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Echocardiographic epicardial fat thickness measurement and cardiovascular risk assessment in patients with systemic lupus erythematosus

Sistemik lupus eritematozus hastalarında ekokardiyografik epikardiyal yağ kalınlığı ölçümü ve kardiyovasküler risk değerlendirilmesi

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ABSTRACT

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune inflammatory disease. Traditional cardiovascular (CV) risk factors are more prevalent in SLE patients than in the general population. Risk scores which take into account traditional risk factors for CV diseases underestimate true CV risk in SLE. Therefore, risk predictors of atherosclerosis including carotid intima-media thickness (c-IMT), high-sensitivity C-reactive protein (hs-CRP) have been investigated in SLE to show the actual CV risk. Increased c-IMT and hs-CRP levels in SLE patients have been reported. Epicardial fat also strongly influences the formation and the progress of coronary artery disease. However, there is limited data comparing the epicardial fat thickness (EFT) of SLE patients with that of the normal population. This study was designed with the aim of further evaluating whether SLE patients have greater EFT values with increased c-IMT and hs-CRP levels when compared with a healthy group. The population of this study was comprised of 38 consecutive SLE patients and 34 healthy volunteers. C-IMT was measured through ultrasonographic imaging of the common carotid arteries using a linear array transducer. Transthoracic echocardiography was used to measure EFT. SLE patients had significantly higher EFT values than those of healthy volunteers (4.5±1.1 vs. 3.9±0.9, p=0.01). There were also direct correlations between EFT values and SELENA-SLEDAI index, c-IMT and hs-CRP of study population. As a conclusion; the echocardiographic EFT measurement can be used as a reproducible and practical tool for evaluation of cardiovascular risk with c-IMT and hs-CRP in patients with SLE.

Keywords: *Systemic lupus erythematosus, epicardial fat thickness, atherosclerosis*

ÖZ

Sistemik Lupus Eritematozus (SLE) multisistemik ve otoimmün inflamatuvar bir hastalıktır. Geleneksek kardiyovasküler (KV) risk faktörleri SLE'li hastalarda normal populasyona göre daha sıktır. Ancak geleneksek KV risk faktörlerini hesaplayan risk skorlamaları SLE'li hastalardaki gerçek kardiyovasküler riski olduğundan daha düşük göstermektedir. Bu nedenle karotis intima media kalınlığı (KİMK) ve yüksek duyarlıklı C reaktif protein (yd-CRP) gibi aterosklerotik prediktörler, SLE'lu hastalardaki gerçek KV riski değerlendirmek için bu grup hastalarda araştırılmıştır. SLE'lu hastalarda KİMK ve yd-CRP değerlerinde artış saptanmıştır. Epikardiyal yağ dokusu da koroner arter hastalığının oluşumunu ve gelişimini kuvvetli bir şeklide etkilemektedir.Ancak, SLE'lu hastalarda epikardiyal yağ kalınlığının (EYK) normal popülasyona göre karşılaştırılması ile ilgili sınırlı veri mevcuttur. Bu nedenle bu çalışma SLE'lu hastalarda artmış KİMK ve yd-CRP düzeyleri ile birlikte EYK'da normal popülasyona göre artış olup olmadığını araştırmak için tasarlanmıştır. Çalışmamıza 38 ardışık SLE hastası ve 34 sağlıklı gönüllü çalışmaya dahil edildi. KİMK ölçümleri lineer bir transdüserle, ultrasonografik olarak karotis arterlerden yapıldı. EYK ölçümü için transtorasik ekokardiyografi cihazı kullanıldı. SLE'lu hastaların EYK ölçümleri sağlıklı gönüllülere göre anlamlı derecede yüksek bulundu ((4.5±1.1 vs. 3.9±0.9, p=0.01). EYK ölçümleri ile SELENEA-SLEDAI indeksi, KİMK ve yd-CRP değerleri arasında direkt korelasyonlar tespit edildi. Sonuç olarak, Ekokardiyografik EYK ölçümü KİMK ve yd-CRP değerleri ile birlikte SLE'lu hastalarda gerçek kardiyovasküler risk değerlendirmesinde tekrarlanabilir ve kolay bir yöntem olarak kullanılabilir.

