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Increased epicardial adipose tissue volume predicts insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome

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ABSTRACT

Background/objectives: Epicardial adipose tissue (EAT) reportedly secretes various adipokines that evoke insulin resistance in patients with obesity or metabolic syndrome. However, it remains unclear whether EAT also plays a role in the development of insulin resistance in lean subjects. The purpose of this study was to investigate the impact of EAT volume on the presence of insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome.

Methods: We prospectively studied 624 consecutive patients who underwent multidetector computed tomography (MDCT) and measured EAT volume between January 2009 and June 2011. Obesity was defined as body mass index ≥25 kg/m^2, and metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria. After we excluded 385 patients with obesity or metabolic syndrome, 239 patients were enrolled in the present study.

Results: There were 102 (42.7%) subjects with insulin resistance (homeostasis model assessment ratio [HOMA-R] >2.5) and 88 (36.8%) subjects with coronary artery disease. After adjusting for age, gender, and body mass index, increased EAT volume (≥35 ml mean EAT volume) was independently associated with insulin resistance (odds ratio 2.6, 95% confidence interval 1.5–4.8). Furthermore, increased EAT volume was also associated with coronary artery disease (odds ratio 1.9, 95% confidence interval 1.0–3.6) after adjustment of age, gender, body mass index, and the presence of insulin resistance.

Conclusion: Increased EAT volume may play a key role in the development of insulin resistance and coronary artery disease, even in non-obese subjects without metabolic syndrome.

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1. Introduction

The prevalence rates of obesity and overabundance of visceral fat are increasing in developed countries [1]. It is obvious that obesity and increased visceral fat are associated with impaired glucose tolerance and the development of metabolic syndrome [2,3], which is a cluster of risk factors for coronary artery disease [4]. Abdominal visceral fat can produce large quantities of various adipokines that are strongly associated with coronary artery disease development [5]. Although the prevalence of obesity is still markedly lower in Japan compared to Western countries (body mass index ≥25 kg/m^2, 28% in male and 22% in female; ≥30 kg/m^2, 2.9% in male and 3.4% in female), the Japanese prevalence rates of obesity and obesity-linked diseases have recently increased [6–9].

Because epicardial adipose tissue (EAT) surrounding the heart is adjacent to major coronary arteries, EAT is thought to be a source of several inflammatory mediators involved in the development of coronary artery disease [10,11]. Increased EAT volume and high levels of inflammatory mediators are significantly related to insulin resistance and coronary artery disease in obese subjects or patients with metabolic syndrome [11,12]. We previously reported that high EAT volume was associated with coronary artery disease in both obese and non-obese patients [13]. A recent study described that insulin resistance is increasingly prevalent among Japanese subjects without obvious obesity [14]. However, little is known about the pathological role of EAT in subjects without obesity or metabolic syndrome.

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The purpose of this study was to investigate the impact of increasing EAT volume on the presence of insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome.

2. Methods

2.1. Study population

We performed multi-detector row computed tomography (MDCT) in 624 consecutive patients at the Yamagata University Hospital between September 2009 and October 2011. We excluded 82 patients who had metabolic syndrome, 189 patients with obesity, and 115 patients without fasting insulin level data. The remaining 239 patients were included in the present study (Fig. 1). All subjects provided written informed consent prior to their participation, and the protocol was approved by the institution's Human Investigation Committee. The procedures were performed in accordance with the Helsinki Declaration.

2.2. Definition of metabolic syndrome

Height and body weight were measured, and venous blood samples were collected before MDCT. We defined metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III criteria [15]. We modified these criteria for abdominal obesity by using body mass index ≥25 kg/m^2 in place of waist circumference [16]. Metabolic syndrome requires at least three of the following five criteria: body mass index ≥25 kg/m^2, elevated triglyceride ≥150 mg/dl, reduced high-density lipoprotein cholesterol (HDLc) <40 mg/dl in men and <50 mg/dl in women, elevated fasting plasma glucose ≥110 mg/dl or previously diagnosed diabetes mellitus, elevated blood pressure (systolic blood pressure ≥130 mm Hg, and/or diastolic blood pressure ≥85 mm Hg) or antihypertensive medication.

