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Impact of abdominal fat distribution, visceral fat, and subcutaneous fat on coronary plaque scores assessed by 320-row computed tomography coronary angiography

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HIGHLIGHTS

- Abdominal visceral fat area correlated with coronary plaque scores, whereas abdominal subcutaneous fat area inversely correlated with those scores.
- Higher SAT and lower VAT were inversely correlated with the extent and severity of coronary artery plaques.
- Fat distribution may be a useful tool for evaluating risk and prognosis of coronary artery disease.

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ABSTRACT

Background and aims: Obesity is a risk factor for coronary artery disease (CAD), but the association between fat distribution, i.e., visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), and coronary artery plaque morphology remains unclear. This study explored the association between abdominal fat distribution and coronary artery plaques.

Methods: We retrospectively evaluated 4327 consecutive patients without CAD history, undergoing coronary computed tomography (CT) angiography. Plaques were assessed using segment stenosis score (SSS) and segment involvement score (SIS). We evaluated abdominal VAT and SAT areas using CT images. Patients were categorized into four groups: low VAT (< median)/low SAT (< median); low VAT/high SAT (≥median); high VAT (≥median)/low SAT; and high VAT/high SAT.

Results: Mean age was 65 years (men, 66.4%). VAT area correlated with SSS (β-coefficient = 0.11, $p < 0.001$) and SIS (β-coefficient = 0.006, $p < 0.001$), whereas SAT area was inversely correlated with SSS (β-coefficient = −0.007,$p < 0.001$) and SIS (β-coefficient = −0.004, $p < 0.001$). The low VAT/high SAT group had the lowest risk of higher SSS (≥5) and SIS (≥5) (odds ratio [OR] using low VAT/low SAT group as the reference category, 0.76, 95% confidence interval [CI], 0.61–0.95, $p < 0.05$; OR, 0.68, 95% CI, 0.53–0.88, $p < 0.01$, respectively) in multivariate analysis adjusted for age, sex, and traditional CAD risk factors. In the obese population (body mass index ≥25, n = 1694), the low VAT/high SAT group had the lowest risk of higher coronary plaque scores.

Conclusions: Higher SAT and lower VAT were inversely correlated with the extent and severity of coronary artery plaques. Fat distribution may be useful for evaluating risk and prognosis of CAD.

1. Introduction

Worldwide prevalence of obesity has increased in the past decades. Mean body mass index (BMI) has increased worldwide by 0.4 kg/m^2 per decade for men and 0.5 kg/m^2 for women [1]. Obesity is considered a risk factor for coronary artery disease (CAD) [2]. Since obesity is associated with increased blood pressure, dyslipidemia, and type 2 diabetes mellitus [3,4], obese individuals are more likely to develop cardiovascular disease.

Recently, many large studies and meta-analyses have demonstrated the presence of an “obesity paradox”: obese patients with CAD (BMI, 25.0–34.9 kg/m^2) have a better prognosis than those with a normal BMI

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(18.5–24.9 kg/m^2) [3,5,6]. This suggests that the metabolic effects of obesity may be protective against the development of CAD [7].

Previous studies have investigated body composition and adipose tissue distribution [8]. Abdominal visceral fat correlates with prevalence of CAD and mortality [9,10], whereas subcutaneous fat may play a protective role against the development of CAD through the improvement of insulin sensitivity or secretion of adipokines [11–13]. Distribution of adipose tissue, i.e. visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), may be associated with the development and prognosis of CAD. However, association between the extent and severity of coronary artery plaques and abdominal fat distribution remains unclear.

The recent introduction of multidetector coronary computed tomographic angiography (CCTA) offers a novel noninvasive approach for the evaluation of CAD [14]. In addition to high diagnostic accuracy for detection of CAD and high negative predictive value for excluding the presence of obstructive CAD [15], CCTA enables prediction of prognosis in individuals with stable CAD using CCTA scores, which are calculated from the severity and extent of coronary artery plaques, segment stenosis score (SSS), and segment involvement score (SIS) [16].

The aim of this study was to evaluate the association between fat distribution and severity and extent of coronary artery plaque assessed by CCTA plaque scores.

2. Patients and methods

2.1. Study population

We retrospectively evaluated 5756 consecutive patients who underwent CCTA at our institution between January 2009 and May 2017. Of these, 1429 patients with a prior history of percutaneous coronary intervention or coronary artery bypass graft were excluded, leaving a total of 4327 patients. All patients provided written informed consent prior to study enrollment and the identities of these patients have been protected. The study protocol was approved by the medical ethical committee.

