Epicardial Adipose Tissue Predicts Severe Mitral Annular Calcification in Patients Aged ≥60 Years

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Background: Epicardial adipose tissue (EAT) has been shown to be associated with diabetes mellitus (DM), hypertension (HT), coronary artery calcification, and atherosclerotic disease. Mitral annular calcification (MAC) is also associated with atherosclerosis. The purpose of this study was to assess the relationship between EAT and severe MAC.

Material/Methods: The study enrolled 102 patients who had severe MAC and 107 patients who did not have MAC, as determined by echocardiographic examination. EAT was measured by transthoracic echocardiography. The parasternal long-axis view was used to measure the maximal EAT thickness.

Results: Patients with severe MAC were older (p<0.001) and were more likely to be female (p<0.001). Epicardial adipose tissue (p=0.001) and urea (p=0.004) were also higher and eGFR was lower (p<0.001) in patients with severe MAC. EAT (OR: 15.96, CI %: 1.04–24.604, p<0.05), female sex, CAD, DM, eGFR, and age were independent predictors of severe MAC. The AUC for the EAT to predict severe MAC was 0.699 (95%, CI: 0.625–0.774, p<0.001).

Conclusions: Our data suggest that EAT is an independent predictor for the presence of severe MAC. Routine echocardiographic assessment of EAT is a cheap and noninvasive method for evaluating patient cardiovascular risk classification.

MeSH Keywords: Adipose Tissue • Aging • Mitral Valve

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Background

Epicardial adipose tissue (EAT) is a visceral fat tissue found between the myocardium and the pericardium [1]. It is usually located in the interventricular and atrioventricular grooves and along the coronary arteries. There is no fascia between EAT and the myocardium; therefore, they have similar microcirculation. EAT excretes anti-atherogenic and anti-inflammatory mediators and supplies energy for the myocardium [2]. However, under pathological conditions, EAT appears to play an important role in atherosclerosis and progression of metabolic diseases (e.g., obesity, insulin resistance, diabetes mellitus, and hypertension). Interleukin-6, tumor necrosis factor alpha, and monocyte chemoattractant protein-1 are secreted from EAT [3] and directly affect atherosclerosis [4,5]. Consequently, increased EAT is associated with atherosclerosis [6].

MAC is a degenerative and chronic process of the mitral valve annulus [7]. The prevalence of MAC is 8–15% [8–11], but the etiology is unclear. In early stages of the disease, histological findings include calcium deposits with necrotic and apoptotic interstitial cell material [12]. However, the pathogenesis of MAC still remains unclear.

There are many similarities between EAT and MAC regarding cardivascular risk factors and outcomes. Several previous studies have examined the relationship between aortic valve sclerosis, mitral annular calcification (MAC), and EAT, showing that EAT has an acritical role in the progression of aortic valve sclerosis and coronary atherosclerosis [13], and that there is a strong association between mitral and aortic calcification and EAT [14]. It has been shown that increasing EAT is associated with hypertension, elevated LDL, and low HDL [15]. EAT was found to be related to mortality in patients with coronary artery disease [16]. Risk factors for MAC are similar to risk factors for cardivascular diseases, including age, hypertension, hyperlipidemia, diabetes, and obesity. Also, MAC has been associated with an increased risk of ischemic stroke, coronary atherosclerosis, coronary events, and all-cause mortality [17]. There are limited data on the association between epicardial fat thickness (EFT) and MAC [14,18]. In the present study, we assessed the relationship between EAT and MAC.

Material and Methods

We included 102 patients with severe MAC detected by echocardiography and 107 subjects without MAC, aged ≥60 years and admitted to the cardiology outpatient clinic. Exclusion criteria were mild or moderate MAC, restrictive and hypertrophic cardiomyopathy, acute myocarditis, active infection, renal failure requiring dialysis, autoimmune-inflammatory and connective tissue diseases, malignancy, pregnancy and age <60 years. The demographic data included sex, age, body mass index (BMI), a history of CAD, hypertension (HT), DM, and atrial fibrillation (AF). The echocardiographic data involved epicardial adipose tissue, ejection fraction (EF), left ventricle end-diastolic diameter (LVEDD), left atrium (LA) diameter, right ventricle (RV) diameter, pulmonary artery systolic pressure (PASP), left ventricular hypertrophy (LVH), mitral, aortic, tricuspid regurgitation, and aortic stenosis.

