

# Epicardial adipose tissue: a review of physiology, pathophysiology, and clinical applications

*Epikardiyal yağ dokusu: Fizyoloji, patofizyoloji ve klinik uygulamalar hakkında bir derleme*

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## ABSTRACT

Visceral fat tissue is an important predictor of cardio-metabolic diseases, carrying more risk than general fat accumulation. Epicardial fat, a particular form of visceral fat deposited around the heart, is considered an important cardiovascular risk predictor, in view of producing and releasing several adipo-cytokines. There is growing evidence about the physiological and metabolic importance of epicardial fat. Epicardial fat thickness and volume have both strong correlation between obesity, impaired fasting glucose, insulin resistance, metabolic syndrome, hypertension, diabetes mellitus, and atherosclerosis. Epicardial fat can be assessed by transthoracic echocardiography, cardiac magnetic resonance imaging, and computed tomography. In this article, we reviewed the anatomy, physiology, function, and the methods of assessment of epicardial fat tissue. We also have tried to discuss its relationship to metabolic syndrome and coronary atherosclerosis in the lights of recent findings. (*Anadolu Kardiyol Derg 2013; 13: 261-5*)

**Key words:** Epicardial fat, visceral fat, cardiac imaging, cardiometabolic risk

## ÖZET

Kardiyo-metabolik hastalıkların önemli bir belirteci olan visseral yağ dokusu genel yağ birikiminden daha fazla risk oluşturmaktadır. Visseral yağın kalp etrafında depolanan özel bir şekli olan epikardiyal yağ, çok sayıda adipo-sitokin üretme ve salma yeteneği sayesinde önemli bir kardiyovasküler risk belirteci olarak düşünülmektedir. Epikardiyal yağın fizyolojik ve metabolik önemine dair artan deliller mevcuttur. Epikardiyal yağ kalınlığı ve hacminin her ikisinin de obezite, bozulmuş glikoz intoleransı, metabolik sendrom, hipertansiyon, diyabet ve ateroskleroz ile güçlü korelasyonları mevcuttur. Epikardiyal yağ transtorasik ekokardiyografi, kardiyak manyetik rezonans ve bilgisayarlı tomografi ile değerlendirilebilir. Bu yazıda epikardiyal yağ dokusunun anatomisini, fizyolojisini, fonksiyonunu ve değerlendirme metotlarını gözden geçirdik. Aynı zamanda metabolik sendrom ve koroner ateroskleroz ile ilişkisini son bilgiler ışığında tartışmaya çalıştık. (*Anadolu Kardiyol Derg 2013; 13: 261-5*)

**Anahtar kelimeler:** Epikardiyal yağ, visseral yağ, kardiyak görüntüleme, kardiyometabolik risk

## Introduction

### Anatomy and physiology of EAT

Cardiac fat tissue resides in three locations: epicardium, pericardium, and intracellular fat. Epicardial adipose tissue (EAT) is present on the surface of the heart between the myocardium and visceral pericardium and covers more than three quarters of the surface of the heart (1). EAT is concentrated in the atrioventricular and interventricular grooves, along the

major branches of the coronary arteries, around the atria, over the free wall of the right ventricle (RV) and over the apex of the left ventricle (LV) (2) in the normal adult population. EAT is supplied by side-branches of the coronary arteries similar to the microcirculation of the myocardium. Therefore, EAT can locally modulate both myocardium and coronary arteries (3, 4). There are sufficient data suggesting that there are differences between EAT and other visceral adipose tissue of the body. Microscopically EAT is composed of adipocytes which are smaller than those in cutaneous and other visceral fat depots, and inflammatory, stro-

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movascular and immune cells (5), but interestingly the number of adipocytes per gram of tissue is greatest in EAT. As fatty acid synthesis is greater in EAT, the rate of fatty acid breakdown is significantly higher than other fat depots of the body.

