

# Visceral adipose tissue influences on coronary artery calcification at young and middle-age groups using computed tomography angiography

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## ABSTRACT

**Purpose:** The purpose of the study was to evaluate the impact of excessive visceral adipose tissue (VAT) on subclinical coronary atherosclerosis and coronary artery calcifications (CAC) in young and middle-age groups using multislice computed tomography. **Methods:** This study is a single center, cross-sectional study. Eligible patients ( $n = 159$ ), who under the age of 61 years, with chest pain and mild to moderate probability to have coronary artery disease (CAD) were enrolled. Coronary calcium score and epicardial adipose tissue (EAT) were measured at the level of the left main coronary artery while VAT was measured at the level of the iliac crest. **Results:** The average age was ( $48 \pm 8$  years). The mean VAT was ( $38 \pm 21 \text{ cm}^2$ ) with no significant difference between men and women ( $38 \pm 22$  vs.  $37 \pm 19$   $P = 0.8$ ) respectively. Student's  $t$ -test analysis showed significantly higher VAT in patients with detectable CAC than patients with no CAC ( $48 \pm 24$  vs.  $33 \pm 18$   $P = 0.00002$ ), respectively. Univariate regression analysis showed that VAT and EAT, are strong predictor for CAC (hazard ratio [HR] 1.034, 95% confidence interval [CI]: 1.016–1.052].  $P < 0.001$  and [HR] 1.344, 95% CI: [1.129–1.601]  $P = 0.001$ ), respectively. **Conclusion:** Excessive VAT is significantly associated with positive CAC. VAT can strongly predict subclinical CAD in individuals at young and middle-age groups.

**Key words:** Computed tomography-angiography, coronary artery calcifications, visceral adipose tissue

## INTRODUCTION

Obesity is a well-recognized risk factor for coronary artery disease (CAD).<sup>[1]</sup> Higher mortality was observed in both sexes older than age 50 in all racial and ethnic groups with increased body mass index (BMI).<sup>[2]</sup> Furthermore, adiposity has a causative effect on other risk factors of CAD including diabetes mellitus (DM), hypertension (HTN), and metabolic syndrome.<sup>[3,4]</sup> Metabolic syndrome is independently associated with CAD extension and poor outcome as well in patients with acute coronary syndrome.<sup>[5]</sup> Waist circumference, which is used as one of the diagnostic criteria for metabolic syndrome,<sup>[6]</sup> may reflect the effect of body fat accumulation on cardiac events and mortality better than

BMI.<sup>[7,8]</sup> At older ages, excessive visceral adipose tissue (VAT) measured by computed tomography angiography (CTA) is an independent predictor of CAD severity, coronary artery calcifications (CAC), and may contribute to the atherosclerosis extension.<sup>[9,10]</sup> However, there are Limited data on the relationship between VAT and CAD in young and middle-age patients. We hypothesized that increased VAT accumulation is associated with increased CAC score and hence subclinical CAD in young and middle age individuals.

## METHODS

In this cross-sectional study, we enrolled a total of 159 patients between March 13, 2013 and July 28, 2014, all of them underwent

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multi-slice computed tomography. Eligible patients were under the age of 61 years, presented with chest pain with mild to moderate pretest probability for CAD and were referred for coronary CTA due to chest pain. All patients older than 60 years, had past history of coronary revascularization, and patients with a high probability of CAD were excluded. Coronary calcium score (CCS) and epicardial adipose tissue (EAT) were measured at the level of left main (LM) coronary artery while VAT was measured at the level of the iliac crest.

### Data collection

Patients' demographics, medical and surgical history were obtained from the medical records. Data collected included age, sex, race, smoking history, drug history, past history, family history of CAD, DM, HTN, dyslipidemia, patient's weight and height. Patient's weight, height, waist and hip circumference and waist-hip ratio (WHR) were measured, and BMI was calculated. We reported the traditional risk factors for CAD including DM, HTN, smoking, family history of premature CAD, and hyper/dyslipidemia. CCS and EAT were measured at the level of LM coronary artery while VAT was measured at the level of the iliac crest. Informed written consent was obtained from all included patients. The study was approved by our center research ethics committee.

