ORIGINAL ARTICLE

Assessment of epicardial adipose tissue thickness and total calcium score in sarcoidosis patients

Sarkoidoz hastalarında epikardiyal yağ dokusu ve total kalsiyum skorunun değerlendirilmesi

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ABSTRACT

Objective: Increased thickness of epicardial adipose tissue (EAT) and the total coronary artery calcium score (TCACS) are independent predictors of atherosclerosis. The aim of this study was to investigate whether EAT thickness, measured using thoracic computed tomography, and TCACS were greater in patients with sarcoidosis.

Methods: This was a retrospective study. The details of participants who presented at the cardiology and pulmonology outpatient clinics between January 2011 and December 2018 with dyspnea, chest pain, or palpitations from the hospital data system were reviewed. Patients with transthoracic echocardiography and thorax computed tomography (CT) (CT) records were identified, and those who were diagnosed with sarcoidosis, had no other health problems, and did not take any medication were included in the study.

Results: A total of 45 controls and 78 sarcoidosis patients were enrolled. The mean age of the controls was 46.15±13.1 years, while it was 46.26±12.37 years in the sarcoidosis group, which represented no significant difference between the groups (p>0.05). When the groups were compared in terms of a fasting blood test, erythrocyte sedimentation rate (ESR), TCACS, EAT thickness, levels of C-reactive protein (CRP), total cholesterol, low-density lipoprotein (LDL), and triglycerides, it was observed that CRP and EAT thickness were higher in the sarcoidosis group.

Conclusion: The results of this study indicated that the thickness of EAT calculated using thorax CT was greater in sarcoidosis patients; however, the TCACS was similar in both groups. In addition, there was a positive correlation between EAT thickness and the level of total cholesterol, LDL, triglycerides, CRP, and the sedimentation rate. These findings suggest that atherosclerosis may start earlier in those with sarcoidosis than in the healthy population.

ÖZET

Amaç: Epikardiyal yağ dokusu (EYD) kalınlığında ve total koroner arter kalsiyum skorunda (TKAKS) artış aterosklerozun bağımsız bir öngördürücüsüdür. Bu çalışmada, sarkoidoz hastalarında bilgisayarlı toraks tomografisi ile ölçülen EYD kalınlığında ve TKAKS'de artış olup olmadığı araştırılmak istendi.

Yöntemler: Çalışma geriye dönük olarak düzenlendi. Ocak 2011 ve Aralık 2018 arasında kardiyoloji ve göğüs hastalıkları polikliniğine dispne, göğüs ağrısı veya çarpıntı nedeniyle başvuran olgular tarandı ve transtorasik ekokardiyografi ve toraks bilgisayarlı tomografisi (BT) olanlar belirlendi. Bu olgular arasından sarkoidoz hastalığı yeni tespit edilen ve tedavi almayanlar ile sağlık sorunu tespit edilmeyenler çalışmaya alındı.

Bulgular: Çalışma 45 kontrol ve 78 sarkoidoz hastasından oluşuyordu. Kontrol grubunun yaş ortalaması 46.15±13.1 iken; sarkoidoz grubunun ise 46.26±12.37 idi ve gruplar arasında anlamlı bir fark yoktu (p>0.05). Gruplar açlık kan testleri, eritrosit sedimentasyon hızı (ESH), TKAKS ve EYD kalınlığı, C-reaktif protein (CRP) seviyesi, total kolesterol, düşük dansiteli lipoprotein (LDL), trigliserit, bakımından karşılaştırıldığında; sarkoidoz grubunda CRP ve EAT kalınlığının daha yüksek olduğu görüldü.

Sonuç: Sonuç olarak, bu çalışmada toraks BT ile hesaplanan EYD kalınlığının sarkoidoz hastalarında arttığı gösterildi. Fakat TKAKS açısından gruplar karşılaştırıldığında sonuçlar benzer bulunmuştur. Buna ek olarak EYD kalınlığı ile total kolesterol, trigliserit, CRP ve ESH arasında pozitif korelasyon saptandı. Bu sonuçlar aterosklerozun sarkoidoz hastalarında sağlıklı popülasyona göre daha erken başlayabileceğini işaret etmektedir.

