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Relationship between the Echocardiographic Epicardial Adipose Tissue Thickness and Serum Adiponectin in Patients with Angina

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Background: It is still unknown whether increased cardiac adiposity is related to the risk factors of coronary artery disease (CAD). We measured epicaridal adopose tissue (EAT) and mediastinal adipose tissue (MAT) using echocardiography and examined their correlations with CAD and serum adiponectin.
Methods: One hundred fifty three patients who underwent elective coronary angiography for chest pain were measured cardiac adiposity by transthoracic echocardiography. The correlations of cardiac adipose tissue with the presence and severity of CAD and the serum adiponectin level were examined.
Results: EAT was thicker in patients with CAD (1.8±1.4 vs. 3.8±1.9 mm, p<0.001), but MAT was not different according to the presence of CAD (2.9±2.8 vs. 3.5±2.5 mm, p=0.121). EAT showed a significant positive correlation with age (r=0.225, p=0.005), homocystein (r=0.289, p=0.001), fasting glucose (r=0.167, p=0.042), and fibrinogen (r=0.218, p=0.009), and a significant negative correlation with serum adiponectin (r=-0.194, p=0.016). EAT thickness (OR 11.53, 95% CI; 3.61-36.84, p<0.001) and low serum adiponectin (OR 2.88, 95% CI; 1.02-8.15, p=0.046) were independent predictors of obstructive CAD. However, MAT thickness was not associated with CAD.
Conclusion: EAT was associated with the severity and risk factors of CAD and correlated with serum adiponectin level. In contrast with EAT, MAT was not associated with CAD and adiponectin.

KEY WORDS: Epicardium · Adiponectin · Coronary artery disease · Echocardiography.

Introduction

Recently, the interest in epicardial adipose tissue (EAT) is rapidly growing. Several clinical and experimental evidences suggest that epicardial fat may play a role in coronary artery disease (CAD) and atherosclerosis.[1-7] Because of its close anatomical relationship to the heart, EAT may locally modulate the coronary arteries and myocardium through paracrine secretion of anti- and pro-inflammatory adipokines. Some studies showed that adipokines and cytokines were locally expressed in EAT and their levels were significantly lower in patients with CAD.[8-10] Additionally, it is well-known that EAT is associated with blood markers such as serum lipid profile, inflammatory marker, and insulin resistance.[2)5)] Accordingly, we presumed that EAT might be related also to serum adiponectin.

When EAT was observed by echocardiography, we can also see mediastinal adipose tissue (MAT) in the outside of parietal pericardium. Pericardial adipose tissue (PAT) is defined as EAT plus MAT. Several studies on both EAT and MAT revealed that cardiac fat is associated with coronary

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risk factors and insulin resistance.[11)12)] However, few clinical studies examined EAT and MAT separately with regard to their relation with CAD. So, we measured EAT and MAT using echocardiography and examined their correlations with CAD and serum adiponectin.

METHODS

STUDY POPULATIONS

One hundred fifty three patients who underwent elective coronary angiography for chest pain were studied. We excluded patients who had myocardial infarction, acute inflammatory disease, heart failure, cardiomyopathy, or pericardial effusion. Moreover, we excluded those whose transthoracic echocardiographic view was inadequate for measuring the epicardial fat thickness.

On admission, blood sampling was performed to measure total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, fibrinogen and high-sensitivity C-reactive protein (hsCRP) in an overnight fasting state. Height (m2) and body weight (kg) were used to calculated body mass index (BMI).

CORONARY ANGIOGRAPHY

In a fasting state, coronary angiography was performed by the Judkins' method following the puncture of femoral artery or via a radial artery approach. The severity of coronary atherosclerotic lesions was evaluated from at least three projections in all the patients. Significant stenosis was defined as a diameter stenosis of 50% or greater in major three epicardial arteries.

Blood sampling for measuring the adiponectin level was obtained at the time of angiography. Serum adiponectin was measured by ELISA (R&D Systems, Inc., USA).

