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Original Article

Evaluation of Subclinical Atherosclerosis with Carotid Intima-Media and Epicardial Fat Thickness in Patients with Sarcoidosis

Hatice Eylül Bozkurt Yılmaz[1], Mustafa Yılmaz[2], Tansel Erol[2], Nazan Şen[1], Zuhal Ekici Ünsal[1], Sibel Kara[1], Mehmet Ali Habeşoğlu[1], Şule Akçay[3]

[1]Department of Pulmonary Medicine, Baskent University School of Medicine, Adana, Turkey
[2]Department of Cardiology, Baskent University School of Medicine, Adana, Turkey
[3]Department of Pulmonary Medicine, Baskent University School of Medicine, Ankara, Turkey

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Abstract

OBJECTIVES: Since many similar mechanisms may play a role in the pathophysiology of sarcoidosis and atherosclerosis, the risk of subclinical atherosclerosis may be increased in patients with sarcoidosis. The aim of this study was to evaluate known markers of subclinical atherosclerosis, namely epicardial fat thickness (EFT) and carotid intima-media thickness (CIMT) in patients with sarcoidosis.

MATERIALS AND METHODS: This cross-sectional study included a total of 183 subjects, including 94 patients with sarcoidosis (patient group) and a control group of 89 healthy individuals. Measurements of EFT and CIMT were taken from all subjects and recorded. The groups were compared, and differences were analyzed statistically.

RESULTS: EFT was higher in patients than in control subjects (6.42±1.12 mm vs 7.13±1.41 mm, p<0.001). CIMT was higher in patients than in control subjects (0.51±0.02 mm vs 0.52±0.02 mm, p=0.003).

CONCLUSION: EFT and CIMT were found to be higher in patients with sarcoidosis than in healthy people. These results indicate that the risk of subclinical atherosclerosis might be increased in these patients.

KEYWORDS: Atherosclerosis, doppler ultrasonography, echocardiography sarcoidosis

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INTRODUCTION

Sarcoidosis is a multisystemic disease characterized by noncaseating granulomatous inflammation [1]. The disease mostly affects the lungs and lymphatic system, but many organs such as the eyes, neural system, skin, heart, liver, spleen, and parotid gland can also be affected [1, 2]. The incidence of the disease is different in each race and society, but the disease is generally more common in women and African-Americans [3]. Although the etiology of sarcoidosis is not entirely known, some environmental risk factors, such as genetics and obesity, have been identified [1-3]. Many complex processes such as increased immune response, inflammation, and oxidative stress play a role in the pathophysiology of the disease [1-3]. Cardiovascular diseases that are mostly caused by atherosclerosis are the most common causes of mortality and morbidity worldwide [4]. Environmental and genetic risk factors for atherosclerosis have been known since a long time [5]. Mechanisms such as increased inflammation and oxidative stress play a role in the pathophysiology of atherosclerosis [6, 7].

In recent studies, it has been shown that epicardial fat thickness (EFT) is a new indicator in the diagnosis of atherosclerotic cardiovascular risk [8]. EFT is identified as the amount of fat between pericardial layers around the heart [8]. Measurement of carotid intima-media thickness (CIMT) is considered a noninvasive method for determining the risk of subclinical atherosclerosis. The success of this measurement in predicting cardiac events has been demonstrated in many studies [9-11]. Since many similar mechanisms play a role in the pathophysiology of sarcoidosis and atherosclerosis, the risk of subclinical atherosclerosis may be increased in patients with sarcoidosis. The aim of this study was to investigate this risk. For this purpose, EFT and CIMT, which are markers of subclinical atherosclerosis, were evaluated in patients with sarcoidosis.

