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EVALUATION OF EPICARDIAL FAT THICKNESS, A NEW INDICATOR OF THE CARDIOVASCULAR RISK FACTOR, IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Aim: Systemic lupus erythematosus (SLE) is a chronic autoimmune rheumatic disease with high cardiovascular mortality. Epicardial adipose tissue (EAD) is the visceral fat located between the myocardium and pericardium. EAD is recognized as an active metabolic and inflammatory tissue capable of producing and releasing various preatherosclerotic and proinflammatory hormones, cytokines. EAD is associated with coronary artery disease, metabolic syndrome, and subclinical atherosclerosis. In this study, we investigated the relationship between EAD and SLE patients.

Material and Methods: A total of 73 patients were recruited from the rheumatology department of a single center as a case-control study. The participants were divided into two groups: 73 patients with SLE (group 1) and 60 age- and sex- matched controls (group 2). Laboratory and radiological results were obtained from the electronic registration database. Data were analyzed and compared between the groups.

Results: There was no significant difference between the groups in terms of age, gender, height, weight, or body mass index (BMI). EAD was found to be significantly higher in SLE patients than in the control group. In the SLE group, EAD was found to be significantly higher in patients with low complement levels than in those without. There was a positive correlation between EAD and age, leukocytes, neutrophils, C-reactive protein (CRP), and BMI, but a negative correlation was found between SLE disease activity index.

Conclusion: Increased EAD was found in SLE patients compared with the control group. In addition, a correlation was found between increased EAD and low complement and CRP. EAD may be a measurable and modifiable potential therapeutic target associated with inflammation and cardiovascular risk in patients with SLE.

Keywords: Epicardial fat thickness, inflammation, systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune rheumatic disease of unknown cause that can affect almost every organ in the body. The reported prevalence of SLE in the United States is 20 to 150 cases per 100,000 (1). 65% of patients with SLE have the onset of the disease between the ages of 16 and 55 (2). Genetic, hormonal, immunological, and environmental factors are thought to play a role in the etiology of the disease (3). The clinical manifestations of SLE range from structural symptoms such as fever, sweating, weight loss, arthralgia, and rash to more severe organ involvement, including cardiovascular, central nervous system, and renal involvement. Cardiac disease is common among patients with SLE and may include the pericardium, myocardium, valves, conduction system, and coronary arteries (4). There is an increased prevalence of atherosclerosis in patients with SLE. Atherosclerosis is an inflammatory process that involves immune cell activation, plaque formation due to inflammation, and subsequent rupture (5). Systemic inflammation is thought to accelerate atherosclerosis (6,7). In mouse models of SLE, the degree of systemic inflammation correlates with the rate of atherosclerosis development. Dysfunctional proinflammatory high-density lipoprotein cholesterol, commonly found among patients with SLE, can accelerate low-density lipoprotein oxidation and atherosclerosis (8,9). The accumulation of immune complexes also stimulates the cholesterol deposition in atherosclerotic plaques (10). Type I interferon (IFN) promotes atherosclerosis by stimulating macrophage recruitment to atherosclerotic lesions in vitro, and type I IFN may have other effects on endothelium and atherogenesis (11,12). Epicardial adipose tissue (EAD) is a surrogate marker of visceral adiposity, and visceral fat may be an independent predictor of metabolic risk. Physiologically, EAD serves as an energy source for the myocardium by providing mechanical protection and plays a cardioprotective role by producing anti-inflammatory adipokines. Metabolically active EAD synthesizes and secretes bioactive molecules. These are transported to the adjacent myocardium via vasocrine and/or paracrine pathways. Recently, a meta-analysis revealed a correlation between EAD thickness and coronary artery disease (13-16). EAD measurement serves as a powerful potential diagnostic tool for assessing cardiovascular risk. The thickness of the EAD can be measured and evaluated using two-dimensional echocardiography, CT, or magnetic resonance imaging (MRI). Ultrasound requires experience, providing a linear measurement rather than a volumetric measurement. In addition, EAD located in the atrioventricular groove or elsewhere cannot be reached by ultrasound. Severely obese patients may have a weak acoustic window that does not allow for optimal visualization of EAD thickness. CT and cardiac MRI can provide a more accurate and volumetric EAD measurement (17). It has been reported that increased EAD measured using CT is associated with further progression of coronary artery calcification (18,19). Few studies have investigated the relationship between EAD and SLE. The aim of our study was to measure EAD thickness, which is known as a new indicator of atherosclerosis and a cardiovascular risk factor, with computed tomography (CT) in SLE patients and to compare it with the control group and to show its relationship with various variables such as demographic characteristics, clinical parameters, laboratory parameters, cardiometabolic risk markers, and disease duration.

