ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2010.06.014

Association Between Visceral Adipose Tissue Area and Coronary Plaque Morphology Assessed by CT Angiography

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OBJECTIVES We sought to investigate the association between visceral adipose tissue (VAT) with the presence, extent, and characteristics of noncalcified coronary plaques (NCPs) using 64-slice computed tomography angiography (CTA).

BACKGROUND Although visceral adiposity is associated with cardiovascular events, its association with NCP burden and vulnerability is not well known.

METHODS The study population consisted of 427 patients (age 67 ± 11 years; 63% men) with proven or suspected coronary artery disease who underwent 64-slice CTA. We assessed the presence and number of NCPs for each patient. The extent of NCP was tested for the difference between high (≥2) and low (≤1) counts. We further evaluated the vulnerable characteristics of NCPs with positive remodeling (remodeling index >1.05), low CT density (≤38 HU), and the presence of adjacent spotty calcium. Plain abdominal scans were also performed to measure the VAT and subcutaneous adipose tissue area.

RESULTS A total of 260 (61%) patients had identifiable NCPs. Multivariate analyses revealed that increased VAT area (per 1 standard deviation, 58 cm^2) was significantly associated with both the presence (odds ratio [OR]: 1.68; 95% confidence interval [CI]: 1.28 to 2.22) and extent (OR: 1.31; 95% CI: 1.03 to 1.68) of NCP. Other body composition measures, including subcutaneous adipose tissue area, body mass index, and waist circumference were not significantly associated with either presence or extent of NCP. Increased VAT area was also independently associated with the presence of NCP with positive remodeling (OR: 1.71; 95% CI: 1.18 to 2.53), low CT density (OR: 1.69; 95% CI: 1.17 to 2.47), and adjacent spotty calcium (OR: 1.52; 95% CI: 1.03 to 2.27).

CONCLUSIONS Increased VAT area was significantly associated with NCP burden and vulnerable characteristics identified by CTA. Our findings may explain the excessive cardiovascular risk in patients with visceral adiposity, and support the potential role of CTA to improve risk stratification in such patients. (J Am Coll Cardiol Img 2010;3:908–17) © 2010 by the American College of Cardiology Foundation

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Manuscript received June 1, 2010; revised manuscript received June 22, 2010, accepted June 25, 2010.

Obesity is widely accepted as a risk factor for coronary artery disease (CAD) (1). In particular, visceral adipose tissue (VAT) accumulation was reported to be a better predictor of metabolic abnormalities and atherosclerosis than total body fat (2,3). Recent epidemiological studies have also suggested that visceral adiposity, as evaluated by the waist-to-hip ratio (4) or computed tomography (CT) scanning (5), is more closely related to cardiovascular events than is body mass index (BMI), a crude marker of total adiposity.

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We previously reported that VAT area is associated with the presence and extent of coronary artery calcium (CAC), independently of BMI, using multidetector CT (6). Whereas the presence and extent of CAC are strongly associated with the overall atherosclerotic plaque burden, it is assumed that noncalcified coronary plaques (NCPs), which contain lipid-rich components and display positive remodeling (PR), are more prone to rupture with subsequent coronary events, according to results of intravascular ultrasound (IVUS) (7) and pathologic (8) studies.

Recent advances in cardiac CT angiography (CTA) have enabled noninvasive detection of NCPs (9–12). Moreover, we previously reported that 64-slice CTA can be used to characterize NCPs in terms of composition (e.g., predominantly fibrous vs. lipid-rich plaques), vascular remodeling, and adjacent calcium morphology. We also reported that 64-slice CTA shows good agreement with IVUS (11).

To our knowledge, very few studies have examined the association between VAT, as an entity, with NCP, particularly regarding its composition and morphology. Determining the associations between VAT area and NCP burden or vulnerable characteristics seems to be important from an etiological perspective. Therefore, in this study, we used 64-slice CTA to quantitatively and qualitatively assess coronary artery plaques to determine whether VAT area is associated with the presence, extent, and vulnerable characteristics of NCPs.

METHODS

Study patients. Between November 2006 and December 2008, we recruited 565 consecutive Japanese patients with proven or suspected CAD, who underwent 64-slice CTA for the follow-up or diagnosis of CAD at our institution. For the present study, we excluded 138 subjects with a history of percutaneous coronary intervention (n = 63) or coronary artery bypass grafting (n = 62), subjects with poor image quality because of motion artifacts or inadequate contrast concentration (n = 6), and subjects with missing information for 1 or more traditional CAD risk factors (n = 7). As a result, 427 patients (267 men and 160 women, 67 ± 11 years) were finally enrolled and included in this study. In all patients, plain cardiac and abdominal scans were performed to measure the CAC score and the VAT area. The study was approved by the hospital's ethical committee, and written informed consent was obtained from all patients.