Both adipocytes and tissue macrophages have secretory properties in EAT and they are capable of producing adipokines and cytokines as in omental and mesenteric visceral adipose tissue. These adipokines and cytokines influence the myocardium and coronary arteries via two mechanisms (i.e. paracrine and vasocrine). Paracrine release of cytokines from EAT can traverse the coronary wall by diffusion from outside-to-inside and interact with cells in each layers of the vessel wall (6). On the other hand, in vasocrine signaling adipokines and free fatty acids might be released from EAT directly into *vasa vasorum* and be transported downstream into the coronary wall (7). Both of these mechanisms may be associated with atherogenesis.

Another function of EAT is the maintenance of fatty acid homeostasis. It may buffer the heart against excessively high circulating levels of fatty acids by its ability to rapidly take up and incorporate fatty acids. Furthermore, this fat depot serves as a local energy source for cardiac muscle in times of high demand (8). EAT might function similar to brown fat in order to defend the myocardium and coronary arteries against hypothermia (9). Finally, it is also proposed to buffer the coronary artery against the torsion induced by the arterial pulse wave and cardiac contraction (10).

EAT has cardioprotective properties through local secretion of anti-inflammatory and anti-atherogenic adipokines such as adiponectin and adrenomedullin. Recently, Iacobellis et al. (11) have demonstrated that chronic coronary artery disease (CAD) down regulated these adipokines. The Framingham offspring cohort revealed that EAT is greater in men than in women (12). However, some of echocardiographic studies disagree with the findings of Framingham cohort (13). There is also controversy whether age influences the amount of EAT. Smith et al. (14) demonstrated that there was no relationship between age and EAT in their autopsy study. Echocardiographic examination measuring the thickness of the EAT has supported their findings in a small subgroup (15). The Framingham offspring cohort demonstrated significant correlation between age and EAT (12).

### Imaging techniques

Epicardial adipose tissue can easily be measured by transthoracic 2D-echocardiography. Echocardiograms can be obtained during cardiac cycles as the subject is the left lateral decubitus position. The investigators usually choose to measure epicardial fat on the free wall of the RV since it is accessible from both parasternal long and short axis views and includes the highest absolute epicardial fat layer thickness. Echo free space can be measured with optimal cursor orientation in each view. Iacobellis et al. (16) reported maximum EAT values at any site over the free wall of the RV is 1.8- 16.5 mm in healthy subjects. Echocardiographic epicardial fat thickness (EFT) reflects visceral adiposity rather than general obesity. Although Abbara et al. (17) demonstrated

that echocardiography cannot give adequate window of all cardiac segments especially in obese subjects and is highly dependent on acoustic windows, the study demonstrated a good reproducibility with a coefficient of variation between two echocardiographers of only 3%. Echocardiography calculation of EFT on the free wall of the RV is in good reliability with EAT measurements with MRI ( $r=0.91$ ,  $p=0.001$ ) (16). EAT measurement with echocardiography in both clinical and research scenarios have several advantages, including its low cost, easy accessibility, rapid applicability and good reproducibility (18). Quantification of EAT with multislice computed tomography (CT) scanning can also easily be obtained. Measurement of the EAT volume on CT is usually performed by tracing the regions of interest on short axis views (19). EAT volume is obtained by adding up the traced areas which are measured from the apex of the heart to the center of the left atrium taking into account of the slice thickness. Automated computer assisted methods for quantification can also be used. In general, multidetector CT measurements of volumetric EAT are considered more reproducible than multidetector CT measurements of EAT. However, EAT is easier to perform and less time-consuming compared to the work for measurements of volumetric EAT; and therefore more suitable for research purposes. CT imaging of EAT can be done with high spatial resolution and atherosclerotic burden can also be measured in the same session. Disadvantages of CT are radiation exposition and high costs, which make it less practical for routine use.

