 85.0*	124 ± 58.5	159 ± 84.7*
HDL cholesterol (mg/dl)	60.4 ± 19.4	51.9 ± 16.5**	59.1 ± 22.7	49.9 ± 15.7**	62.0 ± 14.5	57.0 ± 17.5*
LDL cholesterol (mg/dl)	112 ± 28.4	125 ± 33.4**	109 ± 27.7	123 ± 35.5**	114 ± 29.2	130 ± 29.1**
HbA1c (%)	5.9 ± 1.0	6.5 ± 1.2**	5.9 ± 1.1	6.4 ± 1.2**	5.9 ± 1.0	6.7 ± 1.1**
Uric acid (mg/dl)	5.5 ± 1.6	5.9 ± 1.3**	5.8 ± 1.9	6.2 ± 1.3	5.2 ± 1.2	5.4 ± 1.2
VFA (cm <sup>2</sup> )	99 ± 59.8	160 ± 65.6**	115 ± 67.0	170 ± 67.6**	80 ± 43.4	133 ± 52.0**
SFA (cm <sup>2</sup> )	114 ± 65.5	141 ± 55.8**	106 ± 58.6	134 ± 53.2**	125 ± 72.3	159 ± 58.5**
V/S ratio	1.09 ± 1.11	1.24 ± 0.50**	1.26 ± 0.90	1.37 ± 0.50**	0.72 ± 0.37	0.89 ± 0.32**
WC (cm <sup>2</sup> )	84.6 ± 10.1	92.3 ± 8.1**	86.3 ± 1.1	93.5 ± 0.7**	82.5 ± 9.3	89.4 ± 8.1**
Medication						
Antihypertensive agents, n (%)	14 (13)	67 (31)**	8 (14)	48 (31)*	6 (13)	19 (31)*
Lipid-lowering agents, n (%)	25 (24)	76 (35)*	13 (23)	55 (35)	12 (26)	21 (34)
Hypoglycemic agents, n (%)	26 (25)	62 (29)	8 (14)	42 (27)*	18 (38)	20 (33)

\**p* < 0.05, \*\**p* < 0.001. All data are presented as number of patients (%) or mean ± S.D. CAC, coronary artery calcium; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycohemoglobin A1c; VFA, visceral fat area; SFA, subcutaneous fat area; V/S ratio, visceral fat area/subcutaneous fat area ratio; WC, waist circumference.

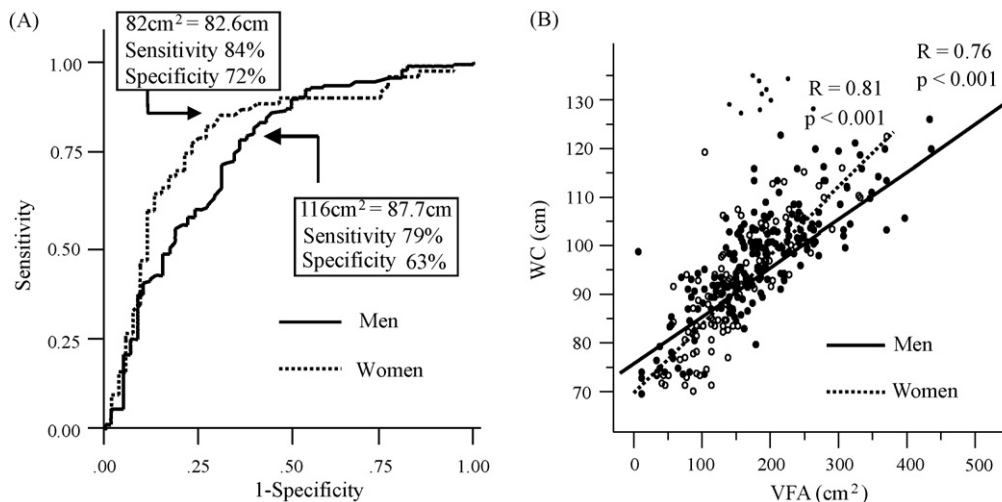


Fig. 2. (A) Receiver operating characteristic (ROC) analysis of the visceral fat area (VFA) to predict the presence of coronary calcium. Solid lines and broken lines depict the ROC curves for men and women, respectively. (B) Correlation between waist circumference (WC) and VFA. Closed circles and open circles indicate the data for men and women, respectively. The solid lines and broken lines represent the men and women, respectively.

values of 87.7 cm and 82.6 cm in men and women, respectively.

Although numerous studies have demonstrated that visceral adiposity is a risk factor for cardiovascular disease, little research has been conducted on the association between visceral adiposity and early atherosclerosis. A number of more recent studies have specifically reported on the effect of excess visceral fat on CAC. In the St. Francis Heart Study, visceral obesity measured by the waist-to-hip ratio or intra-abdominal-fat was positively correlated with CAC

Table 2  
Age- and sex-adjusted Pearson correlation coefficients\*

	VFA	SFA	BMI	WC
VFA	1	0.44	0.51	0.79
SFA	0.44	1	0.6	0.61
BMI	0.51	0.6	1	0.59
WC	0.79	0.61	0.59	1

\* *p* < 0.001 for all correlations.

