Epicardial Adipose Tissue is Associated with Cardiometabolic Risk and the Metabolic Syndrome in Patients with Rheumatoid Arthritis

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Abstract

Objective—Patients with rheumatoid arthritis (RA) have increased coronary atherosclerosis possibly related to increased prevalence of visceral adiposity, insulin resistance, and metabolic syndrome. Epicardial adipose tissue (EAT), a type of visceral fat, may contribute to cardiometabolic risk. The aim of this study was to measure EAT volume in patients with RA and determine its relationship with cardiometabolic risk markers and coronary artery calcium.

Methods—EAT volume and coronary artery calcium score were measured by non-contrast cardiac computed tomography and compared in RA patients (n=162) and controls (N=89). The relationships between EAT volume and markers of cardiometabolic risk in RA were examined with adjustment for age, race and sex.

Results—Among RA patients, EAT volume was positively associated with IL-6 (P=0.03), triglycerides (P=0.004), hypertension (P=0.01), homeostatic model of insulin resistance (HOMA) (P<0.001), smoking history (P=0.04), and homocysteine (P=0.001) and negatively associated with HDL (P=0.005). With further adjustment for waist circumference (a measure of visceral obesity), EAT remained independently associated with triglycerides, HOMA, current smoking and homocysteine (all P<0.05). EAT volume was not associated with corticosteroid use or coronary artery calcium score. Patients with metabolic syndrome had significantly greater EAT volume (P<0.001) and each increase in metabolic syndrome criteria was associated, on average, with a 20% increase (95% CI, 14–26%) in EAT volume (P<0.001).

Conclusion—EAT volume is associated with metabolic syndrome and cardiometabolic risk factors including insulin resistance, triglycerides, current smoking, and homocysteine levels, but not with coronary artery calcium in RA patients.

Keywords

rheumatoid arthritis; epicardial adipose tissue; cardiometabolic risk; insulin resistance; atherosclerosis
factors for cardiovascular disease, are increased in patients with RA (4). However, the cause of accelerated atherosclerosis in RA is unclear and the prevalence of cardiovascular disease remains higher than that of the general population after consideration of traditional cardiovascular risk factors (1). One potential contributor may be visceral adiposity, particularly epicardial adipose tissue (EAT).

Patients with RA are more likely to have central obesity, or visceral adiposity, than control subjects of similar BMI (5). Adipose tissue, particularly visceral adipose tissue, is strongly related to cardiometabolic risk factors such as insulin resistance, hypertension and dyslipidemia in the general population and in RA patients (6, 7). EAT, a fat layer between the myocardium and visceral pericardium, is a type of visceral fat that is emerging as an important cardiovascular risk factor (8, 9). This may be because of local inflammation and paracrine effects resulting from the proximity of EAT to coronary vessels and a shared microcirculation with the myocardium (10–14). In the general population, EAT volume is independently associated with obstructive coronary artery plaque and non-calcified atherosclerotic lesions (15), and is an independent predictor of ischemia (16).

EAT is associated with insulin resistance (17, 18), and is considered a marker of metabolic syndrome in other populations (19–21). Because it is a rich source of bioactive molecules like inflammatory cytokines and adipokines, EAT is regarded as a potential therapeutic target for treatment of the metabolic syndrome (22, 23).

There is little information about EAT in RA. We hypothesized that EAT is a marker of insulin resistance and the metabolic syndrome, as well as a risk factor for coronary atherosclerosis in patients with RA. Thus, the purpose of this study was to measure EAT volume in patients with RA and control subjects and determine its relationship with markers of cardiometabolic risk and coronary artery calcium in RA.

**Methods**

**Study population**

This study included 162 RA patients and 89 control subjects in whom EAT volume was measured. This cohort is part of a group of patients who have been extensively characterized with regard to cardiovascular risk (1, 4, 24–27). Recruitment and study procedures have been described in detail (1). Subjects were enrolled from October 2001 to March 2005. Subjects were older than 18 years of age and patients with RA fulfilled American College of Rheumatology 1987 criteria for RA (28). RA and control groups were frequency-matched for age, race and sex and control subjects did not have RA or other inflammatory disease. The study was approved by the Vanderbilt Institutional Review Board and all subjects gave written informed consent.