MEASUREMENT OF ECHOCARDIOGRAPHIC CARDIAC ADIPOSE TISSUE

Each patient underwent transthoracic echocardiography on the next day after coronary angiography. Echocardiograms were performed with VIVID 7 (GE, USA) instrument by standard techniques with subjects in the left lateral decubitus position.

We measured EAT thickness on the free wall of right ventricle from parasternal long-axis views. EAT was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography and its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole on three cardiac cycles.[13)14)] The measurement was performed at the point on the free wall of the right ventricle along the midline of the ultrasound beam, with the best effort to be perpendicular to the aortic annulus, anatomical landmark (Fig. 1). MAT presenting as an echo-lucent area above the parietal pericardium was also measured at same line. In thin patients whose MAT was indistinguishable, the free wall of the right ventricle was magnified for observation, and if it was still indistinguishable after magnification (11 cases), only PAT thickness was used in statistical analysis. The average value of three cardiac cycles from each echocardiographic view was used for the statistical analysis. The intra-observer and inter-observer correlation coefficients were 0.94 and 0.90, respectively, indicating good reproducibility and reliability.

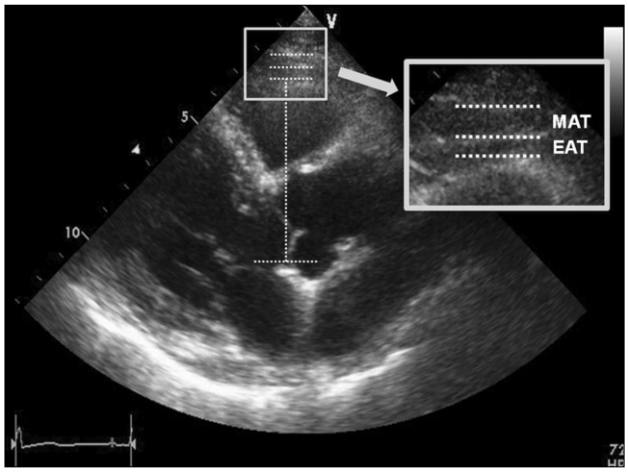

Fig. 1. Echocardiographic measurement of epicardial adipose tissue and mediastinal adipose tissue. EAT: epicardial adipose tissue, MAT: mediastinal adipose tissue.

STATISTICS

Statistical analysis was done using SPSS 11.0 for Windows. All data were expressed as mean±standard deviation or number (percent). Patients' characteristics according to the presence of CAD were compared using independent t-test and Chi-square test. The EAT thickness and serum adiponectin level were compared with other risk factors and coronary atherosclerosis using one-way ANOVA test. The correlations of cardiac adipose tissue with various clinical and biochemical variables were examined by Spearman correlation analysis. Multivariate analysis was performed to determine the factors related to significant coronary artery stenosis. Statistical significance was set at $p<0.05$.

RESULTS

The mean EAT of the patients was 2.88±1.94 mm (range 0.20-9.60 mm), the mean MAT 3.22±2.65 mm (range 0.00-12.70 mm), and the mean PAT 6.10±3.38 mm (range 0.50-18.20 mm). Table 1 shows the baseline clinical characteristics according to the presence of obstructive CAD. Compared to those without significant stenosis, patients with CAD were older (58.1±10.0 vs. 62.5±10.1 years, $p=0.010$),

