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Periaortic adipose tissue index: A new approach to the relationship between coronary stenosis severity/lesion complexity and periaortic adipose tissue

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Abstract

Periaortic adipose tissue (PAT) is associated with atherosclerosis. The severity of coronary stenosis with PAT has not been evaluated with conventional coronary angiography (CAG). The aim of the study is to determine the relationship between PAT and coronary stenosis severity/ complexity, and to evaluate it with the periaortic adipose tissue index (PATI), a new index derived from PAT. Patients who underwent CAG and thoracic computed tomography (CT) between January 2017 and January 2022 were included in the study. PAT volume was calculated by evaluating CT images, and PATI was calculated by dividing the PAT volume by the circumference of the descending aorta. Patients were divided into two groups according to the presence of ≥50% stenosis on CAG. The correlation of PAT and PATI with the SYNTAX score was evaluated. In our study, 263 patients [mean age 64.5(54/72), male 164 (62.4%)] were evaluated. Severe coronary artery disease (CAD) was observed in 181 patients (68.8%). PAT volume and PATI were significantly higher in patients with severe stenosis ($p<0.001$, for both). When PAT and PATI were evaluated alongside CAD risk factors, an independent association between PATI and severe CAD was discovered (β:0.581, p:0.97, β:0.968, p:0.006, respectively). No correlation was found between SYNTAX score and PAT and PATI (r:-0.026, p:0.73, r:-0.019, p:0.19, respectively). In our study, PAT and PATI were higher in patients with severe coronary stenosis, and there was an independent relationship between PATI and severe stenosis. We found no relationship between PAT and PATI and the SYNTAX score.

Keywords: Coronary artery disease, periaortic adipose tissue, syntax score, coronary angiography, computed tomography

1. Introduction

Coronary artery disease (CAD) is a common cause of mortality and morbidity. Although developing diagnosis and treatment methods reduce deaths due to CAD, the number of patients followed as a result of CAD is increasing (1). Many studies have been conducted to identify and treat atherosclerosis risk factors and tests predicting CAD are very beneficial. Although various invasive and non-invasive tests are used, conventional coronary angiography (CAG) is the gold standard method for diagnosis.

Visceral adipose tissue is found in many parts of the body and is named according to the area where it is located; it is especially prevalent around vessel walls (2). It is known that adipose tissue functions as endocrine organs and produces mediators (2-4) and these also cause obesity-related atherosclerosis and vascular damage (3). It is also known that increased visceral adipose tissue is associated with metabolic syndrome parameters (5). Epicardial adipose tissue (EAT) is the visceral adipose tissue type that has been most reported on (6-8). Increased EAT volume and thickness are known to be associated with CAD, cardiovascular events and arrhythmias (6-9). Although we have less research on periaortic adipose tissue (PAT), it is associated with coronary and peripheral vascular disease (10, 11). In addition, it is known that an increase in aortic diameter is associated with an increase in PAT volume (12, 13). In the Framingham Heart Study, PAT was shown to be associated with thoracic and abdominal aortic diameter and was an independent risk factor (12). The relationship between PAT and coronary lesion comes from computed tomography (CT) studies and most of these evaluated subclinical atherosclerosis (2, 10). Although studies have found that PAT is associated with coronary stenosis and calcification, studies supporting these findings are rare (2, 10). To the best of our knowledge, there exists no study evaluating coronary atherosclerosis with

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CAG and investigating its relationship with PAT. In addition, there is no regulation to minimize the effect of aortic diameter when evaluating PAT related conditions.

The aim of the study was to demonstrate the relationship between PAT volume and coronary stenosis severity/complexity with CAG. In addition, we tested this relationship with the periaortic adipose tissue index (PATI), which we defined according to the aortic diameter.

2. Materials and methods

2.1. Study population

Patients who underwent CAG between January 2017 and January 2022 at Baskent University Alanya Application and Research Center were evaluated. Patients over 18 years of age who underwent thorax CT within 6 months (before or after) the CAG date, were included in the study. Patients with previous percutaneous coronary intervention and/or cardiac surgery (such as coronary artery bypass surgery, valve surgery, and aortic surgery), known moderate and/or severe heart valve disease, heart failure, chronic kidney failure, chronic obstructive pulmonary disease (COPD), were excluded from the study. This study was approved by Baskent University Institutional Review Board (Project no: KA 22/212) and supported by Baskent University Research Fund.