2.3. Definitions of insulin resistance and coronary artery disease

Insulin tolerance was evaluated using the homeostasis model assessment ratio (HOMA-R, HOMA-R = fasting insulin levels × fasting plasma glucose × 1 / 405), and insulin resistance was defined as HOMA-R >2.5[17]. We defined coronary artery disease as ≥50% coronary artery stenosis in each axial MDCT based on the Society of Cardiovascular CT guidelines [18].

2.4. Measurement of EAT volume

Cardiac MDCT was performed using a 64-slice MDCT scanner (Aquilion 64, Toshiba, Tokyo, Japan). Nitroglycerin was administered orally before the CT scan was performed. A total of 51–100 ml of contrast media (Iopamidol, Bayer Co. Ltd., Leverkusen, Germany) was injected at a flow rate of 3.0–4.6 ml/s depending on the patient's body weight. The region of interest was placed within the ascending and descending aorta, and scanning was commenced when the CT density reached 250 Hounsfield units at the ascending aorta or 180 Hounsfield units at the descending aorta. The scan was performed between the tracheal bifurcation and the diaphragm. Radiographic parameters were collimation width, 0.5 mm; rotation speed, 0.4 s/rotation; tube voltage, 120 kV; and effective tube current, 400–450 mA. Cardiac images were analyzed at the most motionless phase of the cardiac cycle, which was most frequently the mid-diastolic phase, with retrospective cardiac gating at 75% of the R-wave to R-wave interval.

EAT was defined as the adipose tissue between the surface of the heart and the visceral layer of the pericardium. After manually tracing a single region of interest containing the heart and EAT on cross-sectional images, an EAT image ranging from −200 to −30 Hounsfield units was extracted from the heart image. The EAT area was measured every 5 mm from the atrial appendage to the apex over the diaphragm. EAT volume was automatically calculated as the sum of the EAT areas using analysis software (ZIO station, ZIO SOFT Inc., Tokyo, Japan) [13].

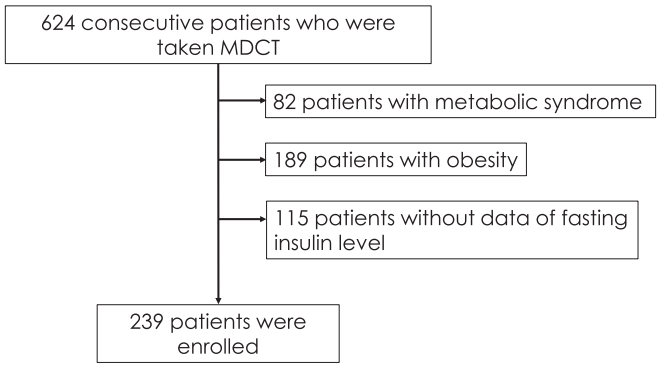

Fig. 1. Recruitment of patients who underwent MDCT at Yamagata University Hospital. MDCT, multidetector computed tomography.

2.5. Statistical analysis

Data are presented as means and standard deviations (SDs). If the data were not normally distributed, they are presented as medians and interquartile range. Unpaired Student's *t*-tests and chi-square tests were used to assess continuous and categorical variables, respectively. Mann–Whitney *U*-tests were employed for data that were not normally distributed. Univariate and multivariate analyses with logistic regression were used to determine significant predictors of insulin resistance and coronary artery disease. Multivariate analysis was adjusted by factors that were found to be significant in univariate analysis. The optimal cutoff value for EAT volume was determined as that with the largest sum of sensitivity plus specificity on the receiver operating characteristic curve. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with a standard statistical program package (JMP version 10; SAS Institute, Cary, North Carolina).