Table 1. Baseline characteristics

	CAD (-) (n=68)	CAD (+) (n=85)	*p* value
Age (years)	58.1±10.0	62.5±10.1	0.010
Male sex (%)	26 (38.2)	44 (51.8)	0.095
Hypertension (%)	36 (52.9)	58 (68.2)	0.053
Diabetes mellitus (%)	10 (14.7)	30 (35.3)	0.004
Current smoker (%)	12 (17.6)	23 (27.1)	0.168
BMI (kg/m^2)	25.1±3.3	25.4±3.1	0.647
Total cholesterol (mg/dL)	189.3±36.8	208.6±43.8	0.004
Triglyceride (mg/dL)	143.5±84.8	169.7±95.5	0.079
HDL cholesterol (mg/dL)	49.9±11.0	46.1±11.0	0.032
LDL cholesterol (mg/dL)	108.6±33.9	125.4±36.8	0.004
baPWV (m/s)	14.9±2.4	15.4±2.7	0.264
Ankle brachial index	1.1±0.7	1.0±1.1	0.001
Epicardial adipose tissue (mm)	1.8±1.4	3.8±1.9	<0.001
Mediastinal adipose tissue (mm)	2.9±2.8	3.5±2.5	0.121
Serum adiponectine (μg/mL)	8.2±7.1	5.9±4.7	0.019

CAD: coronary artery disease, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, baPWV: brachio-ankle pulse wave velocity

Table 2. Correlation between the cardiac adipose tissue thickness and clinical variables

Variables	Epicardial adipose tissue		Mediastinal adipose tissue		Pericardial adipose tissue	
	r	*p*	r	*p*	r	*p*
Age	0.225	0.005*	0.099	0.224	0.210	0.009*
BMI	0.012	0.882	0.185	0.023†	0.183	0.024†
baPWV	0.045	0.502	-0.044	0.634	0.003	0.975
WBC count	0.089	0.275	-0.003	0.974	0.049	0.545
Total cholesterol	0.125	0.124	0.075	0.354	0.126	0.120
HDL cholesterol	-0.146	0.072	0.066	0.417	-0.024	0.769
Homocysteine	0.289	0.001*	0.025	0.769	0.221	0.015†
Glucose	0.167	0.042†	0.011	0.895	0.112	0.172
hsCRP	0.115	0.160	0.020	0.809	0.111	0.171
Fibrinogen	0.218	0.009*	0.057	0.497	0.203	0.015†
Adiponectin	-0.194	0.016†	0.107	0.188	-0.025	0.762

*p<0.01, †p<0.05. BMI: body mass index, baPWV: brachio-ankle pulse wave velocity, WBC: white blood cell, HDL: high density lipoprotein, hsCRP: high sensitivity C-reactive protein

showed higher prevalence of diabetes (14.7 vs. 35.3%, p=0.004), and showed a higher LDL cholesterol level (108.6±33.9 vs. 125.4±36.8 mg/dL, p=0.004) and lower HDL cholesterol level (49.9±11.0 vs. 46.1±11.0 mg/dL, p=0.032). EAT was thicker in patients with CAD (1.8±1.4 vs. 3.8±1.9 mm, p<0.001), but MAT was not different according to the presence of CAD (2.9±2.8 vs. 3.5±2.5 mm, p=0.121). The serum adiponectin level was significantly lower in patients with CAD (8.2±7.1 vs. 5.9±4.7 μg/mL, p=0.019).

EAT showed a significant positive correlation with age (r=0.225. p=0.005), homocystein (r=0.289, p=0.001), fasting glucose (r=0.167, p=0.042), and fibrinogen (r=0.218, p=0.009), and a significant negative correlation with serum adiponectin (r=-0.194, p=0.016) (Table 2). Particularly in male patients, the correlation between MAT and serum adiponectin level was more significant (Fig. 2). MAT showed a correlation with BMI (r=0.185, p=0.023), but not with other biochemical markers.

EAT increased significantly with increase in the severity of CAD (Fig. 3). EAT was 1.76±1.36 mm in patients without significant stenosis (n=68), 3.39±1.64 mm in single vessel disease patients (n=41), 4.12±2.03 mm in multi-vessel disease patients (n=44), showing significant differences among the groups (p<0.001 by ANOVA). However, MAT was not proportional to the severity of CAD. The serum adiponectin level showed the tendency of decreasing with increase in the severity of CAD but the tendency was not statistically significant (p=0.065 by ANOVA).