Risk factor assessment. All patients provided details of their demographics, medical history, and medications at the clinical consultation. Patients were considered current smokers if they had smoked at least 1 cigarette a day within the previous year. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or on antihypertensive therapy. Diabetes mellitus was defined by self-report, a hemoglobin A_{1c} level ≥6.5% (13), or current use of hypoglycemic agents. Hypercholesterolemia was characterized by a fasting serum low-density lipoprotein cholesterol level ≥140 mg/dl on direct measurement (14) or current use of lipid-lowering agents. Height (m) and body weight (kg) were used to calculate BMI.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome
BMI = body mass index
CAC = coronary artery calcium
CAD = coronary artery disease
CT = computed tomography
CTA = computed tomography angiography
IVUS = intravascular ultrasound
NCP = noncalcified coronary plaque
PR = positive remodeling
VAT = visceral adipose tissue

Coronary CT scan protocol and reconstruction. CT examinations were performed using a 64-slice CT scanner (LightSpeed VCT, GE Healthcare, Waukesha, Wisconsin) with a gantry rotation time of 350 ms. To avoid motion artifacts, patients with a resting heart rate ≥60 beats/min were orally administered 40 mg of metoprolol at 60 min before the CT scan. All patients received 0.3 mg of nitroglycerin sublingually just before scanning. A noncontrast-enhanced scan with prospective electrocardiographic gating was performed before CTA to measure the CAC score (sequential scan with 16 × 2.5-mm collimation; tube current, 140 mA; tube voltage, 120 kV). Following a test bolus examination to determine the start of the contrast-enhanced scan, a retrospective electrocardiogram-gated CTA was performed using a helical mode during an

inspiratory breath-hold (64 × 0.625-mm collimation; CT pitch factor, 0.18 to 0.24:1; tube current, 600 to 750 mA with electrocardiogram-correlated tube current modulation; tube voltage, 120 kV). A body weight–adjusted volume (0.6 to 0.7 ml/kg) of contrast material (iopamidol, 370 mg I/ml, Bayer Healthcare, Berlin, Germany) was injected over the course of 10 s, followed by a saline flush of 25 ml. The effective radiation dose was estimated based on the dose-length product and ranged from 15 to 18 mSv (11).

Image reconstruction was retrospectively gated to the electrocardiogram. Depending on the heart rate, either a half-scan (temporal window = 175 ms) or a multisegment (temporal window <175 ms) reconstruction algorithm was selected, and the optimal cardiac phase with the fewest motion artifacts was chosen individually. The reconstructed image data were transferred to a remote computer workstation for post-processing (Advantage Workstation Ver.4.2, GE Healthcare) and were analyzed using dedicated software (CardIQ, GE Healthcare).

CAC scoring. CAC score was assessed by 2 blinded and independent observers using semiautomatic software (Smartscore, version 3.5, GE Healthcare). In each patient, CAC was identified as a dense area in the coronary artery exceeding the threshold of 130 HU, and the total CAC score was calculated based on the Agatston method (15).

Evaluation of plaque characteristics. All coronary segments >2 mm in diameter were evaluated by 2 blinded and independent observers using curved multiplanar reconstructions and cross-sectional images rendered perpendicular to the vessel center line. Atherosclerotic plaques were classified as calcified or noncalcified. Calcified plaques were defined as lesions composed exclusively of structures with a CT density greater than that of the contrast-enhanced coronary lumen, or with a CT density of >130 HU assigned to the coronary artery wall in a plain image. NCPs were defined as a low-density mass >1 mm^2 in size, located within the vessel wall, and clearly distinguishable from the contrast-enhanced coronary lumen and the surrounding pericardial tissue. For the analysis of plaque characteristics, the optimal image display setting was chosen on an individual basis; in general, the window was between 700 and 1,000 HU, and the level was between 100 and 200 HU.

We further evaluated the NCP characteristics on CTA by determining the minimum CT density, the vascular remodeling index, and adjacent calcium morphology, as previously described (11). The minimum CT density was determined as the lowest density of at least 5 regions of interest (area = 1 mm^2), which were placed on each lesion in a random order. Based on our previous comparison of CTA and IVUS data (11), NCP ≤38 HU (corresponding to IVUS-identified hypoechoic plaque) was defined as a low-density plaque. We then measured the cross-sectional vessel area (mm^2) for each NCP site by manually tracing the outer vessel contour (border to low-signal epicardial fat). Vascular remodeling was assessed using the remodeling index, which was calculated by dividing the cross-sectional lesion vessel area by the proximal reference vessel area. PR was defined as remodeling index >1.05 (12). Finally, based on the methods previously described (11,16), we classified calcium deposits in or adjacent to each NCP morphologically according to their length (L) and width (W) versus the vessel diameter (VD) of the coronary artery in which the calcium was observed as follows: none, undetectable; spotty, L < 3/2 of VD and W < 2/3 of VD; long, L ≥ 3/2 of VD and W < 2/3 of VD; wide, L < 3/2 of VD and W ≥ 2/3 of VD; and diffuse, L ≥ 3/2 of VD and W ≥ 2/3 of VD.