For biochemical data, we collected data on levels of hemoglobin (Hb), platelet, white blood cell count (WBC), HbA1c, creatinine, urea, Aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride. Table 1 presents baseline characteristics of patients with and without MAC in echocardiography, and estimated glomerular filtration rate (eGFR) with Modification of Diet in Renal Disease formula is shown.

Transthoracic echocardiography was carried out using the Vivid S5 GE Healthcare system. Each patient underwent two-dimensional transthoracic echocardiography according to recommendations of the European Association of Echocardiography [19]. EAT was defined as echo-free space between the external wall of the myocardium and the visceral pericardium [5]. The parasternal long-axis view was used to measure maximal EAT thickness. The values were measured in 3 cardiac cycles and were averaged.

Severity of MAC was classified in parasternal short-axis view at the plane of the mitral annulus. Mild MAC was defined as a limited and focal increase in echodensity of the mitral annulus. Moderate MAC was defined as a marked echodensity including one third to one half of the ring circumference and severe MAC was defined as a marked echodensity including more than one half of the circumference of the anulus or with intrusion into the left ventricle inflow tract. Maximal MAC thickness measured from the anterior to the posterior margin at its maximal width is used to evaluate MAC severity, with a value>4 mm defining severe MAC [19].

The study was approved by the Institutional Ethics Committee and conducted in accordance with the principles set out in the Declaration of Helsinki.

Statistical analysis

The SPSS 13.0 (SPSS Inc. an IBM company; Chicago, IL, USA) package was used for statistical analyses. Normality tests were carried out for all variables using the Kolmogorov-Smirnov test. Categorical data are presented as percentages and numbers, normally distributed variables are presented

Table 1. Baseline characteristics of patients with and without MAC in echocardiography.

Characteristic	MAC present (n=102)	MAC absent (n=107)	*P*-value
Age (years)	76.3±7.1	72.4±8.3	<0.001
Male/Female	23/79 (22.5–77.5%)	52/55 (48.6–51.4%)	<0.001
Body mass index (kg/m²)	30.7±5.1	28.7±4.4	0.002
Coronary artery disease	53 (52%)	25 (23.4%)	<0.001
Hypertension	80 (78.4%)	71 (66.4%)	0.036
Atrial fibrillation	43 (41.7%)	31 (29%)	0.036
Diabetes mellitus	39 (38.2%)	19 (17.8%)	0.001
Echocardiographic parameters			
Ejection fraction (%)	60 (55–60)	60 (55–60)	0.360
Epicardial adipose tissue (cm)	0.5 (0.4–0.58)	0.38 (0.3–0.5)	<0.001
LVEDD (mm)	48 (46–50)	48 (45–50)	0.446
Left atrium diameter (mm)	39 (36–43)	36 (32–39)	<0.001
Right ventricular diameter (mm)	24 (22–26)	23 (21–25)	0.004
sPAP (mmHg)	30 (20–40)	20 (20–30)	<0.001
Mitral regurgitation			0.008
Grade-1	26 (25.5%)	21 (19.6%)	
Grade-2	21 (20.6%)	10 (9.3%)	
Grade-3	3 (2.9%)	0 (0%)	
Aortic regurgitation			0.776
Grade-1	23 (22.5%)	23 (21.5%)	
Grade-2	14 (13.7%)	13 (12.1%)	
Grade-3	0 (0%)	1 (0.9%)	
Tricuspid regurgitation			0.002
Grade-1	36 (35.3%)	52 (48.6%)	
Grade-2	21 (20.6%)	11 (10.3%)	
Grade-3	14 (13.7%)	3 (2.8%)	
Aortic stenosis			0.006
Grade-1	10 (9.8%)	4 (3.7%)	
Grade-2	7 (6.9%)	0 (0%)	
Grade-3	0 (0%)	0 (0%)	
Left ventricular hypertrophy	51 (50%)	22 (20.6%)	<0.001
Biochemical parameters			
Hemoglobin (g/dl)	12.2±1.9	13.4±1.7	<0.001
Hematocrit (%)	36.8±5.4	40.1±4.5	<0.001

Table 1 continued. Baseline characteristics of patients with and without MAC in echocardiography.