We collected information on the presence of cardiac risk factors for each individual. Systemic arterial hypertension (HTN) was defined as a documented history of high blood pressure or treatment with antihypertensive medications. Diabetes mellitus (DM) was defined as a previous diagnosis of DM or use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as total cholesterol (TC) ≥240 mg/dl, low-density lipoprotein cholesterol (LDL-cholesterol) ≥130 mg/dl, high-density lipoprotein cholesterol (HDL-cholesterol) ≤40 mg/dl, triglycerides (TG) ≥150 mg/dl, and/or treatment with lipid-lowering agents or the previous diagnosis of dyslipidemia. Smoking history was defined as current smoking or cessation of smoking within one month of CCTA. Family history of coronary heart disease was defined based on patient query. Laboratory data including hemoglobin A1c (HbA1c), TC, TG, HDL-cholesterol, LDL-cholesterol, and high-sensitive C-reactive protein (CRP) levels were measured within 1 month of the CT scan.

2.2. Scan protocol and image reconstruction

CCTA scans were performed using a 320-slice multidetector CT scanner (Aquilion One, Canon Medical Systems Ltd., Tochigi, Japan) according to a previously described protocol [17]. Three hours before CCTA, any patient with a heart rate (HR) > 65 bpm received 20 mg of oral metoprolol. For patients with a heart rate > 65 bpm before the scan, 0.125 mg/kg of landiolol (Ono Pharmaceutical Co., LTD., Osaka, Japan) was intravenously administered. Immediately before image acquisition, most patients received 0.3 mg of sublingual nitroglycerin. Scan parameters were a collimation of 320 rows × 0.5 mm, rotation time of 350–400 ms and tube voltage of 120 kV. The tube current (270–400 mA) was selected according to the standard deviation of the noise level measured on the CT projection radiograph. Electrocardiogram-gated non-enhanced scans were obtained, followed by contrast-enhanced scans using Iopamiron 370 mg/mL (Bayer Schering Pharma, Osaka, Japan) injected at a speed of 4.0–5.0 mL/s over 10 s. The scanner's “arrhythmia rejection” software automatically removed irregular beats using the multi-segment acquisition technique. The Phase-NAVI scanner software (Canon Medical Systems Ltd., Tochigi, Japan) automatically determined the appropriate cardiac phase with minimum motion for CT axial image reconstruction. All data acquired with 0.25 mm-thick slices were reconstructed using a standard kernel of FC04.

2.3. CCTA analysis and coronary plaque scores

All CCTA examinations were analyzed by an expert, using the American Heart Association 16-segment classification [18]. In each coronary artery segment, stenosis of atherosclerotic lesions was quantified by visual estimation. Stenosis was graded as none or very mild (< 30% estimated obstruction of coronary luminal diameter), mild (30%–49% estimated obstruction), moderate (50%–69% estimated obstruction), or severe (≥70% estimated obstruction). The percentage obstruction of the coronary artery lumen was based on comparison of the luminal diameter of the obstructed segment to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. Obstructive CAD was defined as at least one coronary segment with ≥50% stenosis.

We assessed each coronary artery using two methods of coronary plaque scoring by CCTA: SSS and SIS. The scoring systems have been previously described [16,19]. The SSS was calculated according to coronary plaque burden. Luminal obstruction of each individual segment was scored from 0 to 3 (normal to severe). Scores of 15 individual segments were summed to give a total score (range: 0 to 45). The SIS was calculated based only on the presence of plaque within a segment, irrespective of the degree of luminal stenosis within each segment (minimum = 0; maximum = 15). We defined the cut-off of CCTA scores using a previous report as SSS ≥5 and SIS ≥5 [16].

The coronary artery calcium score (CACS) was calculated using a workstation (Ziostation 2, Ziosoft, Tokyo, Japan) and expressed as an Agatston score as previously reported [20].

2.4. Quantitative analysis of abdominal visceral and subcutaneous adiposity

Measurement of abdominal visceral fat and subcutaneous adiposity was performed as previously described [21]. Briefly, slices centered at the L4–L5 disc spaces were selected. Visceral fat was defined as the fat enclosed by the visceral cavity. Subcutaneous fat was defined as fat outside the visceral cavity not including that located within the muscular fascia. Fat tissue was identified as tissue with a radiodensity between −190 and −30 Hounsfield units. The total visceral fat area, subcutaneous fat area (in cm^2) and waist circumference (WC, cm) were automatically calculated using a workstation (Ziostation 2, Ziosoft, Tokyo, Japan).

2.5. Statistical analysis

Participants' baseline data were presented as mean ± standard deviation or as median (first quartile, third quartile) for continuous variables and as frequencies or proportions for categorical variables. Continuous variables with skewed distribution including the CACS were log transformed for analysis. The association between variables and coronary plaque scores were expressed as β-coefficients. Unadjusted or multiple linear regression models were used to evaluate the association.

