Atherogenic Indices Can Predict Atherosclerosis in Patients with Sarcoidosis

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Abstract. Background: Sarcoidosis, a multisystemic disease of unknown etiology, is characterized by non-caseating granulomatous inflammation. This study aimed to investigate the efficiency of atherogenic indices and ultrasonographic evaluation of carotid artery on predicting atherosclerosis in patients with sarcoidosis. **Methods:** The study included 44 subjects followed with diagnosis of sarcoidosis and 53 age and gender matched healthy subjects as controls. Laboratory findings, pulmonary function tests and carotid artery ultrasonography of all participants were evaluated. **Results:** Of the participants with sarcoidosis 70.5% was female and the mean age was 35.36±7.18 years, while 64.2% of the control group were female and the mean age was 33.58±8.13 years (P=0.511 and P=0.191, respectively). High-density-lipoprotein cholesterol level in the sarcoidosis group was significantly lower than that of the control group (P=0.017), while other cholesterol levels were higher than those of the controls (P<0.05). Intima-media thickness (IMT) and peak systolic velocity (PSV) of carotid artery were higher in patients with sarcoidosis (P<0.001 and P=0.009, respectively). Atherogenic indices (Atherogenic Index (AI), Atherogenic Coefficient (AC) and Cardiogenic Risk Ratio (CRR)) were higher in sarcoidosis group compared to the controls (P<0.001, for all parameters). IMT was positively correlated with PSV, AI, AC, and CRR. A positive correlation between PSV and atherogenic indices was also detected. **Conclusions:** Sarcoidosis may be a predisposing factor for atherosclerosis. Atherogenic indices, IMT of carotid artery and PSV might be considered predictors for atherosclerosis and cardiovascular diseases in asymptomatic sarcoidosis patients.

Key words: Sarcoidosis; lipid profile; atherogenic index; atherosclerosis; cardiac involvement

Introduction

Sarcoidosis, a multisystemic inflammatory disease of unknown etiology and chronic nature, is characterized by proliferation of non-caseating granulomas.

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The lungs and intrathoracic lymph nodes are the most common sites for involvement. It commonly occurs between the ages of 20 and 50 years (1). In the study published by the Turkish Thoracic Society (TTS) in 2009, the incidence of sarcoidosis in Turkey was estimated at 4 in 100,000 (2).

Atherosclerosis is very common in the population and causes narrowing or occlusion of large and medium sized arteries. The atheromatous plaques occur especially in the branching sites of the vessels. The plaques consist of inflammatory cells, connective tissue cells and calcium as well as LDL (low density lipoprotein) accumulating within the intimal layer of blood vessels (3,4).

The efficacy of atherogenic indices in predicting atherogenic risk and atherosclerosis have been evaluated in Chronic Obstructive Pulmonary Disease (COPD), Familial Mediterranean Fever (FMF), pregnancy induced hypertension, etc.) (5-7). To the best of our knowledge, no study in the current literature evaluated the use of atherogenic indices (Atherogenic Index (AI), Cardiogenic Risk Ratio (CRR) and Atherogenic Constant (AC)) and the thickness of carotid intima-media in predicting atherosclerosis in sarcoidosis.

This study aimed to investigate the use of the serum lipid levels, atherogenic indices and thickness of the intima media layers and systolic flow velocities evaluated via carotid artery Doppler ultrasonography (USG) as a predictor of atherosclerosis in subjects with sarcoidosis.

Figure 1. Flow diagram for inclusion of participants diagnosed with sarcoidosis

Materials and Methods

Patient selection

The study was carried out between October 2017 and February 2018. The study included only the subjects with histopathologically confirmed diagnosis of sarcoidosis and with exclusion of other granulomatous diseases. All patients were contacted by phone call and invited for visit and participation to our study. Fifty-three (96.36%) of the 55 patients followed up with sarcoidosis could be contacted over the phone. Two subjects were excluded because of death within the last 3 months due to non-pulmonary reasons. Three subjects could not apply for thevisits for various reasons, and four subjects were excluded from the study because they had previously used antihyperlipidemic medications, or other criteria that required their exclusion. The flow chart for admittance of patients is given in Figure 1.

Accompanied by clinical and radiological findings, subjects with histopatologically confirmed "non-necrotizing granulomatous inflammation", or mycobacterial infections were excluded. Additionally, all patients were interrogated and the diagnosis confirmed in order to exclude other causes o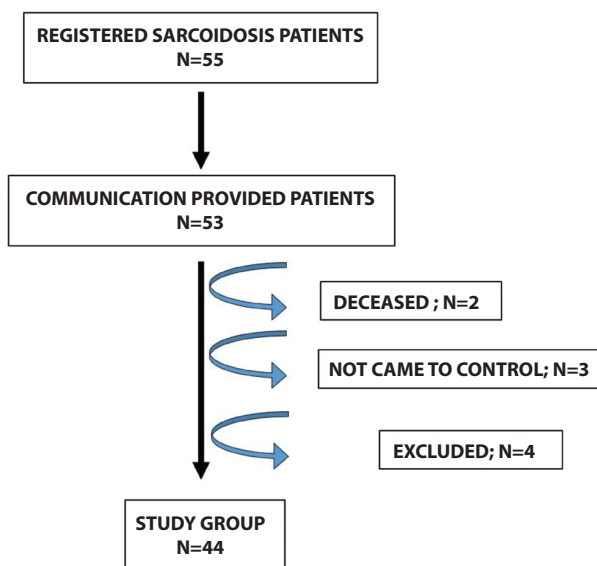f granulomatous inflammation. The subjects with suspected or confirmed granulomatous diseases other than sarcoidosis, those who rejected to participate in the study, who had chronic use of antihyperlipidemic medication, or who had systemic arterial hypertension, coronary artery disease, stroke and vascular dysfunction were excluded.