Characteristic	MAC present (n=102)	MAC absent (n=107)	P-value
WBC (/mm³)	7.6±2.5	6.9±1.9	0.33
Platelet (×10³/µL)	251±75	225±67	0.009
eGFR (ml/min)	60.9 (4.41–77.2)	75.6 (64–89.9)	<0.001
Creatinine (mg/dl)	0.99 (0.79–1.25)	0.89 (0.78–1.08)	0.024
Urea (mg/dl)	50.2±29.5	40.7±15.7	0.004
HbA1c (%)	6.2 (5.7–7.5)	5.9 (5.7–6.2)	0.014
Total cholesterol (mg/dl)	191±43	219±48	0.001
LDL cholesterol (mg/dl)	114±39	130±39	0.008
HDL cholesterol (mg/dl)	47±11	50±12	0.042
Triglyceride (mg/dl)	139 (94–191)	138 (99–194)	0.910
AST (U/L)	20 (17–24)	22 (19–27)	0.025
ALT (U/L)	15 (12–19)	17 (14–24)	0.003

PASP – pulmonary artery systolic pressure; AST – aspartate transaminase; ALT – alanine transaminase; WBC – white blood cell count; LVEDD – left ventricular end diastolic diameter; eGFR – estimated glomerular filtration rate.

Table 2. Significant univariate and multivariate correlates of patients with and without MAC.

Variables	Univariate regression coefficient (95% CI)	P-value	Multivariate regression coefficient (95% CI)	P-value
Age	1.067 (1.028–1.106)	0.001	1.072 (1.019–1.128)	0.007
eGFR (mL/min)	0.964 (0.948–0.981)	<0.001	0.977 (0.957–0.996)	0.019
Diabetes mellitus	0.349 (0.185–0.659)	0.01	0.412 (0.179–0.944)	0.036
Coronary artery disease	0.282 (0.156–0.510)	<0.001	0.244 (0.111–0.536)	<0.001
Hypertension	0.543 (0.292–1.007)	0.053	0.997 (0.442–2.246)	0.993
Female sex	0.308 (0.169–0.561)	<0.001	0.423 (0.190–0.945)	0.036
Epicardial adipose tissue	81.07 (9.13–719.54)	<0.001	15.96 (1.04–24.604)	0.047
Body mass index	1.096 (1.032–1.165)	0.003	1.071 (0.989–1.159)	0,094

eGFR – estimated glomerular filtration rate.

as mean ± SD, and abnormally distributed variables are presented as median. Categorical data and proportions were examined using the Fisher exact test or chi-square, as appropriate. Normally distributed continuous variables were analyzed with the 2-tailed *t* test, and non-normally distributed variables were examined with the Mann-Whitney U test. Pearson and Spearman tests were used for correlation analysis. Spearman correlation analysis was used to evaluate to the relationship between 2 continuous or ordinal variables. Pearson correlation analysis was performed to estimate the linear relationship between 2 continuous

variables. Clinical determinants of the patients with MAC were established using univariate and multivariable logistic regression models. A p value<0.05 was accepted as statistically significant.

Results

A total of 209 patients were separated into 2 groups: Severe MAC present (102 patients) and MAC absent (107 patients). Baseline characteristics and echocardiographic parameters

are summarized in Table 1. Severe MAC was present in 64% of females, 53% of patients with HT, 67% of patients with DM, and 37% of patients with CAD.

