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Title: Evaluation of subclinical atherosclerosis with carotid intima media and epicardial fat thickness in patients with sarcoidosis

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Abstract

Objective: 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 the known markers of

subclinical atherosclerosis of epicardial fat and carotid intima media thickness in patients with sarcoidosis.

Methods: This cross-sectional study included a total of 183 subjects, comprising 94 patients with sarcoidosis and a control group of 89 healthy individuals. Measurements were taken of epicardial fat and carotid intima media thickness from all subjects and recorded. The groups were compared and differences were analysed statistically.

Results: Epicardial fat thickness was higher in the patients than in the control subjects (6.42±1.12 vs. 7.13±1.41, $p < 0.001$). Carotid intima media thickness was higher in the patients than in the control subjects (0.51±0.02 vs. 0.52±0.02, $p = 0.003$).

Conclusion: Epicardial fat and carotid intima media thickness values in patients with sarcoidosis were found to be increased compared to the control group. According to these results, the risk of subclinical atherosclerosis might be increased in these patients.

Keywords: Sarcoidosis, carotid intima media thickness, epicardial fat thickness , atherosclerosis

INTRODUCTION

Sarcoidosis is a multisystemic disease characterized by noncaseating granulomatous inflammation [1]. The disease mostly affects the lungs and the lymphatic system, but many organs like the eyes, neural system, skin, heart, liver, spleen, and parotid gland can be affected [1,2]. The incidence of the disease is different in each race and society, but it is generally more common in females and Afro-Americans [3]. Although the etiology of sarcoidosis is not entirely known, some environmental risk factors like genetics and obesity have been identified [1-3]. Many complex processes such as increase 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 in the world [4]. The environmental and genetic risk factors for atherosclerosis have been known for a long time [5]. Mechanisms such as

similarly increased inflammation and oxidative stress play a role in the pathophysiology of atherosclerosis [6,7].

In recent studies, it has been shown that the 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]. The carotid intima media thickness (CIMT) is considered a noninvasive method of showing the risk of subclinical atherosclerosis. The success of this measurement in predicting cardiac events has been shown 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

The study was conducted as cross sectional. A total of 94 patients who were diagnosed with sarcoidosis between 1 January 2016 and 31 December 2017 or who had previously been diagnosed but had not received treatment were included into the study. Patients who had previously diagnosed but who were receiving treatment for sarcoidosis were excluded from the study. A total of 89 volunteers similar in age and sex to the patient group were included into the control group. The patients were diagnosed with sarcoidosis according to the guidance of the consensus criteria that the American Thoracic Society (ATS) / European Respiratory Society (ERS) had previously published based on histopathological, clinical, and radiological methods, excluding alternative diagnoses that cause noncaseating granulomatous inflammation. Löffgen's syndrome was diagnosed in patients with erythema nodosum, arthralgia, and bilateral hilar lymphadenopathy, and these patients were accepted

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as sarcoidosis without histopathological evidence. In addition to these, the presence of bronchoalveolar lavage above CD4/CD8>3.5 in patients who were clinically and radiologically compatible with sarcoidosis were found to be sufficient for a diagnosis [12].

Patients were excluded from the study if they had any known atherosclerotic cardiovascular disease (coronary artery disease, cerebrovascular disease, peripheral artery disease), heart failure, advanced heart valve disease, active infection, familial hyperlipidemia, diabetes mellitus, 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 if they were not willing to participate in the study.

The 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-hour urinary Ca levels were examined and the values were recorded. Likewise, the chest x-ray, thorax computer tomography, pulmonary function tests, carbon monoxide diffusion capacities, 12 lead ECGs and 2D transthoracic echocardiography were evaluated and the results were recorded. The staging of patients with pulmonary sarcoidosis was done radiologically according to the criteria in the consensus report that had been previously specified. Extrapulmonary movement 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 and measured to whether there was a statistical difference between the groups.

Routine two-dimensional (2D), conventional spectral Doppler and epicardial fat thickness (EFT) data

Echocardiographic evaluations were made using a Philips EPIQ 7 (Seattle, WA, USA) ultrasound system and a Philips X5-1 (Seattle, WA, USA) probe (broadband transducer). In

accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging, standard 2-dimensional (2D) and Doppler examinations were made. The ejection fraction (EF) was calculated with the modified Simpson method. [13]. The 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 3 cardiac beats (Figure-1A). Echocardiographic evaluations were performed twice at different times by 2 different cardiologists blinded to the study groups (sarcoidosis vs. control), and the average of these 4 measurements was used in the analysis.