Table 3  
Multivariable analysis of the association between adiposity measurement and coronary artery calcium

	Multivariable logistic regression analysis <sup>a</sup>					
	All subjects (n = 321)		Men (n = 213)		Women (n = 108)	
	Odds ratio (95%CI <sup>b</sup> )	p value	Odds ratio (95%CI <sup>b</sup> )	p value	Odds ratio (95%CI <sup>b</sup> )	p value
Model 1 <sup>c</sup>						
VFA (cm <sup>2</sup> )	2.01 (1.32–3.27)	0.002	2.37 (1.32–4.53)	0.006	3.70 (1.56–10.1)	0.006
BMI (kg/m <sup>2</sup> )	1.41 (1.01–1.98)	0.04	1.53 (0.98–2.46)	0.06	1.82 (1.03–3.39)	0.04
SFA (cm <sup>2</sup> )	1.27 (0.94–1.82)	0.1	1.60 (0.96–2.76)	0.08	1.67 (0.97–3.01)	0.07
WC (cm)	1.61 (1.10–1.98)	0.01	1.97 (1.17–3.52)	0.02	1.83 (1.00–3.54)	0.05
Model 2 <sup>d</sup>						
VFA (cm <sup>2</sup> )	2.48 (1.23–6.05)	0.02	5.06 (1.14–16.4)	0.04	3.90 (1.26–14.4)	0.02
BMI (kg/m <sup>2</sup> )	1.23 (0.79–1.92)	0.4	1.17 (0.63–2.17)	0.6	1.20 (0.51–2.97)	0.6
SFA (cm <sup>2</sup> )	0.74 (0.38–1.27)	0.3	0.43 (0.12–1.55)	0.2	1.40 (0.57–3.57)	0.4
WC (cm)	1.01 (0.52–1.98)	0.9	1.20 (0.46–3.23)	0.7	0.64 (0.20–1.97)	0.4
Multivariable ordinal regression analysis <sup>e</sup>						
Model 1 <sup>c</sup>						
VFA (cm <sup>2</sup> )	1.82 (1.29–2.60)	0.001	1.64 (1.14–2.44)	0.008	2.85 (1.44–6.18)	0.003
BMI (kg/m <sup>2</sup> )	1.37 (1.05–1.82)	0.02	1.27 (0.93–1.75)	0.1	1.88 (1.12–3.26)	0.02
SFA (cm <sup>2</sup> )	1.29 (0.81–1.71)	0.07	1.36 (0.97–1.93)	0.07	1.55 (0.95–2.62)	0.07
WC (cm)	1.55 (1.13–2.15)	0.006	1.44 (1.02–2.06)	0.04	1.86 (1.09–3.32)	0.02
Model 2 <sup>d</sup>						
VFA (cm <sup>2</sup> )	2.05 (1.18–3.98)	0.02	2.08 (1.05–4.90)	0.05	2.67 (1.66–7.37)	0.04
BMI (kg/m <sup>2</sup> )	1.16 (0.81–1.67)	0.4	1.04 (0.70–1.56)	0.8	1.40 (0.67–3.00)	0.4
SFA (cm <sup>2</sup> )	0.81 (0.49–1.29)	0.4	0.82 (0.39–1.53)	0.5	1.17 (0.57–2.44)	0.7
WC (cm)	1.03 (0.61–1.75)	0.9	0.98 (0.55–1.77)	0.9	0.78 (0.29–2.06)	0.6

<sup>a</sup> The results of logistic regression analysis are presented as the odds ratio of the presence of CAC for one-unit-standard deviation increase in adiposity measurement.

<sup>b</sup> 95% confidence interval.

<sup>c</sup> Adjusted for age, hypertension, diabetes, smoking status, triglycerides, LDL cholesterol, HDL cholesterol, HbA1c, uric acid and medication use. Abbreviations are the same as in Table 1.

<sup>d</sup> Model 1 plus adjustment for VFA, BMI, SFA or WC. Abbreviations are the same as in Table 1.

<sup>e</sup> The results of ordinal regression analysis are presented as the odds ratio of increasing CAC category (0, 1–100 and >100) for one-unit-standard deviation increase in adiposity measurement.

in 50–70-years-old US men and women [17]. The recent CARDIA study has demonstrated that abdominal obesity measured by waist girth or waist-to-hip ratio is associated with CAC in African American and White young adults [18]. With respect to obesity and CAC in diabetic individuals, the PREDICT study showed that the waist-to-hip ratio was a significant predictor of CAC after adjustment for multiple cardiovascular risk factors in 495 diabetic subjects [19]. In another multiethnic study on type 2 diabetes, visceral fat measured by CT predicted CAC [20]. These results support our findings, i.e., visceral fat measured directly using MSCT is an independent predictor of CAC in Japanese patients, in the daily clinical practice.