Patients with severe MAC was older than the patients without severe MAC (p<0.001). We found more CAD (52% *vs.* 23.4%, p<0.001), HT (78.4% *vs.* 66.4%, p=0.036), and DM (41.7% *vs.* 29%, p=0.036) in patients with severe MAC than in patients without MAC. Epicardial adipose tissue (p=0.001), left atrium diameter (p<0.001), right ventricular diameter (p=0.004), and PASP (p<0.001) were higher in patients with severe MAC than in patients without MAC. Mitral regurgitation (p=0.008), tricuspid regurgitation (p=0.002), aortic stenosis (p=0.006), and LVH (p<0.001) were more prevalent in patients with severe MAC. In biochemical analyses, Hba1c (p=0.014) and urea (p=0.004) were higher and eGFR was lower (p<0.001) in patients with severe MAC.

Table 2 shows significant univariate and multivariate correlations of severe MAC calcification with other parameters. In multivariate analysis, we found age, CAD, DM, eGFR, female gender, and EAT (OR: 15.96, CI%: 1.04–24.604, p<0.05) were independent predictors for severe MAC. There was a positive correlation between EAT and age (r=0.232, p=0.001), BMI (r=0.151, p=0.029), HbA1c (r=0.163, p=0.044), creatinine (r=0.184, p=0.009), left atrium diameter (r=0.191, p=0.006), and right ventricle diameter (r=0.149, p=0.032), and a negative correlation with Hb (r=−0.194, p=0.006), Htc (r=−0.200, p=0.004), and eGFR (r=-0.290, p<0.001) (Table 3).

As shown in Figure 1, the area under the curve for EAT to predict severe MAC was 0.699 (95% CI: 0.625–0.774, p<0.001). A EAT of 0.41 was identified as the optimal cut-off value, with sensitivity of 74.5% and specificity of 70.1% for predicting severe MAC.

Discussion

In the present study, we found that EAT was independently associated with the presence of severe MAC. Age, DM, CAD, female sex, and eGFR were also associated with the presence of severe MAC.

EAT acts as an endocrine and paracrine organ. EAT may have many protective effects, but in pathological conditions, EAT has been linked to coronary artery calcium deposits, atherosclerotic disease [20], and metabolic diseases [2] due to secretion of proatherogenic and proinflammatory cytokines. We found that EAT leads to atherogenic and inflammatory phenomena, which may end with valve degeneration and calcification [7]. Histopathologic studies of the valves indicate lesions similar to atherogenic plaques, with accumulation

Table 3. Correlation between clinical-echocardiographical parameters and EAT.

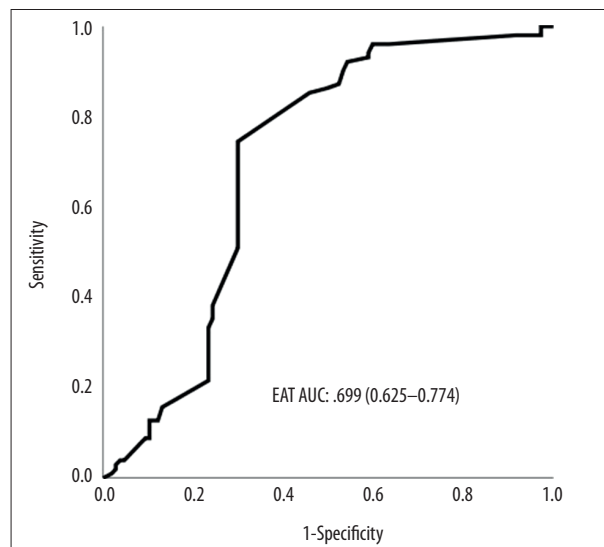| Variables	r-value	P-value
Age	0.232	0.001
Body mass index (kg/m²)	0.151	0.029
HbA1c (%)	0.163	0.044
Creatinine (mg/dl)	0.184	0.009
Left atrium diameter	0.191	0.006
Right ventricle diameter	0.149	0.032
Hemoglobin (g/dl)	−0.194	0.006
Hematocrit (%)	−0.200	0.004
eGFR (ml/min)	−0.290	<0.001

eGFR: Estimated glomerular filtration rate

Figure 1. Receiver operating characteristic (ROC) curves of EAT for prediction MAC.

of inflammatory and atherogenic material [15]. Aortic valve calcification and mitral valve calcification share similar risk factors associated with atherosclerosis [10].