Carotid ultrasonography

Ultrasonographic evaluations were made using a Philips EPIQ 7 (Seattle, WA, USA) ultrasound system with a Philips L12-3 (Seattle, WA, USA) probe (broadband transducer). Manual measurement of CIMT was made from the far walls of the left and right common carotid arteries, in a region 10 mm proximal to the carotid bifurcation. Measurements were made on B-mode duplex ultrasound in the longitudinal plane. CIMT measurements were taken from this image at 3 adjacent sites 1 mm distant from each other (Figure-1B). Ultrasonographic evaluations were performed twice at different times by two different operators blinded to the study groups (sarcoidosis vs. control), and the average of these 4 measurements was used in the analysis

Statistical analyses

Continuous variables were stated as mean±standard deviation (SD) or median (range, interquartile range [IQR]) values and categorical data as percentages. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test. The Chi-square test

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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 commercially available computer program (SPSS version 21.0 for Windows; SPSS, Inc., Chicago, Illinois, US).

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 patient and control groups in terms of demographic, anthropometric, and baseline laboratory values ($p>0.05$). The 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±1.41mm in the patients group, 6.42±1.12 mm in the control group. There was a statistically significant different between the groups in terms of EFT ($p<0.001$). Similarly CIMT was found to be 0.52±0.02 mm in the patients, 0.51±0.02 mm in the control subjects. There was a statistically significant different 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), light density lipoprotein (LDL), creatinine, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), forced expiratory volume in 1 second (FEV_1), forced vital capacity

(FVC), FEV_1/FVC, diffusing capacity of the lung for carbon monoxide (DLCO), serum ACE levels, urine Ca levels, serum Ca levels, CRP levels, duration from first diagnosis time parameters and EFT, CIMT. Correlation analysis showed a statistically significant correlation between EFT and FPG, creatinine, ACE levels, serum Ca levels, CRP (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), between CIMT and HDL, LDL, ACE levels, 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 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), between CIMT and FPG, serum ACE levels (β=0.196, p=0.047, β=0.698, p<0.001, respectively). No significant relationship was found between other variables.

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 of these indicators together in patients with sarcoidosis. According to the results of our study, the CIMT and EFT is thicker in patients with sarcoidosis compared with the control subjects. According to these results, the risk of subclinical atherosclerosis in patients with sarcoidosis may be higher compared with the control population. According to the other results of our study, while levels of serum FPG, creatinine, serum ACE, serum Ca, and CRP levels were correlated with thickness in EFT, levels of HDL, LDL, serum ACE, and serum calcium are correlated with CIMT. In addition to this, while the serum Ca level is an independent predictor for EFT, the levels of FPG and

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serum ACE are independent predictors for CIMT

Even if there are few studies that investigate the risk of atherosclerosis in patients with sarcoidosis, some studies exist. In a study that Tuleta et al., conducted, the 'pulse wave index' was found to be higher in patients with sarcoidosis compared with the normal population. In the results of this study, it was emphasized that early stage atherosclerosis might be greater in patients with sarcoidosis [15]. In another study by Kul et al., a lower coroner flow reserve was found in patients with sarcoidosis compared with the healthy population. In the results of this study, it was concluded that coronary microvascular dysfunction might occur in patients with sarcoidosis [16]. Yong et al. reported that sarcoidosis is associated with increased arterial stiffness and risk of subclinical atherosclerosis [17]. In our study, we found the risk of subclinical atherosclerosis to be higher in patients with sarcoidosis, and the results of our study support the 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 plays a role in the pathophysiology of sarcoidosis [18,19]. In a study by Simonen et al., showed that cholesterol absorption markers in patients with cardiac sarcoidosis were at a higher level compared with the control group, and as a result of this study, they concluded that this could be because of absorption failures in one of the underlying mechanisms in sarcoidosis [20]. In our study, we found that levels of HDL and LDL to correlate with values of CIMT.

Another common mechanism in both diseases is inflammation. Inflammation is a pathophysiological mechanism that plays a key role in many respiratory diseases and may be responsible for the increased risk of atherosclerosis in these 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 the vital processes in both pulmonary sarcoidosis in atherosclerosis [22-24].

Oxidative stress other than inflammation and dyslipidemia are present in the pathophysiology of both diseases. 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 like it is in sarcoidosis, especially in the early stages of atherosclerosis, the role of oxidative stress is well known [27]. All of the aforementioned common pathophysiological mechanisms and similar processes may explain why the risk of subclinical atherosclerosis increases in patients with sarcoidosis.