The distribution of body fat has been focused as a cardiovascular risk. Interestingly, in our study, SFA was lower in men with significant CAC > 400, which raises the possibility that the increasing subcutaneous fat has a favorable effect on atherosclerosis. This finding is relevant as peripheral fat such as subcutaneous or gluteal fat has been shown to be protective against cardiovascular and metabolic outcomes [3,6]. However, more definitive studies will be necessary to validate this hypothesis. Recently, a study from the Framingham Heart Study has shown that pericardial fat, which is an ectopic fat

depot around the heart, is more associated with CAC than visceral fat [21]. It is interesting because the result of this study suggested that pericardial fat may potentially exert local atherosclerotic effects due to anatomical close proximity to the coronary arteries. Further investigation is needed to determine if this finding is true as well as our patient-based sample study.

Several prior studies have identified some plausible mechanisms by which the accumulation of visceral fat could directly accelerate atherosclerosis [4]. It is generally assumed that insulin resistance is one of the most important factors linking visceral fat to the clustering of cardiovascular risk factors. Insulin resistance has also been postulated to be largely responsible for endothelial dysfunction, platelet activation, and the progression of atherosclerosis [22,23]. Visceral adiposity is also associated with increased levels of proinflammatory cytokines like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-6 (IL-6), and less adiponectin. These cytokines are suggested to induce insulin resistance, and play a major role in the pathogenesis of endothelial dysfunction and subsequent atherosclerosis [24,25].

CAC is a marker of atherosclerosis that can be quantified by using MSCT, and it is proportional to the extent and

severity of atherosclerotic disease. In previous large studies, an increased plaque burden was found to be a significant predictor of future cardiovascular events and mortality in symptomatic and asymptomatic subjects [7,8]. The detection and quantification of CAC by MSCT could potentially provide a preventive strategy for cardiovascular events. There is ample evidence demonstrating that individuals with visceral adiposity represent a population at high risk for the progression of atherosclerosis and cardiovascular events. Cassidy et al. reported that several indices of adiposity measurements including waist circumference and waist-to-hip ratio predicted the progression of CAC in patients with a low risk for cardiovascular disease [26]. The strong association between increased amount of visceral fat and quantity of CAC observed in our study could explain, at least in part, the excess risk of atherosclerosis in abdominal obese patients. Therefore, measuring visceral fat is a useful clinical tool for identifying patients with potential future cardiovascular disease risk. Furthermore, our study may still add to the knowledge suggesting that the presence of higher VFA will have a rapid progression of CAC and may still need more aggressive risk modification even if the CAC scores are same across different patients. Considering the cross-sectional nature of this study, causality cannot be established. Ultimately, a trial that specifically focuses on weight reduction and decreases in visceral fat amount would verify a possible causal relationship between visceral adiposity and atherosclerosis.

In the latest Japanese criteria [13], visceral adiposity is a requisite factor in metabolic syndrome. Men and women with a waist circumference greater than 85 cm and 90 cm, respectively, are considered to have an increased risk for more than one obesity-related disease (i.e., hyperglycemia, hypertension, dyslipidemia, hyperuricemia, and cardiovascular disease). These cut-off points were derived from a regression curve that identified the WC values corresponding to a VFA of 100 cm<sup>2</sup>. However, several studies revealed a gender difference in the association of visceral fat accumulation with metabolic syndrome. Hayashi et al. analyzed data from 639 Japanese Americans, and reported that the optimal cut-off points for VFA and WC to predict metabolic syndrome were 96.1 cm<sup>2</sup> and 87.1 cm in men (age, >57 years); and 86.3 cm<sup>2</sup> and 89.0 cm in women (age, >56 years) [27]. Recently, metabolic syndrome has been found to be associated with endothelial dysfunction, a hallmark of early atherosclerotic changes, coronary calcification, and subclinical atherosclerosis of the carotid artery [28,29]. Our study has demonstrated that metabolic syndrome is an independent predictor of CAC, which is consistent with the prior finding [28].

This study had some limitations. First, data were exclusively collected from middle-aged and older Japanese patients with a high risk for cardiovascular disease in a single institute using a retrospective method. As a result, it is uncertain whether our findings can be generalized to other ethnic groups or healthy young subjects. Prospec-

tive and non-randomized investigations should be warranted. Second, we used the CT-measured WC value when calculating the WC cut-off, though anthropometric measured WC values are currently used for the diagnosis of visceral obesity for metabolic syndrome. The relationship between CT and the anthropometric measured WC should be confirmed in Japanese populations. Third, we could not evaluate the relationship between CAC and other confounding factors including inflammatory mediators and adipocytokines, which may not allow us to exclude the potential effects of these influences on CAC. Fourth, although we used 16- and late 64-slice CT to measure CAC, accuracy comparison of both methods could not be evaluated. Horiguchi et al. reported that the sensitivity and specificity in the detection of CAC using 16-slice CT with a threshold of 130 HU were 98.7% and 100%, respectively [30]. Further investigation of the interscanner variability of CAC measurement is needed.

## 5. Conclusions

We found that visceral adiposity measured by MSCT is significantly associated with the presence and extent of CAC in Japanese patients. Follow-up studies are needed to examine the influence of greater visceral fat accumulation on the development of new calcification or the progression of CAC scores.

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