Age and gender matched 55 healthy controls were enrolled in the study. Two of them were excluded from the study for failing to complete the tests. Thus, 53 healthy volunteers completed the study protocol.

For both sarcoidosis and healthy control groups, complete blood count (CBC) and routine biochemical tests, serum lipid panels (triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), and total cholesterol) and C-reactive protein (CRP) were studied. Pulmonary Function Test (PFT), 6-minute walking test (6MWT) and Carotid artery color-Doppler ultrasonography (USG) were applied to all participants in both groups.

Pulmonary Function Tests (PFT)

Pulmonary function test was applied to all participants in accordance with the GOLD guideline with

at least three forced vital capacity (FVC) maneuvers. The procedure was performed by an experienced technician in Pulmonary Function Test Laboratory (ZAN GPI. Applied with 3.00 (Germany)).

6-Minute Walking Test

The procedure was initially explained to the participants in details by an experienced technician of respiratory laboratory. After recording the baseline oxygen saturation rates and blood pressures, the participants were asked to walk for 6 minutes in a lane of 30 meters in length.. In case of desaturation or feeling of poor, the test was discontinued. Otherwise, the patients completed the test. At the end of the sixth minute, the total distance walked, oxygen saturation rates and heart rates were recorded.

Laboratory Investigations

Venous blood samples were collected into dipotassium ethylenediaminetetraacetic acid (dipotassium EDTA) test tubes for CBC test. The Sysmex-XE 2000i (Sysmex, Kobe, Japan) automatic blood cell analyzer were used for analyzes. Biochemical tests, serum triglycerides, high density lipoprotein (HDL), low density lipoproteins (LDL), and very low density lipoprotein (VLDL) measurements were carried out via standard laboratory procedures with the Roche Cobas C501 (Germany) with spectrophotometric methods.

Atherogenic Indices

Atherogenic indices were calculated using the obtained laboratory results;

- *Atherogenic Coefficient (AC):* [(Total Cholesterol (TC) - HDL) / HDL];
- *Cardiogenic risk ratio (CRR):*[TC/HDL]
- *Atherogenic index (AI):* obtained with logarithmic calculation on the website http://www.biomed.cas.cz/fgu/aip/calculator.php (8).

Doppler Ultrasonographic Evaluation

Carotid Doppler Ultrasonography was performed by a trained radiologist with a Terason (U-SMART 3200T) brand portable ultrasonic device, with the patient lying on back, head in hyperextension, neck in neutral position or in an angle of 30-45° opposite to the side being evaluated (Fig. 2A and 2B). In all participants, right Common Carotid Artery (CCA) B-Mode ultrasonography was used to assess intima-media thickness (IMT), and PSV were evaluated using Pulse Wave Doppler. The cut-off value of IMT for atherosclerosis was reported 0.9 mm by European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guideline in 2018 (9).
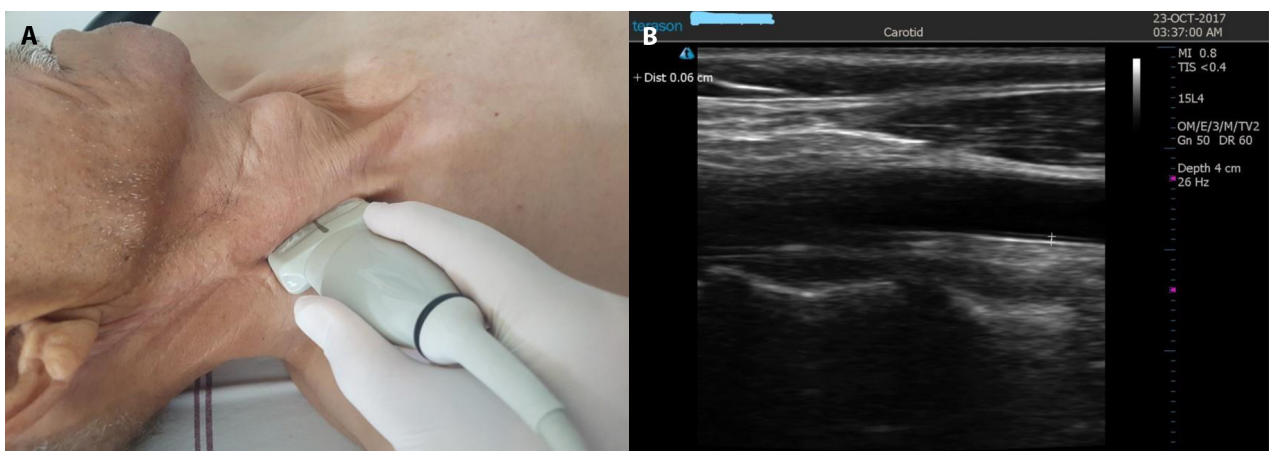

Figure 2. A. Application of carotid Doppler USG. **B**. The measurement of right CCA tunica intima-media thickness.

Etichal Committee Aproval

The study was approved by the local Ethics Committee of Afyonkarahisar Health Sciences University (2017/255).

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences for Windows Version 20.0 (SPSS Inc., Chicago, IL, USA) program. Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Categorical variables were expressed as number and percentage (N (%)). Chi-square test was used to compare group ratios. Normally distributed variables were expressed as mean±standard deviation; non-normally distributed variables were expressed as median (minimum-maximum). In comparison of two groups, the student T-test or Mann-Whitney U test were used according to distribution normality. The Pearson or Spearman Correlation tests according to distribution normality were used for correlation analysis. After setting cut-off value for carotid IMT to predict atherosclerosis as ≥0.9 mm,[9] sensitivity and specificity of ultrasonographic values and atherogenic indices to evaluate atherosclerosis were calculated by analysis of receiver operating characteristic (ROC) curve. The level of statistical significance was set as p<0.05.