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Sarcoidosis is a chronic disease that primarily affects pulmonary tissue and the intrathoracic lymph nodes. The disease may also affect other systems, such as the gastrointestinal system, the eyes, the nervous system, the skin, the cardiovascular system, and the parotid glands. The cardiovascular involvement can include arrhythmia, heart failure, and microangiopathy. Involvement of the coronary arteries is uncommon. Sarcoidosis is characterized by non-caseating granulomas that contain accumulated activated T cells and macrophages. These cells secret cytokines and tumor necrosis factor alpha, which leads to a clinical manifestation of disease.[1] The principal cause of the disease is unknown. Some studies have demonstrated a genetic predisposition. Environmental factors, microbes (such as mycobacterium, propionibacterium), and undefined antigens pull the trigger on an exaggerated immune response. The disease most often appears between 20 and 50 years of age. It is more common in women, and in Scandinavians, Japanese, and Blacks.[1,2]

Abbreviations:

ALT	*Alanine aminotransferase*
AST	*Aspartate aminotransferase*
ATS	*American Thoric Society*
CRP	*C-reactive protein*
CT	*Computed tomography*
EAT	*Epicardial adipose tissue*
ERS	*European Respiratory Society*
ESR	*Erythrocyte sedimentation rate*
HDL	*High-density lipoprotein*
LDL	*Low-density lipoprotein*
TCACS	*Total coronary artery calcium score*

Adipose tissue is one of the biggest organs in the human body and performs complex endocrine tasks. Adipose tissue consists of 2 layers and covers the heart surface and other organs. The epicardial adipose tissue (EAT) is located between the myocardium and visceral pericardium and pericardial adipose tissue is located outside the visceral pericardium. The myocardium and EAT are adjacent with no boundary between them.[3] The adipokines and cytokines released from EAT directly affect the myocardium. These local hormones may be triggered by and/or contribute to the atherosclerotic process. Thus, EAT may be used as a marker of subclinical atherosclerosis.[3,4]

The total coronary artery calcium score (TCACS) is often used to assess patients at low or intermediate risk for coronary artery disease. The TCACS enables early detection of atherosclerosis, which correlates with plaque burden and subsequent subclinical ischemia.[5]This study measured EAT thickness with thorax computed tomography (CT) to determine whether this independent indicator of increased cardiovascular risk and the TCACS were greater than normal in patients with sarcoidosis.

METHODS

Study design

This was a retrospective study. The study design was approved by the İstanbul Training and Research Hospital Ethics Committee (date: 29.03.2019, no: 1762). Participants were enrolled based on hospital data system information from between January 2011 and December 2018. A total of 78 patients who were diagnosed with sarcoidosis according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria and 45 control participants were included. The sarcoidosis cases were newly diagnosed patients and did not use any medication. The disease was inactive in all case, as defined in the consensus statement of the ATS, the ERS, and the World Association of Sarcoidosis and Other Granulomatous Disorders. The control cases were patients who presented at the hospital with dyspnea and/or chest pain, did not have any chronic disease, and were examined using thorax CT. The exclusion criteria were cardiovascular disease, heart failure, moderate or advanced valvular heart disease, pregnancy, age <18 or >75 years, liver or renal failure, any other chronic disease or active infection, diabetes mellitus, hypertension, endocrine disease, or arrhythmia.

Details of anamnesis, fasting blood glucose, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood calcium, blood urea nitrogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), transthoracic echocardiography test, and thorax CT results were obtained from the hospital data system and recorded.