3. Results

3.1. Patient characteristics

The clinical characteristics of the 293 patients enrolled in the present study are listed in Table 1. There were 76 females (32%) and mean age was 63 (13) years old. There were 22 (9%) current smokers and 88 (37%) patients with coronary artery disease. The median EAT volume was 35 ml (interquartile range: 15–51), and the mean body mass index was 22 (2) kg/m^2. There were 102 (43%) patients with insulin resistance, and they exhibited higher serum levels of high-sensitivity C-reactive protein (hsCRP), and low-density lipoprotein cholesterol level (LDLc), as well as higher coronary artery disease prevalence compared to those without it. Furthermore, patients with insulin resistance showed higher EAT volume and were more likely to have undergone coronary artery bypass graft or percutaneous coronary intervention compared with those without insulin resistance.

3.2. Clinical features of patients with coronary artery disease

There were 88 (30%) patients with coronary artery disease in the present study. They were younger and had higher estimated glomerular filtration rate (eGFR), higher serum hsCRP levels, and lower serum HDLc levels compared to those without coronary artery disease (Table 2). Moreover, patients with coronary artery disease exhibited higher EAT volume, a greater prevalence of insulin resistance, and more plaque lesions compared to patients without coronary artery disease.

Table 1
Baseline clinical characteristics.

	All patients ($n = 239$)	Insulin resistance (−) ($n = 137$)	Insulin resistance (+) ($n = 102$)	*P* value
Age, years (SD)	63 (13)	63 (13)	63 (13)	0.759
Male, *n* (%)	163 (68)	96 (70)	67 (66)	0.471
Current smoker, *n* (%)	22 (9)	13 (10)	9 (9)	0.860
Presence of CAD, *n* (%)	88 (37)	25 (18)	63 (62)	<0.001
EAT volume, ml	35 (15–51)	22 (14–35)	34 (17–50)	0.002
Presentation profile				
BMI, kg/m^2 (SD)	22 (2)	21 (2)	22 (2)	0.456
sBP, mm Hg (SD)	128 (22)	125 (21)	124 (22)	0.842
dBP, mm Hg (SD)	73 (12)	74 (13)	72 (11)	0.307
eGFR, ml/min/1.73 m^2 (SD)	72 (22)	71 (20)	72 (22)	0.889
Blood biomarkers				
hsCRP mg/dl (IQR)	0.061 (0.026–0.197)	0.052 (0.026–0.103)	0.072 (0.026–0.218)	<0.001
Fasting plasma glucose, mg/dl (SD)	104 (27)	94 (15)	114 (30)	<0.001
Triglyceride, mg/dl (SD)	102 (55)	106 (71)	101 (47)	0.357
HDLc, mg/dl (SD)	57 (18)	58 (18)	56 (19)	0.449
LDLc, mg/dl (SD)	103 (32)	98 (30)	109 (34)	0.010
Non-HDLc, mg/dl (SD)	118 (36)	117 (35)	120 (37)	0.518
L/H ratio (SD)	1.9 (0.8)	1.9 (0.8)	2.1 (0.8)	0.122
Total cholesterol, mg/dl (SD)	175 (40)	171 (37)	181 (44)	0.066
Characteristics of CAD				
Plaque, *n* (%)	100 (42)	49 (36)	51 (50)	0.030
Unstable plaque, *n* (%)	15 (6)	5 (4)	10 (10)	0.025
Calcification, *n* (%)	146 (61)	82 (60)	64 (63)	0.882
Number of PCI or CABG, *n* (%)	50 (21)	14 (10)	36 (35)	0.012

Data are presented as mean (SD) or % unless otherwise indicated; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; dBP, diastolic blood pressure; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; HDLc, high density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDLc, low density lipoprotein cholesterol; L/H ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PCI, percutaneous coronary intervention; sBP, systolic blood pressure.

3.3. Correlations between EAT and other variables

The correlations between EAT and clinical parameters were examined (Table 3). EAT volume was significantly correlated with body mass index ($r = 0.351$, $P < 0.001$) and HOMA-R ($r = 0.325$, $P < 0.001$). Moreover, EAT volume was weakly correlated with age ($r = 0.234$, $P = 0.001$) and levels of hsCRP levels ($r = 0.156$, $P = 0.025$), fasting plasma glucose ($r = 0.154$, $P = 0.017$), triglyceride

Table 2
Clinical characteristics of patients with or without coronary artery disease.