### Calcium score acquisition

Imaging was performed using dual-source CT scanner (Definition Flash; Siemens Healthcare, Forchheim, Germany; 280-ms rotation, 2\_128\_0.6 mm collimation) in deep inspiration. The scan begins with a scout imaging of the entire chest and abdomen, to define the view fields of coronary calcium and then for VAT acquisitions. The former acquired by prospective electrocardiogram-triggering scan with (3 mm slice thickness tube current 35 mA) then the raw data Reconstruction using Multi-Modality Workplace (SyngoMMWP VE40A, Siemens Medical Solutions, Forchheim, Germany) and calcium score software (VE40A) to calculate coronary calcium using Agatston method.

### Adipose visceral tissue calculation

Nongated abdominal scan with 3 mm slice thickness was done at the level of the iliac crest to analyze VAT. Manual tracing of intraperitoneal fat at single slice used to calculate visceral fat volume using SyngoMMWP workstation, volume software (VE40A), and set the attenuation values within a range of  $-190$  to  $-50$  hounsfield units to define fat. We measured subcutaneous adipose tissue (SAT) volume by tracing extraperitoneal fat area [Figure 1a].

### Epicardial adipose tissue

Using calcium score data to select a 3 mm slice at the level LM coronary artery then manual tracing of epicardial fat

tissue to estimate the EAT applying the same parameter of fat definition used for analyzing VAT with SyngoMMWP workstation and volume software (VE40A), [Figure 1b].

### Computed tomography angiography data

Coronary stenosis was graded by quantitative measurements using SyngoMMWP workstation into four categories: Normal if no stenosis, mild ( $>0$ – $30\%$  stenosis), moderate ( $31$ – $70\%$  stenosis), and severe ( $>70\%$ ).

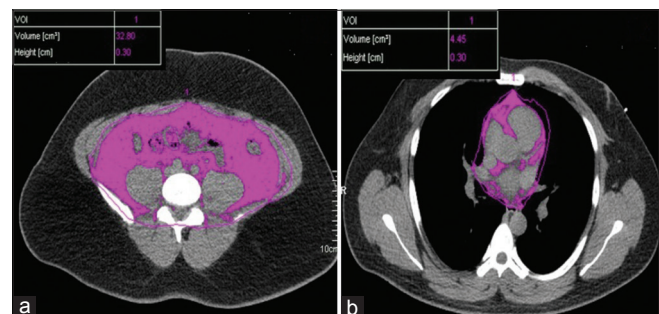
### Statistical analysis

Clinical characteristics were presented as a percentage (%) for categorical variables, mean  $\pm$  standard deviation for normally distributed continuous variables and median (interquartile range) for nonnormally distributed continuous variables. For normally distributed continuous variables two-sample *t*-test were performed, and Wilcoxon rank-sum tests were used for nonnormally distributed continuous variables; Chi-square or Fisher's exact tests were run for categorical variables. Multivariable logistic regression models were used to assess the association between VAT and CAC in middle and young age group. All baseline characteristics were considered for inclusion into the model. A  $P < 0.05$  was considered statistically significant for all tests. All statistical analyses were performed using SPSS for Windows (Version 19.0 SPSS Inc., Chicago, IL, USA).

## RESULTS

### Clinical characteristics

Table 1 shows the clinical characteristics of cohort subjects. A total of 159 patients with a mean age of  $48 \pm 8$  years and mean BMI ( $30.5 \pm 5.6$ ), with women having higher BMI than men ( $31.8 \pm 5.4$  vs.  $29.8 \pm 5.6$ ,  $P = 0.03$ ), respectively. The prevalence of overweight and obese patients with BMI  $> 25$  is ( $132/159$ ,  $83\%$ ) while  $5\%$  are morbidly obese and have BMI  $> 40$ .