Measurement of VAT area. In addition to cardiac scans, abdominal scans were performed at the 4th to 5th lumbar levels in the spinal position, and 12 slices at 5-mm thickness were obtained during a breath-hold after normal expiration. The adipose tissue areas and waist circumference in each subject were determined from an image taken at the level of the umbilicus using dedicated software (Virtual Place, AZE Inc., Tokyo, Japan). Subcutaneous adipose tissue was defined as extraperitoneal fat between the skin and muscles, with attenuation ranging from −150 to −50 HU. Intraperitoneal fat with the same density as the subcutaneous adipose tissue layer was defined as VAT. The adipose tissue areas were determined by automatic planimetry. Waist circumference was determined at the umbilicus level using a mobile caliper.

Statistical analysis. Categorical variables are presented as the number of patients (percentage), and continuous variables are expressed as mean ± SD or medians (interquartile range). We compared sex-specific clinical and CTA characteristics between patients divided by the median values of VAT area. Differences between patients with high and low VAT area were evaluated using chi-square tests for categorical variables and the Student *t* test or Mann-Whitney *U* test for continuous variables. The presence of plaque was assessed as a binary

outcome. The extent of NCP was defined as a dichotomous variable for high (≥2) and low (≤1) NCP counts. Stratified analyses were also performed according to the vulnerable NCP characteristics (PR, low CT density, and spotty calcium). Multivariate logistic regression analyses were performed to determine whether the association between VAT area and the presence and extent of NCP was independent of age, sex, and traditional risk factors (hypertension, hypercholesterolemia, diabetes mellitus, and current smoking). We further assessed the relationship between VAT area and the presence of vulnerable NCP characteristics using age- and sex-adjusted, and multivariate logistic regression models in a hierarchal fashion. All analyses were done using JMP 5.0.1 statistical software (SAS Institute Inc., Cary, North Carolina). A p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics. Table 1 lists the clinical characteristics of the study patients according to the median VAT area (men, 126 cm^2; women, 91 cm^2). Compared with patients with low VAT area, those with high VAT area had a higher BMI, waist circumference, and subcutaneous adipose tissue area, and a higher prevalence of hypertension, hypercholesterolemia, and diabetes mellitus, in both sexes. In addition, the triglyceride and hemoglobin A_{1c} levels were higher and the high-density lipoprotein cholesterol level was lower in patients with high VAT, in both sexes. With respect to medications, patients with high VAT area had a higher prevalence of using antihypertensive agents in men, and hypoglycemic agents in both sexes.

CTA plaque characteristics. Of 427 patients, 95 (22%) had no coronary plaques. Of the remaining 332 (78%) patients, calcified plaques alone were observed in 72 (17%) patients, and NCPs were detected in 260 (61%, 189 men) patients. A total of 576 NCPs were visualized (mean 2.2 ± 1.1 per patient), and the NCPs were localized to the left main trunk (n = 57), left anterior descending artery (n = 245), left circumflex artery (n = 103), and the right coronary artery (n = 171). Of the 427 patients, 120 (28%) had a ≥50% stenotic lesion in at least 1 coronary vessel. The number of patients with NCPs with PR (remodeling index >1.05), low CT density (≤38 HU), and adjacent spotty calcium deposits was 166 (39%), 159 (37%), and 114 (27%), respectively. Seventy-one patients (17%) had NCP with all 3 characteristics.