To better quantify the importance of abdominal fat distribution, the cohort was stratified into 4 groups for quantitative analysis of VAT area and SAT area: low VAT (< median)/low SAT (< median) group; low VAT/high SAT (≥median) group; high VAT (≥median)/low SAT

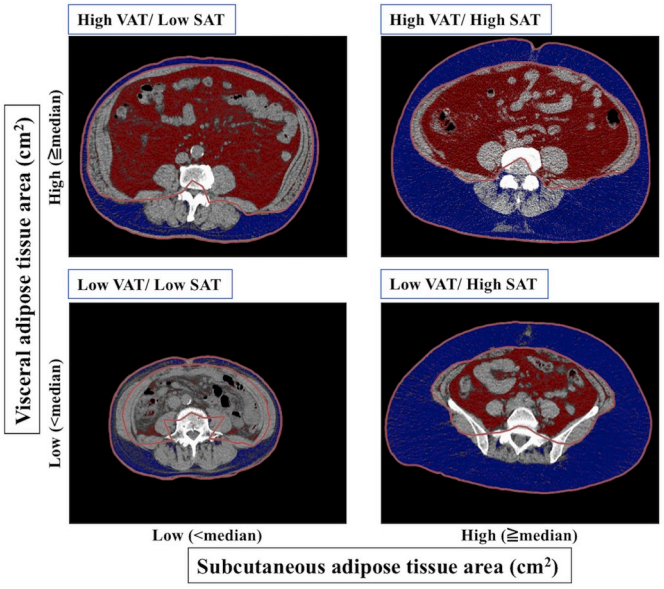

Fig. 1. Grouping according to quantitative analysis of abdominal fat distribution.
Abdominal fat distribution was categorized into 4 patterns depending on the amount of abdominal visceral adipose tissue (VAT) area and subcutaneous adipose tissue (SAT) area measured by multi-detector computed tomography data: low VAT/low SAT, low VAT/high SAT, high VAT/low SAT and high VAT/high SAT. Regions in red and blue indicate visceral fat area and subcutaneous fat area, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

group; and high VAT/high SAT group (Fig. 1 and Supplemental Fig. 1). Furthermore, patients with high BMI ($\geq 25\,kg/m^2$) were divided into four groups, as described above, using the medians of VAT and SAT.

A one-way analysis of variance or Student t tests were used to examine differences between the four VAT/SAT groups for continuous variables in comparison to the low VAT/low SAT group. Categorical variables were compared using a chi-square test. To correct for multiple comparisons between groups, the Turkey test or Steel-Dwass test were used.

Multivariable logistic regression models or multivariable linear regression models were used to assess predictors of higher coronary plaque scores. Models were analyzed in two ways: Model 1 was adjusted for age and sex, both of which should be considered for abdominal fat area; Model 2 was adjusted for all covariates in Model 1 plus HTN, dyslipidemia, DM, smoking status, and family history of CAD. The strength of the associations is presented as odds ratios (ORs, 95% confidence interval [CI]). The differing risks of higher coronary plaque scores between the four VAT/SAT groups were expressed as ORs in comparison with the low VAT/low SAT group. Statistical significance was set at $p < 0.05$. All analyses were conducted using JMP (version 13, for Windows, SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Clinical characteristics of the study population

Table 1 shows the baseline characteristics of the study population (4327 patients). The mean age was 65.0 ± 11.9 years, and 66% were male. The mean BMI was 24.4 ± 4.0 kg/m^2. The median VAT area, SAT area, and WC of the study population were 113.3 cm^2 (interquartile range, 71.7, 156.5), 139.5 cm^2 (98.4, 184.5), and 85.3 cm (78.4, 92.1), respectively. Both BMI and WC significantly correlated to VAT area or SAT area (Supplemental Table 1).

The baseline characteristics of the four fat composition groups based on VAT area and SAT area are shown. There were differences in age, sex, BMI, creatinine, estimated glomerular filtration rate, hemodialysis, TC, LDL-cholesterol, HDL-cholesterol, TG, HbA1c, and CRP between the four groups. The proportions of traditional CAD risk factors, including hypertension, dyslipidemia, diabetes, smoking, and family history, were also significantly different between the four groups. In contrast, there was no significant difference in the proportion undergoing statin therapy.

3.2. Univariate and multivariate predictors of coronary plaque scores

The VAT area was significantly correlated with coronary plaque scores, both SSS (β-coefficient = 0.11, $p < 0.0001$) and SIS (β-coefficient = 0.006, $p < 0.001$) (Table 2A and B), whereas the SAT area showed inverse correlations with both scores (SSS: β-coefficient = −0.007, $p < 0.001$; SIS: β-coefficient = −0.004, $p < 0.001$). Age, sex, DM, HTN, dyslipidemia, and current smoking were also associated with increased SSS and SIS. In contrast, BMI, WC, and family history did not correlate with coronary plaque scores. Neither VAT area nor SAT area was significantly correlated with coronary plaque scores in the multivariate analysis adjusted for age, sex, and traditional CAD risk factors. However, high SAT area showed a trend to correlate with low SSS (β-coefficient = −0.025, $p = 0.09$).