The results of multivariate logistic regression analysis for prediction of CAD were presented in Table 3. In addition to the well-known CAD risk factors, such as age, diabetes, LDL cholesterol and hsCRP, EAT thickness and serum

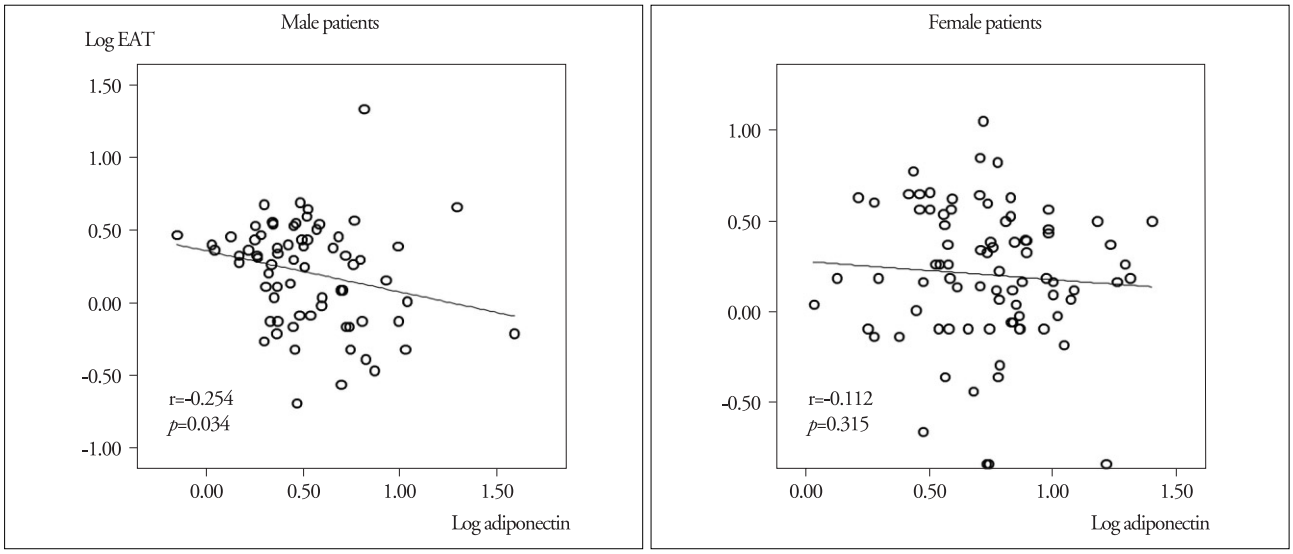

Fig. 2. Correlation between serum adiponectin level and epicaridal adipose tissue according to gender. EAT: epicardial adipose tissue.