Table 1. Characteristics of the Study Patients With High and Low VAT Area

	Men (n = 267)		Women (n = 160)	
	High VAT (n = 133)	Low VAT (n = 134)	High VAT (n = 80)	Low VAT (n = 80)
Age, yrs	65 ± 10	64 ± 12	71 ± 10	68 ± 11
BMI, kg/m^2	25.7 ± 2.7†	22.4 ± 3.1	24.7 ± 3.4†	22.1 ± 3.4
WC, cm	95.8 ± 7.5†	84.7 ± 7.6	93.7 ± 7.7†	82.3 ± 8.4
SAT, cm^2	143 ± 53†	99 ± 46	190 ± 71†	141 ± 61
Hypertension, n (%)	92 (69)*	76 (57)	48 (60)*	35 (44)
Hypercholesterolemia, n (%)	80 (60)*	61 (46)	48 (60)*	32 (40)
Diabetes mellitus, n (%)	79 (59)†	50 (37)	41 (51)†	23 (29)
Current smoking, n (%)	73 (55)	66 (49)	13 (16)	6 (8)
Total cholesterol, mg/dl	201 ± 34	196 ± 41	203 ± 39	204 ± 51
Triglycerides, mg/dl	156 (109–231)†	111 (83–157)	146 (110–210)†	98 (75–133)
HDL cholesterol, mg/dl	48 ± 14†	59 ± 18	57 ± 16†	68 ± 17
LDL cholesterol, mg/dl	119 ± 29	114 ± 32	119 ± 35	119 ± 47
HbA_{1c}, %	6.3 ± 1.3†	5.8 ± 1.3	6.3 ± 1.2†	5.8 ± 1.2
Medications				
Antihypertensive agents, n (%)	49 (37)*	32 (24)	20 (25)	22 (28)
Lipid-lowering agents, n (%)	39 (29)	32 (24)	22 (28)	18 (23)
Hypoglycemic agents, n (%)	43 (32)*	27 (20)	28 (35)*	15 (19)

Values are expressed as number (percent), mean ± SD, or medians (interquartile range). High VAT indicates VAT area greater than the sex-specific median value (men, 126 cm^2; women, 91 cm^2), and low VAT indicates VAT area less than the median value. *$p < 0.05$; †$p < 0.01$ versus low VAT group.
BMI = body mass index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue; WC = waist circumference.

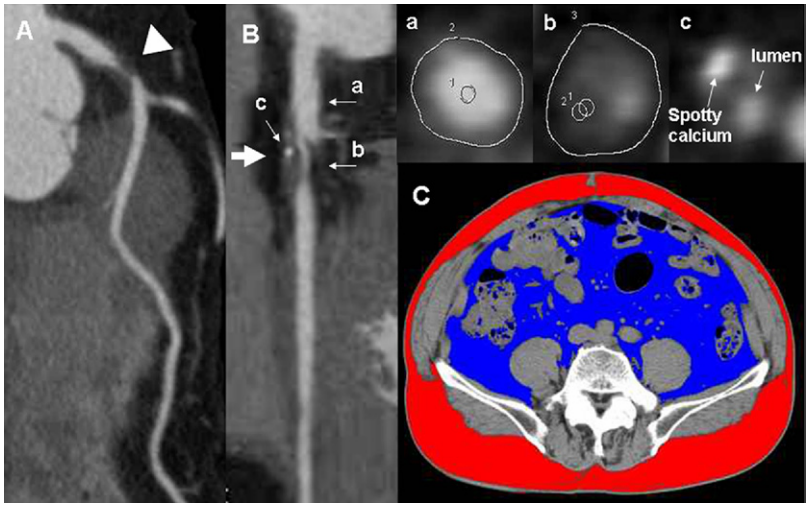

Figure 1. Coronary CT Angiography in a 74-Year-Old Man With High VAT Presenting With Unstable Angina Pectoris

(A) Shows a significant stenotic lesion in the proximal left anterior descending artery **(arrowhead)**. The stretched multiplanar reconstruction image of the vessel shows obstructive NCP with positive remodeling and adjacent spotty calcium **(B, arrow)**. The cross-sectional vessel areas of the reference site **(a)** and the lesion **(b)** are 26 and 32 mm^2, respectively. Therefore, the remodeling index is 1.23. The minimum computed tomography (CT) density of the lesion is 21 HU **(b)**. The **small circles** within the outer vessel boundaries indicate regions of interest (area = 1 mm^2) **(a, b)**. Adjacent spotty calcium can be observed in the cross-sectional image **(c)**. **(C)** Shows the abdominal adipose tissue areas at the level of the umbilicus. Regions of **blue** and **red** color indicate visceral (162 cm^2) and subcutaneous (151 cm^2) adipose tissue, respectively. CT = computed tomography; NCP = noncalcified coronary plaque; VAT = visceral adipose tissue.

Comparisons of plaque burden and vulnerable characteristics between patients with high and low VAT area. Figure 1 shows a representative CTA finding in a patient with high VAT area presenting with unstable angina pectoris. Figure 2 shows the prevalence of plaque characteristics in patients with high and low VAT area. Compared with patients with low VAT, men (71% vs. 56%, p = 0.01) and women (61% vs. 36%, p = 0.002) with high VAT were more likely to have calcified plaque. Similarly, men (82% vs. 60%, p < 0.0001) and women (56% vs. 33%, p = 0.003) with high VAT were more likely to have NCP. In analyses stratified for vulnerable NCP characteristics, patients with high

