Increased epicardial fat thickness is associated with low grade systemic inflammation in metabolic syndrome

Metabolik sendromda epikardın yağ kalınlığında artış düşük dereceli sistemik yangı ile birliktedir

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ABSTRACT

Objectives: Epicardial fat tissue is a type of visceral adipose tissue that functions as a metabolically active endocrine organ. Most components of metabolic syndrome (MetS), especially visceral obesity, are associated with a low-grade systemic inflammatory state. In this study, we aimed to assess the relationship between echocardiographic epicardial fat thickness (EFT), MetS, the components of MetS, and high sensitivity C-reactive protein (hs-CRP) levels in patients with MetS.

Study design: Forty-six patients (25 males, mean age 47.3±6.5 years) with the diagnosis of MetS (according to the Adult Treatment Panel III update criteria) but without clinical coronary artery disease, and 44 age and gender matched healthy volunteers (18 males, mean age 46.0±6.1 years) were included in the study. EFT, which was measured by transthoracic echocardiography, as well as clinical and biochemical parameters were compared between the two groups.

Results: Waist circumference, total and LDL-cholesterol, fasting glucose, triglycerides, systolic and diastolic blood pressure levels, hs-CRP, and uric acid levels were significantly higher in patients with MetS. EFT was also significantly increased in patients with MetS (8.7±0.2 mm *vs.* 4.8±0.1 mm, p<0.001). Multiple regression analysis determined that MetS itself (β=0.929, p<0.001) and hs-CRP (r=-0.181, p=0.007) are independent predictors of increased EFT.

Conclusion: This study demonstrates that EFT is higher in patients with MetS, and that MetS and hsCRP are independent predictors of this increased EFT. Increased EFT, which is associated with low-grade systemic inflammation, may play a role in the pathogenesis of atherosclerosis in MetS patients.

ÖZET

Amaç: Epikardın yağ dokusu, metabolik aktif endokrin organ gibi görev yapan bir viseral yağ dokusu tipidir. Metabolik sendrom (MetS) komponentlerinin çoğu, özellikle de viseral obezite, düşük dereceli sistemik yangı ile ilişkilidir. Bu çalışmada, MetS'li hastalarda ekokardiyografi ile ölçülen epikardın yağ dokusu kalınlığı (EYK) ile MetS, MetS komponentleri ve yüksek duyarlıklı C-reaktif protein (hs-CRP) arasındaki ilişki değerlendirildi.

Çalışma planı: Çalışmaya güncellenmiş ATP III ölçütlerine göre MetS tanısı konan ve koroner arter hastalığının klinik bulguları olmayan ardışık 46 hasta (25 erkek, ort. yaş 47.3±6.6 yıl) ve yaş ve cinsiyet olarak eşleştirilmiş 44 sağlıklı gönüllü (18 erkek, ortalama yaş 46.0±6.1 yıl) alındı. Transtorasik ekokardiyografi ile EYK ölçüldü. Gruplar arasında EYK, klinik ve biyokimyasal değişkenler karşılaştırıldı.

Bulgular: MetS'li hastalarda bel çevresi, toplam kolesterol, LDL-kolesterol, açlık kan şekeri, trigliserit, sistolik ve diyastolik kan basınçları, hs-CRP ve ürik asit düzeyleri anlamlı olarak yüksek bulundu. MetS'li hastalarda kontrol grubuna kıyasla EYK'da anlamlı yükseklik saptandı (8.7±0.2 mm ve 4.8±0.1 mm, p<0.001). Çoklu değişken regresyon analizinde, MetS (β=0.929, p<0.001) ve hs-CRP düzeyi (r=-0.181, p=0.007) artmış EYK'nın bağımsız belirteçleri olarak bulundu.

Sonuç: Bu çalışmada MetS'li hastalarda EYK'nın daha yüksek olduğu ve MetS'in varlığının ve hs-CRP'nin artmış EYK'nın bağımsız prediktörleri olduğu görülmüştür. MetS'li hastalarda düşük dereceli sistemik yangı ile ilişkili olan EYK, ateroskleroz patogenezinde rol oynuyor olabilir.