Study limitation: Our work had 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 with a large number of patients. According to the results of our study, the risk of subclinical atherosclerosis increases in patients, 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 taken manually, and measurement operator is dependent. To minimize the margin of error, measurements were taken twice by two different operators blind to the patient and control groups.

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Conclusion

According to the results of our study, CIMT and EFT in patients increased statistically significantly compared to the control group. According to these results, the risk of subclinical atherosclerosis might have increased in these patients.

Conflict of Interest, Disclosure Statement: The authors declare that they have no conflicts of interest. The authors have indicated they have no financial relationships relevant to this article to disclose.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (KA18/24).

Informed Consent Statement: After giving detailed information about the study, Informed consent (writing) was obtained from all individual participants included in the study.

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Table-1. Baseline clinic, 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 (gr/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 (beat/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, % of predicted±SD	92.8±14.8	NA	-
FVC, % of predicted±SD	100.26±15.7	NA	-
FEV_1/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 second, FPG: Fasting plasma glucose, FVC: Forced vital capacity, HDL: High density lipoprotein,IQR: Interquartile range, LDL: Light density lipoprotein, NA: Non available, SBP: Systolic blood pressure, WBC: White blood cell

Table-2. Baseline clinic characteristics of the patients with sarcoidosis

Stage	
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)
Norosarcoidosis, n (%)	2 (2.12)
Hepatic sarcoidosis, n (%)	4 (4.25)
Oculersarcoidosis, n (%)	6 (6.38)
Spleniksarcoidosis, n (%)	1 (1)
Skin sarcoidosis, n (%)	9 (9.57)

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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, LVEDV: Left ventricle end diastolic diameter, LVESV: Left ventricle end systolic diameter

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	
Variables	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

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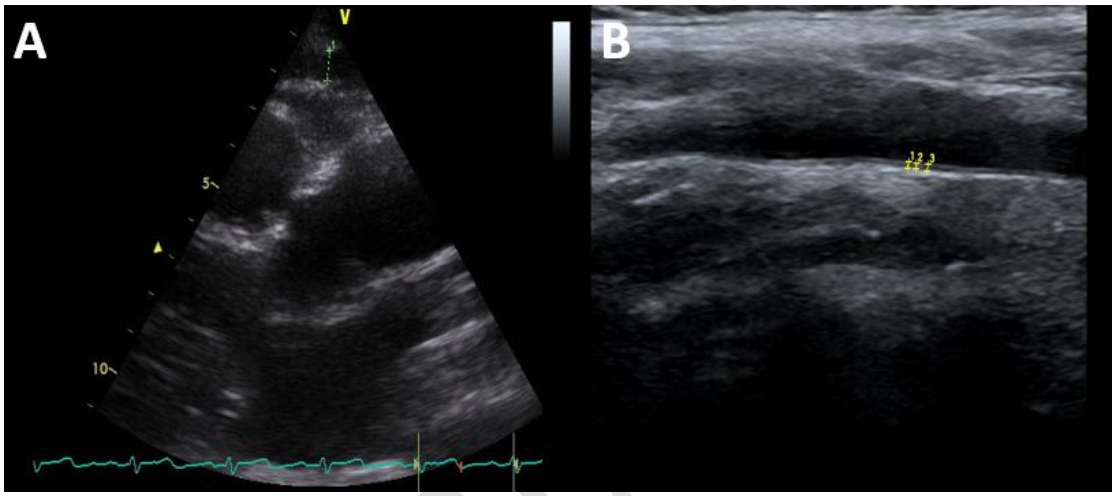
FEV_1	-0.071	0.497	0.048	0.645	0.321	0.397	-0.046	0.883
FVC	-0.069	0.512	0.071	0.495	-0.442	0.234	0.009	0.978
FEV_1/FVC	-0.105	0.315	-0.052	0.621	-0.116	0.485	-0.045	0.746
DLCO	-0.022	0.832	0.097	0.354	-0.022	0.850	0.018	0.851
ACE level	**0.307**	**0.003**	**0.653**	**<0.001**	0.253	0.079	**0.698**	**<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, Cr: Creatinine, 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 second, FPG: Fasting plasma glucose, FVC: Forced vital capacity, HDL: High density lipoprotein,LDL: Light density lipoprotein, SBP: Systolic blood pressure

Figure Legends

1. **Figure-1** (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.



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