Hospitalization diagnoses were evaluated during the CAG period, and the patients were divided into two groups according to the presence of acute coronary syndrome (ACS) in this period (14-16). The patients were divided into two groups as; 1- Severe CAD, 2-Normal coronary/noncritical CAD based on the presence of ≥50% of coronary lesion severity. In addition, the complexity of coronary lesions was evaluated with the SYNTAX score by consensus by two cardiologists.

Demographic characteristics and laboratory results during the CAG period were obtained using the hospital database. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate the glomerular filtration rate (GFR) (17).

2.2. Measurement of periaortic and epicardial adipose tissue volumes

Chest CT images with and without contrast were used in the retrospective evaluation. Chest CT scans were performed with a two-slice multi-detector CT scanner (Somatom Spirit, Siemens). Chest CT protocol with tube voltage of 130 kVp and tube current of 160 mA were used for non-overlapping images with a thickness of 5 mm. The diameter of the descending thoracic aorta was measured from the outer edge of the aortic wall at its widest point, in the anteroposterior plane. All image analyses (GE, Advantage, AW) were performed on the workstation with the semi-automatic method that requires manual tracking of the borders. A CT attenuation range width of -195 to -45 Hounsfield units was used to determine adipose tissue. The volume of adipose tissue was automatically calculated in the areas monitored for PAT and EAT via the integrated software. The PAT was anatomically defined, similar to the Framingham heart study, as the region anteriorly between the area immediately surrounding the thoracic aorta (defined by a horizontal line drawn from the oesophagus connected to the left costovertebral joint) and posteriorly, between the right lateral edge of the vertebral body and the anterior edge of the vertebral body (Fig. 1) (12). The EAT volume was calculated by manually scanning the area surrounding the adipose tissue between the visceral layer of the pericardium and the heart surface (Fig. 1). PATI was calculated by dividing the PAT volume by the aortic circumference in cm.

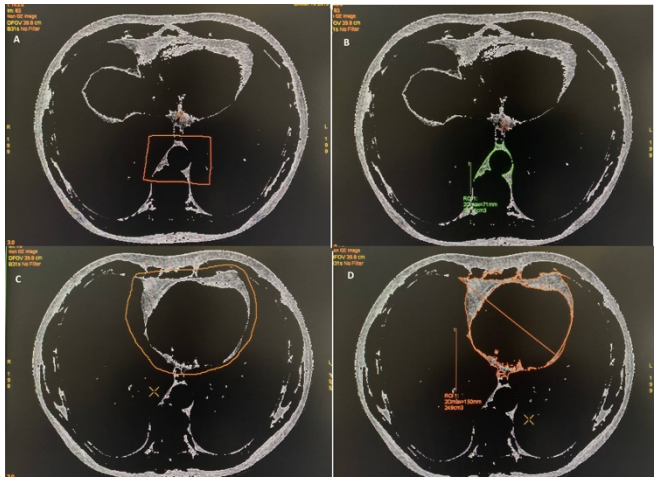

Fig.1. Evaluation of periaortic and epicardial adipose tissue volume on CT image. A-B; Appearance and evaluation of periaortic adipose tissue in computed tomography, C-D; Appearance and evaluation of epicardial adipose tissue in computed tomography

2.5. Statistical analysis

Statistical analysis was performed with the SPSS 25.0 statistical analysis software. The normality of the distribution of continuous variables was examined using the Kolmogorow-Smirnow test. Normally distributed continuous variables were expressed as mean and standard deviation, while non-normally distributed ones were expressed as medians and quartiles. Categorical variables were expressed as numbers and percentages. Normally distributed continuous variables between the groups were compared with the Student's T test, non-normally distributed continuous variables were compared with the Mann-Whitney U test, and categorical variables were compared with the Chi-Square test. The correlation of adipose tissue measurements with the SYNTAX score was analysed by Pearson correlation analysis. Relationships between coronary artery disease, adipose tissue, and other possible variables, were examined via directed acyclic graphs (DAG). DAG was plotted and analysed with the Dagitty v3.0 software (18). The relationship between variables detected as a result of the DAG analysis and fat measurements with the

presence of severe CAD, was analysed separately using the conditional forward method in binary regression analysis. The power, sensitivity and specificity values of the fat measurements in terms of detecting the presence of severe CAD were made via ROC curve analysis. All analyses were two-way and statistical significance was accepted as p<0.05.