MATERIAL AND METHODS

Study Population and Design

In this retrospective study, 73 patients over the age of 18 years and 60 controls, who applied to the rheumatology outpatient clinic of a tertiary hospital between January 2019 and January 2021, were diagnosed with SLE according to the 2012 Systemic Lupus International Collaboration Clinics criteria, were included in the study. Routine biochemical, whole blood samples, complete urinalysis and complement (C3-C4), antibodies against double-stranded DNA (dsDNA) levels, antinuclear antibody (ANA), and ANA profiles of SLE patients were retrospectively analyzed from the patient file. The laboratory and tomography results of the patients were retrospectively obtained by scanning the archives of the HBYS and PACS systems. Thorax CT images were analyzed at the workstation. SLE disease activity index (SLEDAI)-2K was used to evaluate the disease activity of patients with SLE. Patients who were the same age and gender as the patient group, had normal blood tests, had no known chronic disease, applied to the internal medicine outpatient clinic due to cough and dyspnea, underwent elective thoracic tomography, and had no pathological findings were selected as the control group. The radiological data of these patients were also scanned retrospectively from the PACS system archive. This single-center study was approved by the Sulçuk University Ethics Committee (decision no: 2021/320, date: 02.06.2021) and was conducted according to the principles. Written informed consent forms were obtained from all participants before the study.

Statistical Analysis

The Statistical Package for Social Sciences software was used for all procedures (IBM SPSS Statistics 21.0, IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality distribution of the scale variables.

For continuous numerical variables, descriptive statistics are presented as mean standard deviation. Categorical variables are represented by the number of cases and percentage. The chi-square test was used to compare categorical variables, and the Student's t-test was used to compare continuous numerical variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate diagnostic performance. If the area under the curve (AUC) was found to be significant, the Youden index was used to determine the best cut-off point. The sensitivity and specificity of the diagnostic performance indicators were calculated. To determine the relationship between epicardial fat tissue and laboratory values, Pearson correlation analysis was used. Unless otherwise specified, the results were deemed statistically significant at p=;0.05.

RESULTS

The study included 73 patients with SLE, with 9.6% males and 90.4% females, a mean age of 47.58±10.98 years, and a mean disease duration of 7.52±5.68 years (range, 1-20 years). The control group included 60 age- and gender-matched healthy individuals. Tables 1 and 2 show the demographic and clinical characteristics of patients with SLE and the healthy control group. The groups did not differ significantly in terms of age, gender, height, weight, or BMI (p>0.05). Epipericardial fat tissue was found to be significantly higher in the SLE patient group than in the healthy control group (Table 1) (p=0.002). Within the SLE patient group, epipericardial fat tissue was significantly higher in patients with low complement levels than in those without (p=0.022). In addition, the renipericardial fat tissue did not differ significantly between SLE patients with anti-dsDNA positivity and comorbidity (p>0.05). The clinical characteristics and laboratory test results for the patients with SLE are shown in Table 2.

Table 1. Demographic and clinical characteristics of SLE patients and control group

	SLE patients	Healthy control	p-value
Gender (female)	n (%)* 66/73 (90.4)	51/60 (85.0)	0.425
Age, (years)**	47.58±10.98	49.78±11.99	0.270
Weight (kg)**	56.91±7.07	54.98±5.92	0.096
Height (cm)**	160.59±5.20	160.28±5.67	0.747
BMI**	22.17±3.38	21.52±3.07	0.253
Epipecardial fat tissue (cm^3)**	145.65±68.18	109.86±61.60	**0.002**

*Chi-square test's, data are presented as counts, with percentages in brackets, **Independent sample t-test, data are presented as mean ± standard deviation
SLE: Systemic lupus erythematosus, BMI: Body mass index

Table 3 shows the results of the ROC analysis. Epipericardial fat tissue demonstrated satisfactory diagnostic performance in differentiating SLE patients from healthy volunteers. The AUC was 0.662 (p=0.001), with a sensitivity of 75.3% and a specificity of 55.0% at a cut-off value of 96.95. Pearson correlation analysis was performed to determine the relationships between the epicardial fat tissue and laboratory values of patients with SLE (Table 4). There was a weak positive correlation between renipericardial fat tissue and age, leukocyte count, neutrophil count, and CRP (p=0.05). A strong positive correlation was found between epicardial fat tissue and BMI (p=0.001). However, in our study, healthy volunteers with BMI indices similar to those of SLE patients were included, and no significant difference in BMI was found (p>0.05). A weak negative correlation was found between epicardial fat tissue and SLEDAI (p=0.001).