**Figure 1:** (a) Visceral adipose tissue measurement by manually tracing the intraperitoneal adipose area at the level of the iliac crest. (b) Epicardial adipose tissue measurements by tracing the epicardial area at the level of the left main coronary artery. VAT: Visceral adipose tissue; EAT: Epicardial adipose tissue; LM: Left main coronary artery

### Coronary artery calcifications score analysis

Coronary calcium detected in 49 patients (31%), with higher prevalence in men (36%) than in women (21%). The average CCS is  $(39 \pm 153)$ .

Association between the coronary calcification (CAC) and VAT: Patients were divided into two groups according to the CAC: Group (A) with no calcification and group (B) with detectable CAC. The result of Student's *t*-test analysis comparing group A and B showed that VAT and EAT are significantly higher in group B than in group A, ( $48 \pm 24$  vs.  $33 \pm 18$   $P = 0.00002$ ) for VAT and ( $4.7 \pm 2.6$  vs.  $3.4 \pm 1.7$   $P = 0.0002$ ) for EAT, respectively, with no significant difference in SAT ( $57 \pm 38$  vs.  $58 \pm 35$ ,  $P = 0.22$ ), respectively. Patients in group B were older in age ( $52 \pm 6$  vs.  $46 \pm 9$   $P < 0.0001$ ), and had significantly higher prevalence of Diabetes ( $26/49$  [53%] vs.  $29/110$  [27%]) and smoking (27% vs. 14%) ( $P = 0.002$ ). Other parameters did not show a significant difference, [Table 1].

Univariate logistic regression analysis showed that VAT, EAT, age, DM, and dyslipidemia are strong predictor for CAC. Family history, smoking, HTN and Male sex showed a strong trend towards significance for predicting CAC [Table 2a].

Multivariate logistic regression analysis was done while controlling for important clinical variables including the following: Age, Sex, BMI, DM, HTN, dyslipidemia, family history, smoking, VAT, EAT, and WHR showed that VAT is the strongest independent predictor of CAC in the model (hazard ratio [HR] = 1.034, 95% confidence interval [CI: 1.013–1.055]  $P = 0.001$ ). When VAT is not controlled for in the multivariate logistic model, EAT is an independent predictor of CAC (HR = 1.277, 95% CI: [1.055–1.571]  $P = 0.013$ ), [Table 2b and c].

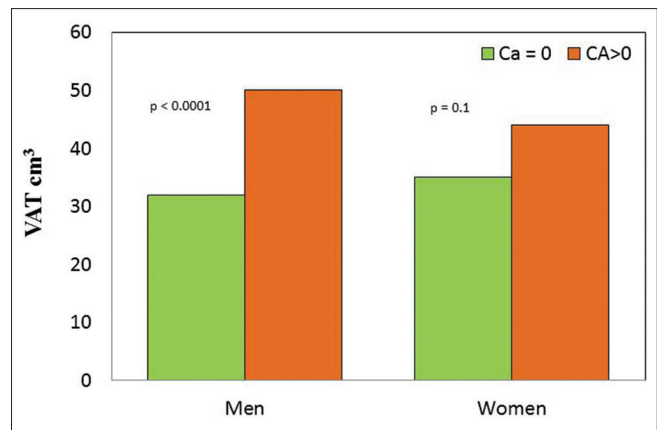
Student's *t*-test analysis of subset groups showed that VAT is significantly higher in patients with CAC than in patients without CAC ( $50 \pm 23$  vs.  $32 \pm 18$ ,  $P < 0.0001$ ) for men but not significant in women ( $44 \pm 26$  vs.  $35 \pm 17$   $P = 0.1$ ), respectively, [Table 3, Figures 2A and 2B].