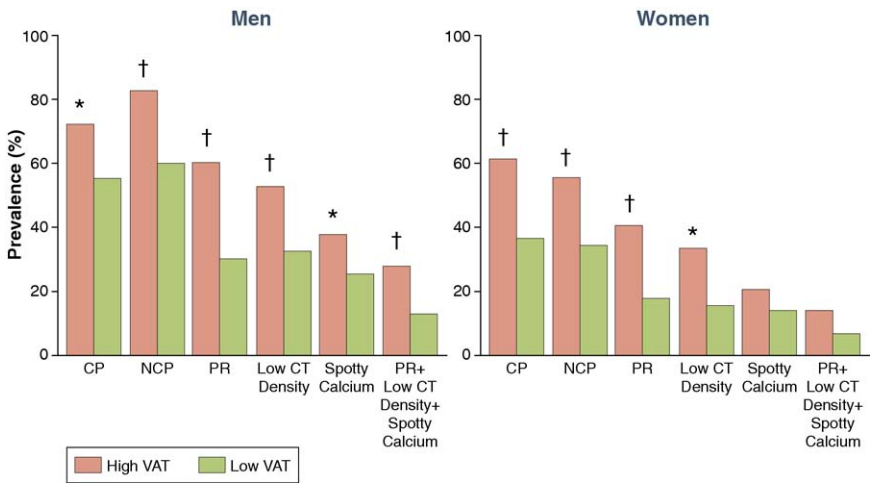

Figure 2. Prevalence of Plaque Characteristics in Patients With High and Low VAT

High VAT **(pink bars)** indicates VAT area greater than the sex-specific median value (men 126 cm^2, women 91 cm^2) and low VAT **(green bars)** indicates VAT area less than the median. CP = calcified coronary plaque; PR = positive remodeling; other abbreviations as in Figure 1. *p < 0.05; †p < 0.01.

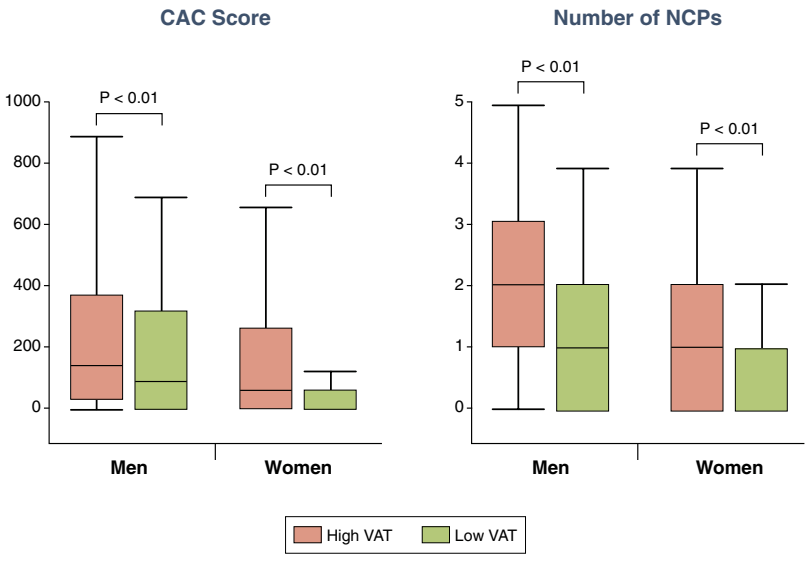

Figure 3. CAC Score and the Number of NCPs in Patients With High versus Low VAT Area

The patients with higher VAT had significantly higher median levels of CAC scores and the number of NCPs in both sexes. **Boxes** indicate 25th and 75th percentiles; **lines** indicate 5th and 95th percentiles for the data. CAC = coronary artery calcium; other abbreviations as in Figure 1.

VAT had a higher prevalence of NCP with PR (59% vs. 30%, $p < 0.0001$), low CT density (55% vs. 34%, $p = 0.0007$), and adjacent spotty calcium (41% vs. 26%, $p = 0.01$) in men, and PR (41% vs. 18%, $p = 0.001$) and low CT density (34% vs. 16%, $p = 0.01$) in women. The frequency of patients with NCP with all 3 characteristics was higher in men with high VAT (29% vs. 13%, $p = 0.001$). Figure 3 shows the CAC score and the number of NCPs for patients with high and low VAT. In both sexes, patients with high VAT area were more likely to have high CAC scores (138 [18 to 342] vs. 60 [0 to 292], $p = 0.008$ in men, 46 [0 to 246] vs. 0 [0 to 45], $p = 0.0001$ in women) and a greater extent of NCP distribution (2 [1 to 3] vs. 1 [0 to 2], $p = 0.004$ in men, 1 [0 to 2] vs. 0 [0 to 1], $p = 0.003$ in women) than those with low VAT.