Results

The study included 44 participants with sarcoidosis and 53 healthy individuals as controls. Of the participants, 31 (70.5%) were female in the sarcoidosis group, and 34 (64.2%) were female in the control group (P=0.511). The average age of patients with sarcoidosis was 35.36 years, and that of the control group was 33.58 years (P=0.191). The vast majority of those with sarcoidosis were in early stage (Stage 1 and 2) (Table 1).

The laboratory findings of all participants are given in Table 2. Mean Platelet Volume (MPV) was found to be significantly low in sarcoidosis group, while their RDW (%) values were significantly higher

Table 1. Demographic features (gender, age and body compositions) of all participants and stages, involvement sites and steroid treatment status of sarcoidosis patients in the study.

	Sarcoidosis N=44	Control N=53	P
Gender			
Male, N (%)	13 (29.5)	19 (35.8)	0.511
Female, N (%)	31 (70.5)	34 (64.2)	
Age, year (Average± SD)	35.36±7.18	33.58±8.13	0.191
Smoking patient, N (%)	9 (20.5)	14 (26.4)	0.492
Cigarette consumption, pack-years	15.50±7.76	16.93±7.43	0.647
Weight, kg	76.39±14.18	74.84±14.01	0.380
Height, cm	164.68±9.74	168.68±8.84	**0.039**
Body mass index (BMI), kg/m²	27.84±5.20	26.22±4.23	0.066
Sarcoidosis stage			
Stage 1	21 (47.7)		
Stage 2	13 (29.5)		
Stage 3	8 (18.2)		
Stage 4	2 (4.5)		
Steroid treatment reception status			
Current receiver of steroid	5 (11.4)		
Previous receiver of steroid	21 (47.7)		
Organ involvements of sarcoidosis			
Lung	44 (100)		
Lymph node	37 (84.1)		
Skin	10 (22.7)		
Eye	3 (6.8)		
Neurological	1 (2.3)		
Other	2 (4.6)		

(respectively, P=0.001 and P=0.018). C-reactive protein was significantly higher in the sarcoidosis group (P<0.001).

Serum lipid parameters are given in Table 3. HDL cholesterol was significantly lower in sarcoidosis

Table 2. Complete blood count and biochemical test results of the study groups.

Laboratory parameters	Sarcoidosis	Control	P
CBC			
WBC, 10^3/uL	8.18±3.23	7.40±1.98	0.147
Hemoglobin, (g/dL)	13.66±1.70	14.00±1.67	0.320
MCV, fL	86.45 (63.10-99.70)	88.50 (63.70-102.70)	0.063
MPV, (fL)	9.45 ± 1.04	10.17 ± 1.07	**0.001**
RDW,%	14.10 (12.40-21.20)	13.50 (12.20-18.20)	**0.018**
Plt, 10^3/uL	274.07±77.89	263.74±63.80	0.474
PDW, fL	15.94±0.43	16.08 ±0.36	0.075
PCT (plateletcrit), %	0.24 (0.10-0.41)	0.25 (0.17-2.21)	0.323
Biochemical Parameters			
Glucose, mg/dl	97.05 (71.40-126.70)	89.90 (66.20-104.00)	**<0.001**
Urea (mg/dL)	27.65 (14.00-66.00)	24.60 (14.20-48.40)	0.029
Blood Urea Nitrogen (BUN), mg /dl	12.92 (6.54-31.12)	11.50 (6.64-22.60)	0.031
Creatinine, mg / dl	0.75 (0.46-1.51)	0.79 (0.54-1.20)	0.264
AST, U/L	17.20 (10.90-49.00)	17.40 (11.00-36.50)	0.510
ALT, U/L	16.90 (9.90-46.20)	14.10 (7.70-40.90)	0.101
Sodium, mmol/L	140.70±2.58	139.49±2.66	0.026
Potassium, mmol/L	4.48±0.40	4.49±0.34	0.957
Chloride, mEq / l	101.43±2.45	101.78±2.58	0.498
C-Reactive Protein (CRP), mg/dl	0.57 (0.10-21.90)	0.23 (0.11-0.80)	**<0.001**

Table 3. Lipid profile results of the sarcoidosis and control groups.

Serum Lipid Variables	Sarcoidosis	Control	P
Cholesterol, mg / dL	191.62±37.99	171.31±24.18	**0.002**
VLDL, mg/dl	35.23±17.82	20.27±8.64	**<0.001**
LDL, mg/dl	127.12±32.21	106.02±20.08	**<0.001**
HDL, mg/dl	44.49±10.92	51.00±14.65	**0.017**
Triglyceride, mg/dl	175.72±89.37	101.35±43.22	**<0.001**

group; however the remaining lipid panel results were significantly higher in the sarcoidosis group compared to the controls.

In the spirometric tests, FVC (%), Forced expiratory volume at first second (FEV_1) (%), FEV_1/FVC (%) and Forced Expiratory Flow at 25-75% of the pulmonary volume (FEF_{25-75}) (%) values were lower in the sarcoidosis group (P<0.001, P=0.002, P<0.001 and P<0.001, respectively) (Table 4). Regarding the participants' exercise capacities, the total walking distance of the sarcoidosis group was significantly lower in the 6-minute walk test compared to the control group(P<0.001).

The atherogenic indices of the both groups are also outlined in Table 5. All indicators were significantly higher in the sarcoidosis group.

Table 4. Results of spirometric measurements and exercise capacities of the study groups.