**Clinical data**

Clinical information, laboratory measurements, and coronary artery calcium scores were obtained as previously described (1). Disease activity of RA was determined by the 28 joint count disease activity score (DAS28) (29). Body mass index (BMI) was calculated and expressed as kg/m². Patients were categorized as having the metabolic syndrome based on the National Cholesterol Education Program Adult Treatment Panel III definition (NCEP) (30). The NCEP definition requires that three or more of the following criteria are present: waist circumference ≥102 cm in men and ≥88 cm in women, triglycerides ≥150 mg/dl, HDL <40mg/dl in men and <50mg/dl in women, high blood pressure ≥130/85 mmHg or use of medication for high blood pressure, and fasting glucose ≥10 mg/dl (30).
Fasting glucose, erythrocyte sedimentation rate (ESR), fasting cholesterol panel, and high-sensitivity C-reactive protein (CRP) were measured by the Vanderbilt University Medical Center Clinical Laboratory except in 40 patients in whom CRP concentrations were measured by ELISA (Millipore). Tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and fasting insulin were measured by multiplex ELISA (Lincoplex Multiplex Immunoassay Kit, Millipore Corp., Billerica MA, USA). The homeostatic model assessment of insulin resistance (HOMA) was used to quantify insulin resistance and was calculated as [serum insulin (uIU/ml) x glucose (mmol/l)]/22.5 (31).

Assessment of epicardial adipose tissue volume

EAT volume was measured on the same images used for coronary artery calcium score analysis, using the volume analysis software tool of the Leonardo workstation (Leonardo, Siemens, Erlangen, Germany), blinded to the clinical status of subjects, as previously described and performed by us (32, 33). The epicardium was manually traced in axial view and a threshold of −190 to −30 Hounsfield units was applied to determine the fat-containing voxels. These were summed to give total EAT volume in cm³.

Statistical analysis

Descriptive statistics were calculated as median with interquartile range (median [IQR]) for continuous variables, and frequency and proportions for categorical variables. Wilcoxon’s rank sum tests were used to compare continuous variables and Pearson’s chi-square test to compare categorical variables.

The independent association between disease status (RA or control) and EAT volume was assessed with multivariable linear regression models with adjustment for age, race and sex. Subsequent analyses were performed on RA patients only. Spearman’s rank correlation coefficients (rho) were calculated to assess the correlation between EAT and continuous variables among patients with RA. Using multivariable linear regression models, the independent association of clinical and laboratory measures with EAT were assessed with adjustment for age, race and sex. Waist circumference was then added to the model. Proportional odds logistic regression was used to assess association between EAT and coronary artery calcium score as the outcome with adjustment for age, race and sex. The association of EAT volume with the number of NCEP metabolic syndrome criteria included as a linear term was assessed with multivariable linear regression model with adjustment for age, race, and sex.

Triglycerides, homocysteine, CRP, IL-6, TNF-α, HOMA, leptin, adiponectin, and EAT volume were natural logarithm-transformed to improve normality of residuals. Statistical analyses were performed using R version 2.15.1 (http://www.r-project.org). Two-sided P values less than or equal to 0.05 were considered statistically significant.

Results

Clinical characteristics

Clinical characteristics of patients with RA and control subjects are presented in Table 1. As previously reported (1), patients with RA had larger waist circumference, were more likely to be smokers, had higher diastolic blood pressure, and lower total and LDL cholesterol compared to controls (all P<0.05). Among RA patients, 13.0% had known cardiovascular disease prior to the study, 71.0% had known cardiovascular disease prior to the study, 71.0% were rheumatoid factor positive, 71.0% were current methotrexate users, 20.4% were current anti-TNF-α users, and 13.0% were current statin users.
**Association of clinical variables and EAT**

RA patients had a borderline significant trend toward higher EAT volume (108.2 cm³ [77.0–144.6 cm³] compared to controls 93.9 cm³ [69.9–133.1 cm³], P=0.06, and after adjustment for age, race and sex, P =0.11). In RA patients EAT volume correlated significantly with waist circumference (rho=0.52), BMI (rho=0.34), and waist/hip ratio (rho=0.45) in unadjusted analysis and after adjustment for age, race and sex (all P values <0.001) (Table 2). There was no significant association between EAT volume and cumulative or current corticosteroid exposure, current use or duration of methotrexate use, current use or duration of anti-TNF-α inhibitor use, disease activity measured by the DAS 28 score, or rheumatoid factor positivity (all P values >0.05) (Table 2).