Assessment of blood sample tests

Levels of fasting blood glucose, total cholesterol, LDL, HDL, triglycerides, creatinine, AST, ALT, blood calcium, and blood urea were evaluated using colorimetric analysis (Cobas 8000; Roche Diagnostics, Basel, Switzerland) and the details were extracted from the hospital database. Hemogram parameters (BS-200; Mindray Medical International Co., Ltd., Shenzhen, China), CRP (turbidimetric method, AU5800; Beckman Coulter Inc., Brea, CA, USA) and ESR (Ves-matic Cube 200; Diesse Diagnostica Senese, SpA, Siena, Italy) were also recorded.

Echocardiographic evaluation

The data of heart chamber diameters, valvular pathology, and ejection fraction measured using the Simpson rule from the apical and parasternal axes with a 2.5 MHz transducer and echocardiography (Vivid 5; GE Healthcare, Inc. Chicago, IL, USA) were scanned from the files and documented.

Computed thorax tomography

Non-contrast thorax CT images of the study cases were retrieved. The measurements were performed using 64-slice CT (Aquilion 64; Toshiba Medical Systems Corp., Otawara-shi, Japan). The standard Agatston's method was used to calculate the degree of total coronary calcium score.[6,7] The total coronary calcium score and EAT thickness were calculated by the a single radiologist after the images were processed.

Statistical analysis

IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. Descriptive statistics of mean and SD were used to define some of the data, and skewness and kurtosis tests were used to assess the normality of distribution of the variables. The non-normally distributed variables of triglycerides, sodium, CRP, ESR, ALT, AST, TCACS, and EAT thickness were assessed with the Mann-Whitney U test, while normally distributed variables were assessed with an independent sample Student's t-test. The categorical variables were analyzed with a chi-squared test. Correlation analysis was used to examine the relationships between data. The relationships between EAT thickness and total cholesterol, LDL, HDL, triglycerides, CRP, and ESR were calculated using univariate regression analysis. Multivariate regression analysis was employed to examine EAT thickness and total cholesterol, LDL, and ESR, which had a p value of <0.05 in the univariate regression analysis. A p value of <0.05 was accepted as statistically significant.

RESULTS

The study included a total of 123 cases (45 controls and 78 sarcoidosis patients). In the control group, 27 (60%)

Table 1. General characteristics and biochemical test results of the groups

	Sarcoidosis group			Control group			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			46.26±12.37			46.15±13.1	0.646
Gender*							
Female	56	71		27	60		
Male	22	29		18	30		0.179
Smoking*	68	87.17		10	22.22		0.003
Glucose (mg/dL)			97.48±12.65			96.91±14.03	0.264
Total cholesterol (mg/dL)			227.7±28.23			212.19±40.5	0.019
LDL (mg/dL)			132.08±25.44			124.93±34.26	0.023
HDL (mg/dL)			43.7±8.27			43.26±9.6	0.211
Triglycerides (mg/dL)**			258.02±80.79			214.71±74.75	0.000
Urea (mg/dL)			31.41±9.91			31.94±9.8	0.704
Creatinine (mg/dL)			0.76±0.2			0.73±0.18	0.746
Sodium (mEq/L)**			139.15±1.85			139.25±3.55	0.41
Potassium (mmol/L)			4.45±0.43			4.2±0.38	0.219
Calcium (mg/dL)			9.72±0.48			9.69±0.57	0.164
AST (U/L)**			21.97±6.8			22.76±13.2	0.296
ALT (U/L)**			23.31±5.8			26.04±19.89	0.823

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HDL: High density lipoprotein; LDL: Low density lipoprotein; SD: Standard deviation. *Chi squared. **Mann-Whitney U test.