	Coronary artery disease (−) ($n = 151$)	Coronary artery disease (+) ($n = 88$)	*P* value
Age, years (SD)	66 ± 12	61 ± 13	0.002
Male, *n* (%)	101 (67)	62 (70)	0.568
Current smoker, *n* (%)	18 (12)	4 (5)	0.057
Presence of IR, *n* (%)	37 (25)	65 (74)	<0.001
EAT volume, ml (SD)	28 (14–37)	37 (18–49)	0.007
Presentation profile			
BMI, kg/m^2 (SD)	22 (3)	22 (2)	0.121
sBP, mmHg (SD)	125 (22)	123 (21)	0.424
dBP, mm Hg (SD)	74 (12)	71 (11)	0.068
eGFR, ml/min/1.73 m^2 (SD)	68 (23)	75 (20)	0.032
Blood biomarkers			
hsCRP mg/dl (IQR)	0.063 (0.025–0.151)	0.087 (0.026–0.214)	<0.001
Fasting plasma glucose, mg/dl (SD)	101 (25)	110 (29)	0.016
Triglyceride, mg/dl (SD)	106 (59)	114 (73)	0.345
HDLc, mg/dl (SD)	60 (19)	53 (16)	0.010
LDLc, mg/dl (SD)	101 (32)	106 (32)	0.187
Non-HDLc, mg/dl (SD)	114 (35)	122 (37)	0.085
L/H ratio (SD)	1.7 (0.7)	2.1 (0.8)	0.001
Total cholesterol, mg/dl (SD)	175 (41)	175 (40)	0.957
Characteristics of CAD			
Plaque, *n* (%)	37 (25)	63 (72)	0.010
Unstable plaque, *n* (%)	-	15 (17)	-
Calcification, *n* (%)	88 (58)	58 (66)	0.556
Number of PCI or CABG, *n* (%)	–	50 (57)	–

Data are presented as mean (SD) or % unless otherwise indicated; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; dBP, diastolic blood pressure; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; IR, insulin resistance; LDLc, low-density lipoprotein cholesterol; L/H ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PCI, percutaneous coronary intervention; sBP, systolic blood pressure.

Table 3
Relationships between clinical parameters, biomarkers, and EAT.

	EAT	
	r	*P* value
Age	0.234	0.001
BMI	0.354	<0.001
Blood biomarkers		
hsCRP	0.156	0.025
Fasting plasma glucose	0.154	0.017
Insulin	0.006	0.929
Triglyceride	0.232	0.001
HDLc	−0.178	0.022
LDLc	0.256	<0.001
Non-HDLc	0.075	0.249
L/H ratio	0.048	0.460
Total cholesterol	0.193	0.010
HOMA-R	0.325	<0.001

BMI, body mass index; EAT, epicardial adipose tissue; HDLc, high-density lipoprotein cholesterol; HOMA-R, homeostasis model assessment ratio; hsCRP, high-sensitivity C-reactive protein; LDLc, low-density lipoprotein cholesterol; L/H ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

($r = 0.232$, $P = 0.001$), HDLc ($r = -0.178$, $P = 0.022$), LDLc ($r = 0.256$, $P < 0.001$), and total cholesterol ($r = 0.193$, $P = 0.010$). However, insulin, non-HDLc, and the LDLc to HDLc ratio (L/H ratio) were not correlated with EAT.

3.4. Predictors of insulin resistance

Univariate and multivariate analyses with logistic regression for predicting the presence of insulin resistance are shown in Table 4. Increased EAT volume (odds ratio 1.23, 95% confidence interval 1.05–1.44) was independently associated with insulin resistance after adjustment for age, gender, body mass index, and systolic blood pressure.

3.5. Predictors of coronary artery disease

Univariate and multivariate analyses with logistic regression for predicting the presence of coronary artery disease are shown in Table 5. Increased EAT volume (odds ratio 1.20, 95% confidence interval 1.07–1.36) was independently associated with coronary artery disease after adjustment for age, gender, body mass index, and diastolic blood pressure.