3.3. Prevalence of coronary plaque scores in fat distribution groups

Coronary plaque scores, SSS and SIS, are shown in Table 3. The fat distribution groups were low VAT/low SAT (n = 1444), low VAT/high SAT (n = 720), high VAT/low SAT (n = 720), and high VAT/high SAT (n = 1443). The median SSS and SIS in the study population were 4 (1, 10) and 3 (0, 6), respectively. Patients with low VAT/high SAT had the lowest coronary plaque scores (SSS: 2 [0, 7], SIS: 2 [0, 4]), whereas patients with high VAT/low SAT had the highest plaque scores (SSS:5 [1, 12], SIS: 3 [1, 7]). These differences were statistically significant ($p < 0.05$).

A total of 34% of the patients had significant stenosis. The proportion of obstructive CAD was highest in the high VAT/low SAT group (41%) and lowest in the low VAT/high SAT group (24%).

Patients with low VAT/high SAT had the lowest CACS (Log CACS:1.8 [0, 5.0]). In contrast, patients with low VAT/low SAT, high VAT/low SAT, and high VAT/high SAT had a high CACS (3.8 [0, 6.0], 4.2 [0, 6.0], 3.6 [0, 5.6], respectively), and these groups had a statistically higher rate of patients with severe coronary artery calcification (CACS > 400 Agatston Units) compared to low VAT/high SAT group ($p < 0.05$).

In each fat distribution group, both BMI and WC significantly correlated to VAT area or SAT area (Supplemental Table 1). We assessed the association of BMI and WC with SSS or SIS in each fat distribution group (Supplemental Table 2). In low VAT/low SAT group or low VAT/high SAT group, BMI or WC had significant association with SSS or SIS in univariate analysis, however, in multivariate analysis these relationships were not significant.

3.4. Association between fat distribution and coronary plaque scores

We analyzed the predictive value of fat distribution for high coronary plaque scores (SSS ≥5, SIS ≥5). In the multivariate analysis adjusted for age, sex, and traditional CAD risk factors, fat distribution was an independent predictor of high coronary plaque scores. In particular, patients with low VAT/high SAT scores had the lowest risk of high SSS and SIS (odds ratio [OR] using the low VAT/low SAT group as the reference category, 0.76, 95% confidence interval [CI], 0.61–0.95, $p < 0.05$; OR, 0.68, 95% CI, 0.53–0.88, $p < 0.01$, respectively). The low VAT/high SAT group also had a significantly lower risk compared to the high VAT/low SAT group or high VAT/high SAT group. There were no statistical differences between the low VAT/low SAT group,

Table 1
Patients baseline characteristics.

Parameters	All	Low VAT/Low SAT	Low VAT/High SAT	High VAT/Low SAT	High VAT/High SAT	*p* value
	n = 4327	n = 1444	n = 720	n = 720	n = 1443	
Age (years)	65.0 ± 11.9	66.5 ± 12.2	65.5 ± 12.2	65.5 ± 10.8	62.9 ± 11.9 *	< 0.0001
Male, n (%)	2873 (66)	962 (67)	181 (25) *	677 (94) *	1053 (73) *	< 0.0001
BMI (kg/m^2)	24.4 ± 4.0	21.3 ± 2.60	24.4 ± 3.05 *	24.2 ± 2.29 *	27.7 ± 3.75 *	< 0.0001
Hypertension	2755 (63)	778 (54)	419 (58)	504 (70) *	1054 (73) *	< 0.0001
Diabetes mellitus	1259 (29)	363 (25)	149 (21) *	253 (35) *	494 (34) *	< 0.0001
Dyslipidemia	2354 (54)	650 (45)	391 (54) *	402 (56) *	911 (63) *	< 0.0001
Current smoker	2155 (49)	684 (47)	230 (32) *	461 (64) *	780 (54) *	< 0.0001
Family history	1058 (25)	323 (22)	204 (28) *	162 (23)	369 (26) *	0.008
eGFR (ml/min/1.73m^3)	69.7 ± 19.7	67.6 ± 21.9	71.1 ± 18.1	68.5 ± 18.3	71.6 ± 18.7 *	< 0.0001
Hemodialysis, n (%)	263 (6)	115 (8)	20 (3) *	57 (8)	71 (5) *	< 0.0001
Total cholesterol (mg/dL)	198 ± 55	194 ± 61	203 ± 39	196 ± 78	200 ± 38 *	0.001
LDL-cholesterol (mg/dL)	114.4 ± 33.2	111.8 ± 31.9	118.7 ± 34.6 *	109.9 ± 32.4	117.1 ± 33.6 *	< 0.0001
HDL-cholesterol (mg/dL)	56.4 ± 23.1	60.6 ± 33.1	62.1 ± 17.4 *	52.3 ± 15.4 *	51.4 ± 13.1 *	< 0.0001
Triglycerides (mg/dL)	135 ± 101	106 ± 67	110 ± 60 *	161 ± 120 *	163 ± 122 *	< 0.0001
HbA1c (%)	6.1 ± 1.5	6.1 ± 2.0	6.0 ± 0.9	6.2 ± 1.1 *	6.2 ± 1.1 *	0.001
High-sensitive CRP (mg/dL)	0.28 ± 0.95	0.35 ± 1.20	0.22 ± 1.01	0.27 ± 0.83 *	0.26 ± 0.64 *	0.02
Use of statin, n (%)	885 (20)	267 (18)	158 (18)	142 (20)	318 (22) *	0.08
VAT area (cm^2)	113.3 (71.7, 156.5)	62.4 (34.7, 82.0)	84.6 (67.5, 101.2) *	146.5 (126.5, 170.7) *	163.1 (136.7, 198.7) *	< 0.0001
SAT area (cm^2)	139.5 (98.4, 184.5)	88 (62.7, 112.0)	177.7 (155.7, 215.8) *	113.5 (97.0, 125.4) *	188.0 (162.0, 233.9) *	< 0.0001
WC (cm)	85.3 (78.4, 92.1)	76.0 (71.8, 80.4)	84.8 (81.3, 89.0) *	85.5 (82.1, 89.0) *	94.3 (89.9, 99.8) *	< 0.0001