were female, and 56 (71%) members of the sarcoidosis group were female. The mean age of the controls was 46.15±13.1 years, while it was 46.26±12.37 years in the sarcoidosis group, with no significant difference between the groups (p=0.646). Among the controls, 29 (64%) were smokers, and 68 (87%) in the patient group were smokers, which represented a significant difference. Smoking was more common in the sarcoidosis group (p=0.003). All of the participants had a sinus rhythm. The sarcoidosis patients had been recently diagnosed and had not been treated with any medication. Comparisons between the groups of the fasting blood glucose, total cholesterol, LDL, HDL, and triglyceride levels were conducted. The total cholesterol, LDL, and triglyceride levels were higher in the sarcoidosis group (p=0.019, 0.023, 0.000, respectively), but there was no meaningful significant difference in the fasting blood glucose and HDL values between the groups (p=0.264, 0.211, respectively). The other biochemical test and hemogram parameter results were also similar (p>0.05). When the groups were compared in terms of the acute phase reactants of CRP and ESR, the CRP level was higher in the sarcoidosis group (p=0.000), while there was no difference between the groups with regard to the ESR level (p>0.05). The groups were also similar in terms of ejection fraction. The results are summarized in Tables 1–3.

Thorax CT scans performed for any reason were compared in terms of EAT thickness and TCACS. There was no significant difference between groups in the TCACS (p=0.907); however, the EAT thickness in

Table 2. Hemogram parameters and acute-phase reactant results

	Sarcoidosis group	Control group	*p*
Hemoglobin (g/dL)	13.76±1.76	13.6±1.76	0.82
White blood cell (10^9/L)	7.77±2.46	8.21±2.19	0.238
Platelet (10^9/L)*	277.93±85.16	271.93±57.2	0.642
Erythrocyte sedimentation rate (mm/h)	22.97±18.3	21.88±13.7	0.495
C-reactive protein (mg/dL)*	8.46±9.67	2.07±2.05	0.000

*Mann-Whitney U test.

Table 3. Echocardiography and computed thorax tomography results

	Sarcoidosis group	Control group	*p*
Ejection fraction (%)	64.1±1.93	64.11±1.92	0.981
EAT thickness (mm)*	5.67±2.47	3.38±0.91	0.000
Total coronary artery calcium score*	14.95±68.75	22±75.31	0.907

EAT: Epicardial adipose tissue; Ejection fraction was calculated via echocardiography, and EAT thickness and total coronary artery calcium score were measured via computed tomography of the thorax. *Mann-Whitney U test.

Table 4. The correlation analysis of some parameters

No	Variable	1	2	3	4	5	6	7
1	Total cholesterol	1						
2	Low-density lipoprotein	0.791**	1					
3	High density lipoprotein	-0.268**	-0.54**	1				
4	Triglycerides†	0.616**	0.228**	-0.127	1			
5	C-reactive protein†	0.301**	0.257**	-0.085	0.226*	1		
6	Erythrocyte sedimentation rat	0.058	0.032	0.079	0.001	0.225*	1	
7	Epicardial adipose tissue thickness†	0.328**	0.265**	-0.012	0.26**	0.455**	0.24*	1

*p<0.05; **p<0.01. †Spearman correlation analysis.

the sarcoidosis group was greater than that of the controls (p=0.000).The results are presented in Table 3.

Correlation analysis revealed that there was a positive correlation between EAT thickness and total cholesterol, LDL, triglycerides, CRP, and ESR. These results indicated that EAT thickness increased when these other variables increased. The results of correlation analysis are displayed in Table 4.

Univariable and multivariable regression analysis in sarcoidosis group of the relationship between EAT thickness and some laboratory variables revealed a positive association between ESR and EAT thickness. The results of regression analysis are shown in Tables 5 and 6.

Table 5. The univariable regression analysis of EAT thickness and some laboratory variables in the sarcoidosis group

Variable	EAT thickness		
	R^2	β&CI	*p*
Total cholesterol	0.05	0.020 (0.000 to 0.039)	0.049
LDL	0.083	0.028 (0.007 to 0.049)	0.011
HDL	0.011	-0.031 (-0.099 to 0.037)	0.367
Triglycerides	0.000	0.000 (-0.007 to 0.007)	0.964
ESR	0.104	0.043 (0.014 to 0.073)	0.005
CRP	0.009	0.024 (-0.034 to 0.082)	0.41

CI: Confidence interval, CRP: C-reactive protein; EAT: Epicardial adipose tissue; ESR: Erythrocyte sedimentation rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; R^2: Coefficient of determination.