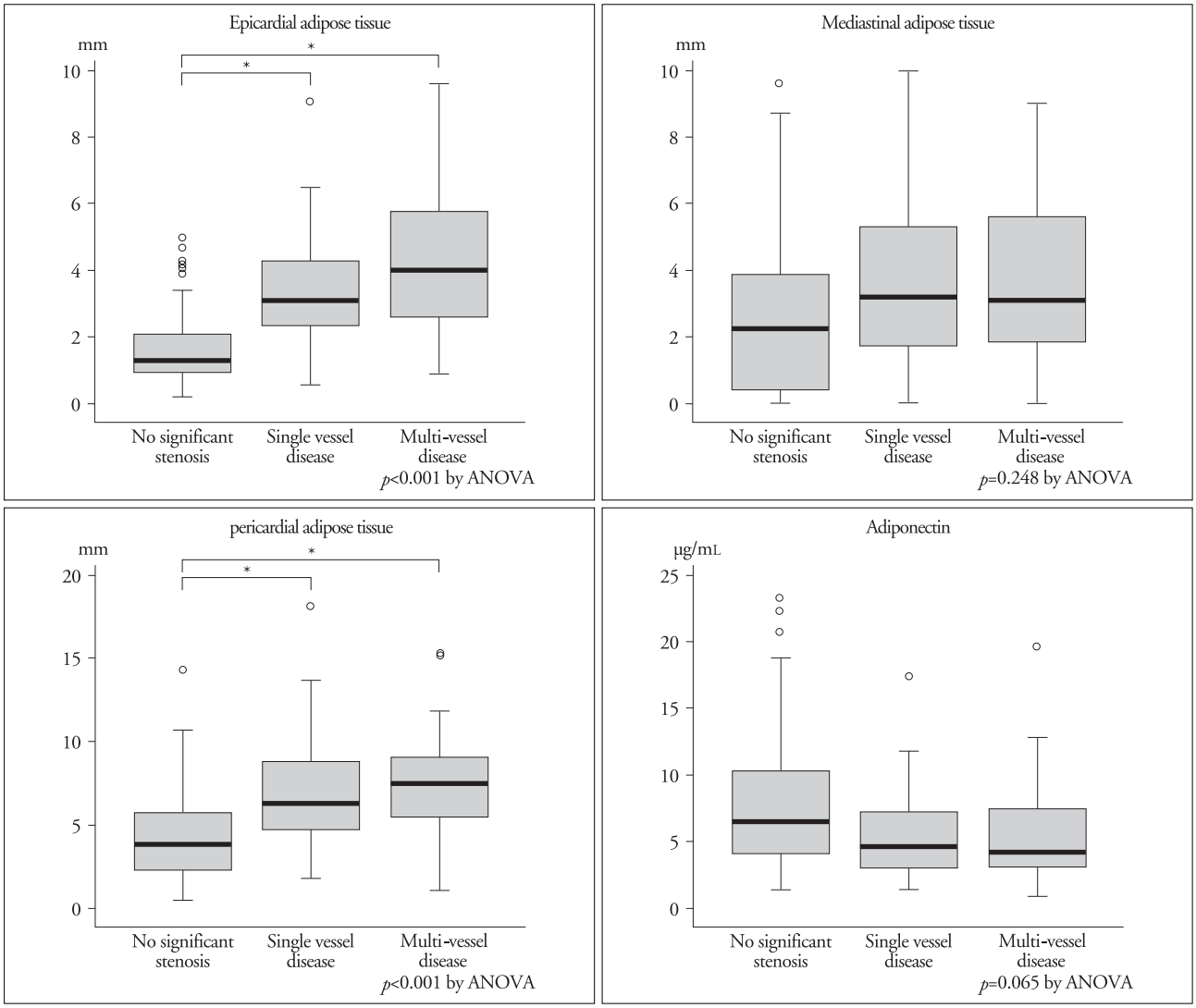

Fig. 3. Cardiac adipose tissue and serum adiponectin level according to the severity of coronary artery disease. *p<0.05.

Table 3. Multiple regression analysis for prediction of the presence of significant coronary artery disease

Variable	OR (99% CI)	*p* value
EAT thickness (≥2.6 mm)	11.53 (3.61-36.84)	<0.001
hsCRP (≥1.1 mg/L)	6.16 (2.19-17.33)	0.001
Diabetes	4.99 (1.48-16.82)	0.009
Age (≥65 years)	3.72 (1.33-10.39)	0.012
LDL cholesterol (≥118 mg/dL)	3.31 (1.27-8.58)	0.014
low serum adiponectin (<5.5 μg/mL)	2.88 (1.02-8.15)	0.046
PAT thickness (≥5.7 mm)	2.51 (0.65-9.70)	0.182
Hypertension	1.73 (0.60-4.98)	0.314
low HDL cholesterol (<46 mg/dL)	1.35 (0.51-3.52)	0.545
MAT thickness (≥3.2 mm)	1.45 (0.42-4.97)	0.555
Serum creatinine (≥0.99 mg/dL)	1.02 (0.39-2.65)	0.973

For continuous variables, the median value was used as a cut-off point. EAT: epicardial adipose tissue, hsCRP: high sensitivity C-reactive protein, LDL: low density lipoprotein, PAT: pericardial adipose tissue, HDL: high density lipoprotein, MAT: mediastinal adipose tissue

adiponectin were independent predictors of obstructive CAD. However, MAT thickness was not associated with CAD.