Data are presented as mean ± SD, medians (interquartile ranges), or n (%).
BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; CRP, C-reactive protein; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; WC, waist circumference.
The data are the means and standard derivations. *$p < 0.05$: *vs*. Low VAT/Low SAT group.

Table 2
Association of VAT, SAT, BMI or WC with SSS (A) and SIS (B).

A

	Univariate analysis			Multivariate analysis		
Parameters	β-coefficients	95% CI	*p* value	β-coefficients	95% CI	*p* value
VAT area (cm^2)	0.11	0.007–0.01	< 0.0001	−0.001	−0.004–0.003	0.70
SAT area (cm^2)	−0.01	−0.010–−0.004	< 0.0001	−0.03	−0.006–0.0004	0.09
BMI (kg/m^2)	0.03	−0.02–0.09	0.23	−0.02	−0.07–0.04	0.54
WC (cm)	0.01	−0.01–0.03	0.30	−0.02	−0.04–0.003	0.10
Age (years)	0.16	0.14–0.17	< 0.0001			
Male	1.16	0.94–1.39	< 0.0001			
Diabetes mellitus	1.62	1.39–1.86	< 0.0001			
Hypertension	1.61	1.39–1.83	< 0.0001			
Dyslipidemia	0.74	0.53–0.96	< 0.0001			
Current smoker	0.95	0.73–1.16	< 0.0001			
Family history	0.09	−0.16–0.34	0.47			

B

	Univariate analysis			**Multivariate analysis**		
Parameters	**β-coefficients**	**95% CI**	***p* value**	**β-coefficients**	**95% CI**	***p* value**
VAT area (cm^2)	0.01	0.004–0.007	< 0.0001	−0.00004	−0.002–0.002	0.99
SAT area (cm^2)	−0.004	−0.005–−0.002	< 0.0001	−0.001	−0.003–0.001	0.18
BMI (kg/m^2)	0.02	−0.01–0.04	0.25	0.001	−0.03–0.03	0.94
WC (cm)	0.01	−0.004–0.02	0.22	−0.004	−0.014–0.006	0.46
Age (years)	0.09	0.08–0.100	< 0.0001			
Male	0.55	0.43–0.66	< 0.0001			
Diabetes mellitus	0.81	0.69–0.93	< 0.0001			
Hypertension	0.86	0.75–0.98	< 0.0001			
Dyslipidemia	0.41	0.30–0.53	< 0.0001			
Current smoker	0.46	0.34–0.57	< 0.0001			
Family history	0.004	−0.13–0.14	0.95			

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; WC, waist circumference; CI, confidence interval. The multivariate analysis was adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, current smoker, and family history of CAD.

Table 3
Plaque scores and CACS in fat distribution groups.