3. Results

In our study, 263 patients [mean age 64.5(54/72), male 164 (62.4%)] were evaluated. Severe CAD was seen in 181 (68.8%) patients, and male gender was more common in patients with severe lesions (p=0.001). In addition, the number of patients who underwent CAG with the diagnosis of acute coronary syndrome was higher (p<0.001). Angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) use and statin use were higher (p=0.033, p=0.015, respectively). The group with severe CAD had higher glucose levels at admission and high-density lipoprotein cholesterol (HDL-C) levels (p=0.002, p=0.005, respectively). When visceral fat tissue was evaluated between groups, EAT, PAT, and PAT-derived PATI were found to be higher in those with severe CAD (p=0.014, p<0.001, p<0.001, respectively). There was no difference between the groups in other demographic data (p>0.05 for all) (Table 1).

When the relationship between SYNTAX score and EAT, PAT, PATI was examined in the correlation analysis, no significant correlation was found between them (r:-0.026, p= 0.73, r:-0.026, p= 0.73, r:-0.019, p=0.19, respectively) (Fig. 2).

ROC curve analysis was applied to evaluate the relationship between severe CAD and EAT, PAT, PATI. A significant correlation was found between EAT, PAT, PATI and severe CAD (AUC: 0.595, 95% CI: 0.522 to 0.688, p=0.014, AUC: 0.644, 95% CI: 0.573 to 0.716, p<0.001, AUC: 0.644, 95% CI: 0.574 to 0.714, p<0.001, respectively) (Fig.3 and Table 2).

Sensitivity and specificity of PAT in predicting severe CAD were 59.7% and 59.8%. While the sensitivity and specificity of PATI were 63% and 62.2%, EAT was found to be 55.2% and 54.9% (Table 3).

Factors associated with CAD and PAT were analysed in DAG analysis (Fig. 4). Age, GFR, Glucose, HDL-C, low density lipoprotein cholesterol, sex and smoking were found to be associated with severe CAD. These parameters were taken into regression analysis with PAT and PATI separately (Tables 4 and 5).

Table 1. Clinical and laboratory findings of patients with and without severe coronary stenosis ASA; acetylsalicylic acid, ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, BP; blood pressure, CCB; calcium channel blocker, CRP; C-reactive protein, EAT; Epicardial adipose tissue, GFR; glomerular filtration rate, HDL-C; high-density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, PAT; periaortic adipose tissue; PATI; periaortic adipose tissue index

Parameter	Coronary stenosis <50%	Coronary stenosis ≥50%	Total	p value
Number	82	181	263	
Age, years	64.5(54/72)	66(56/76.5)	65 (56/75)	0.160
Male/female, N(%)	39(47.6)/43(52.4)	125(69.1)/56(30.9)	164(62.4)/ 99(37.6)	**0.001**
Systolic BP, mmHg	130(120/140)	130(120/145)	130 (120/140)	0.190
Diastolic BP, mmHg	80(70/85)	80(71/90)	80 (70/90)	0.082
Hypertension, N (%)	43(52.4)	110(60.8)	153 (58.2)	0.204
Diabetes, N (%)	23(28)	71(39.2)	94 (35.7)	0.080
Active smoking, N (%)	15(18.3)	32(17.7)	47 (17.9)	0.904
Acute coronary sydrome, N(%)	35(42.7)	149(82.3)	184 (70)	**<0.001**
Medications, N (%)				
ASA	20(24.4)	66(36.5)	86 (32.9)	0.053
ACEi/ARB	27(32.9)	85(47.6)	112 (42.6)	**0.033**
Beta blocker	22(26.8)	57(31.3)	79 (30)	0.445
CCB	17(20.7)	47(26)	64 (24.3)	0.359
Statin	10(12.2)	46(25.4)	56 (21.3)	**0.015**
Hemoglobin, g/dl	12.8±1.9	13.2±2.2	13.1±2.1	0.160
Glucose, mg/dl	112(98.5/136.5)	130.5(105/173)	121 (103/162.5)	**0.002**
GFR, ml/min/1.73 m2	77.8(45.8/92)	79(57/94)	79 (56.7/92.3)	0.396
CRP, mg/L	7.7(1.5/22.5)	5.1(1.7/26.6)	6 (1.6/24)	0.329
Total Cholesterol, mg/dl	190(175/213)	193(166/213)	192 (169/213)	0.975
HDL-C, mg/dl	44(41/52)	43(35/47)	43 (38/47)	**0.005**
LDL-C, mg/dl	115(96/136)	116(96/143)	115 (96/138)	0.527
Triglyceride, mg/dl	149(101/163)	149(118/192)	149 (115/171)	0.166
EAT volume, ml	167(120/215)	189(135/261)	181 (130/250)	**0.014**
PAT volume, ml	27(20/38)	34(25/51.5)	32 (24/46)	**<0.001**
Aortic diameter, mm	28(25/31)	29(26/31.5)	28 (26/31)	0.387
PATI, ml/cm	4.38(3,51/5.89)	5.5(4.13/7.76)	5.1 (3.9/7.16)	**<0.001**