Values	Sarcoidosis	Control	P
FVC, lt	3.07±1.18	4.14±0.99	**<0.001**
FVC, %	84.29±20.44	98.96±14.15	**<0.001**
FEV_1, lt	2.43±0.96	3.42±0.81	**<0.001**
FEV_1, %	86.89±22.51	95.72±13.99	**0.020**
FEV_1/FVC, %	80.50 (55.00-100.00)	82.00 (72.00-97.0)	**<0.001**
FEF_{25-75}, lt	63.70±10.66	95.00±6.19	**<0.001**
6MWT	372.50 (120.00-550.00)	480.00 (300-740)	**<0.001**
Male, 6MWT, m	450.00 (120.00-540.00)[¥]	480.00 (360.00-740.00)[γ]	0.054
Female, 6MWT, m	360.00 (120.00-550.00)	450.00(300.00-660.00)	**<0.001**

FEV1: Forced expiratory volume at 1st second; FVC: Forced Vital Capacity; FEF_{25-75}: Forced expiratory flow at 25-75% of vital capacity. 6MWT: 6 minute walking test
[¥] Within the Sarcoidosis group, for the 6MWT distance between the genders, P= 0.098
[γ] Within the Control group, for the 6MWT distance between the genders, P= 0.174

Table 5. Intima-media thickness (IMT) and Peak Systolic Flow Velocity (PSV) evaluated by superficial carotid artery ultrasonography and color Doppler Ultrasonography in study groups, and Atherogenic markers used for prediction of atherogenic risk; Atherogenic Index (AI), Atherogenic Coefficient (AC), and Cardiogenic Risk Ratios (CRR)

	Sarcoidosis	Control	P
Ultrasonographic Evaluation of Carotid artery			
Intima-media layer thickness (IMT), mm	0.56±0.10	0.48±0.09	**<0.001**
Peak Systolic Flow Velocity (PSV), cm/s	82.73±20.80	73.52±12.84	**0.009**
Atherogenic Indices			
Atherogenic index (AI)	0.55±0.28	0.28±0.25	**<0.001**
Atherogenic coefficient (AC)	3.51±1.25	2.56±0.94	**<0.001**
Cardiogenic risk ratio (CRR)	4.51±1.25	3.55±0.94	**<0.001**

Carotid artery superficial and color Doppler ultrasonography revealed that the thickness of the intima-media layer in the sarcoidosis group was significantly higher (0.56±0.10 mm) than that of the control group (0.48±0.09 mm) (P<0.001). Moreover, peak systolic flow velocity (PSV) was lower in the control group (P=0.009) (Table 5).

In sarcoidosis group, IMT was positively correlated with PSV and the Atherogenic index (AI) (R=0.586, p=<0.0001, for both). Similarly, a positive correlation was detected between PSV and AI in the sarcoidosis group (R=0.810, P<0.001). All data regarding correlations for the groups were presented in Tables 6 and 7.

In addition, Figures 3 and 4 represent the correlations between AI, ultrasonographic findings (IMT and PSV) of the sarcoidosis and the control groups.

While 7 (15.9%) of the sarcoidosis patients had IMT of higher than 0.9 mm (cutoff) to diagnose atherosclerosis, there was only 1 (1.9%) participant in the control group (P=0.012). Among 26 sarcoidosis patients who received steroid treatment (current or previous steroid user), IMT was higher than the cut-off value in 7 (26.9%) participants. On the other hand, IMT was lower than the cut-off value in non-steroid users (N=28 patients) (P=0.016). Other results of ROC analysis to predict atherosclerosis are given in Table 8.

Table 6. Correlations of common carotid artery (CCA) linear ultrasonographic findings (Intima-media thickness- IMT) with other variables in Sarcoidosis and control groups.

	Sarcoidosis		Control	
	R	P	R	P
Body Mass Index (BMI)	-0.077	0.621	0.146	0.297
6-minute walking test	-0.286	0.060	-0.155	0.266
Cigarette Consumption	0.640	**0.046**	-0.010	0.970
Peak Systolic Flow Rate (PSV)	0.586	**<0.001**	0.214	0.123
AI	0.586	**<0.001**	0.337	**0.014**
CRR	0.302	**0.046**	0.512	**<0.001**
AC	0.302	**0.046**	0.512	**<0.001**
CRP	0.068	**0.660**	-0.139	0.320
HDL	-0.364	**0.015**	-0.420	**0.002**
TG	0.496	**0.001**	0.153	0.275
Total Cholesterol	-0.067	0.666	0.092	0.510
VLDL	0.496	**0.001**	0.153	0.275
LDL	-0.168	0.276	0.191	0.170

Table 7. Correlations of common carotid artery (CCA) color Doppler ultrasonographic evaluation (PSV (Peak Systolic Flow Rate)) with other variables in Sarcoidosis and control groups.

	Sarcoidosis		Control	
	R	P	R	P
Body Mass Index (BMI)	-0.100	0.520	0.126	0.369
6-minute walking test	0.035	0.823	-0.231	0.096
Cigarette consumption	0.401	0.250	-0.441	0.099
Intima-media thickness	0.586	**<0.001**	0.214	0.123
AI	0.810	**<0.001**	0.419	**0.002**
CRR	0.665	**<0.001**	0.228	0.100
AC	0.665	**<0.001**	0.228	0.100
C-Reactive Protein	0.218	0.156	-0.175	0.210
HDL	-0.685	**<0.001**	-0.185	0.185
TG	0.642	**<0.001**	0.384	**0.005**
Total Cholesterol	0.004	0.981	0.041	0.773
VLDL	0.641	**<0.001**	0.384	**0.005**
LDL	-0.007	0.962	-0.056	0.693

Discussion

Sarcoidosis patients (N=44) and age and gender matched healthy participants (N=53) were included in the study. The participants with sarcoidosis had no cardiac involvement within the tests for initial diagnosis. We aimed to evaluate the risk of atherosclerosis for the control and study groups by assessing certain biochemical markers, indices with reported validity for prediction of atherosclerosis (AI, AC, CRR), and vascular ultrasonography (5-7,10,11). The present study revealed that atherogenic indices used for prediction of atherosclerosis (AI, AC, and CRR) were higher in the sarcoidosis group compared to the controls. Additionaly, the intima-media layer of the carotid artery was thicker and PSV values were significantly higher in sarcoidosis group compared to the controls.