Discussion

The present study demonstrated that EAT was an independent predictor of CAD and negatively correlated with serum adiponectin level. In contrast with EAT, MAT was not associated with CAD and adiponectin.

It has been reported that EAT plays a role in the pathogenesis of CAD. The studies using epicardial fat obtained during coronary artery bypass surgery revealed that significantly higher expression of interleukin-1, interleukin-6, and tumor necrosis factor-a mRNA was shown in epicardial fat than in leg subcutaneous adipose tissue.[8] In addition, the expression of adiponectin, a protective cytokine, was significantly lower in the EAT of patients with CAD than in that of patients without CAD.[9][10] EAT thickness was also correlated with LDL cholesterol, HDL cholesterol, fasting glucose, hsCRP and blood pressure.[2][5][14][15] Accordingly, EAT is believed to be closely related with the incidence and development of CAD, and in our study as well, EAT was an independent predictor of obstructive CAD. Recently, it is reported that EAT is correlated not only with tissue expression but also with serum pro-inflammatory mediator interleukin-6, monocyte chemoattractant protein-1, visfatin, and plasminogen activator inhibitor-1.[16][17] In this study, the serum adiponectin level showed a negative correlation with EAT. These evidences suggested that EAT plays as a endocrine organ of the heart.

Several imaging modalities have been used for the assessment of epicardial fat. Since Iacobellis et al.[13] introduced the measurement of EAT thickness using echocardiography for the first time in 2003, epicardial fat measuring on the right ventricular free wall has been generalized. It is common recently to measure the volume of epicardial fat using multislice computed tomography (MSCT) or magnetic resonance imaging (MRI).[1][4][6] Fat volume also shows a high correlation with coronary calcium score or the risk of CAD. Because EAT is a three-dimensional structure, it may be more accurate to measure the fat volume, but as its high correlation with echocardiographic measurement has been proved, MSCT or MRI may not be necessary if it is only for the evaluation of cardiac adiposity.

When we examine cardiac fat, we can see that adipose tissue is divided by the parietal pericardium. The tissue between the epicardium and the parietal pericardium is called EAT, and the tissue in the outside is called MAT, and the whole of the tissues is called PAT.[18] Research using CT reported that PAT shows a correlation with abdominal fat and is associated with coronary risk factors.[12] In our study, MAT did not show a correlation with coronary risk factors, so the association of PAT, the sum of EAT and MAT, with such factors appeared weak. Furthermore, although PAT was related with the severity of CAD, it was not an independent factor of CAD. In fact, EAT is a different type of tissue from MAT. EAT originates from the splanchnopleuric mesoderm associated with gut. On the other hand, MAT originates from the primitive thoracic mesenchyme, which splits to form the parietal pericardium and the outer thoracic wall. EAT is supplied by branches of the coronary arteries, whereas MAT is supplied by the branches of the internal mammary arteries.[18] Accordingly, it is believed that, compared to MAT, EAT is more closely associated with the incidence of CAD and the development of atherosclerosis.

Our analysis was limited by the studied population because it included only those patients pre-selected to undergo coronary angiography. A prospective cohort study might be necessary to elucidate the clinical significance of EAT and MAT in the general population. In addition, as epicardial adipose tissue has a three-dimensional distribution, two-

dimensional echocardiography may not assess the total amount of epicardial adiposity completely. When we measure EAT on the free wall of the right ventricle, we may measure from the parasternal long axis view and from the short axis view and obtain the mean of the two values, but because the two measurements are highly correlated with each other, some studies including ours use only the value measured from the parasternal long axis view.[5)19)]

In conclusion, compared to MAT, EAT showed higher association with the severity and risk factors of CAD, and a good negative correlation with the serum adiponectin level. Echocardiographic epicardial fat measurement might be used as an easy and reliable cardiovascular risk indicator.