DISCUSSION

SLE may present with clinical features ranging from mild joint and skin involvement to life-threatening renal, hematological, and central nervous system involvement. Heart disease is common among patients with SLE. There is an increased prevalence of atherosclerosis in SLE patients. Excessive oxidative stress in SLE increases inflammation, resulting in apoptotic cell

Table 2. Clinical characteristics of SLE patients (n=73)

Disease duration*	7.52±5.68
Additional disease**	29 (39.7)
HL**	4 (5.5)
ANA positivity**	73 (100)
Anti-DNA positivity**	11 (15.1)
Low complement levels**	44 (60.3)
Leukocyte (10^9/L)*	6.12±1.84
Hemoglobin (g/L)*	12.63±1.92
Platelet (10^9/L)*	239.18±82.17
PCT*	0.26±0.83
Neutrophile (10^9/L)*	3.61±1.43
Monocyte (10^9/L)*	0.47±0.16
Lymphocyte (10^9/L)*	1.76±0.65
Red cell distribution width (RDW) (%)*	14.94±2.32
Mean platelet volume (MPV) (FL)* SLEDAI *8.30±5.12	8.52±0.86
C-reactive protein (CRP) (mg/L)*	4.92±3.69
Erythrocyte sedimentation rate (ESR) (mm/h)*	24.52±16.23

*Data are presented as mean ± standard deviation, **Data are presented as counts, with percentages in brackets
SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, PCT: Platelets

Table 3. ROC analysis results of epipericardial fat tissue used for diagnosis of patients with SLE

	AUC (95% CI)	p-value	Cut-off	Sensitivity	Specificity
Epipericardial fat tissue	0.662 (0.568-0.756)	0.001	>96.95	75.3	55.0
Regression model (EAD, age and BMI)	0.757 (0.674-0.838)	<0.001	-	68.5	75.0

AUC: Area under the curve, 95% CI: 95% confidence interval, BMI: Body mass index, ROC: Receiver operating characteristic, EAD: Epicardial adipose tissue

Table 4. Correlation of epicardial fat tissue with disease activity, duration and laboratory findings in SLE patients (n=73)

	rs	p-value
Epicardial fat tissue - age	0.397	<0.001
Epicardial fat tissue - BMI	0.867	<0.001
Epicardial fat tissue - disease duration	-0.076	0.523
Epicardial l fat tissue - disease activity	-0.368	0.001
Epicardial fat tissue - hemoglobin	0.026	0.826
Epicardial fat tissue - leukocyte	0.267	0.022
Epicardial fat tissue - platelet	0.059	0.620
Epicardial fat tissue - neutrophile	0.250	0.033
Epicardial fat tissue - PCT	-0.080	0.499
Epicardial fat tissue - monocyte	-0.047	0.695
Epicardial fat tissue - lymphocyte	0.180	0.127
Epicardial fat tissue - RDW	0.010	0.935
Epicardial fat tissue - MPV	-0.145	0.219
Epicardial fat tissue - CRP	0.276	0.018
Epicardial fat tissue - ESR	0.018	0.877

rs: Pearson's rho correlation coefficients, BMI: Body mass index, MPV: mean platelet volume, RDW: Red cell distribution width, PCT: Platelets, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SLE: Systemic lupus erythematosus