MRI allows an accurate but more expensive and cumbersome measurement of EAT. Maximum EFT at the right ventricular free wall can be measured in different views: in a transversal 4-chamber view and in consecutive short-axis views covering the whole ventricle. In addition, mean EFT can be calculated by averaging results from the long-axis and short-axis measurements. MRI also allows quantitative assessment of the amount of EAT at the end diastole in the short-axis views covering the entire left and right ventricle by using the modified Simpson's rule with integration over the image slices (20).

## Cardiometabolic risk and EAT

### Metabolic syndrome

Metabolic syndrome (MS) is a cluster of several cardiovascular risk factors, which are found to be associated with two fold increase in risk of cardiovascular disease (CVD), mortality and stroke, and a 1.5-fold increase in risk of all-cause mortality (21). Insulin resistance and central obesity are the key components of MS, leading to glucose intolerance and dyslipidemia. The identification of predictors for premature atherosclerosis is crucial because subclinical atherosclerosis develops years before the clinical manifestations of CVD. EAT in MS influences on oxidative stress, endothelial dysfunction and vascular remodeling by adipokines. Recent findings suggest that EAT as a kind of visceral adipose tissue is associated with various components of metabolic syndrome as well as MS itself (22). Gorter et al. (19) docu-

mented in a CT study that patients with high body mass index ( $>27$  kg/m<sup>2</sup>) have more EAT volume than those with a BMI  $<27$  kg/m<sup>2</sup>. Both MRI and echocardiographic studies support that EAT strongly and independently reflect intra-abdominal visceral fat (18-20).

Interestingly epicardial fat decreases after a very low calorie diet (6-month long weight loss program mean 20 kg by adhering to 900 kcal/day), bariatric surgery induced weight loss (average weight loss of 40 kg), or moderate aerobic exercise (23). The decrease in epicardial fat during weight loss is quicker and larger than the decrease in common indices of body fatness. This might be used for therapeutic target during weight-loss interventions including exercise or pharmaceutical treatments (24).

Glucose metabolism contributes to the development of atherosclerosis and relationship of EAT with it has been recently addressed. There is a strong correlation exists between fasting plasma glucose and EAT measured with echocardiography and CT (22). Recent studies demonstrated that both glucose transporter -4 and retinol binding protein levels affect local unfavorable glucose profile in EAT (25). Additionally, the relationship between epicardial fat and plasma insulin and mRNA expression of resistin which is a molecule linked with insulin resistance has been documented (16). Therefore, EAT seems to contribute to the development of insulin resistance. Iacobellis et al. (26) showed that cut-off value of EFT was 9.5 mm when insulin resistance was considered separately. In this study, highest values of EFT were found in patients with extremely high intra-abdominal fat and insulin resistance. In a recent study, an association has been found with the EAT volume and presence and extent of CAD in diabetic or non-diabetic patients (27).

Excess visceral fat is associated with increased blood pressure presumably through the renin-angiotensin system. The association of epicardial fat with hypertension has been demonstrated in some recent studies (28). We have demonstrated that EAT quantity increases in the non-hypertensive healthy patients with exaggerated blood pressure response to exercise stress testing. All these individuals were in risk for future hypertension (29). Echocardiographic EFT was found to be increased in untreated hypertensive patients with non-dipper blood pressure pattern (30). Increased EFT is also associated with changes in LV and RV mass and diastolic function (31). LV hypertrophy is related to a proportionate increase in EAT independent from obesity and age. Mechanical and biomolecular mechanisms could explain these associations (32).