REFERENCES

1. Gorter PM, de Vos AM, van der Graaf Y, Stella PR, Doevendans PA, Meijs MF, Prokop M, Visseren FL. *Relation of epicardial and pericoronary fat to coronary atherosclerosis and coronary artery calcium in patients undergoing coronary angiography. Am J Cardiol 2008;102:380-5.*
2. Ahn SG, Lim HS, Joe DY, Kang SJ, Choi BJ, Choi SY, Yoon MH, Hwang GS, Tahk SJ, Shin JH. *Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart 2008;94:e7.*
3. Eroglu S, Sade LE, Yildirir A, Bal U, Ozbicer S, Ozgul AS, Bozbas H, Aydinalp A, Muderrisoglu H. *Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. Nutr Metab Cardiovasc Dis 2009;19:211-7.*
4. Sarin S, Wenger C, Marwaha A, Qureshi A, Go BD, Woomert CA, Clark K, Nassef LA, Shirani J. *Clinical significance of epicardial fat measured using cardiac multislice computed tomography. Am J Cardiol 2008;102:767-71.*
5. Jeong JW, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK, Rhee SJ, Lee EM, Lee J, Yoo NJ, Kim NH, Park JC. *Echocardiographic epicardial fat thickness and coronary artery disease. Circ J 2007;71:536-9.*
6. Djaberi R, Schuijf JD, van Werkhoven JM, Nucifora G, Jukema JW, Bax JJ. *Relation of epicardial adipose tissue to coronary atherosclerosis. Am J Cardiol 2008;102:1602-7.*
7. Hwang JW, Choi UJ, Ahn SG, Lim HS, Kang SJ, Choi BJ, Choi SY, Yoon MH, Hwang GS, Tahk SJ, Shin JH, Kang DK. *Echocardiographic plains reflecting total amount of epicardial adipose tissue as risk factor of coronary artery disease. J Cardiovasc Ultrasound 2008;16:17-22.*
8. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y. *Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003;108:2460-6.*
9. Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G, Gallo P, di Gioia CR. *Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. Cytokine 2005;29:251-5.*
10. Iacobellis G, di Gioia CR, Cotesta D, Petramala L, Travaglini C, De Santis V, Vitale D, Tritapepe L, Letizia C. *Epicardial adipose tissue adiponectin expression is related to intracoronary adiponectin levels. Horm Metab Res 2009;41:227-31.*
11. Sironi AM, Gastaldelli A, Mari A, Ciociaro D, Positano V, Buzzigoli E, Ghione S, Turchi S, Lombardi M, Ferrannini E. *Visceral fat in hypertension: influence on insulin resistance and beta-cell function. Hypertension 2004;44:127-33.*
12. Taguchi R, Takasu J, Itani Y, Yamamoto R, Yokoyama K, Watanabe S, Masuda Y. *Pericardial fat accumulation in men as a risk factor for coronary artery disease. Atherosclerosis 2001;157:203-9.*
13. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, Leonetti F. *Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304-10.*
14. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, Di Mario U, Leonetti F. *Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163-8.*
15. Park EM, Choi JH, Shin IS, Yun KH, Yoo NJ, Oh SK, Kim NH, Jeong JW. *Echocaridographic epicardial fat thickness on short term prognosis in patients with acute coronary sydrome. J Cardiovasc Ultrasound 2008;16:42-7.*
16. Malavazos AE, Ermetici F, Cereda E, Coman C, Locati M, Morricone L, Corsi MM, Ambrosi B. *Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitor-1 levels in visceral obesity. Nutr Metab Cardiovasc Dis 2008;18:523-30.*
17. Malavazos AE, Ermetici F, Coman C, Corsi MM, Morricone L, Ambrosi B. *Influence of epicardial adipose tissue and adipocytokine levels on cardiac abnormalities in visceral obesity. Int J Cardiol 2007;121:132-4.*
18. Sacks HS, Fain JN. *Human epicardial adipose tissue: a review. Am Heart J 2007;153:907-17.*
19. Iacobellis G, Willens HJ, Barbaro G, Sharma AM. *Threshold values of high-risk echocardiographic epicardial fat thickness. Obesity (Silver Spring) 2008;16:887-92.*