MATERIALS AND METHODS

In this cross-sectional study, a total of 94 patients who were diagnosed with sarcoidosis between January 1, 2016 and December 31, 2017 or who had previously been diagnosed but had not received treatment were included. Patients who had previously been diagnosed but were receiving treatment for sarcoidosis were excluded from the study. A total of 89

Address for Correspondence: Hatice Eylül Bozkurt Yılmaz, Department of Pulmonary Medicine, Başkent University School of Medicine, Adana, Turkey
E-mail: b_eylul@yahoo.com

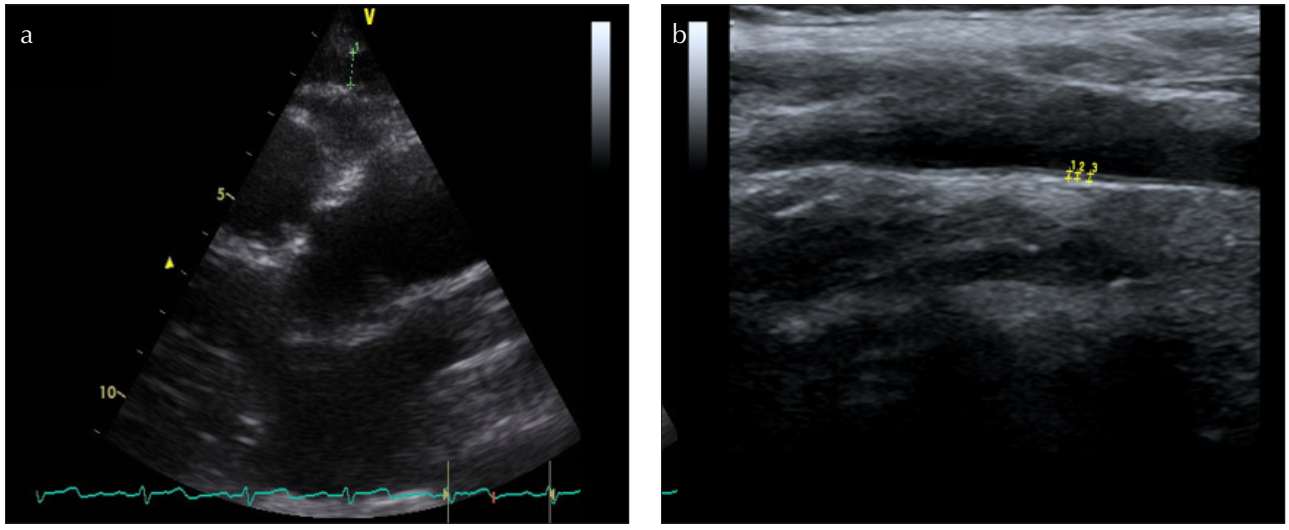

Figure 1. a, b. (a) Measurements of epicardial fat thickness on the free wall of the right ventricle from the parasternal long-axis views, (b) Measurement of carotid intima media thickness at the far wall of common carotid arteries

volunteers similar in age and sex to the patient group were included in the control group. Patients were diagnosed with sarcoidosis according to the guideline that the American Thoracic Society/European Respiratory Society had previously published based on histopathological, clinical, and radiological methods, excluding alternative diagnoses that cause noncaseating granulomatous inflammation. Lofgren's syndrome was diagnosed in patients with erythema nodosum, arthralgia, and bilateral hilar lymphadenopathy, and these patients were accepted as sarcoidosis without histopathological evidence. In addition, the presence of bronchoalveolar lavage above CD4/CD8>3.5 was found sufficient for diagnosis in patients considered clinically and radiologically as sarcoidosis [12].

Patients were excluded from the study if any of the following criteria were met: any known atherosclerotic cardiovascular disease (coronary artery disease, cerebrovascular disease, or peripheral artery disease), heart failure, advanced heart valve disease, active infection, familial hyperlipidemia, diabetes mellitus, history of smoking uncontrolled hypertension, malignancy, chronic renal disease requiring dialysis, chronic liver disease, autoimmune diseases, use of systemic steroids, pregnancy, age <18 years or >65 years, pulmonary hypertension or chronic obstructive pulmonary disease, or unwillingness to participate in the study.