**Inflammation, adipokines and EAT**

IL-6 was associated with EAT volume in univariate analysis and after adjustment for age, race, and sex (rho=0.19, P adjusted=0.03) (Table 2). However, there was no significant association between EAT volume and TNF-α, CRP, ESR or adiponectin in unadjusted or adjusted analysis (Table 2). Leptin was not correlated with EAT in unadjusted analysis (rho=0.09, P=0.24), but was after adjustment for age, race and sex (P <0.001).

**Metabolic syndrome and EAT**

RA patients with metabolic syndrome (n=56) had significantly higher EAT volume (124.2 cm³ [98.1–174.8 cm³]) compared to those without metabolic syndrome (n=101) (103.4 cm³ [69.5–132.2 cm³]), P adjusted for age, race, and sex <0.001 (Figure 1). Each increase in metabolic syndrome criteria count was associated on average with a 20% increase (95% CI, 14–26%) in EAT volume (P<0.001) independent of age, race and sex (Figure 2).

**Cardiometabolic risk and EAT**

Triglycerides (rho=0.25, P adjusted=0.004), HOMA (rho=0.32, P adjusted <0.001), and homocysteine (rho=0.31, P adjusted=0.001) were positively associated with EAT volume in univariate analyses and after adjustment for age, race, sex. HDL cholesterol (rho=−0.27, P adjusted=0.005) was negatively associated with EAT volume (Table 3). Hypertension was also associated with EAT volume (P adjusted= 0.01); however, presence of diabetes was not (P adjusted =0.35). Pack-year smoking history was associated with EAT volume (rho=0.22) in unadjusted (P=0.005) and adjusted analysis (P=0.04). However, current smoking status was not (P=0.14). Coronary artery calcium score was not significantly correlated with EAT volume in unadjusted or adjusted analysis (rho=0.28, P adjusted= 0.24) (Table 3).

**EAT as a risk factor independent of traditional visceral fat measure**

Given that EAT is a type of visceral fat, we performed analyses additionally adjusting for waist circumference as a measure of visceral adiposity. Total cholesterol (P =0.04), triglycerides (P = 0.01), current smoking status (P = 0.003), HOMA (P =0.02), and homocysteine (P <0.001) remained significantly associated with EAT volume.

**Discussion**

The major findings of this study are that EAT volume is associated with cardiometabolic risk factors and the metabolic syndrome, but not with coronary artery calcium score in patients with RA.

EAT is considered by some to be a surrogate measure of visceral adiposity (18, 34, 35). Concordant with this, we found EAT to be more strongly correlated with waist circumference than BMI in RA patients. The trend toward increased EAT volume in RA patients had a borderline significant trend toward higher EAT volume (108.2 cm³ [77.0–144.6 cm³] compared to controls 93.9 cm³ [69.9–133.1 cm³], P=0.06, and after adjustment for age, race and sex, P =0.11). In RA patients EAT volume correlated significantly with waist circumference (rho=0.52), BMI (rho=0.34), and waist/hip ratio (rho=0.45) in unadjusted analysis and after adjustment for age, race and sex (all P values <0.001) (Table 2). There was no significant association between EAT volume and cumulative or current corticosteroid exposure, current use or duration of methotrexate use, current use or duration of anti-TNF-α inhibitor use, disease activity measured by the DAS 28 score, or rheumatoid factor positivity (all P values >0.05) (Table 2).

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patients was mainly due to greater overall visceral adiposity, as the RA patients had a larger waist circumference. Also, our findings that EAT volume in RA was associated with hypertension and triglycerides, and inversely with HDL are concordant with findings in RA and the general population that visceral obesity was associated with hypertension and dyslipidemia (6, 7). A relationship between EAT and homocysteine has not been described previously, but is biologically plausible. Human adipose tissue from subcutaneous and omental tissue expresses large amounts of nicotinamide N-methyltransferase, an enzyme which produces homocysteine. Also, cultured adipocytes are capable of producing homocysteine (36), and in patients with type 2 diabetes, those with hyperhomocysteinemia had a significantly higher visceral to subcutaneous adiposity ratio than those with normal homocysteine levels (37).