Parameters	All	Low VAT/Low SAT	Low VAT/High SAT	High VAT/Low SAT	High VAT/High SAT	*p* value
	n = 4327	n = 1444	n = 720	n = 720	n = 1443	
SSS	4 (1, 10)	4 (0, 10)	2 (0, 7) *	5 (1, 12) *	4 (1, 10)	< 0.0001
SIS	3 (0, 6)	3 (0, 6)	2 (0, 4) *	3 (1, 7) *	3 (1, 6)	< 0.0001
Obstructive CAD, n (%)	1492 (34)	503 (35)	174 (24) *	295 (41) *	520 (36)	< 0.0001
CACS						
Log (CACS + 1)	3.6 (0, 5.7)	3.8 (0, 6.0)	1.8 (0, 5.0) *	4.2 (0, 6.0)	3.6 (0, 5.6)	< 0.0001
CACS > 400, n (%)	924 (21)	355 (25)	98 (14) *	179 (25)	292 (21) *	< 0.0001

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SSS, segment stenosis score; SIS, segment involvement score; CAD, coronary artery disease; CACS, coronary artery calcium score.
The data are medians and interquartile ranges. *$p < 0.05$: *vs*. Low VAT/Low SAT group.

Table 4
Association of fat distribution groups with high SSS (SSS≧5) (A) and high SIS (SIS≧5) (B).

A

	Univariate analysis			Multivariate analysis: Model 1			Multivariate analysis: Model 2		
Parameters	OR	95%CI	*p* value	OR	95%CI	*p* value	OR	95%CI	*p* value
Fat distribution									
Low VAT/Low SAT	1 [reference]			1 [reference]			1 [reference]		
Low VAT/High SAT	0.57	0.47–0.69	< 0.001[a]	0.84	0.68–1.04	0.10[a]	0.76	0.61–0.95	0.02[a]
High VAT/Low SAT	1.35	1.13–1.61	0.001[a]	1.17	0.97–1.42	0.11[a]	0.97	0.79–1.18	0.74[a]
High VAT/High SAT	1.02	0.88–1.18	0.81[a]	1.23	1.05–1.44	0.01[a]	0.97	0.82–1.15	0.82[a]
BMI (kg/m^2)	1.00	0.99–1.02	0.79	1.03	1.01–1.05	0.001	1.00	0.98–1.01	0.60
WC (cm)	1.00	1.00–1.01	0.63	1.01	1.00–1.01	0.01	1.00	0.99–1.00	0.31
Age (years)	1.05	1.05–1.06	< 0.001	1.07	1.06–1.07	< 0.001	1.06	1.06–1.07	< 0.001
Male	1.82	1.59–2.08	< 0.001	2.51	2.13–2.94	< 0.001	2.23	1.86–2.68	< 0.001
Hypertension	2.48	2.17–2.84	< 0.001				1.84	1.59–2.14	< 0.001
Diabetes mellitus	2.21	1.94–2.53	< 0.001				1.80	1.55–2.09	< 0.001
Dyslipidemia	1.38	1.22–1.57	< 0.001				1.24	1.08–1.43	0.002
Current smoker	1.58	1.40–1.79	< 0.001				1.28	1.10–1.49	0.001
Family history	1.07	0.93–1.23	0.38				1.24	1.06–1.45	0.008

B

	Univariate analysis			**Multivariate analysis: Model 1**			**Multivariate analysis: Model 2**		
Parameters	**OR**	**95%CI**	***p* value**	**OR**	**95%CI**	***p* value**	**OR**	**95%CI**	***p* value**
Fat distribution									
Low VAT/Low SAT	1 [reference]			1 [reference]			1 [reference]		
Low VAT/High SAT	0.52	0.42–0.65	< 0.001*	0.74	0.58–0.95	0.02*	0.68	0.53–0.88	0.003*
High VAT/Low SAT	1.35	1.11–1.63	0.002*	1.22	0.99–1.49	0.06*	1.00	0.81–1.24	0.99*
High VAT/High SAT	1.06	0.90–1.24	0.50*	1.29	1.08–1.53	0.004*	1.01	0.84–1.21	0.90*
BMI (kg/m^2)	1.01	0.99–1.02	0.33	1.04	1.02–1.06	< 0.001	1.00	0.98–1.02	0.75
WC (cm)	1.00	1.00–1.00	0.20	1.01	1.00–1.02	< 0.001	1.00	0.99–1.01	0.93
Age (years)	1.05	1.05–1.06	< 0.001	1.06	1.06–1.07	< 0.001	1.06	1.05–1.07	< 0.001
Male	1.76	1.51–2.03	< 0.001	2.23	1.87–2.65	< 0.001	1.84	1.51–2.25	< 0.001
Hypertension	2.72	2.33–3.18	< 0.001				2.01	1.70–2.38	< 0.001
Diabetes mellitus	2.25	1.95–2.59	< 0.001				1.79	1.54–2.09	< 0.001
Dyslipidemia	1.50	1.31–1.72	< 0.001				1.35	1.16–1.57	< 0.001
Current smoker	1.66	1.45–1.90	< 0.001				1.43	1.21–1.68	< 0.001
Family history	0.98	0.79–0.84	0.79				1.10	0.93–1.31	0.26