Renal function tests, liver function tests, blood counts, C-reactive protein (CRP) levels, serum angiotensin-converting enzyme (ACE) levels, serum calcium (Ca) levels, and 24-h urinary Ca levels were examined, and the values were recorded. Chest radiography, thorax computed tomography, pulmonary function tests, 12-lead Electrocardiogram (ECGs), and two-dimensional (2D) transthoracic echocardiography were performed, and the results were recorded. The staging of patients with pulmonary sarcoidosis was performed radiologically according to the criteria in the consensus report that had been previously specified. Extrapulmonary sarcoidosis was diagnosed based on radiologic and pathologic data [12]. Demographic, anthropometric, laboratory, and clinical data were recorded from all subjects in the study. CIMT and EFT were measured in both groups to determine whether there was a statistical difference between the groups.

MAIN POINTS

- Sarcoidosis and atherosclerosis are inflammatory disease.
- Similar risk factors might play role in the pathophysiology of sarcoidosis and atherosclerosis.
- Risk of subclinical atherosclerosis in patients with sarcoidosis may be high.

Routine 2D, Conventional Spectral Doppler, and EFT Data

Echocardiographic evaluations were performed using a Philips EPIQ 7 ultrasound system (Seattle, WA, USA) and a Philips X5-1 probe (broadband transducer; Seattle, WA, USA). In accordance with the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging, standard 2D and Doppler examinations were performed. Ejection fraction was calculated using the modified Simpson method [13]. EFT was defined as the area between the myocardium free wall and the pericardium visceral layer where there was no echo [14]. On the parasternal long-axis image, EFT was measured perpendicular to the right ventricular free wall, at the end of diastole and on three cardiac beats (Figure 1a). Echocardiographic evaluations were performed twice at different times by two different cardiologists blinded to the study groups (sarcoidosis vs control), and the average of these four measurements was used in the analysis.

Carotid ultrasonography

Ultrasonographic evaluations were performed using a Philips EPIQ 7 ultrasound system with a Philips L12-3 probe (broadband transducer Seattle, WA, USA). Manual measurement of CIMT was performed from the far walls of the left and right common carotid arteries, in a region 10 mm proximal to the carotid bifurcation. Measurements were performed using B-mode duplex ultrasound in the longitudinal plane. CIMT measurements were taken at three adjacent sites 1 mm distant from each other (Figure 1b). Ultrasonographic evalua-

Table 1. Baseline clinical, demographic, anthropometric, and pulmonary function test characteristics of the study population

	Sarcoidosis (n=94)	Control (n=89)	p
Age (years)	52.52±11.41	50.13±7.95	0.104
Female gender, n (%)	73 (77.65)	61 (68.53)	0.164
BMI (kg/m^2)	30.99±4.25	30.42±4.21	0.369
Hypertension, n (%)	26 (27.65)	30 (33.7)	0.375
Creatinine (mg/dL)	0.78±0.27	0.76±0.11	0.476
Hemoglobin (g/dL)	13.48±1.52	13.6±1.4	0.567
WBC (/mm^3)	7431±2332	7592±1405	0.576
Platelets (100/mm^3)	287 (252-337, IQR=85)	300 (279-321, IQR=42)	0.25
Total cholesterol (mg/dL)	214.71±41.77	212.19±45.54	0.697
LDL (mg/dL)	142.30±39.76	139.34±41.65	0.624
HDL (mg/dL)	48.15±12.35	48.67±12.75	0.78
Triglyceride (mg/dL)	112 (85-146, IQR=61)	110 (82-153, IQR=71)	0.989
FPG (mg/dL)	111.35±35.05	113.76±37.33	0.654
SBP (mm Hg)	129.51±9.92	129.36±11.13	0.923
DBP (mm Hg)	80.95±8.32	82.66±8.59	0.172
Heart rate (beats/min)	79.27±12.99	76±13.26	0.094
Serum Ca level (mg/dL)	9.47±0.61	NA	-
Urine Ca level (g/day)	0.28±0.14	NA	-
Serum ACE level (U/L)	75.12±46.4	NA	-
CRP (mg/L)	5.9±4.98	NA	-
FEV_1 (%)	92.8±14.8	NA	-
FVC (%)	100.26±15.7	NA	-
FEV1/FVC, ratio±SD	78.16±6.52	NA	-
DLCO (mmol/(min/kPa))	85.15±12.26	NA	-
DFFD (months)	41 (11-62, IQR=51)	NA	-