Anahtar kelimeler: *Sistemik lupus eritematozus, epikardiyal yağ kalınlığı, ateroskleroz*

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune inflammatory disease of multifactorial aetiology. SLE development is characterized by the production of autoantibodies and immune complex formation and deposition, which trigger inflammation and damage affecting several organs[1]. Development of SLE seems to be due to the interaction between environmental triggers (e.g., viruses, drugs, pollution, and stress hormones, etc.) and a favorable genetic background, characterized by the combination of common variants of several susceptibility loci[2].

Traditional cardiovascular (CV) risk factors are more prevalent in SLE patients than in the general population, yet they cannot fully account for the increased prevalence and risk of cardiovascular diseases (CVD) compared with age-and sex-matched controls from the general population. Indeed, both the Framingham Risk Score and the Reynolds Risk Score, which take into account traditional risk factors for CVD, have underestimated the true CV risk in SLE[3].

Early atherosclerosis is reflected on increased carotid artery intima-media thickness (c-IMT). Increased c-IMT is a result of cumulative atherogenetic processes and may predict cardiovascular events[4].

High-sensitivity C-reactive protein (hs-CRP) is a circulating acute phase reactant that represents active systemic inflammation and has been reported as a strong predictor of future cardiovascular events in large prospective trials[5].

Epicardial fat is a true visceral adipose tissue, deposited in the proximity to the atrium, the free wall of the right ventricle, and the left ventricular apex of the heart[6]. As has been demonstrated in a recent study, epicardial fat strongly influences both the formation and the advance of coronary artery disease (CAD)[7].

Epicardial fat may also play a role in the screening of patients with intermediate CAD risk[8]. Recent studies have demonstrated that c-IMT is related to the risk of atherosclerosis in SLE patients[9]. However, there is limited data which compared the epicardial fat thickness (EFT) of SLE patients with that of the normal population. The relations between c-IMT, hs-CRP and EFT in SLE patients are also unclear at present.

Therefore, this study was designed with the aim of further evaluating whether SLE patients have greater EFT values with increased c-IMT and hs-CRP levels when compared with a healthy control group; we also investigated the association between EFT values and SLE disease activity.

MATERIAL and METHODS

Study population

The population of this study was comprised of 38 consecutive SLE patients referred to the outpatient clinic of our department of rheumatology (5 men; median age, 40 (29-46)) and 34 age-matched healthy volunteers, were also included as a control group (4 men; median age, 38 (34-40) years). Characteristics of all our SLE patients were found to fall within the revised criteria (1997) of the American College of Rheumatology[10]. SLE diagnosis was based on histopathological and clinical examination of each patient.

Age, gender, disease duration, body mass index (BMI), fasting blood glucose, hs-CRP, triglyceride levels, hemoglobin, total cholesterol, high (HDL-C) and low-density lipoprotein (LDL-C) cholesterol, as well as systolic and diastolic blood pressures and heart rate were recorded. Calculations of BMI were made by dividing body weight in kilograms by the square of height in meters (kg/m^2).

Disease activity was assessed with one of the most popular instruments used to capture flare of the disease as the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) SLE Disease Activity Index (SELENA SLEDAI)[11], which is based on clinical and laboratory experience and calculated at patient admission.

Control subjects had not any systemic organ or cardiovascular disease. None of the patients had hypertension (systolic BP >140 mmHg or diastolic BP >90 mmHg), diabetes mellitus (venous plasma concentration after overnight fast >110 mg/dL), renal failure (values of serum creatinine >1.3 mg/dL), heart failure, the reduced left ventricle's (LV) ejection fraction (lower than 50%), moderate to severe valvular stenosis or regurgitation, CAD, chronic obstructive pulmonary disease, cancer, nor any pregnancy or infectious diseases. Any patients with suboptimal echocardiographic imaging results were excluded fromthe study.. Each patient and member of the control group gave informed consent in writing before participation. Our local ethics committee approved this study, which was conducted in accordance with the guidelines contained in the Helsinki Declaration on Biomedical Research İnvolving Human Subjects.

Measurement of C-IMT:

The intima-media thickness (IMT) of carotid artery was also measured in all patients. C-IMT values were established through ultrasonographic imaging of the left and right common carotid arteries using a linear array transducer of 7.5 MHz (Vivid 7 dimension, General Electric Medical Systems, Horten, Norway). In using the transducer care was taken that the closer, and remote walls of the common carotid artery, were aligned parallel with the footprint of the transducer, and also such that the diameter of the lumen lied maximally on longitudinal plane. The region found 1 cm proximal of the bifurcation of the carotid artery was located, and the far wall's IMT was taken as the distance from the interface of the lumen and intima to that of the media and adventitia. Four IMT measurements were performed on contiguous sites with an interval of 1 mm, and the average of measurements was estimated. After obtaining measurements of the right and left common carotid arteries in this way the values of either side were averaged. Every measurement was made manually using stills taken during the sonographic scanning. Any thicknesses of 1.2 mm or greater not uniformly involving the artery was defined as a plaque. The variability of ultrasonographic measurements between observers was <4%. Each examination was performed by an experienced examiner blinded to biochemical as well as clinical data.