We found a significant relationship between EAT volume and smoking. It is possible that smoking may contribute to increase in visceral fat (38) and specifically EAT volume (39). Concordant with EAT being a type of visceral adipose tissue, we found that patients with RA and metabolic syndrome had higher EAT volume than those without, which is similar to findings in other populations (19–22). Moreover, increases in metabolic syndrome criteria were associated with increases in EAT volume. Also, EAT volume was associated with higher HOMA, an index of insulin resistance. This association remained significant after we adjusted additionally for waist circumference, suggesting that EAT may be associated with insulin resistance independent of a traditional measure of visceral adiposity. It is possible that EAT, a relatively small collection of adipose tissue, may be a marker of visceral obesity and thus insulin resistance and the metabolic syndrome, or it may have direct systemic effects that contribute to insulin resistance and development of the metabolic syndrome.

EAT has characteristics that suggest a particular association with inflammation. Compared to subcutaneous fat, EAT has higher levels of IL-6, TNF-α and leptin mRNA expression (40). Moreover, in monozygotic twins with discordant obesity, epicardial fat was associated with CRP levels independent of measured total visceral fat (12). Given the possibility that EAT may have independent effects on inflammation, we evaluated the relationship between EAT and inflammatory mediators and adipokines which are hypothesized to contribute to EAT’s effects (12, 20, 40).

Overall, we found no significant relationship between CRP and EAT volume, and a weak relationship with serum IL-6 and leptin concentrations. Thus, EAT volume was not strongly associated with markers of systemic inflammation and circulating adipokines in patients with RA. However, we cannot exclude the possibility that there may be local changes in cytokines and adipokines related to EAT.

We did not find an association between EAT and coronary artery calcium score in patients with RA. Studies reporting significant associations between EAT and coronary artery calcium and coronary events (15, 16, 41) were performed in other populations of patients undergoing CT scanning or CT angiography. Possible reasons for the lack of association between EAT and coronary artery calcium score in RA are our modest sample size, or that the effects of systemic inflammation in RA may obscure any contribution of EAT to coronary atherosclerosis. Our findings in RA contrast with a previous study in patients with SLE in which we found a significant association between EAT volume and coronary artery calcium score (33). In SLE patients, cumulative corticosteroid exposure was associated with higher EAT volume; however, RA patients in the current study had considerably lower cumulative corticosteroid exposure (median [IQR], 3015 mg [625–9125mg]) than the SLE patients (11,428mg [2,732–27,375mg]) (33).
Some of the limitations of this study are that we were not able to measure non-calcified plaque, which is more vulnerable to rupture (15, 42); we did not measure other markers of cardiovascular risk like carotid intima media thickness, or ankle brachial indices; and that we do not have long term follow-up data on cardiovascular events. Additionally, this was a cross sectional study, therefore we cannot infer a causal relationship between EAT and development of insulin resistance or metabolic syndrome.

Conclusion

In conclusion, EAT is associated with cardiometabolic risk factors and the metabolic syndrome but not with coronary atherosclerosis measured by coronary artery calcification in patients with RA.

Acknowledgments

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References


29. Prevoo ML, van ’t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a

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Significance and Innovations

- Among patients with rheumatoid arthritis, epicardial adipose tissue volume is independently associated with cardiometabolic risk factors and the metabolic syndrome.
- Although epicardial adipose tissue volume is associated with atherosclerosis and cardiovascular events in the general population, in this study it is not associated with coronary artery calcium score in patients with rheumatoid arthritis.
Figure 1.
Epicardial adipose tissue volume is increased in RA patients with metabolic syndrome. RA patients with metabolic syndrome (n=56) had significantly higher EAT volume (124.2 cm$^3$ [98.1–174.8 cm$^3$]) compared to those without metabolic syndrome (n=101) (103.4 cm$^3$ [69.5–132.2 cm$^3$]), P adjusted for age, race, and sex <0.001.
Figure 2.
Epicardial adipose tissue volume is increased with each increase in metabolic syndrome criteria met in RA patients. Each increase in metabolic syndrome criteria count was associated with a 20% increase on average (95% CI, 14–26%) in EAT volume independent of age, race and sex (P<0.001).
Table 1