death. Reactive species and free radical production in SLE and antiphospholipid syndrome are thought to contribute to chronic inflammation of tissues and lead to dyslipidemia and accelerated atherogenesis (20,21). A systematic review of 28 studies found that the risk of cardiovascular disease (CVD) among SLE patients was at least doubled compared to the general population (22). In a study, 105 patients with SLE and rheumatoid arthritis (RA) and 105 controls were compared (23). Coronary artery calcification was observed in 47.6 percent of SLE patients, 47.6 percent of RA patients, and 35.2 percent of controls. This increased frequency was strongly associated with inflammation, apart from other cardiac risk factors. EAD is a surrogate marker of visceral adiposity and it has been shown that visceral fat may be an independent predictor of metabolic risk. In the general population, EAD volume is independently associated with obstructive coronary artery plaque and noncalcified atherosclerotic lesions and is an independent predictor of ischemia (15,16). Mazurek et al. (24) compared epicardial and subcutaneous adipose tissue, and it was determined that epicardial tissue produced more inflammatory cytokines such as chemokines (monocyte chemotactic protein 1), leptin, interleukin-1B, interleukin 6 and tumor necrosis factor-alpha (TNF-α). In the light of these findings, they hypothesized that the presence of proinflammatory mediators such as TNF-α in the tissues surrounding the coronary arteries may lead to an increase in vascular inflammation and neovascularization via apoptosis (25). In our study, a weak positive correlation was found between EAD and leukocytes, neutrophils and CRP ($p<0.05$). This illustrates the link between EAD and inflammation. EAD is recognized as an active metabolic and inflammatory tissue capable of producing and releasing various proatherosclerotic and proinflammatory hormones, cytokines. There are studies in the literature showing its increase in autoimmune diseases. There are many studies showing increased EAD thickness in patients with RA. A cross-sectional study conducted with a cohort of 34 female RA patients and 16 controls matched for age and body mass index (BMI) showed greater EAD thickness in female patients with RA. Another age- and sex-matched cross-sectional study, including 76 patients with RA and 50 controls, reported a greater EAD thickness in RA patients (26,27). Increased EAD thickness is associated with endothelial dysfunction in spondyloarthritis (28). It suggests that EAD thickness is a candidate for atherosclerotic risk assessment in patients with systemic sclerosis without open heart disease (29). A systematic review and meta-analysis also shows that familial Mediterian fever patients have a higher risk of developing EAD than controls (30). In a study evaluating EAD thickness and total calcium score in sarcoidosis patients, EAD thickness calculated using thorax CT was found to be higher in sarcoidosis patients. The prognostic value of EAD measurements with CT: A systematic review of the literature also shows that most studies show that EAD quantification is significantly related to clinical outcomes and provides incremental prognostic value over coronary artery calcium scoring. Concerns with CT include the difficulty of integrating it into practice due to the radiation hazard, relatively high cost, and increased time required for measurements (31). A meta-analysis showed that EAD thickness was significantly higher in patients with metabolic syndrome (MetS) than in patients without (18). MetS is common among patients with SLE (32,33). In SLE, CVD risk factors (diabetes, hyperlipidemia, hypertension, family history of coronary heart

Table 5. Multivatiate analysis

	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Epipericardial_fat	-0.034	0.009	15.387	1	0.000	0.966	0.950	0.983
Gender (1)	-1.098	0.642	2.922	1	0.087	0.333	0.095	1.175
Age	0.043	0.020	4.734	1	0.030	1,044	1.004	1.086
BMI	0.438	0.171	6.604	1	0.010	1,550	1.110	2.166
Constant	-6.618	2.904	5.193	1	0.023	0.001		

EAD, age and BMI were found to be independent predictive parameters in SLE patients
SLE: Systemic lupus erythematosus, EAD: Epicardial adipose tissue, BMI: Body mass index, 95% CI: 95% confidence interval

disease, obesity, sedentary lifestyle and smoking), glucocorticoid use, disease duration and disease activity are associated with increased risk (34-36). Clinical factors associated with CVS in patients with SLE include: Higher disease activity, chronic nephritis, low serum C3 levels, anti-dsDNA, antiphospholipid antibodies, and high CRP (37). In our study, EAD in SLE patients was found to be significantly higher in patients with low complement levels (p=0.022).

In addition, EAT volume did not differ significantly in SLE patients with anti-dsDNA positivity and comorbidity (p>0.05). In addition, EAD predicted CVS events independent of conventional risk factors and BMI in the Multi-Ethnic Atherosclerosis Study MESA and another observational study (38). Lipson et al. (39) found increased EAD in SLE patients, similar to our study. However, the causes of increased EAD in SLE patients are still unknown. In our study, EAD was measured higher in SLE patients than in the control group, regardless of BMI. As noted above, inflammation is an important risk factor for atherosclerosis. This study also shows that increased EAD may be an independent risk factor for CVD in SLE patients (Table 5)

Study Limitations

Our study has limitations that must be acknowledged. First, due to its retrospective nature, it was impossible to standardize the point at which testing was performed in the natural history of the disease. The small number of patients, the fact that the study was conducted in a single center is another limitation of the study.

CONCLUSION

In our study, we observed increased EAD in patients with SLE compared with the control group. In addition, a correlation was found between increased EAD and low complement and CRP. EAD may be a measurable, modifiable potential therapeutic target associated with inflammation and cardiovascular risk in patients with SLE.

Ethics

Ethics Committee Approval: This single-center study was approved by the Sulçuk University Ethics Committee (decision no: 2021/320, date: 02.06.2021) and was conducted according to the principles.

Informed Consent: Written informed consent forms were obtained from all participants before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.H., S.Y., H.Ö., Ö.F.T., A.K., D.T., Concept: S.H., S.Y., D.T., M.K.K., Design: S.H., S.Y., H.Ö., Ö.F.T., A.K., D.T., Data Collection or Processing: S.H., S.Y., D.T., Analysis or Interpretation: S.H., H.Ö., Ö.F.T., A.K., M.K.K., Literature Search: S.H., D.T., Writing: S.H., S.Y., D.T., M.K.K.

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