Measurement of Epicardial Fat Thickness:

Transthoracic echocardiography (GE Vivid 7 system GE-Vingmed Ultrasound AS, Horten, Norway) was used to measure EFT of the participants positioned left-laterally. Echocardiographic examinations were performed by cardiologists with considerable specialized experience in echocardiography blind to clinical data. Subsequently all data was transmitted for analysis to an EchoPAC 6.1 workstation (GE Vingmed Ultrasound AS). EFT was visualized and measurements taken parasternally in a long-axis view, as has been described and legitimized[12]. EFT was defined to be anechoeic area of the pericardial layers during 2D echocardiography; Thickness of the free wall of the right ventricle was measured perpendicularly during end-systole over a period of three to ten cardiac cycles. Measurements were obtained at the ultrasound beam's midline when focused on the right ventricular free wall and with the aortic annulus perpendicular to the beam. EFT values were quantified twice each and the RR interval percentages showing the smallest amount of motion were selected as being maximally conducive to research confidence.

Statistical analyses:

All calculations were performed using the statistical software package SPSS 16.0 for Windows (SPSS Inc. Chicago. IL.). The variables were examined by using analytic (Kolmogorov-Smirnov/Shapiro-Wilk's test) and visual (histogram) methods defining whether they are normally distributed or not. Descriptive statistics were used to summarize the data. Categorical variables were expressed as percentages, continous variables as mean ± standart deviation and medians (25-75 percentiles). The statistical analysis was performed with computer software (SPSS version 13.0, SPSS Inc. Chicago, IL, USA). Numeric variables were analysed with a Student's t-test and a Mann-Whitney

U-test. Categorical variables were analysed with a chi-square test and Fisher's exact test, as appropriate. The data were expressed as numeric variables and as percentages (%) for categorical variables. Correlation analysis was performed using Spearman's correlation test. A p value of <0.05 was considered statistically significant.

RESULTS

Study Population:

Characteristics of both the patient and control groups are shown in Table 1. There were no significant differences in terms of age, gender, BMI and conventional risk factors such as blood pressure, diabetes, fasting glucose, creatinine, hemoglobin, and cholesterol levels between SLE and control group (Table 1). There was a significant difference between hs-CRP values of the patients with SLE and healthy volunteers (6.3 (2.7-12.5) vs.1.5 (1.0-2.7), p<0.001).

Table 1.Comparison of demographic, biochemical and echocardiographic measurements of the study population:

	Patients with SLE (n=38)	Healthy controls (n=34)	P
Age (years)	40 (29-46)	38 (34-40)	0.49
Male/Female (n/n)	5/33	4/30	0.85
c-IMT (mm)	56 (50-62)	50 (45-56)	0.03
SELENA-SLEDAI index	4 (3-5)		-
BMI (kg/m^2)	27.6 (24.7-29.1)	27.7 (26.1-29.0)	0.91
Systolic BP (mmHg)	120 (110-120)	120 (110-130)	0.48
Diastolic BP (mmHg)	75 (70-80)	80 (70-80)	0.16
Heart Rate (beat/min)	74 (71-77)	74 (66-84)	0.61
Total Cholesterol (mg/dl)	178±37	178±26	0.99
HDL-C (mg/dl)	43 (38-52)	41 (35-47)	0.29
LDL-C (mg/dl)	110±27	111±21	0.90
Triglyceride (mg/dl)	86 (63-172)	112 (87-154)	0.11
Glucose (mg/dl)	92 (87-97)	90 (87-96)	0.43
Hemoglobin (g/dl)	14.0±1.4	14.1±1.1	0.79
Hs-CRP (mg/l)	6.3 (2.7-12.5)	1.5 (1.0-2.7)	<0.001
EFT (cm)	4.5±1.1	3.9±0.9	0.01

BP: Blood pressure, Hs-CRP: high sensitive C-reactive protein, EFT: epicardial fat thickness, SELENA-SLEDAI index: Safety of Estrogens in Lupus Erythematosus: National Assessment SLE Disease Activity Index

Measurement of the Carotid Intima Media Thickness:

Helathy volunteers had significantly lower C-IMT values than the patients with SLE (50 (45-56) vs.56 (50-62), p=0.03), (Table 1).