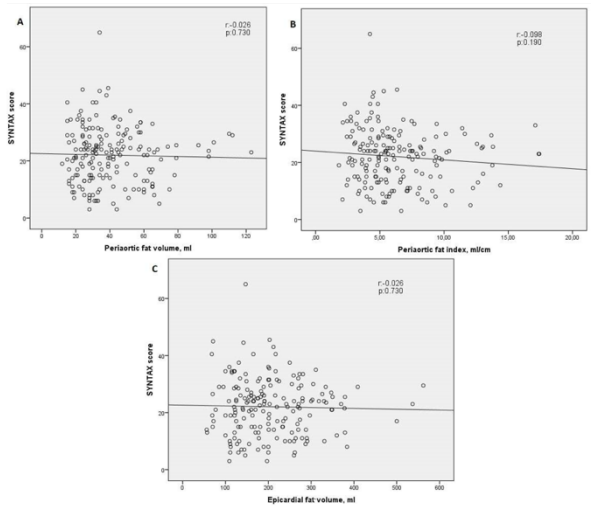

Fig.2. Correlation of Syntax score with visceral adipose tissue markers

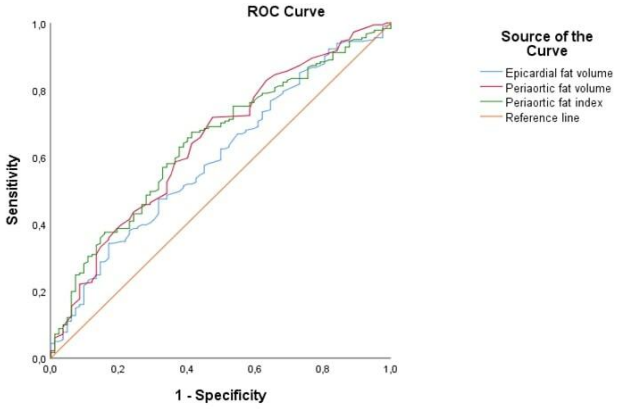

Fig.3. ROC curve analysis of visceral adipose tissue markers to predict significant coronary stenosis

Table 2. ROC curve analysis of visceral adipose tissue parameters to predict significant coronary stenosis

Variables	Area under curve	Significance	95% Confidence Interval
EAT volume, ml	0.595	0.014	0.522-0.668
PAT volume, ml	0.644	<0.001	0.573-0.716
PATI, ml/cm	0.644	<0.001	0.574-0.714

EAT; Epicardial adipose tissue, PAT; periaortic adipose tissue; PATI; periaortic adipose tissue index.

Table 3. Sensitivity and specificity of visceral adipose tissue parameters in the prediction of presence of significant coronary stenosis

Parameter	Value	Sensitivity, %	Specificity, %
EAT volume, ml	177.50	55.2	54.9
PAT volume, ml	30.50	59.7	59.8
PATI, ml/cm	4.8429	63.0	62.2

EAT; Epicardial adipose tissue, PAT; periaortic adipose tissue; PATI; periaortic adipose tissue index.

An independent relationship was found between PATI and the presence of severe CAD (β: 0.968, p=0.006) (Table 4). This association with PAT disappeared when evaluated together with other risk factors (β: 0.581, p=0.097) (Table 5). Age, GFR, HDL-C, sex, and glucose were independently associated with severe CAD in both analyses (Tables 4 and 5).