Multivariate association of VAT area with calcified plaques. Calcified plaques were observed in 247 (58%, 169 men) patients. Multivariate association of VAT area with the presence of calcified plaque is presented in Table 2. As well as age, hypertension, hypercholesterolemia, and diabetes mellitus, increased VAT area was significantly associated with the presence of calcified plaque.

Multivariate associations of VAT area with NCP burden and vulnerable characteristics. Table 3 shows the association between VAT area and clinical variables with the presence and extent of NCP in all patients. In addition to age, sex, and traditional coronary risk

Table 2. Associations With the Presence of Calcified Plaque

	Univariate		Multivariate	
	OR (95% CI)*	p Value	OR (95% CI)*	p Value
Age, per 11 yrs	1.41 (1.16–1.72)	0.0006	1.60 (1.28–2.03)	<0.0001
Sex, men	1.81 (1.22–2.70)	0.003	1.56 (0.96–2.55)	0.07
VAT, per 58 cm^2	1.71 (1.37–2.15)	<0.0001	1.34 (1.05–1.73)	0.02
Hypertension	2.29 (1.55–3.41)	<0.0001	1.62 (1.05–2.50)	0.03
Hypercholesterolemia	1.73 (1.17–2.55)	0.006	1.58 (1.03–2.42)	0.04
Diabetes mellitus	2.33 (1.57–3.49)	<0.0001	2.04 (1.32–3.16)	0.001
Current smoking	1.71 (1.14–2.58)	0.01	1.44 (0.89–2.34)	0.1

*Odds ratio (95% confidence interval) for the presence of calcified plaque associated with the presence of covariates in dichotomous variables or a 1 SD increase in continuous variables.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

Table 3. Associations With the Presence and Extent of NCP

	Presence				Extent			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)*	p Value	OR (95% CI)*	p Value	OR (95% CI)†	p Value	OR (95% CI)†	p Value
Age, per 11 yrs	1.21 (1.00–1.47)	0.05	1.45 (1.15–1.86)	0.002	1.28 (1.06–1.57)	0.01	1.53 (1.20–1.97)	0.0007
Sex, men	3.04 (2.02–4.59)	<0.0001	2.37 (1.44–3.91)	0.0007	2.42 (1.60–3.70)	<0.0001	1.85 (1.11–3.10)	0.02
VAT, per 58 cm^2	2.13 (1.71–2.82)	<0.0001	1.68 (1.28–2.22)	0.0002	1.74 (1.41–2.18)	<0.0001	1.31 (1.03–1.68)	0.03
Hypertension	2.18 (1.46–3.25)	0.0001	1.34 (0.85–2.11)	0.20	3.13 (2.08–4.79)	<0.0001	2.31 (1.46–3.68)	0.0004
Hypercholesterolemia	2.35 (1.59–3.52)	<0.0001	2.00 (1.28–3.14)	0.002	1.65 (1.12–2.44)	0.01	1.48 (0.95–2.30)	0.08
Diabetes mellitus	2.03 (1.36–3.04)	0.0005	1.61 (1.02–2.55)	0.04	2.63 (1.78–3.92)	<0.0001	2.36 (1.52–3.70)	0.0001
Current smoking	2.93 (1.91–4.57)	<0.0001	2.22 (1.33–3.74)	0.002	2.42 (1.62–3.64)	<0.0001	1.95 (1.21–3.19)	0.007

*Odds ratio (95% confidence interval) for the presence of NCP associated with the presence of covariates in dichotomous variables or a 1-SD increase in continuous variables; †odds ratio (95% confidence interval) for high NCP counts (≥2; n = 177) versus low counts (≤ 1; n = 250).
NCP = noncalcified coronary plaque; other abbreviations as in Tables 1 and 2.

factors such as hypertension, hypercholesterolemia, diabetes mellitus, and current smoking, increased VAT area (per 1 SD, 58 cm^2) was significantly associated with both the presence (odds ratio [OR]: 1.68; 95% confidence interval [CI]: 1.28 to 2.22) and extent (OR: 1.31; 95% CI: 1.03 to 1.68) of NCP. Age- and sex-adjusted Pearson's correlations between adiposity measurements are provided in Table 4. Despite the positive correlations that were found between these variables, only VAT remained an independent predictor of the presence and extent of NCP after adjustment for clinical variables (Table 5). Further adjustment for BMI, waist circumference, and subcutaneous adipose tissue area did not change the significant association of VAT with NCP (presence: OR: 1.79; 95% CI: 1.25 to 2.83, extent: OR: 1.56; 95% CI: 1.08 to 2.29). Table 6 shows the results of age- and sex-adjusted and multivariate analyses of the association between VAT and vulnerable NCP characteristics. Increased VAT area was independently associated with the presence of NCP with PR, low CT density, and adjacent spotty calcium.