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; BMI, body mass index; WC, waist circumference; SSS, segment stenosis score; SIS, segment involvement score; OR, odds ratio; CI, confidence interval. Model 1 was adjusted for age and sex; Model 2 was adjusted for all covariates in Model 1 plus hypertension, dyslipidemia, diabetes mellitus, smoking status, and family history of coronary artery disease. [a] *p* value comparing to Low VAT/Low SAT group.

high VAT/low SAT group, and high VAT/high SAT group (Table 4A and B). Age, sex, and traditional CAD risk factors, such as hypertension, diabetes, dyslipidemia, and current smoking, were independent predictors of SSS and SIS. Family history was not an independent predictor of SSS and SIS. Additional results using each cut-off value of VAT and SAT determined by receiver operating characteristic curve analysis to categorize the fat distribution group instead of each median of VAT and SAT are shown in Supplemental Fig. 2 and Table 3. These results were consistent with analysis using each median of VAT and SAT as cut-offs.

3.5. Analysis of fat distribution in the obese population

We assessed the association between fat distribution and coronary plaque scores in the obese population (BMI ≥25 kg/m^2). A total of 1694 patients were recruited for the analysis. The baseline characteristics are shown in Supplemental Table 4A. Mean age and BMI were 62.7 ± 12.0 and 28.3 ± 3.1, respectively; 73% of the patients were male.

In the obese population, VAT area was correlated with SSS (β-coefficient = 0.01, $p < 0.0001$) and SIS (β-coefficient = 0.006,

$p = 0.0007$), whereas SAT area showed inverse correlations with SSS (β-coefficient = −0.01, $p < 0.0001$) and SIS (β-coefficient = −0.005, $p < 0.0001$) (Supplemental Tables 4B and C). However, in the multivariate analysis, the correlations were not statistically significant.

In the analysis of fat distribution, patients with low VAT/high SAT had the lowest SSS (2.0 [0, 8]) and SIS (2 [0, 5]) (Supplemental Table 4D). In multivariate analysis, fat distribution was associated with coronary plaque scores (Supplemental Tables 4E and F). Patients with low VAT/high SAT had the lowest risk of high SSS and SIS (OR with the low VAT/low SAT group as the reference category, 0.67, 95% CI, 0.48–0.94, $p < 0.05$; OR, 0.65, 95% CI, 0.45–0.93, $p < 0.05$, respectively). The differences between the low VAT/low SAT, high VAT/low SAT, and high VAT/high SAT groups were not significant.

4. Discussion

This study demonstrates that abdominal fat distribution, VAT and SAT, are associated with coronary plaque scores—SSS and SIS assessed by CCTA. Neither VAT area nor SAT area was an independent predictor of high coronary plaque score (SSS ≥5 or SIS ≥5); however, the combination of VAT area and SAT area was an independent predictor. Patients with lower VAT area and higher SAT area had lower coronary plaque scores than those in other groups, which suggested that both increases in subcutaneous fat and decreases in visceral fat were inversely correlated with the severity and extent of coronary artery plaques. These associations were independent of sex and age. A previous study also reported the association between VAT alone or SAT alone and SIS; however, a smaller cohort was evaluated and fat distribution and the severity of coronary plaques were not assessed [22].To the best of our knowledge, this is the first study to show the relationship between adipose tissue composition and the extent and severity of coronary artery plaques.

Recently, CCTA evaluations have not only provided diagnostic information regarding CAD but also prognostic information from patients with CAD, which can be used in addition to traditional risk factors [23]. The study reported measurement of coronary plaque severity, global coronary artery plaque extent, coronary artery plaque distribution, presence of left main or left anterior descending artery plaque, and 3-vessel coronary artery plaques as methods to assess CAD prognosis and determine coronary plaque scores calculated from CCTA findings [16]. Among coronary plaque scores, SSS and SIS were shown to have predictive value in terms of all-cause mortality during short-to intermediate-follow up in patients with CAD. Coronary plaque scores assessed by CCTA are useful for evaluation of the prognosis of patients with CAD.

In this study, we retrospectively evaluated coronary plaque scores, SSS and SIS, of 4327 consecutive patients using CCTA images. Considering the predictive value of these coronary plaque scores, the findings suggest that patients with low VAT and high SAT area have a better prognosis than other patients. This finding may aid improvements in risk discrimination and reclassification of obesity and CAD. Body weight, BMI, WC, and waist to hip ratio have been previously used for assessment of obesity and risk classification of CAD. However, recent studies revealed that these measurements were not sufficient for prognosis of CAD [3,5,6]. The distribution of abdominal visceral and subcutaneous fat is a novel classification that can be used to distinguish risks not differentiated by body size, such as BMI or WC. Assessment of abdominal fat distribution should be considered in clinical practice. We suggest initiation or intensification of therapies considering patients' fat distribution, to reduce the risk of CAD, such as diet and exercise therapy. Further studies to investigate whether reduction of visceral fat and increased subcutaneous fat improves clinical outcomes are necessary.