The receiver operating characteristic curve for EAT volume as a predictor of coronary artery disease is shown in Fig. 2. The area under the receiver operating characteristic curve for predicting coronary artery disease was 0.624. EAT volume ≥40 ml had a sensitivity of 56% and a specificity of 61% for predicting coronary artery disease.

4. Discussion

In the present study, we demonstrated that increased EAT volume was associated with the presence of insulin resistance and coronary artery disease in non-obese Japanese subjects without metabolic syndrome. The cut-off value of EAT volume to predict coronary artery disease was ≥40 ml in non-obese subjects without metabolic syndrome.

The worldwide prevalence rates of obesity and overabundance of visceral fat are increasing. The World Health Organization (WHO) and the U.S. National Institutes of Health defined obesity as body mass index ≥30 kg/m^2 [1]. However, the prevalence of obesity is markedly lower in Japan (2–3%), in contrast to 10–20% in Western populations [7]. Therefore, the Japan Society for the Study of Obesity has defined obesity as body mass index ≥25 kg/m^2 [6]. Many reports have shown that excess visceral fat is more closely related the obesity-linked diseases (i.e., hypertension, dyslipidemia, gout, and coronary artery disease) than obesity itself in Japan [3,19,20]. Our data showed that increased EAT volume was associated with the presence of insulin resistance and coronary artery disease even in non-obese subjects. These results were consistent with previous reports [3,19,20].

EAT volume was also reported to be significantly related to coronary artery disease in subjects with metabolic syndrome [21]. EAT produces various cytokines and promotes a catabolic state due to chronic adipose tissue inflammation and insulin resistance in individuals with metabolic syndrome [22]. In the present study, we showed that increased EAT volume was associated with the presence of insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome independent of body mass index. These data suggest that there is a causal relationship between increased EAT and coronary artery disease.

The mechanism by which EAT impairs insulin signaling and promotes coronary artery disease is thought to be associated with increased levels of inflammatory mediators (i.e., tumor necrosis factor-alpha, interleukin-6, and plasminogen activator inhibitor-1) induced by EAT [23,24]. We previously demonstrated that increased EAT volume and adipocyte size were associated with impaired adiponectin secretion in pericardial fluid, which may facilitate the development of coronary artery disease in non-obese subjects [13]. EAT volume was weakly but

Table 4
Univariate and multivariate analyses of factors predicting insulin resistance.

	Univariate analysis			Multivariate analysis		
	Unadjusted OR	95% CI of OR	*P* value	Adjusted OR[a]	95% CI of OR	*P* value
Age, per 10-year increase	1.23	1.01–1.49	0.036	1.05	0.85–1.32	0.635
Gender (male)	1.72	0.94–3.14	0.077	1.61	0.85–3.06	0.147
Presentation profile						
BMI, per 1 SD increase	1.12	1.11–1.49	<0.001	1.39	1.26–1.50	0.003
sBP, per 10 mm Hg increase	1.13	1.00–1.28	0.049	1.08	0.95–1.23	0.236
dBP, per 10 mm Hg increase	1.03	0.83–1.31	0.767			
Blood biomarkers						
hsCRP, per 1 SD increase	1.27	0.90–1.78	0.170			
Triglyceride, per 1 SD increase	1.12	0.72–1.18	0.534			
HDLc, per 1 SD decrease	1.12	0.84–1.49	0.466			
LDLc, per 1 SD increase	1.21	0.91–1.17	0.188			
Non-HDLc, per 1 SD increase	1.11	0.70–1.20	0.516			
L/H ratio, per 0.1 increase	1.03	0.94–1.01	0.124			
Total cholesterol, per 1 SD increase	1.25	0.93–1.68	0.145			
EAT, per 10 ml increase	1.23	1.07–1.42	0.003	1.23	1.05–1.44	0.010

BMI, body mass index; CAD, coronary artery disease; dBP, diastolic blood pressure; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; HDLc, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDLc, low-density lipoprotein cholesterol; L/H ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; sBP, systolic blood pressure.