Demographics and clinical features of rheumatoid arthritis patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls N=89</th>
<th>RA patients N=162</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53 [45–60]</td>
<td>54 [45–63.8]</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>63%</td>
<td>70%</td>
<td>0.27</td>
</tr>
<tr>
<td>Race, % Caucasian</td>
<td>84%</td>
<td>89%</td>
<td>0.29</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>88.8 [80–96]</td>
<td>94.6 [83.8–104.1]</td>
<td>0.01</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 [24.7–31.6]</td>
<td>28.3 [24–32.9]</td>
<td>0.40</td>
</tr>
<tr>
<td>Current Smoker, %</td>
<td>9%</td>
<td>23%</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>4%</td>
<td>10%</td>
<td>0.10</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>20%</td>
<td>36%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>40%</td>
<td>53%</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>128.5 [115–138]</td>
<td>134.5 [119–145.5]</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>72.5 [67.5–77]</td>
<td>75.25 [68.5–82]</td>
<td>0.05</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dl</td>
<td>196 [171–218.2]</td>
<td>185 [156.5–210.8]</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>123 [105–147]</td>
<td>113 [89.2–134.8]</td>
<td>0.006</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>45 [39–54]</td>
<td>43 [37–54]</td>
<td>0.54</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>102.5 [73.5–137]</td>
<td>109.5 [80–151]</td>
<td>0.32</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>89 [83–95]</td>
<td>87 [82–93.8]</td>
<td>0.55</td>
</tr>
<tr>
<td>EAT volume, cm³</td>
<td>93.9 [69.9–133.1]</td>
<td>108.2 [77–144.6]</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Wilcoxon rank sum test for continuous variable or Chi-square test for categorical variables.

Continuous variables are presented as median [interquartile range]. Categorical variables are presented as percentages. Data for NCEP metabolic syndrome was available for 156 RA and 84 controls.

BP= blood pressure, LDL= low density lipoprotein, HDL= high density lipoprotein, EAT= epicardial adipose tissue volume.
## Table 2

Relationship between EAT volume and clinical and laboratory measures in RA patients

<table>
<thead>
<tr>
<th></th>
<th>Spearman (rho)</th>
<th>P value*</th>
<th>Adj P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropomorphic measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.34</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.45</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease or treatment measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative corticosteroid use</td>
<td>0.13</td>
<td>0.09</td>
<td>0.90</td>
</tr>
<tr>
<td>Current corticosteroid use</td>
<td>-</td>
<td>-</td>
<td>0.72</td>
</tr>
<tr>
<td>DAS 28 score</td>
<td>0.03</td>
<td>0.72</td>
<td>0.28</td>
</tr>
<tr>
<td>Positive RF</td>
<td>-</td>
<td>0.99</td>
<td>0.51</td>
</tr>
<tr>
<td>Inflammatory markers and cytokines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.08</td>
<td>0.35</td>
<td>0.10</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.19</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.15</td>
<td>0.06</td>
<td>0.16</td>
</tr>
<tr>
<td>ESR</td>
<td>−0.07</td>
<td>0.39</td>
<td>0.99</td>
</tr>
<tr>
<td>Adipokines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td>0.09</td>
<td>0.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>0.01</td>
<td>0.88</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Spearman correlation coefficient P values.

**P value adjusted for age, race and sex.

EAT= epicardial adipose tissue volume, RF= rheumatoid factor, CRP= high sensitivity C-reactive protein, IL-6= interleukin 6, TNF-α= tumor necrosis factor alpha, ESR= erythrocyte sedimentation rate.
# Table 3

Relationship between EAT volume and cardiometabolic risk markers in RA patients

<table>
<thead>
<tr>
<th>Cardiometabolic risk factors</th>
<th>Spearman (rho)</th>
<th>P value*</th>
<th>Adj P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>0.01</td>
<td>0.87</td>
<td>0.55</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.27</td>
<td>0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.05</td>
<td>0.50</td>
<td>0.31</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.25</td>
<td>0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>-</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
<td>0.35</td>
</tr>
<tr>
<td>Current smoking</td>
<td>-</td>
<td>-</td>
<td>0.14</td>
</tr>
<tr>
<td>Smoking history (pk yr)</td>
<td>0.22</td>
<td>0.005</td>
<td>0.04</td>
</tr>
<tr>
<td>HOMA</td>
<td>0.32</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>0.31</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC score</td>
<td>0.28</td>
<td>0.06</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* Spearman correlation coefficient P values.

** P value adjusted for age, race and sex.

EAT= epicardial adipose tissue volume, HDL= high density lipoprotein, LDL= low density lipoprotein, pk yr= pack year, HOMA= homeostatic model assessment of insulin resistance, CAC=coronary artery calcium.