In the literature, pulmonary involvement was reported to occur in 85-95% of the sarcoidosis patients (12). Although there are inconsistencies in the literature regarding the data about the rates of extrapulmonary involvement, the rate is 40.6% in the TTD study and 36% in the ACCESS study (3,13). Especially, cardiac and progressive pulmonary involvements are most frequently associated with mortality in sarcoidosis (14).

It is known that lipoprotein profile changes occur in sarcoidosis. These changes may occur in all patients even if they do not receive treatment (especially steroid treatment) (15,16). The level of HDL cholesterol, in particular, was reported to be lower in sarcoidosis patients, whereas no significant changes in total Cholesterol, LDL and Triglyceride levels were reported (15). In the study of Ivanišević et al. a significant decrease in HDL cholesterol levels and significant increase in the triglyceride levels were reported in sarcoidosis patients (17). In accordance with the previous studies, HDL cholesterol was lower in the sarcoidosis group
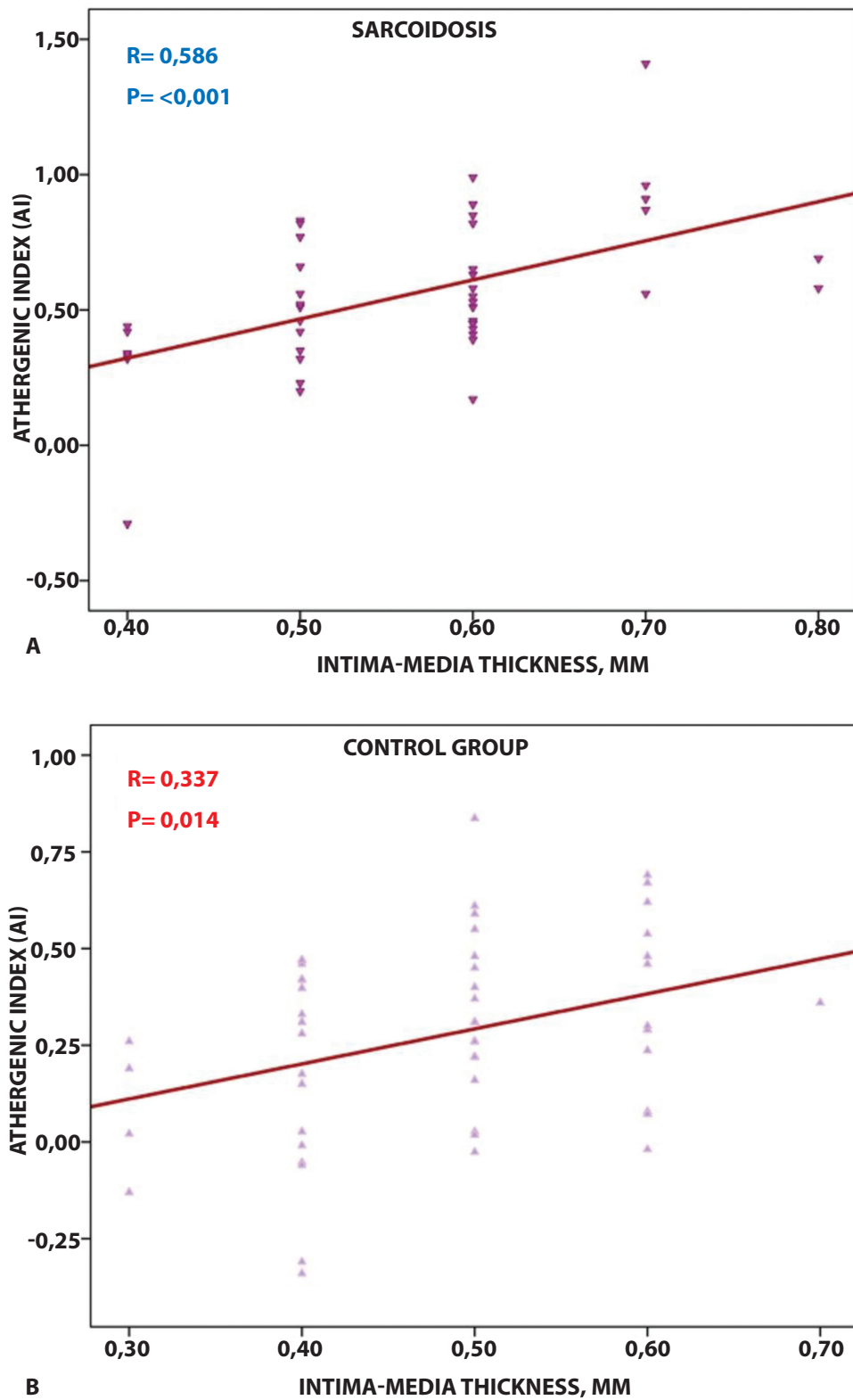
Figure 3. Correlation chart of the Atherogenic Index (AI) and the common carotid artery intima media layers in the Sarcoidosis (A) and Control (B) groups.
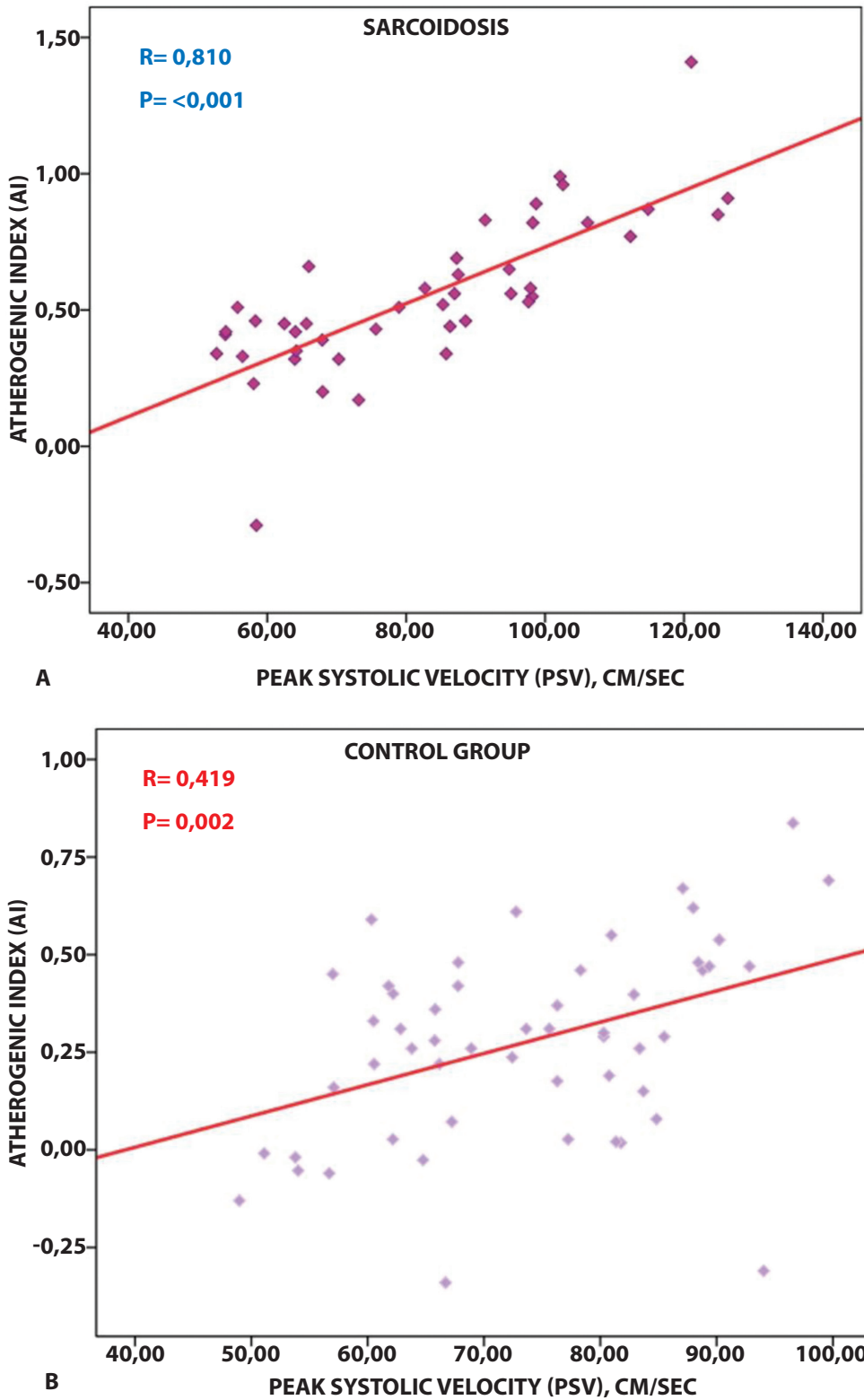
Figure 4. Correlation chart of the Atherogenic Index (AI) and the common carotid artery Peak Systolic Flow Rate (PSV) values in the Sarcoidosis (A) and Control (B) groups.