[a] Adjusted OR after adjustment for age, gender, body mass index, and systolic blood pressure.

Table 5
Univariate and multivariate analyses of factors predicting coronary artery disease.

	Univariate analysis			Multivariate analysis		
	Unadjusted OR	95% CI of OR	*P* value	Adjusted OR[a]	95% CI of OR	*P* value
Age, per 10-year increase	1.01	0.83–1.18	0.930	1.00	0.82–1.22	0.967
Gender (male)	1.17	0.71–2.12	0.472	1.16	0.64–2.10	0.636
Presentation profile						
BMI, per 1 SD increase	1.04	0.80–1.34	0.775			
sBP, per 10 mm Hg increase	1.07	0.84–1.04	0.225			
dBP, per 10 mm Hg increase	1.23	1.00–1.54	0.050	1.21	0.84–1.50	0.087
Blood biomarkers						
hsCRP, per 1 SD increase	1.13	0.85–1.49	0.393			
Triglyceride, per 1 SD increase	1.06	0.72–1.18	0.571			
HDLc, per 1 SD decrease	1.06	0.81–1.36	0.703			
LDLc, per 1 SD increase	1.03	0.80–1.33	0.827			
Non-HDLc, per 1 SD increase	1.24	0.31–13.07	0.087			
L/H ratio, per 0.1 increase	1.06	1.02–1.10	0.002	1.06	1.02–1.10	0.003
Total cholesterol, per 1 SD increase	1.06	0.72–1.18	0.570			
EAT, per 10 ml increase	1.25	1.15–1.46	0.009	1.20	1.07–1.36	0.047

BMI, body mass index; dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EAT, epicardial adipose tissue; HDLc, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IR, insulin resistance; LDLc, low-density lipoprotein cholesterol; L/H ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; sBP, systolic blood pressure.
[a] Adjusted OR after adjustment for age, gender, body mass index, and diastolic blood pressure.

significantly correlated with the serum hsCRP level in the present study. Increased EAT volume may be associated with adipocytokine secretion, which induces insulin resistance and coronary artery disease even in non-obese subjects without metabolic syndrome.

4.1. Study limitations

There were several limitations in the present study. First, we did not measure adipocytokine level. Because EAT volume was weakly but significantly correlated with serum hsCRP in this study, EAT-released adipocytokines may promote inflammation. Second, this was a cross-sectional study and therefore could not identify a cause–effect relationship. Future prospective study about the impact of EAT volume on cardiovascular events is needed. Thirdly, sensitivity and specificity of EAT for predicting coronary artery disease were not so high. It was because we enrolled not only the patients who were suspected with coronary artery disease but also those who were not. Future prospective study with patients who were suspected with coronary artery disease only is needed.

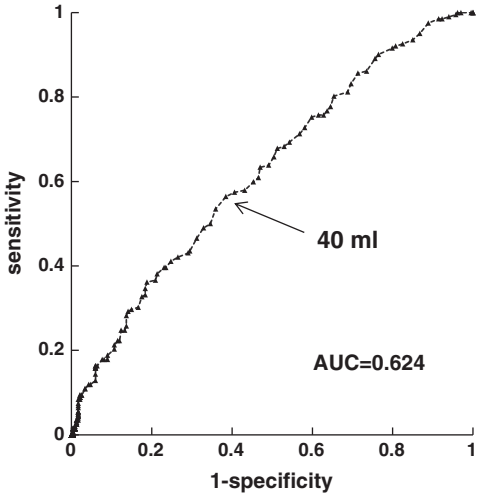

Fig. 2. The receiver operating characteristic curves for EAT volume to predict coronary artery disease in non-obese subjects. The receiver operating characteristic curves and area under the curve for coronary artery disease (cut-off value = 40 ml, area under the curve = 0.624). EAT, epicardial adipose tissue.

4.2. Conclusions

In conclusion, increased EAT volume was associated with the presence of insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome. These results suggest that increased EAT may play a role in coronary artery disease through insulin resistance in lean subjects who do not have metabolic syndrome.

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