Measurement of Epicardial Fat Thickness:

Patients with SLE had significantly higher EFT values than those of healthy volunteers (4.5±1.1 vs. 3.9±0.9, p=0.01). There were also direct correlations between EFT values and SELENA-SLEDAI index, c-IMT and Hs-CRP of study population (Figure 1), (Figure 2), (Figure 3).

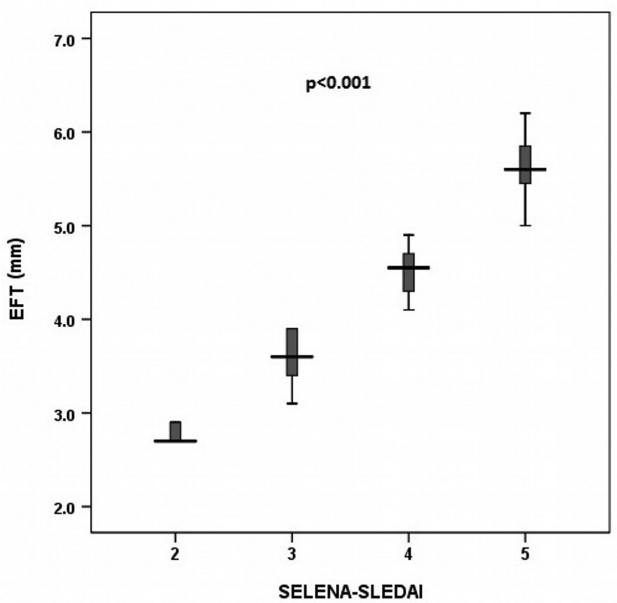

Figure 1. Correlation Between EFT and SELENA-SLEDAI Index.

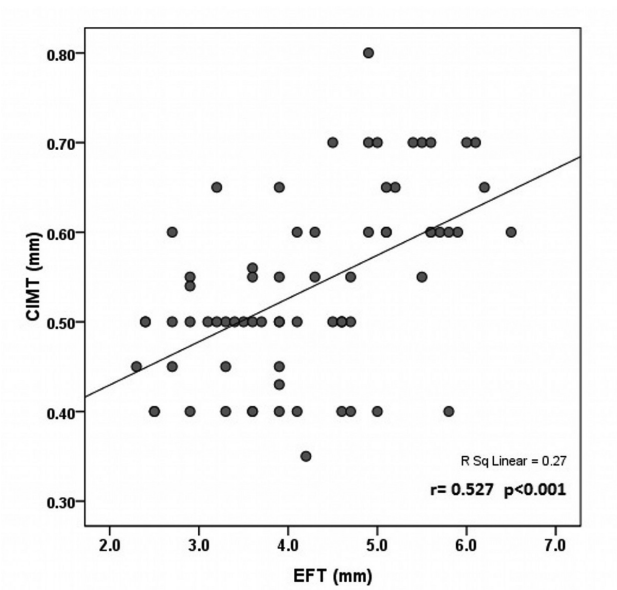

Figure 2. Correlation Between EFT and CIMT.

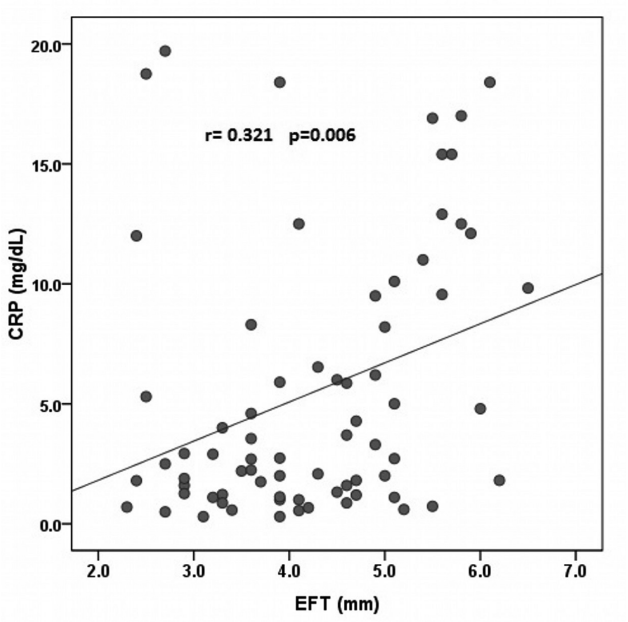

Figure 3. Correlation Between EFT and Hs-CRP.