compared with the control group in our study. Additionally, similar to the results stated by Ivanišević et al., the triglyceride levelswere lower than those of the control group. On the contrary, the remaining serum cholesterol levels (Total Cholesterol, LDL and VLDL) were significantly higher in sarcoidosis group than the controls in our study.

The changes in the lipid metabolism and the accompanying increased oxidative stress lead to damage in the plasma membranes, and bronchial and pulmonary capillary endothelium (18-20). Mochizuki et al. explained that they play a role in the progression of the disease even in the early stages via the endothelial cells as seen with the inspection of respiratory samples (19). Recently, alterations in lipid profile in sarcoidosis patients were reported to be associated with increased risk of atherosclerosis (21-22). In our study, atherogenic indices were used for predicting atherosclerosis in sarcoidosis for the first time. According to our results; AI, AC, and CRR were higher in sarcoidosis compared to the control group.

Steroid treatment gives rise to adverse effects on the vascular system and the endothelial layer by suppressing proinflammatory cytokines. There are studies reporting the inhibition of endothelial nitric oxide synthase enzyme through steroid use, thus resulting in diminished levels of nitric oxide, which in turn result in elevated arterial pressure and level of norepinephrine (23). Also, corticosteroid use in sarcoidosis was reported to increase the tendency towards metabolic syndrome (24). However, there are also studies that report no associations between steroid use and vascular parameters (25). Samancı et al. studied the effect of corticosteroid use on IMT of sarcoidosis patients. They could find no significant effect of steroid use on IMT of patients with sarcoidosis (26). In our study, 5 (11.4%) participants were currently receiving corticosteroid treatment and 21 participants had used corticosteroid previously. Regarding participants with history of steroid use (N=26), IMT of 7 patients was higher than the cut-off value, which was statistically higher than that of the non-steroid users (P=0.016).