ACE: angiotensin-converting enzyme; BMI: body mass index; Ca: calcium; CRP: C-reactive protein; DBP: diastolic blood pressure; DFFD: duration from first diagnosis; DLCO: diffusing capacity of the lung for carbon monoxide; FEV_1: forced expiratory volume in 1 s; FPG: fasting plasma glucose; FVC: forced vital capacity; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; NA: not available; SBP: systolic blood pressure; WBC: white blood cell

tions were performed twice at different times by two different operators blinded to the study groups (sarcoidosis vs control), and the average of these four measurements was used in the analysis

Statistical Analyses

Continuous variables were presented as mean±standard deviation or median (range, interquartile range) and categorical data as percentages. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. The chi-square test was applied in the analysis of categorical parameters, and the unpaired t-test was applied to continuous variables with normal distribution. The Mann Whitney U-test was applied to continuous variables not showing normal distribution. Correlations between continuous variables were evaluated using Pearson or Spearman correlation tests, as appropriate. Standard multiple linear regression analysis was applied to determine independent determinants of EFT and CIMT. A two-sided value of $p<0.05$ was accepted as statistically significant. Statistical analysis was performed using a commercially available computer program Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp.; Armonk, NY, USA).

Table 2. Baseline clinical characteristics of patients with sarcoidosis

Stage	n (%)
Stage 0, n (%)	8 (8.51)
Stage 1, n (%)	43 (45.74)
Stage 2, n (%)	37 (39.36)
Stage 3, n (%)	6 (6.38)
Stage 4, n (%)	0 (0)
Pulmonary sarcoidosis, n (%)	94 (100)
Neurosarcoidosis, n (%)	2 (2.12)
Hepatic sarcoidosis, n (%)	4 (4.25)
Ocular sarcoidosis, n (%)	6 (6.38)
Splenic sarcoidosis, n (%)	1 (1)
Skin sarcoidosis, n (%)	9 (9.57)

RESULTS

A total of 183 individuals, including 94 patients with sarcoidosis and 89 healthy volunteers, were included in this study. There was no statistically significant difference between the patient and control groups in terms of demographic, anthropometric, and baseline laboratory values ($p>0.05$). Demographic, anthropometric, and laboratory values of both groups are shown in Table 1. Basal clinical features and organ involvement of patients with sarcoidosis are shown in Table 2. In addition, there was no statistically significant difference between the two groups in terms of baseline echocardiographic measurements and cardiac cavity measurements ($p>0.05$). Echocardiographic measurements are summarized in Table 3.

EFT was found to be 7.13±1.41 mm in the patient group and 6.42±1.12 mm in the control group. There was a statistically significant difference between the groups in terms of EFT ($p<0.001$). Similarly, CIMT was found to be 0.52±0.02 mm in the patient group and 0.51±0.02 mm in the control group. There was a statistically significant difference between the groups in terms of CIMT ($p=0.003$). Table 4 shows the results of correlation analyses and linear regression analysis between age, fasting plasma glucose (FPG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, systolic blood pressure, diastolic blood pressure, body mass index, forced expiratory volume in 1 s (FEV_1), forced vital capacity

(FVC), FEV_1/FVC, diffusing capacity of the lung for carbon monoxide, serum ACE levels, urine Ca levels, serum Ca levels, CRP levels, duration from first diagnosis and EFT and CIMT. Correlation analysis showed a statistically significant correlation between EFT and FPG, creatinine, ACE levels, serum Ca levels, and CRP levels (r=0.214, p=0.038; r=0.248, p=0.016; r=0.307, p=0.003; r=354, p<0.001; r=0.325, p=0.001, respectively) and between CIMT and HDL, LDL, ACE, and serum Ca levels (r=-0.252, p=0.014; r=0.302, p=0.003; r=0.653, p<0.001; r=0.326, p=0.001). No significant correlation was found between the other variables. In multiple linear regression analysis, there was a statistically significant relationship between EFT and serum Ca levels (β=0.260, p=0.046) and between CIMT and FPG and serum ACE levels (β=0.196, p=0.047; β=0.698, p<0.001, respectively). No significant relationship was found between the other variables.