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Metabolic syndrome (MetS) is a cluster of several cardiovascular risk factors and is associated with an increased risk for cardiovascular disease.[1] Visceral obesity and insulin resistance have been reported to play a key role in the development of MetS.[2] Based on previous reports, we believe that visceral adipose tissue may also be an important risk factor for MetS.

Epicardial fat tissue, which is defined as the adipose tissue between the surface of the myocardium and the epicardium, can easily be visualized and measured using standard two-dimensional echocardiography.[3] Epicardial fat thickness (EFT) is used a measure of visceral adiposity rather than of general obesity.[4] EFT correlates with MetS, insulin resistance, coronary artery disease (CAD), and subclinical atherosclerosis, and may also serve as a simple tool for the prediction of cardiometabolic risk.[3,5,6] Epicardial fat tissue functions as lipid storage that secretes hormones, inflammatory cytokines, and chemokines, and is hypothesized to play a causative role in the development of MetS.[7]

MetS is considered to be a pro-inflammatory condition, and most of the components of MetS, especially visceral obesity, are associated with low-grade systemic inflammation.[2] C-reactive protein (CRP) is one of the most important markers of inflammation, and elevated high sensitive CRP (hs-CRP) is known to be associated with cardiovascular risk factors[8,9] and is recognized as a strong predictor of future cardiovascular events.[10]

In this study, we aimed to assess the relationship between the components of MetS, echocardiographic EFT, and hs-CRP levels.

PATIENTS AND METHODS

Study group

Forty-six patients (25 males, mean age 47.3±6.5 years) with the diagnosis of MetS (according to the Adult Treatment Panel III update criteria)[11] but without clinical CAD were included in the study. Forty-four age and gender matched healthy subjects (18 males, mean age 46.0±6.1 years) were recruited for the control group. Patients were defined as having hypertension (HT) if their systolic pressure was >140 mmHg, their diastolic pressure was >90 mmHg, or they were using an antihypertensive medication.[12] Patients were designated as having diabetes mellitus (DM) if they had a history of taking an oral antidiabetic or insulin medication, or if their fasting blood glucose was ≥126 mg/dl at the start of the study.[13] Patients were excluded from the study if they had coronary heart disease, severe valvular disease, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, malignancy, congenital heart disease, chronic heart failure, a cardiac rhythm other than sinus, uncontrolled HT prior to the study, a systemic disease such as collagenosis, chronic autoimmune, hemolytic, hepatic, or chronic renal disease, or inadequate transthoracic echocardiographic images. Patients were defined as having CAD if they had the presence of one of the following: a past history of myocardial infarction/revascularization, typical angina, ST-segment or T-wave changes specific to myocardial ischemia, Q waves on an electrocardiogram, wall motion abnormality on echocardiography, a non-invasive stress test demonstrating ischemia or any perfusion abnormality, or coronary artery stenosis on angiography.

Abbreviations:

BMI	*Body mass index*
CAD	*Coronary artery disease*
CRP	*C-reactive protein*
DM	*Diabetes mellitus*
EFT	*Epicardial fat thickness*
hs-CRP	*High sensitive C-reactive protein*
HT	*Hypertension*
MetS	*Metabolic syndrome*

Systolic and diastolic blood pressures were measured after at least five minutes of resting. Blood samples were obtained after overnight fasting. Plasma glucose, total cholesterol, HDL- and LDL-cholesterol, triglycerides, hs-CRP, and uric acid levels were measured using standard methods. Height and weight were measured according to a standardized protocol, and body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Waist circumference was measured to the nearest 0.5 cm on bare skin during mid-respiration at the natural indentation between the tenth rib and the iliac crest. Demographic data including classical risk factors for atherosclerosis (HT, dyslipidemia, and smoking) were noted. The study protocol was approved by the local ethics committee and informed consent was obtained from each subject.