Atherosclerosis can affect the whole arterial tree including coronary and carotid arteries. It is known that coronary flow reserve may diminish significantly in sarcoidosis patients compared to healthy controls,

which in turn result in atherosclerotic changes (27-29). Hu et al. (14) reported that 2 of 4 cardiac deaths in sarcoidosis patients were associated with coronary atherosclerosis especially in older ages (≥ 60 years).

Intima-media thickness, generally evaluated in the B-Mode of linear ultrasonography, is obtained by the measurement of the combined intima and media layer thickness of the carotid artery. The thickening of the combined layers plays a role in the development and progression of atherosclerosis (30).

It has been reported that the evaluation of carotid artery IMT with ultrasonography can be used for detecting subclinic and asymptomatic atherosclerotic vascular diseases and help to catch the development of primordial atherosclerosis at an early stage. Some studies reported that IMT of carotid artery was correlated with atherosclerotic changes in other parts of the body (30-32). In our study, IMT of carotid artery in the sarcoidosis group was higher than that of the healthy controls. Additionally, a positive and significant correlation was detected between atherogenic markers (AI, AC, and CRR) and IMT in sarcoidosis patients. Furthermore, the correlation of both atherogenic indices and IMT help physician to predict pre-atherosclerotic and atherosclerotic lesions and to refer for further evaluations to decrease cardiac mortality and morbidity in asymptomatic patients.

The ultrasonographic evaluation of carotid arterial stenosis is widely used recently. PSV, in particular, increases with the narrowing of arterial caliber. There is an association between flow rate and constricted vascular bed caliber. This association was firstly defined by Spencer and Reid and named as "Spencer's Curve" (33,34). According to this principle the flow velocity of the blood passing through the stenosis site increases (35). Yong et al recently reported that, the pulse wave velocity (PWV) used to compare aortic stiffness was found to be higher in sarcoidosis patients than in the control group (36). In accordance with the literature, in our study, the PSV was also increased in sarcoidosis patients compared to the control group. Additionally, a positive correlation was detected between PSV and the intima-media thickness evaluated by ultrasonography. However, there are many studies in the literature, that specify the index of carotid artery PSV could not be used alone to determine carotid artery stenosis.

However, the index of NASCET (North American Symptomatic Carotid Endarterectomy Trial) in which the PSV is evaluated together with "end-diastolic velocity" is a correct indicator for the degree of stenosis (35,37-39).

LIMITATIONS

The present study has several limitations. First one is the limited number of study population. Second; the number of patients with advanced stage sarcoidosis was also limited. Therefore, the association between atherogenic state and advanced stage of sarcoidosis could not be assessed. The third limitation is the absence of data on the duration of the disease in the study protocol. So, the effect of duration of disease on development of atherosclerosis could not be evaluated. Another limitation was that carotid artery PSV alone was used to predict atherosclerosis. We believe that further studies should be performed to evaluate the predictor efficacy of "*NASCET index*" in sarcoidosis patients.

CONCLUSION

In conclusion, atherogenic indices are increased in sarcoidosis patients, and are associated with increased IMT. The use of Doppler ultrasonographic data of carotid artery alone as a "predictor" of atherosclerosis seems illogical, since it shows only pre-atherosclerotic and atherosclerotic lesions. Given that atherogenic indices correlate with Doppler ultrasonographic data, sarcoidosis patients should be referred to cardiology clinic for further evaluation of atherosclerosis.

Authorship Statement: Conception and design (OS, EG, EK); performance of the field, clinical, data collection (OS, EG, EK, AD, Ç, SG); data analysis and interpretation-n (EG, SG, GO); preparation of the draft manuscript (OS, EG, SG); literature analysis (SG, AD) revisions or critique and overall and/or sectional scientific management (OS, EG, EK, GÖ, Ç, AD, SG).

REFERENCES

1. Spagnolo P, Rossi G, Trisolini R, Sverzellati N, Baughman RP, Wells AU. Pulmonary sarcoidosis. Lancet Respir Med. 2018;6(5):389-402.
2. Musellim B, Kumbasar OO, Ongen G, Cetinkaya E, Turker H, Uzaslan E, et al. Epidemiological features of Turkish patients with sarcoidosis. Respir Med. 2009; 103:907-912.
3. Heikkilä HM, Trosien J, Metso J, Jauhiainen M, Pentikäinen MO, Kovanen PT, Lindstedt KA. Mast cells promote atherosclerosis by inducing both an atherogenic lipid profile and vascular inflammation. J Cell Biochem. 2010;109:615-623.
4. Simonen P, Lehtonen J, Gylling H, M Kupari. Cholesterol metabolism in cardiac sarcoidosis. Atherosclerosis. 2016;248:210-215.
5. Gunay S, Sariaydin M, Acay A. New Predictor of Atherosclerosis in Subjects With COPD: Atherogenic Indices. Respir Care. 2016;61:1481-1487.
6. Acay A, Ulu MS, Ahsen A, Ozkececi G, Demir K, Ozuguz U, Yuksel S, Acarturk G. Atherogenic index as a predictor of atherosclerosis in subjects with familial Mediterranean fever. Medicina 2014;50:329-333.
7. Singh M, Pathak MS, Paul A. A study on atherogenic indices of pregnancy induced hypertension patients as compared to normal pregnant women. J Clin Diagn Res 2015;9:BC05-BC08.
8. Dobiasova M. Czech Calculator of atherogenic risk. Available from: http://www.biomed.cas.cz/fgu/aip/calculator. php (Last accessed date 05/06/2018).
9. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al; ESC Scientific Document Group. 2018 ESC/ ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–104
10. Caminhotto Rde O, Fonseca FL, Castro NC, et al. Atkins diet program rapidly decreases atherogenic index of plasma in trained adapted overweight men. Arch Endocrinol Metab. 2015;59:568-571.
11. Bakry OA, El Farargy SM, Ghanayem N, et al. Atherogenic index of plasma in non-obese women with androgenetic alopecia. Int J Dermatol. 2015;54:339-344.
12. Rizzato G, Fraioli P, Montemurro L. Long-term therapy with deflazacort in chronic sarcoidosis. Chest. 1991;99:301-309.
13. Rybicki BA, Iannuzzi MC, Frederick MM, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). Am J Respir Crit Care Med. 2001; 164:2085-2091.