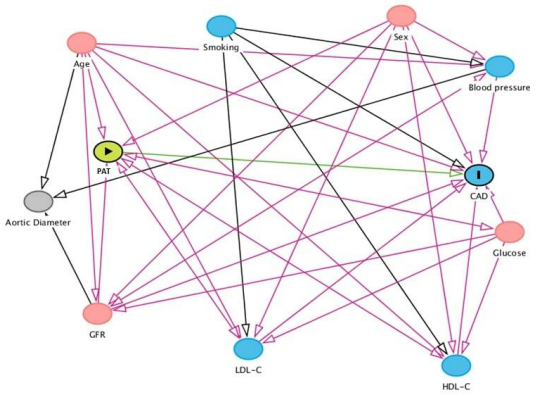

Fig. 4. Directed acyclic graph that show associations of periaortic adipose tissue, coronary artery disease and possible covariates. CAD; coronary artery disease, GFR; glomerular filtration rate, HDL-C; high density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, PAT; periaortic adipose tissue

Table 4. Binary logistic regression analysis of periaortic adipose tissue index and possible covariates for the association with significant coronary stenosis

Variables	B	S.E.	Sig.	Exp (B)
Age*	2.557	0.817	0.002	12.897
GFR*	0.925	0.31	0.003	2.521
HDL-C*	-1.483	0.673	0.028	0.227
Glucose*	1.464	0.492	0.003	4.322
Sex **	-0.886	0.312	0.005	0.412
PATI*	0.968	0.354	0.006	2.631

Model: Age, GFR, Glucose, HDL-C, LDL-C, PATI, sex and smoking. *Natural logarithm of non-normally distributed parameters was used. ** Male sex, GFR; glomerular filtration rate, HDL-C; high-density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, PATI; periaortic adipose tissue index

Table 5. Binary logistic regression analysis of periaortic adipose tissue volume and possible covariates for the association with significant coronary stenosis

Variables	B	S.E.	Sig.	Exp (B)
Age*	2.237	0.812	0.006	9.363
GFR*	0.908	0.307	0.003	2.480
HDL-C*	-1.492	0.667	0.025	0.225
Glucose*	1.460	0.489	0.003	4.307
PAT*	0.581	0.351	0.097	1.789
Sex **	-0.832	0.319	0.009	0.435

Model: Age, GFR, Glucose, HDL-C, LDL-C, PAT, sex and smoking. *Natural logarithm of non-normally distributed parameters was used. ** Male sex, GFR; glomerular filtration rate, HDL-C; high-density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, PAT; periaortic adipose tissue.

4. Discussion

To the best of our knowledge, this is the first study comparing PAT with stenosis severity and lesion complexity in patients undergoing CAG. PAT volume was significantly higher in patients with severe CAD, while PATI was higher and showed an independent association with severe CAD. However, we did not observe any relationship between EAT, PAT, PATI and SYNTAX score.

CAD risk factors have been evaluated numerous times before and used in risk modification, namely male gender, age, diabetes mellitus (DM), hyperlipidemia and smoking (15, 16). In our study, male gender, high glucose levels and low HDL-C were observed more frequently in the group with severe CAD. Although age and GFR were not different between the groups, regression analysis revealed an independent risk factor for severe CAD in addition to male gender, glucose and low HDL-C. Smoking was not different between the groups. Although the frequency of DM and HT was more frequent in the group with severe CAD, there was no statistical difference. No difference was observed between the groups in other cholesterol parameters except HDL-C. This may be due to the fact that we grouped them according to the severity of stenosis, instead of grouping them according to the presence of atherosclerosis. In addition, it may be due to the significantly higher use of statins in the group with severe stenosis.