The mechanisms underlying the relationship between epicardial fat and MAC are not fully established. The close anatomic relationship of epicardial adipose tissue with the adjacent myocardium suggest possible local interactions between these tissues. The effect of secreted numerous hormones, inflammatory mediators, and cytokines by EAT may be a potential trigger mechanism in progression of MAC and CAD. Alnabelsi et al. evaluated the relationship between EAT and aortic-mitral annular calcium by CT in patients aged >65 years, finding a significant association between EAT and

calcium deposits in the mitral annulus and aortic valve [8]. Mahabadi et al. examined the relationship between severe aortic valve stenosis and EAT thickness, reporting a strong association between EAT and severe aortic stenosis, independent of other common cardiovascular factors [21]. They used CT imaging, but they did not evaluate MAC, and they used EAT area instead of thickness. Although the used a different imaging technique (computed tomography), their findings are compatible with the results of our study. Guler et al. was the only study using echocardiography to evaluate the relationship between EAT and MAC [18]. Although they did not classify the severity of the MAC, their results were similar to ours.

EAT is associated with coronary artery disase and cardiovascular risk factors. Risk factors for atherosclerotic CAD such as diabetes mellitus and chronic kidney disease are also risk factors for MAC. There is an association between MAC and age, female sex, CAD, and hyperlipidemia. A previous study found that MAC was correlated with age [13], as in our study. Female sex has been associated with MAC [22]. It has been suggested that bone demineralization in postmenopausal women causes calcium accumulation in tissues [23]. Similarly, the rate of MAC was higher in females in the present study. However, the increased prevalence of MAC in female patients compared with male patients warrants further research. Our findings demonstrated remarkably higher prevalence of MAC in patients with CAD, which is consistent with previous studies [20,24]. It has been shown that DM is associated with presence of MAC. In our study, MAC was more frequent in patients with DM.

CKD is associated with irregularity of phosphate and calcium metabolism, which causes tissue calcification [25]. Previous studies have demonstrated increased prevalence of MAC in patients with CKD [26,27]. In our study, although dialysis-dependent patients were excluded, eGFR was significantly correlated with presence of MAC. Overall, there was a tendency of increased prevalence of MAC with declining eGFR.

Increased prevalence of MAC in patients with cardiovascular risk factors such as hypercholesterolemia has been frequently reported in the literature [28]. Several studies found no association between MAC and hypercholesterolemia [11,29]. On the contrary, in our study, LDL and total cholesterol were lower in patients with MAC. Use of statin therapy was significantly higher in patients with MAC compared to patients without MAC (29–14%, p=0.006), because patients with MAC are more likely to have CAD.

The major finding of this study is the significant association between EAT and MAC. Moreover, echocardiography is an non-invasive technique and is less expensive than computerized tomography. Therefore, routine echocardiographic assessment of EAT might be useful for determining severe MAC associated with an increased risk of ischemic stroke, coronary atherosclerosis, coronary events, and all-cause mortality.

Conclusions

In our study we found that EAT is an independent predictor for the presence of severe MAC. EAT assessment by echocardiography requires very little time and can be easily applied for evaluation of MAC associated with cardiovascular risk factors and cardiovascular disease.

Limitations

The sample size of our study was small and we only included patients with severe MAC. Echocardiography may not be the most suitable technique for measuring epicardial fat because it is a linear measurement in one location; therefore, it may not reflect the variability of fat thickness or total epicardial fat volume. Multidetector computed tomography is more sensitive and specific than echocardiography in measuring fat thickness in deeper epicardial fat layers.

Conflict of Interests

None.

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