14. Hu X, Carmona EM, Yi ES, et al. Causes of death in patients with chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33(3):275-280.

15. Salazar A, Mañá J, Pintó X, et al. Corticosteroid therapy increases HDL-cholesterol concentrations in patients with active sarcoidosis and hypoalphalipoproteinemia. Clin Chim Acta. 2002;320:59-64.

16. Salazar A, Pintó X, Mañá J. Serum amyloid A and high-density lipoprotein cholesterol: serum markers of inflammation in sarcoidosis and other systemic disorders. Eur J Clin Invest. 2001;31:1070-1077.

17. Ivanišević J, Kotur-Stevuljević J, Stefanović A, et al. Dyslipidemia and oxidative stress in sarcoidosis patients. Clin Biochem. 2012;45:677-682.

18. Mochizuki I, Kubo K, Honda T. Relationship between mitochondria and the development of specific lipid droplets in capillary endothelial cells of the respiratory tract in patients with sarcoidosis. Mitochondrion. 2011;11:601-606.

19. Mochizuki I, Kubo K, Hond T. Widespread heavy damage of capillary endothelial cells in the pathogenesis of sarcoidosis–Evidence by monoclonal von Willebrand factor immunohistochemistry in the bronchus and lung of patients with sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2014; 31:182-190.

20. Psathakis K, Papatheodorou G, Plataki M, et al. 8-Isoprostane, a marker of oxidative stress, is increased in the expired breath condensate of patients with pulmonary sarcoidosis. Chest. 2004;125:1005-1011.

21. Tuleta I, Pingel S, Biener L, et al. Atherosclerotic Vessel Changes in Sarcoidosis. Adv Exp Med Biol. 2016;910:23-30.

22. Bargagli E, Rosi E, Pistolesi M, et al. Increased Risk of Atherosclerosis in Patients with Sarcoidosis. Pathobiology. 2017;84:258-263.

23. Siasos G, Tousoulis D, Gialafos E, et al. Association of sarcoidosis with endothelial function, arterial wall properties, and biomarkers of inflammation. Am J Hypertens. 2011;24:647-653.

24. Tuleta I, Skowasch D, Biener L, et al. Impaired Vascular Function in Sarcoidosis Patients. Adv Exp Med Biol. 2017;980:1-9.

25. Hellmann M, Dudziak M, Dubaniewicz A. Increased pulse wave velocity in pulmonary sarcoidosis: a preliminary study. Pol Arch Med Wewn. 2015;125:475-477.

26. Samancı NS, Poturoglu S, Samancı C, et al. Evaluation of carotid intima-media thickness with vascular endothelial growth factor and malondialdehyde levels in patients with sarcoidosis. Diagn Interv Imaging. 2017;98:557-561. doi: 10.1016/j.diii.2017.04.004.

27. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-952.

28. Santos-Gallego CG, Weiss AJ, Sanz J. Non-cardiac sarcoid actually affects the heart by reducing coronary flow reserve. Atherosclerosis. 2017;264:74-76.

29. Kul S, Kutlu GA, Guvenc TS, et al. Coronary flow reserve is reduced in sarcoidosis. Atherosclerosis. 2017;264:115-121.

30. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21:93-111.

31. Kasliwal RR, Bansal M, Desai D, Sharma M. Carotid intima-media thickness: Current evidence, practices, and Indian experience. Indian J Endocrinol Metab. 2014;18:13-22.

32. Yılmaz HEB, Yılmaz M, Erol T, en N, Ünsal ZE, Kara S, Habeşoğlu MA, Akçay Ş. Evaluation of Subclinical Atherosclerosis with Carotid Intima-Media and Epicardial Fat Thickness in Patients with Sarcoidosis. Turk Thorac J. 2020 May;21(3):174-179. doi:10.5152/TurkThoracJ.2019.19017.

33. Spencer MP, Reid JM. Quantitation of carotid stenosis with continuous-wave (C-W) Doppler ultrasound. Stroke. 1979;10:326 –330.

34. Alexandrov AV. The Spencer's Curve: clinical implications of a classic hemodynamic model. J Neuroimaging. 2007;17:6-10.

35. Von Reutern GM, Goertler MW, Bornstein NM, et al. Grading carotid stenosis using ultrasonic methods. Stroke. 2012;43:916-921.

36. Yong WC, Sanguankeo A, Upala S. Association between sarcoidosis, pulse wave velocity, and other measures of subclinical atherosclerosis: a systematic review and meta-analysis. Clin Rheumatol. 2017.

37. Hathout GM, Fink JR, El-Saden SM, Grant EG. Sonographic NASCET index: a new doppler parameter for assessment of internal carotid artery stenosis. AJNR Am J Neuroradiol. 2005;26:68-75.

38. Eliasziw M, Rankin RN, Fox AJ, et al. Accuracy and prognostic consequences of ultrasonography in identifying severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Stroke 1995;26:1747–1752.

39. Grant EG, Benson CB, Moneta GL, et al. Carotid artery stenosis: gray-scale and Doppler US diagnosis--Society of Radiologists in Ultrasound Consensus Conference. Radiology. 2003; 229:340-346.