DISCUSSION

Serum levels of hs-CRP and c-IMT values are well-known predictors of atherosclerosis used for the assessment of cardiovascular risk in patients with SLE. In our present study we have investigated whether echocardiographic EFT measurement may also be used as a novel predictor of atherosclerosis in SLE patients.

Several traditional and disease-related risk factors that affect CV risks in patients with SLE were identified. Moreover, certain imaging techniques hold promise in further improving risk stratification. Traditional risk factors include age (postmenopausal status in particular), male sex, positive family history for premature coronary artery diseases, obesity, arterial HTN, DM, dyslipidemia, metabolic syndrome, hyperhomocysteinemia, and smoking[13].

The majority of these factors have been reported with increased frequency in patients with SLE[13]. Further, disease characteristics, such as activity and medications used, can substantially affect the severity of SLE[14].

Hs-CRP is defined as a systemic marker for inflammation. Recent prospective trials showed that the pathogenesis of atherosclerosis is associated with a chronic low-grade inflammation, and increased hs-CRP level is described as a risk factor for coronary artery disease[15,16].

Barnes et al.[17] have demonstrated that hs-CRP levels of patients with SLE was significantly higher than those of the healthy population and hs-CRP levels of the patients with SLE were directly correlated with disease activity.

In the present study we also found that hs-CRP levels of the patients with SLE were significantly higher than the healthy control group similar to Barnes' study. C-IMT is a measure of subclinical atherosclerosis associated with cardiovascular risk factors4.

In a meta-analysis including 71 studies, 4814 SLE patients showed significantly higher CIMT than the 3773 controls using a random-effects model. This data were associated with increased atherosclerotic risk in patients with SLE by the authors[18].

In the present study, we found increased CIMT values in patients with SLE in comparison to control patients. These results were similar to previous studies.

Increased epicardial fat quantity is associated with incident CAD in addition to major adverse cardiovascular outcomes[19]. These relations occur independently from BMI and other conventional risk factors. Epicardial fat tissue actually is one of the factors contributing to CAD compared to other visceral fat tissues[20,21]. In a recent meta-analysis of 2.872 patients, Xu et al.[22] reported that EFT and epicardial fat tissue volumes were significantly increased in patients with CAD as compared with the healthy group.

In a cohort of 190 asymptomatic patients, Bachar et al.[8] reported that EFT was associated with subclinical coronary atherosclerosis, demonstrated by computed tomoghraphic calcium score. A recent study demonstrated an independent relationship existing

between arterial stiffness and EFT, suggesting that echocardiographic measurement of EFT could serve as an easily quantifiable tool for the early detection of subclinical atherosclerosis[23].

There is limited data about EFT values of the patients with SLE in the literature. Lipson et al.[24] found that volume of epicardial adipose tissue (EAT) measured by CT in SLE patients were significantly higher than those in the healthy population. This result shows that there is an increased cardiovascular risk burden in patients with SLE. Quantification can be performed with automated, computerized methods, as in Lipson's study; however, disadvantages of CT include radiation exposure and expense, making it less practical in routine practice. Echocardiographic assessment of EFT on the free wall of teh right ventricle is reliable with EAT measurements with MRI (r=0.91, p=0.001)[13]. Echocardiographic EFT measurement seems to be more practical and applicable as compared to CT, due to the latter's disadvantages such as high cost and radiation exposure.

In the present study EFT measurements of patients with SLE were compared with those of the healthy population and it was found that the echocardiographic EFT values of patients with SLE were significantly higher than those of the healthy population. There were direct correlations between EFT and atherosclerotic predictors including c-IMT and hs-CRP values of the study population. We also found a direct correlation between EFT values of the patients with SLE and a disease activity index, namely the SELENA-SLEADI index. Therefore, we conclude that echocardiographic EFT measurements can be used as a reproducible and practical tool for evaluation of cardiovascular risk in patients with SLE.

Conflict of Interest

Because of one of the co-authors is a member of the journal's editorial board, he has been excluded from evaluation processes of the manuscript for publication.

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