Transthoracic echocardiography

All of the patients underwent transthoracic echocardiography using a Vivid 7 (GE Pro/Expert) machine with a 3.5 MHz transducer. Two dimensional, M-

Table 1. Comparison of clinical, laboratory and transthoracic 2D-echocardiography data from the two groups

	Metabolic syndrome (n=46)			Controls (n=44)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			47.3±6.47			46.0±6.1	0.015
Gender (men)	25	54.3		18	40.9		0.214
Smoker	20	43.5		13	29.5		0.195
Hypertension	29	63.0		0	0		**<0.001**
Diabetes mellitus	3	3.3		0	0		0.242
Body mass index (kg/m^2)			31.9±4.1			24.0±3.4	**<0.001**
Systolic blood pressure (mmHg)			131.4±15.3			110.0±10.6	**<0.001**
Diastolic blood pressure (mmHg)			74.6±10.8			68.4±7.5	0.002
Waist circumference (cm)			107.1±8.7			84.9±8.7	**<0.001**
Fasting glucose (mg/dl)			106.1±18.3			90.0±7.8	**<0.001**
Total cholesterol (mg/dl)			213.1±33.2			186.2±33.1	**<0.001**
LDL-cholesterol(mg/dl)			127.7±35.7			114.2±26.6	0.046
HDL-cholesterol (mg/dl)			37.7±8.3			53.1±10.6	**<0.001**
Triglycerides (mg/dl)			243.6±64.3			95.8±32.7	**<0.001**
hs-C-reactive protein (mg/L)			3.6±3.0			2.1±2.1	0.008
Uric acid (mg/dl)			5.4±1.2			4.5±1.3	0.002
Left ventricular mass index (g/m^2)			107.5±17.2			80.7±10.6	0.001
Ejection fraction (%)			65.1±2.1			61.8±1.6	0.214
Epicardial fat thickness (mm)			8.7±0.2			4.8±0.1	0.001

mode, and transthoracic Doppler echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography.[14] Images were digitally stored and analyzed by an experienced echocardiographer blinded to the study protocol. Left ventricular mass was calculated from M-Mode records taken on parasternal long-axis images according to Devereux's formula.[15]

Epicardial fat thickness was identified as the echo-free space between the epicardial layers on two-dimensional images. Its thickness was measured on the free wall of the right ventricle from both the parasternal long-axis and short-axis views at the end-diastole in three cardiac cycles. The maximum value at every site was measured, and the average value was recorded. To assess the reproducibility of the echocardiographic measurements, EFT thickness was measured by two independent echocardiographers in 24 randomly selected patients, and the inter-observer correlation coefficients were calculated. Echocardiographic measurements were repeated 1 day later in the same group of patients to calculate the intra-observer correlation coefficients. The variability between measurements was taken as the mean of differences between measurements.

Statistical analysis

Statistical analyses were performed using SPSS software (Version 15.0, SPSS Chicago, USA). Continuous data were presented as median ± IQR (interquartile range) or mean ± standard deviation (SD). Comparisons of multiple mean values were performed with either a Student's t-test or a Mann-Whitney U-test, and a Kolmogorov-Smirnov test was utilized to determine the distribution pattern. Categorical variables were reported as percentages and compared with either a chi-square test or a Fisher's exact test, while correlations were evaluated by the Pearson correlation test. Independent parameters associated with EFT were determined by a standard multiple linear regression analysis. A p value <0.05 was considered to be statistically significant.

RESULTS

Demographic and clinical characteristics as well as the laboratory results of the study and control groups are summarized in Table 1. The mean age and gender were similar between the groups. As expected, the prevalence of HT, serum fasting glucose, triglycerides, hs-CRP, uric acid levels, waist circumference, and BMI were significantly higher, while the serum HDL-cholesterol levels were significantly lower in MetS patients when compared with control subjects. There were no significant differences in end-diastolic volume, end-systolic volume, or ejection fraction between the groups, but the left ventricular mass indices were significantly higher in patients with MetS ($p<0.001$). EFT was also significantly higher in patients with MetS (8.7±0.2 mm for MetS patients *vs.* 4.8±0.1 mm for controls, $p<0.001$).

Epicardial fat thickness was positively correlated with age ($r=0.236$, $p=0.025$), BMI ($r=0.643$, $p<0.001$), waist circumference ($r=0.665$, $p<0.001$), LDL-cholesterol ($r=0.247$, $p=0.020$), triglycerides ($r=0.492$, $p<0.001$), fasting glucose ($r=0.385$, $p<0.001$), uric acid ($r=0.308$, $p=0.003$), white blood cell count ($r=0.225$, $p=0.033$), systolic blood pressure ($r=0.537$, $p<0.001$), diastolic blood pressure ($r=0.289$, $p=0.006$) and hs-CRP levels ($r=0.230$, $p=0.029$), and negatively correlated with HDL-cholesterol.