DISCUSSION

In the present study, we show that VAT area is significantly associated with the presence and extent of NCP, as detected by 64-slice CTA. This association is independent of traditional coronary risk factors. Taken together with our previous reports (6), the present data indicate that visceral adiposity is associated with a higher likelihood of having CAD and, if present, more diffuse CAD compared with patients without visceral adiposity. Importantly, the study also demonstrates that high VAT area is significantly associated with the presence of NCP with PR, low CT density, and spotty calcium, which may represent vulnerable characteristics, as previously described (9,11,12). Thus, our data suggest that the accumulation of VAT may contribute to the acceleration of atherosclerosis and to plaque vulnerability.

Association between VAT area and coronary plaque burden in 64-slice CTA. We have previously reported that the accumulation of VAT is an independent predictor of the presence and extent of CAC detected by multidetector CT (6). Although several epidemiological studies have been done, there is a paucity of data regarding direct associations between VAT and the distribution of NCP. Whereas the quantification of CAC is considered to provide prognostic information (17), a recent CTA study suggested that the number of NCPs with a calcified component (namely, mixed plaques) was an independent predictor of acute cardiac events (18). In the present study, we found a positive association between VAT accumulation and NCP burden using 64-slice CTA. These findings may have important therapeutic implications because information about the plaque burden determined by CTA may help to identify patients with visceral adiposity at high risk for cardiovascular events. The identification of such patients is essential to initiate aggressive therapeutic strategies, such as lifestyle modification and pharmacological interventions.

Table 4. Age- and Sex-Adjusted Pearson's Correlation Coefficients

	VAT	SAT	BMI	WC
VAT	—			
SAT	0.53	—		
BMI	0.65	0.70	—	
WC	0.77	0.79	0.77	—

$p < 0.0001$ for all correlations. Abbreviations as in Table 1.

Table 5. Associations of Adiposity Measurements With the Presence and Extent of NCP

	Presence				Extent			
	Univariate		Multivariate*		Univariate		Multivariate*	
	OR (95% CI)†	p Value	OR (95% CI)†	p Value	OR (95% CI)‡	p Value	OR (95% CI)‡	p Value
VAT (per 58 cm^2)	2.13 (1.71–2.82)	<0.0001	1.68 (1.28–2.22)	0.0002	1.74 (1.41–2.18)	<0.0001	1.31 (1.03–1.68)	0.03
SAT (per 65 cm^2)	0.82 (0.67–1.00)	0.04	0.97 (0.77–1.23)	0.8	0.84 (0.68–1.02)	0.08	0.96 (0.75–1.22)	0.7
BMI (per 3.5 kg/m^2)	1.13 (0.94–1.37)	0.2	1.02 (0.81–1.28)	0.9	1.08 (0.89–1.32)	0.4	0.96 (0.76–1.21)	0.7
WC (per 9.6 cm)	1.37 (1.13–1.69)	0.002	1.25 (0.99–1.58)	0.06	1.23 (1.02–1.50)	0.03	1.08 (0.86–1.37)	0.5

*Adjusted for age, sex, hypertension, hypercholesterolemia, diabetes mellitus, and current smoking; †odds ratio (95% confidence interval) for the presence of NCP associated with a 1 − SD increase in adiposity measurements. ‡Odds ratio (95% confidence interval) for high NCP counts (≥2; n = 177) versus low counts (≤1; n = 250).
NCP = noncalcified coronary plaque; other abbreviations as in Tables 1 and 2.

Recent studies have suggested that increased epicardial adipose tissue (19) or low levels of adiponectin (20) are more associated with NCP rather than calcified plaque. In accordance with these results, we found that VAT had stronger association with NCP (OR: 1.68, p = 0.0002) than with calcified plaque (OR: 1.34, p = 0.02). These findings may suggest that release of inflammatory adipocytokines from VAT may sustain an active atherosclerotic process as proven by the presence of NCP. The presence of mere CAC (calcified plaque), instead, could represent a more advanced and stable phase of the atherosclerotic disease process.

The present data suggest that VAT accumulation accelerates atherosclerosis independently of traditional cardiovascular risk factors such as hypertension, hypercholesterolemia, and diabetes. These observations may contribute to our understanding that nontraditional risk factors such as hyperinsulinemia and elevated apolipoprotein B and small low-density lipoprotein particles, which are commonly found in patients with visceral adiposity, may increase the risk of CAD beyond that predicted by the presence of traditional risk factors (21). Notably, the odds ratios for NCP were higher with smoking than with VAT in a multivariate model, suggesting that smoking may facilitate the accumulation of VAT. Taking into account a previous report that smoking habits are independently related to VAT (22), smoking may confound the relationship between VAT and CAD risk.