### Computed tomography angiography data analysis

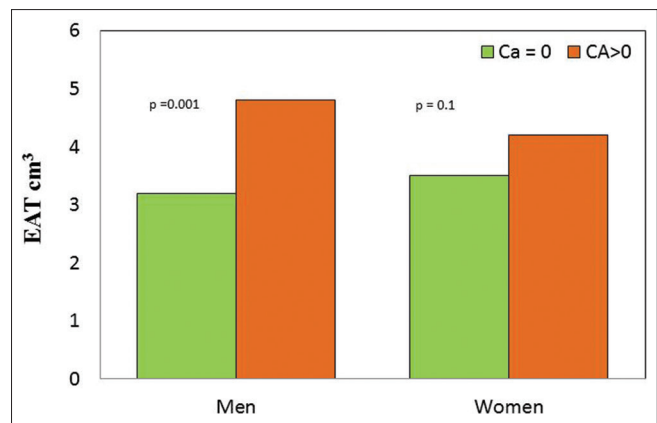
All patients underwent CTA except two patients due to very high CAC score. Patients with detectable calcium have significantly higher prevalence of coronary stenosis, [Figure 3].

## DISCUSSION

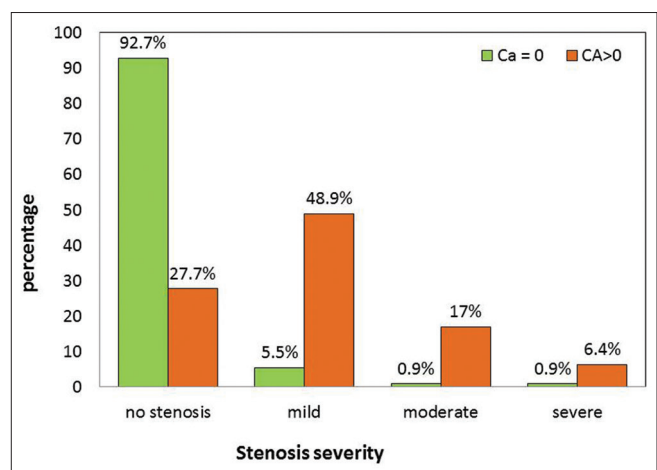
Obesity is a well-established independent risk factor for cardiovascular disease.<sup>[11]</sup> Obese men and women are at



**Figure 2A:** Visceral adipose tissues and epicardial adipose tissues are significantly higher in men with coronary calcification than men without calcification. No difference is seen in women regardless of the coronary calcification status



**Figure 2B:** Visceral adipose tissues and epicardial adipose tissues are significantly higher in men with coronary calcification than men without calcification. No difference is seen in women regardless of the coronary calcification status



**Figure 3:** Coronary angiographic data showed significantly higher grade of stenosis in the presence of calcium. Mild (>0–30%), moderate (31–70%), and severe stenosis (>70%)

increased risk of CAD.<sup>[12]</sup> The reported all-cause mortality is higher in white adults with BMI of >25,<sup>[13]</sup> however,

**Table 1: Patients baseline clinical characteristics and comparison between patients with no coronary calcium (group A), and patients with detectable coronary calcium (group B)**

Variable	All patients (N=159)	Group A (N=110)	Group B (N=49)	P value
<b>Demographics</b>				
Age (years)	48±8	46±9	52±6	<0.0001
Sex (male)	103 (65)	66 (60)	37 (75)	0.14
Weight (kg)	82±15.6	81.7±15	82.5±15	0.7
BMI (kg/m <sup>2</sup> )	30.5±5.6	30.6±6	30.6±5	0.9
Waist (cm)	99±21	98±20	102±23	0.2
WHR (≥0.9)	135 (85)	91 (82)	44 (90)	0.25
<b>Past medical history</b>				
Diabetes mellitus	55 (35)	29 (27)	26 (53)	0.002
Hypertension	70 (44)	43 (39)	27 (56)	0.08
Smoker	28 (17)	15 (14)	13 (27)	0.054
Dyslipidemia	44 (28)	25 (23)	19 (40)	0.077
Family history of CAD	11 (7)	5 (5)	6 (13)	0.18
<b>Medications</b>				
Statin	13 (8.2%)	7 (6.4)	6 (12.2)	0.22
Beta-blocker	6 (3.7)	4 (3.6)	2 (4)	0.9
ACEI	33 (20.7)	22 (20)	11 (22.4)	0.8
<b>Adipose tissue data</b>				
VAT cm <sup>3</sup>	38±21	33±18	48±24	0.00002
EAT cm <sup>3</sup>	3.8±2	3.4±1.7	4.7±2.6	0.0002
SAT cm <sup>3</sup>	57±37	57±38	58±35	0.22
<b>Coronary artery involvement</b>				
CCS	39±153		127±255	
LM involvement n (%)	8 (5)		8 (16)	
LAD involvement n (%)	36 (23)		36 (73)	
LCX involvement n (%)	21 (13)		21 (43)	
RCA involvement n (%)	28 (18)		28 (57)	