When EFT was taken as a dependent variable and the presence of MetS, age, LDL-cholesterol, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure, white blood cell count, uric acid, fasting glucose, BMI, waist circumference, and hs-CRP were taken as independent variables, we found that hs-CRP (ß=-0.181, $p=0.007$) and MetS (ß=0.929, $p<0.001$) were independent predictors of EFT (Table 2).

Table 2. Multiple linear regression analysis*

Independent variables	Correlation coefficients	*p*
Age	-0.034	0.601
HDL-cholesterol	0.106	0.239
Triglycerides	0.001	0.986
Fasting glucose	-0.039	0.580
Uric acid	0.081	0.234
hs-C-reactive protein	-0.181	0.007
White blood cell	-0.043	0.488
Systolic blood pressure	-0.052	0.576
Diastolic blood pressure	0.040	0.603
Body mass index	0.112	0.213
Waist circumference	0.153	0.398
Metabolic syndrome	0.929	**<0.001**

* $r^2=0.772$; $p<0.001$.

DISCUSSION

This study demonstrates that EFT is increased in patients with MetS, and that hs-CRP and MetS are independent predictors of this increment. Since inflammation is known to play an important role in the pathogenesis of atherosclerosis,[16] we speculate that increased EFT might reflect the presence of low-grade inflammation, which may play a role in the pathogenesis of atherosclerosis in this patient population.

Metabolic syndrome, the clustering of obesity, dyslipidemia, DM or impaired glucose tolerance, and HT are closely associated with cardiovascular mortality.[17] Visceral obesity appears to play a key role in the development of all MetS components.[2] Epicardial fat is the true visceral fat deposit of the heart.[18,19] It strongly reflects the intraabdominal accumulation of visceral fat as measured via MRI and is a better indicator than waist circumference.[20] EFT (as measured by echocardiography) is associated with increased left ventricular mass, endothelial dysfunction, the presence and severity of CAD, and subclinical atherosclerosis.[21] It is also independently associated with blood pressure, LDL-cholesterol, fasting glucose, and both traditional and novel cardiovascular risk factors.[3] In the literature, EFT has been reported to be significantly higher in patients with MetS than in subjects without MetS, as we found in our study,[3,5] but the pathogenetic importance of this finding has never been fully elucidated.

Epicardial fat is an endocrine and paracrine source of cytokines, and its thickness is correlated with several circulating proatherogenic and proinflammatory adipokines such as visfatin, plasminogen activator inhibitor-I, monocyte chemoattractant protein-I, and CRP.[3,18,22] However, it is inversely related to adiponectin, an anti-inflammatory and antiatherogenic adipokine.[5] Although epicardial fat is a source of bioactive molecules, it is not clear whether this activity is directly related to the quantity of fat accumulation.[3] It is hypothesized that the local secretion of pro-

inflammatory cytokines from the epicardial fat may be predominant and would therefore down-regulate the production of protective and anti-inflammatory cytokines. Several components of MetS, including visceral obesity, are associated with a low-grade inflammatory state.[2] hs-CRP is a well-known systemic inflammatory marker, and its elevation within the upper normal range indicates a systemic low-grade inflammation, which has been known to be associated with cardiovascular risk factors,[8,9] and is recognized as a strong predictor of future cardiovascular events.[10] Many epidemiological studies have shown associations between increased hs-CRP levels and components of MetS.[23-25] Danesh et al.[26] reported that CRP is significantly correlated with obesity, but is not correlated with any of the other features of MetS. However, MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) investigators found that the concentration of CRP increases as BMI or blood pressure increases and HDL cholesterol decreases.[27] However, a major controversy exists as to whether increased CRP contributes to disease pathogenesis or is just a secondary response to the inflammatory disease processes in MetS patients.[28]

In conclusion, our study proposes that echocardiographic EFT is independently associated with hs-CRP levels and MetS in MetS patients. Although a direct causative relationship could not be derived from this study, interaction among low-grade inflammation, MetS, and EFT may be a subject of great interest in future studies.

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