### Atherosclerosis

An increase of the quantity of EAT is associated with incident CAD and with major adverse cardiac events (33). Associations are independent from body mass index and other traditional risk factors. EAT is actually one of the factors contributing to CAD compared with other visceral adipose tissue (34). A recent meta-analysis of 2872 patients, Xu et al. (35) concluded that EFT and EAT volume are significantly increased in the CAD group compared to the non-CAD group. Patients in the higher

EAT tertile ( $\geq 100$  mL) were more likely to have CAD compared with those in the lower EAT tertile ( $<100$  mL) (risk ratio 0.69, 95% CI: 0.52, 0.92,  $p=0.01$ ). The authors pointed that patients with coronary plaque had increased EAT volume compared with patients without coronary plaque. Another study demonstrated that EAT had significant correlation between both non-stenotic lesions and non-calcified plaque. Higher EAT volume was found in patients with noncalcified plaques than in patients with calcified plaques (36). This may be relevant for the development of acute coronary syndromes as non-calcified parts of a plaque contribute to plaque vulnerability (37). Furthermore, EAT volume is a strong and independent determinant of the presence of total coronary occlusions (38). EAT might affect the coronary microvascular function. Sade et al. (39) found that EFT was an independent predictor of diminished coronary flow reserve in women with angiographically normal coronary arteries.

EAT might also be used for screening the patients with intermediate risk of CAD. Bachar et al. (40) noted a strong positive correlation between EFT and coronary atherosclerosis quantified by the CT calcium score in 190 asymptomatic subjects with  $>1$  cardiovascular risk factors. Therefore, EFT with low dose or without injection of contrast medium may be used as a coronary risk screening examination (40). A recent study has demonstrated an independent relationship between EFT and arterial stiffness, suggesting that echocardiographic EFT measurement could be an easy-to-measure tool for early detection of subclinical target organ damage (41).

EAT mediates the inflammatory process within the atherosclerotic plaque (42). The paracrine or vasocrine secretion of epicardial inflammatory adipokines, such as tumor necrosis factor alpha, plasminogen activator inhibitor-1, interleukin-6, interleukin -1b, monocyte chemo-attractant protein-1, and resistin contribute to the metabolic and inflammatory milieu that promotes atherogenesis (43). Whether the atherogenic effect of EAT occurs through vasocrine or paracrine pathway is unknown. Two longitudinal studies have reported results that supported the hypothesis of 'outside to inside signaling' as a cause of atherosclerosis. Oxidative stress also plays a role in the development of atherosclerosis. EAT exhibits higher reactive oxygen species and includes lower catalase activities compared with subcutaneous fat tissue (44). However, the relation of epicardial fat and oxidative stress is more complex and involves other cytokines and vasoactive factors such as leptin and angiotensin II (36). Besides, all these other inflammatory mediators and soluble intercellular adhesion molecules participate in several stages of the atherosclerotic process including chemotaxis, smooth-muscle cell proliferation, foam-cell development and migration, and plaque destabilization (45).

EAT may contribute to atherosclerosis not only through the secretion of bioactive molecules but also through specific mechanical effects. For instance, atherosclerotic plaque in coronary arteries leads to an asymmetric expansion of the vessel wall named positive remodeling (46). Because of its intrinsic compressibility, epicardial fat has been suggested to play a per-

missive role in vessel expansion. Coronary lesions, which are surrounded by the epicardial fat undergo expansion more easily than those lesions surrounded by the myocardium since the myocardium is relatively incompressible. This hypothesis is demonstrated in postmortem studies as well as in studies using CT by absence of atherosclerosis in coronary artery segments with myocardial bridges (47).

## Conclusion

EAT is a unique fat depot in the body in terms of the size of its adipocytes, biochemical composition, and metabolic activity. EAT has significantly higher rates of lipolysis and lipogenesis compared to other visceral fat depots. Given its anatomical proximity to the heart, it interacts locally with the coronary arteries and the myocardium through paracrine or vasocrine pathways. EAT has strong correlation with visceral obesity, MS, diabetes mellitus, and CVD. It can be easily detected and measured by imaging modalities such as echo, CT and MRI. Understanding the role of epicardial fat in atherosclerosis is still unclear. Future clinical and experimental studies should aim to elucidate the function of epicardial fat in different physiological conditions.

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