Table 3. Comparison of two-dimensional echocardiographic parameters between the groups

	Sarcoidosis (n=94)	Control (n=89)	p
EF	57.78±3.21	57.31±2.89	0.298
LVEDD (mm)	43.61±3.01	43.24±2.11	0.340
LVESD (mm)	27.36±2.48	27.58±2.57	0.552
Left atrium (mm)	30.69±3.08	30.62±2.66	0.863
Right ventricle (mm)	28.99±2.24	29.16±2.25	0.614
IVS (mm)	0.98±0.13	0.96±0.11	0.405
Right atrium (mm)	29.89±2.01	29.65±1.84	0.399

EF: ejection fraction; IVS: interventricular septum; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter

DISCUSSION

In our study, we aimed to investigate whether the risk of subclinical atherosclerosis increases in patients with sarcoidosis. For this purpose and using ultrasonographic methods, we measured CIMT and EFT, which are indicators of subclinical atherosclerosis. Our study is the first study in the literature that evaluates both these indicators together in patients with sarcoidosis. According to the results of our study, CIMT and EFT are larger in patients with sarcoidosis than in control subjects. According to these results, the risk of subclinical atherosclerosis may be higher in patients with sarcoidosis than in control subjects. According to the other results of our study, serum FPG, creatinine, serum ACE, serum Ca, and CRP levels correlated with EFT, while HDL, LDL, serum ACE, and serum Ca levels correlated with CIMT. In addition to this, while serum Ca level is an independent predictor for EFT, the levels of FPG and serum ACE are independent predictors for CIMT.

There are limited number of studies that have investigated the risk of atherosclerosis in patients with sarcoidosis. In a study

Table 4. Correlation and multiple linear regression analysis of epicardial fat/carotid intima media thickness and various clinical variables

	Correlation analysis				Multiple linear regression analysis			
	EFT		CIMT		EFT		CIMT	
Variable	r	p	r	p	β	p	β	p
Age	0.187	0.070	0.051	0.626	0.847	0.400	-0.005	0.955
FPG	**0.214**	**0.038**	-0.147	0.158	0.079	0.506	**-0.196**	**0.047**
HDL	0.129	0.215	**-0.252**	**0.014**	0.154	0.140	-0.099	0.248
LDL	0.124	0.234	**0.302**	**0.003**	-0.175	0.180	-0.057	0.593
Cr	**0.248**	**0.016**	0.179	0.085	<0.001	0.998	-0.087	0.428
SBP	0.061	0.560	0.001	0.995	0.104	0.399	0.024	0.817
DBP	-0.122	0.240	0.007	0.950	-0.091	0.453	0.021	0.834
BMI	0.040	0.705	0.079	0.446	0.097	0.400	0.101	0.287
FEV_1	-0.071	0.497	0.048	0.645	0.321	0.397	-0.046	0.883
FVC	-0.069	0.512	0.071	0.495	-0.442	0.234	0.009	0.978
FEV_1/FVC	-0.105	0.315	-0.052	0.621	-0.116	0.485	-0.045	0.746
DLCO	-0.022	0.832	0.097	0.354	-0.022	0.850	0.018	0.851
ACE level	**0.307**	**0.003**	**0.653**	**<0.001**	0.253	0.079	**0.698**	**<0.001**
Urine Ca	0.034	0.748	0.113	0.283	0.03	0.976	-0.029	0.727
Serum Ca	**0.354**	**<0.001**	**0.326**	**0.001**	**0.260**	**0.046**	0.068	0.524
CRP	**0.325**	**0.001**	-0.118	0.255	0.175	0.194	-0.103	0.350
DFFD	-0.157	0.132	-0.161	0.121	-0.130	0.227	-0.113	0.203