ACEI: Angiotensin converting enzyme inhibitor, SAT: Subcutaneous adipose tissue, LM: Left main, LAD: Left anterior descending artery, LCX: Left circumflex, RCA: Right coronary artery, CCS: Coronary calcium score, mean±SD

abdominal adipose tissue distribution measured by WHR found to predict cardiovascular sequelae, stroke, and death better than BMI.<sup>[14,15]</sup>

Subcutaneous fat are less pathogenic than visceral fat accumulation, as the latter considered metabolically more active tissue that contributes to higher adipocyte dysfunction.<sup>[16]</sup> This results in hypersecretion of adipocytokines such as interleukin-6, tumor-necrosis factor-alpha, and plasminogen activator inhibitor type-1 with decrease secretion of adiponectin.<sup>[17-20]</sup> The net effect of these abnormalities leads to metabolic changes that play a major role in increase insulin resistance, DM, metabolic syndrome, and atherosclerosis with adiposity.<sup>[21]</sup>

Multidetector CT (MDCT) is an important tool for quantification of abdominal fat distribution and can accurately distinguish VAT from Subcutaneous fat.<sup>[22]</sup> Furthermore, MDCT with a low radiation dose can reliably assess the extent and number of CAC.<sup>[23]</sup> The severity of calcifications is expressed as numbers using different

**Table 2: (A) Univariate logistic regression for variables associated with CAC shows that VAT, EAT, Age, DM and Dyslipidemia are strong predictors for CAC. (B) multivariate logistic regression for variables associated with CAC. (C) Multivariate logistic regression for variables associated with CAC when VAT is not put in the model**

<b>(A) Univariate logistic regression for variables associated with CAC</b>		
Variable	HR (95% CI)	P value
VAT	1.034 (1.016-1.052)	<0.001
EAT	1.344 (1.129-1.601)	0.001
SAT	0.997 (0.987-1.008)	0.559
WHR (≥0.9)	1.837 (0.644-5.244)	0.256
Dyslipidemia	2.153 (1.040-4.457)	0.039
Family history	0.341 (0.099-1.178)	0.089
Smoking	0.437 (0.190-1.009)	0.052
Hypertension	1.912 (0.968-3.778)	0.062
DM	3.157 (1.563-6.379)	0.001
Sex (M)	2.056 (0.966-4.372)	0.061
Age	1.136 (1.073-1.203)	<0.001
<b>(B) Multivariate logistic regression for variables associated with CAC</b>		
Variable	HR (95% CI)	P value
VAT	1.032 (1.012-1.052)	0.002
EAT	1.089 (0.832-1.425)	0.534
Smoking history	3.147 (1.181-8.389)	0.022
DM	2.811 (1.465-8.303)	0.011
Age	1.131 (1.061-1.206)	<0.001
<b>(C) Multivariate logistic regression for variables associated with CAC when VAT is not put in the model</b>		
Variable	HR (95% CI)	P value
EAT	1.277 (1.055-1.545)	0.012
Smoking history	2.667 (1.018-6.984)	0.046
DM	2.995 (1.363-6.582)	0.006
Age	1.124 (1.055-1.197)	<0.001

CI: Confidence interval, CAC: ???, EAT: ???, HR: ???, DM: ???, WHR: ???

scoring methods such as Agatston scoring that is most widely used.<sup>[24]</sup>

Detection of CAC at one or more of the coronary arteries confirm the presence of atherosclerotic cardiovascular disease (ASCVD), and the existence of calcium as a part of atheroma composition places the plaque under the definition of advanced types of atherosclerotic lesions.<sup>[25]</sup> CAC can provide a sensible estimation of the total coronary atheroma including noncalcified plaque (NCP) burden.<sup>[23]</sup> The extent of calcifications has an independent prognostic value in long-term follow-up for the prediction of cardiovascular death, myocardial infarction and provides more accurate prediction of all-cause mortality than standard CAD risk factors.<sup>[26-29]</sup>

Our cross-sectional study results demonstrated that the presence of CAC is significantly associated with higher VAT volume in patients with CAC than in patients without. The age of our patients is between 25 and 60 years old. Furthermore, we found that VAT has a stronger association with CAC than the other traditional risk factors of CAD.