The differing effects of type of adipose tissue is one of the mechanisms underlying the "obesity paradox." A high volume of abdominal visceral fat is associated with increased CAD and mortality [9,10]. Furthermore, a high visceral fat area is also associated with coronary plaque morphology, independent of traditional coronary risk factors, among patients with suspected CAD [24]. Adverse effects of VAT have been attributed to adipokines, free fatty acids, and other metabolites released from adipose tissue [25]. The beneficial effects of subcutaneous fat in suppression of adverse effects of visceral fat have also been demonstrated. In recent studies, a loss of both visceral and subcutaneous fat was associated with severe insulin resistance [26] and patients with high visceral fat and high subcutaneous fat had lower levels of insulin resistance than did patients with high visceral fat alone [27]. Furthermore, in mouse models, SAT was found to be both anatomically and intrinsically different from VAT acting systemically to improve glucose metabolism via the production of adipokines [28]. In addition to this endocrine function, recent studies indicated that subcutaneous adipose tissue was able to buffer an energy surplus due to excess energy intake or reduced energy expenditure [29]. The effect of subcutaneous adipose tissue to store excess energy prevents from ectopic fat deposition, such as the liver, the skeletal muscle, and the heart, which results in impaired insulin sensitivity. Additionally, subcutaneous fat reduces postprandial increase in serum lipid level through quick storage of lipid, which may suppress the adverse effect of postprandial lipedema in the development of atherosclerosis. These hypotheses indicate that, to consider the metabolic effects of adipose tissue in terms of the development of atherosclerosis, the distribution of visceral fat and subcutaneous fat is more important than the amount of visceral fat alone.

Previous studies have shown that distribution of fat is a predictor of cardiovascular outcomes and mortality [30,31]. These studies demonstrated that a higher ratio of VAT to SAT was associated with an increased risk of poor cardiovascular outcomes, suggesting that an increase in VAT and a decrease in SAT correlate with cardiovascular outcomes. The findings from this study are consistent with these results, showing low VAT/high SAT patients have lower coronary plaque scores. In previous studies, the high VAT/low SAT group and the low VAT/low SAT group were assessed as the same group; however, we evaluated the two groups separately and demonstrated that these two groups had different risks of coronary plaque scores in multivariate analysis adjusting only age and sex.

Patients with low VAT/low SAT had similar coronary plaque scores to those with high VAT/low SAT and high VAT/high SAT. This could be explained by the frailty of these patients, in addition to the reduction of protective effects of subcutaneous fat against atherosclerosis. The patients in the low VAT/low SAT group were significantly older and had a lower BMI than those in other groups. A previous study demonstrated an association between frailty and subclinical coronary atherosclerosis including coronary artery calcification [32]. Coronary plaque scores (SSS and SIS) do not account for coronary plaque characteristics such as calcified plaque or lipid-rich plaque. However, coronary calcium scoring demonstrated that the groups with low VAT and low SAT had the highest rate of the severe coronary calcification (CACS > 400 AU). Considering this finding, frailty may be a cause of coronary atherosclerosis via coronary artery calcification in patients with low VAT and low SAT.

We demonstrated the association between coronary plaque scores and fat distribution in obese patients, as seen in the overall population. In the obese population, patients with high SAT and low VAT had the lowest coronary plaque scores. This finding indicates that among obese patients with large amount of adipose tissue, the risk of CAD may vary depending on the region of adiposity and that the distribution of adipose tissue may offer clues to aid understanding of the obesity paradox.

4.1. Study limitations

This study has several limitations. First, because this is a retrospective single-center cross-sectional study, the causality of the association between coronary plaque scores and the fat distribution cannot

be established. Second, the study population consisted of patients who were suspected of having CAD and underwent CCTA in a single center; thus, this study had a sampling bias, and our results cannot be generalized to all patients.

4.2. Conclusion

We demonstrated that an increase in SAT and a decrease in VAT were associated with low coronary plaque scores, as assessed by CCTA. Given that these scores represent the severity and extent of coronary artery plaques and predict all-cause mortality, the fat distribution may be useful for evaluating the risk and prognosis of CAD. In addition, fat distribution was also correlated with coronary plaque scores for obese patients. This finding suggests that there are differences in the risk of CAD among obese patients and that fat distribution could provide clues for understanding the obesity paradox.

Conflicts of interest

Dr. Tanabe receives remuneration from Canon Medical Systems. The remaining authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.06.910.

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