ACE: angiotensin-converting enzyme; BMI: body mass index; Ca: calcium; CIMT: carotid intima-media thickness; Cr: creatinine; CRP: C-reactive protein; DBP: diastolic blood pressure; DFFD: duration from first diagnosis; DLCO: diffusing capacity of the lung for carbon monoxide; EFT: epicardial fat thickness; FEV_1: forced expiratory volume in 1 s; FPG: fasting plasma glucose; FVC: forced vital capacity; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure

conducted by Tuleta et al. [15], the "pulse wave index" was found to be higher in patients with sarcoidosis than in a normal population. The results of this study that early stage atherosclerosis might be more observed in patients with sarcoidosis. In another study by Kul et al.[16], a lower coronary flow reserve was found in patients with sarcoidosis than in a healthy population. They concluded that coronary microvascular dysfunction might occur in patients with sarcoidosis. Yong et al.[17] reported that sarcoidosis is associated with increased arterial stiffness and risk of subclinical atherosclerosis. In our study, we found the risk of subclinical atherosclerosis to be higher in patients with sarcoidosis than in control subjects, and the results of our study support the results of studies in the literature.

Some common pathophysiological mechanisms that play a role in the pathophysiology of both sarcoidosis and atherosclerosis may explain why the risk for atherosclerosis is high in patients with sarcoidosis. It has been shown in some earlier studies that disorders in lipid metabolism play a role in the pathophysiology of sarcoidosis [18, 19]. A study by Simonen et al. [20] showed that the levels of cholesterol absorption markers in patients with cardiac sarcoidosis were higher than those in control individuals; they concluded that absorption failures could be one of the underlying mechanisms in sarcoidosis. In our study, we found that levels of HDL and LDL correlated with CIMT.

Another common mechanism in sarcoidosis and atherosclerosis is inflammation. Inflammation is a pathophysiological mechanism that plays a key role in many respiratory diseases [21]. Similarly, both atherosclerosis and sarcoidosis are activated by some cytokines that are released by macrophages, and the inflammatory process is initiated. The chitinase 1 enzyme, which is released from activated macrophages, plays an important role in vital processes in both pulmonary sarcoidosis and atherosclerosis [22-24].

Another mechanism in the pathophysiology of both diseases is oxidative stress. In one study, it was reported that there was an increase in oxidative stress in patients with sarcoidosis and that there could be an increase in the risk of atherosclerosis in these patients [25]. In another recent study, it was shown that serum oxidative stress markers increased in patients with sarcoidosis and that this increase might be responsible for the onset of atherosclerosis in patients with sarcoidosis [26]. Oxidative stress might be responsible for the onset of atherosclerosis as it is in sarcoidosis, the role of oxidative stress is well known especially in the early stages of atherosclerosis [27]. All the aforementioned common pathophysiological mechanisms and similar processes may explain why the risk of subclinical atherosclerosis increases in patients with sarcoidosis.

Our study has some limitations. The study was conducted in one center, and the patients in this population might not reflect the general population. The number of patients may be relatively small, and these results must be confirmed with larger-scale studies. According to the results of our study, the risk of subclinical atherosclerosis increases in patients with sarcoidosis, and it is not known whether this result is of clinical importance. Additionally, it is not known whether this risk that increased in patients with sarcoidosis will get better with treatment. Measurements of CIMT and EFT were performed manually, and the measurement is operator dependent. To minimize the margin of error, measurements were performed twice by two different operators blinded to the patient and control groups.

To conclude, CIMT and EFT was significantly higher in the patient group than in the control group. According to these results, the risk of subclinical atherosclerosis might have increased in these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from Başkent University Institutional Review Board (KA18/24, 03/26/2018).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.E.B.Y., N.Ş.; Design - H.E.B.Y.; Supervision - M.A.H., Ş.A.; Resource - Z.E.Ü., S.K.; Materials - N.Ş., S.K., Z.E,Ü.; Data Collection and/or Processing - H.E.B.Y.; Analysis and /or Interpretation - H.E.B.Y, M.Y.; Literature Search - H.E.B.Y, T.E., M.Y.; Writing - H.E.B.Y., M.Y.; Critical Reviews - Ş.A, N.Ş.

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