**Table 3: Subset analysis of men vs. women showed more association between VAT and CAC in men**

Variable	Men (n=103)			Women (n=56)		
	CCS=0 (n=66)	CCS>0 (n=37)	P value	CCS=0 (n=44)	CCS>0 (n=12)	P value
Age (years)	45±9	52±6	<0.0001	47±6	52±6	0.02
Weight (kg)	84±18	85±15	0.5	78.6±12	72.5±11	0.1
BMI (kg/m <sup>2</sup> )	29.4±5.6	30.8±5	0.2	32.3±5.7	29.7±4.3	0.1
Waist (cm)	98±20	102±25	0.3	97±20	103±12	0.3
WHR	0.97±0.05	0.99±0.06	0.096	0.94±0.1	0.966±0.07	0.4
VAT cm <sup>3</sup>	32±18	50±23	<0.0001	35±17	44±26	0.1
EAT cm <sup>3</sup>	3.2±1.9	4.8±2.8	0.001	3.5±1.4	4.2±2	0.1
SAT cm <sup>3</sup>	47±30	60±36	0.061	74±44	53±33	0.1
DM n (%)	12 (18%)	18 (49%)	0.001	17 (39%)	8 (67%)	0.08
Hypertension n (%)	19 (29%)	19 (51%)	0.023	24 (55%)	8 (67%)	0.4
Smoker n (%)	14 (21%)	11 (30%)	0.3	0	0	
Dyslipidemia n (%)	8 (12%)	17 (46%)	<0.0001	17 (39%)	2 (17%)	0.1
Family history of CAD n (%)	2 (3%)	4 (11%)	0.1	3 (9%)	2 (17%)	0.2

CCS: Coronary calcium score, SAT: Subcutaneous adipose tissue, WHR: ???, VAT: ???, EAT: ???, DM: ???, CAD: ???

Many studies investigated the relationship between VAT and CAD. Our results are consistent with those of previous reports. Marques *et al.*<sup>[30]</sup> which showed that visceral fat area (VFA), determined at different intervertebral levels, were significantly related to CAD with odds ratio of 2.85 when VFA is >145 cm<sup>2</sup> at the intervertebral level T12–L1, while other anthropometric adiposity measurements (BMI, waist and hip circumferences) had no significant association. In addition, Imai *et al.*<sup>[31]</sup> found VFA positively associated with progressing of NCP burden but not with calcified plaque after 38 months follow-up. Ohashi *et al.*<sup>[9]</sup> reported that NCP burden and features of vulnerable plaque are significantly associated with higher VAT area. Another report by Ohashi *et al.*<sup>[10]</sup> found VAT is significantly associated with the extent of CAC. These reports support the role of excessive adipose tissue distribution on increase prevalence of CAD. We suggest further studies in the same age group that calculate total abdominal VAT volume with including NCP extension and severity. Inability to follow-up by MDCT to see the effect of excess VAT on the progression of CAC was a limitation to our study. Furthermore, we did not study the association of VAT with NCP, which may provide better idea about the severity of ASCVD at early stages of plaque formation. Our study is a cross-sectional analysis of VAT that is less accurate and more variable than volumetric assessment and finally, we excluded patients with a high probability of having CAD.

## CONCLUSION

Young and middle age group of patients with detectable CAC tend to have a higher VAT than patients with no CAC. VAT can strongly predict subclinical CAD, mainly in men. Further studies to investigate the effect of VAT on the development of ASCVD at younger age group are required.

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