BMI was not significantly associated with NCP in the present study. We also found that BMI and VAT area were only moderately related, indicating that BMI and VAT convey different information. Interestingly, we found that subcutaneous adipose tissue was protective against NCP in univariate analyses, which may confirm previous results that subcutaneous adiposity has favorable effects on CAD (4).

Association between VAT area and the vulnerability of NCP. Several epidemiological studies have suggested that visceral adiposity is linked to the development of acute coronary syndrome (ACS) (4,5). However, the association between visceral adiposity and coronary plaque vulnerability is unclear. Several prior CTA studies have shown that NCP is associated, more so than calcified coronary plaque, with the occurrence of ACS (9). Moreover, we previously documented that PR, low CT density, and adjacent spotty calcium represent CTA-detected plaque vulnerability (12). In the present study, using 64-slice CTA, we provide definitive evidence for increased coronary plaque vulnerability in patients with visceral adiposity.

Although there are many pathways by which visceral adiposity is causally linked to atherosclerosis, 1 possible mechanism is that adipocytokines secreted from VAT, including tumor necrosis factor-α, IL-6, free fatty acids, adiponectin, and plasminogen activator-1, may directly influence the vessel wall atherogenic environment by regulating gene expression and the function of endothelial and arterial smooth muscle, and macrophage cells (23). For example, insulin resistance, which is promoted by free fatty acids, is thought to increase atherogenesis and atherosclerotic plaque instability by inducing proinflammatory activity in vas-

Table 6. Relationship Between VAT and NCP Characteristics in CT Angiography

	Age- and Sex-Adjusted		Multivariate*	
	OR (95% CI)†	p Value	OR (95% CI)†	p Value
Positive remodeling	2.00 (1.57–2.57)	<0.0001	1.71 (1.18–2.53)	0.005
Low CT density	1.66 (1.33–2.11)	<0.0001	1.69 (1.17–2.47)	0.006
Spotty calcium	1.69 (1.34–2.17)	<0.0001	1.52 (1.03–2.27)	0.04
All 3 characteristics	1.89 (1.47–2.54)	<0.0001	1.58 (1.05–2.41)	0.03

*Adjusted for age, sex, BMI, SAT, WC, hypertension, hypercholesterolemia, diabetes mellitus, and current smoking; †odds ratio (95% confidence interval) for the presence of each CT characteristic per 1 − SD (58 cm^2) increase in VAT.
CT = computed tomography; NCP = noncalcified coronary plaque; other abbreviations as in Tables 1 and 2.

cular and immune cells (24). Furthermore, increased levels of plasminogen activator-1 can inhibit plasminogen-induced migration and proliferation of vascular smooth muscle cells, leading to the formation of plaques with thin fibrous caps, necrotic cores, and rich in macrophages that are prone to rupture (25).

Taken together, our findings may partially explain the excess cardiovascular risk in patients with visceral adiposity, suggesting that excess VAT accumulation is associated with a proinflammatory metabolic profile that is predictive of an unstable atherosclerotic plaque. Therefore, stabilization of the atherosclerotic plaque may offer a legitimate therapeutic target to reduce the risk of ACS in patients with visceral adiposity.

Study limitations. First, although our data support the notion that VAT is an important factor in the pathogenesis of atherosclerosis, causality cannot be established because this is a cross-sectional study. Prospective and larger population studies are needed to elucidate whether the occurrence of CTA-detected vulnerable NCPs, in combination with increased VAT area, might help to identify patients at high risk for cardiovascular events. Second, the study population comprised patients with proven or suspected CAD; thus, our results do not apply to patients with a lower probability of CAD. Third, inflammatory markers were not measured in the present study. The previous article (26) demonstrates that epicardial adipose tissue in patients with critical CAD has higher expressions of inflammatory mediators compared with their subcutaneous adipose tissue. Further studies are needed to clarify which inflammatory markers mediate the association between VAT and atherosclerosis. Finally, the current appropriate clinical guidelines do not recommend screening with CTA because of the high radiation exposure, the use of contrast agents, cost effectiveness and limited evidence (27). However, investigational studies using CTA should be encouraged to better understand the role of detecting the plaque burden and vulnerability in patients with visceral adiposity, which may help improve risk prediction and the prevention of such events.

CONCLUSIONS

We have demonstrated that increased VAT is significantly associated with the presence, extent, and vulnerable characteristics of NCPs, as assessed by 64-slice CTA. Our findings support the hypothesis that the accumulation of VAT may contribute to the progression and instability of coronary atherosclerotic plaques. Long-term studies of the cardiovascular event risk in patients with visceral adiposity are important, and 64-slice CTA may offer an approach to improve risk stratification in such patients.

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Key Words: 64-slice computed tomography angiography ■ noncalcified coronary plaque ■ plaque vulnerability ■ visceral adipose tissue.