As expected, the frequency of ACS was higher in the group with severe CAD in patients who underwent CAG. In the other group, in addition to coronary imaging with the diagnosis of stable angina, coronary imaging was required before valve surgery or aortic surgery. In our study, the severity of the coronary lesion and the complexity of the lesion were evaluated as a number of previous studies have shown that EAT is associated with coronary lesion severity (7, 8). However, lesion complexity differs in studies (6-8): Kaya et al. evaluated 93 patients in their study, while the EAT volume was higher in patients with severe CAD, they did not find a relationship between lesion complexity and EAT (7). On the contrary, in a different CT study, patients with familial hypercholesterolemia were evaluated and it was found that EAT volume was associated with lesion complexity (8). Similarly, Erkan et al. evaluated EAT thickness in 183 patients echocardiographically in their study (6). EAT thickness was associated with the SYNTAX score and the Gensini score, which assesses the extent of atherosclerosis (6). In our study, EAT volume was higher in patients with severe CAD, but no correlation was found between this result and the SYNTAX score.

Obesity is one of the cardiovascular risk factors like DM and is associated with increased visceral fat volume (19, 20). The relationship between the criteria used in the diagnosis of metabolic syndrome and PAT volume has been shown (5). An increase in PAT volume was observed with the presence of each criterion defining the metabolic syndrome (5). Pro-inflammatory cytokine release increases with increasing adipose tissue (3, 21, 22). An increased pro-inflammatory response causes atherosclerosis and vascular damage (3, 21, 22). Mazotta et al. evaluated the relationship of pro-atherogenic mediators with PAT. In their study, they evaluated samples taken from PAT in patients who were going to have coronary, valve or aortic surgery. They showed that pro-atherogenic mediators were higher in those with CAD (21).

PAT volume has been shown to be associated with coronary and peripheral artery disease (10, 11, 23). Increased PAT volume has been demonstrated in patients with COPD and patients undergoing peritoneal dialysis (24, 25). In addition, in a study evaluating PAT volume in ischemic stroke, higher periaortic fat attenuation was observed while there was no change in PAT volume in cardioembolic strokes (26). In peripheral arterial disease, PAT was demonstrated to be an independent risk factor in the Framingham heart study, and in this study, increased PAT volume was associated with lower ankle brachial index and claudication (11). The relationship between carotid intima-media thickness and plaque size was investigated by Yun et al. and associated with PAT volume (5).

Mamopoulos et al. showed that the assessment of periaortic adipose tissue, aortic size and calcification is reliable and comparable in advanced and undeveloped devices, regardless of imaging parameters (slice thickness or CT) (27).

Subclinical disease has generally been evaluated in studies associated with PAT and coronary atherosclerosis, as well as studies evaluating the relationship of severe CAD are rare (2, 10). Contrary to EAT and to the best of our knowledge, there are no studies evaluating lesion complexity. The relationship between PAT and atherosclerosis has been principally evaluated with CT, and one of the most important of these reports is the Framingham Heart Study (2, 10). This study shows that PAT is associated with coronary calcification and is a risk factor for cardiovascular disease (2).It should be noted that the purpose of this study was not to compare stenosis severity and lesion complexity, but to demonstrate increased atherogenic mediators in PAT in those with CAD (21). Efe et al. evaluated the relationship between PAT and severe CAD in their study and observed more severe stenosis in the group with high PAT volume. PAT volume and coronary stenosis severity were determined by CT. However, when they evaluated PAT volume with other risk factors, they did not detect an independent risk factor (10). Our study supports the CT study.

It is known that PAT volume is associated with aortic enlargement as well as with atherosclerosis (12). In the Framingham heart study, it was shown that PAT tissue is associated with thoracic and abdominal aortic diameters and

is an independent risk factor (12). This association may possibly be stronger than that of coronary atherosclerosis. As the aortic diameter increases, it is expected that the surrounding fatty tissue will increase. We aimed to eliminate the effect of aortic width in all patients by dividing the PAT by the aortic circumference, instead of just evaluating the volume. PATI represents the volume of adipose tissue per cm relative to the aortic circumference and has been associated with coronary lesion severity, and this relationship was found to be an independent risk factor when evaluated together with CAD risk factors. PATI can thus be used to balance PAT volume due to a change in aortic diameter.

We found that PAT volume is associated with severe CAD. However, we did not observe a relationship between PAT and SYNTAX score. PATI derived from PAT and calculated according to aortic circumference was both associated with severe CAD and was found to be an independent risk factor, when evaluated together with CAD risk factors.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: E.A., S.A., Design: E.A., AC., Data Collection or Processing: E.A., I.U., Analysis or Interpretation: S.A., A.A., I.H.M., Literature Search: E.A., S.A., Writing: E.A., S.A.

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