Table 6. Multivariable regression analysis of EAT thickness and total cholesterol, LDL, and ESR in the sarcoidosis group

Variable	EAT thickness	
	β&CI	*p*
Total cholesterol	-0.067 (-0.229 to 0.095)	0.412
LDL	0.093 (-0.070 to 0.256)	0.261
HDL	0.059 (-0.117 to 0.234)	0.506
Triglycerides	0.013 (-0.018 to 0.045)	0.404
ESR	0.042 (0.012 to 0.072)	0.008
CRP	0.007 (-0.051 to 0.065)	0.820

CI: Confidence interval, CRP: C-reactive protein; EAT: Epicardial adipose tissue; ESR: Erythrocyte sedimentation rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein. Adjusted R^2=0.121; p=0.021.

DISCUSSION

In recent studies, it has been established that an increase in EAT thickness was related to coronary artery disease and atherosclerosis.[8] This study sought to determine whether EAT thickness was greater in patients with sarcoidosis. To the best of our knowledge, this is the first such study in the literature. EAT thickness was calculated using thorax CT in patients with sarcoidosis. According to the findings of the study, EAT was thicker in patients with sarcoidosis than in healthy subjects. There was a positive correlation between EAT thickness and total cholesterol, LDL, triglycerides, ESR, and CRP. Multivariable regression analysis determined a relationship only between EAT thickness and ESR.

EAT is localized between the myocardium and visceral pericardium, with vascularization supplied by branches of the coronary arteries. EAT has multiple metabolic and endocrine functions. Therefore, EAT protects the cardiovascular system from some mechanical and metabolic damage.[8,9] However, when EAT thickness increases, these properties are reversed. The levels of many proinflammatory and atherogenic mediators, such as leptin, resistin, visfatin, interleukin 1, and tumor necrosis factor alpha, increase in the blood. As a result, it has been suggested that the EAT volume is associated with coronary artery disease, vulnerable plaque, and TCACS.[10,11] Some subclinical markers, such as an increase in carotid intima media thickness, increase with EAT thickness, and might help to establish an early diagnosis of disease. There are a few studies that have investigated the existence of atherosclerotic cardiovascular disease in patients with sarcoidosis. It has been reported that arterial stiffness, a marker of atherosclerosis, increased in sarcoidosis.[12] Tuleta et al.[13] found that pulse wave index measurements were higher in a sarcoidosis group. In another recently published study, it was observed that coronary flow reserve was reduced in patients with sarcoidosis compared with healthy subjects.[14] Our study results indicated that sarcoidosis patients had a greater EAT thickness.[14] Thorax CT is used in the diagnosis and follow-up of sarcoidosis, and can provide information about EAT thickness. Indications of greater EAT thickness could prompt a review modifiable cardiovascular risks.

Like an increase in EAT thickness, TCACS is a well-recognized and useful marker of the presence

and burden of subclinical coronary atherosclerosis. In addition, TCACS provides information about the progression of coronary atherosclerosis.[15] Research has yielded significant evidence of important associations between an elevated TCACS and the risk of future cardiovascular disease.[16,17] In a study that compared a normal population against participants wit type I diabetes mellitus, the TCACS of healthy group was lower than that of the diabetes group.[18] In our study, there was no significant difference in the TCACS between groups, which may be related to the duration of disease. Only newly diagnosed sarcoidosis patients were recruited for this study.

Sarcoidosis is a systemic granulomatosis disease. Activated proliferative T cells and mononuclear phagocytes secret several mediators, such as interleukins. It has been reported that in inflammatory disease, endogenous agents affected serum lipoprotein concentration and metabolism.[19] Simonen et al.[20] investigated changes in the lipid metabolism of patients with cardiac sarcoidosis. They found that the levels of lipid absorption markers were higher in the patients than in the healthy controls. In our study, the levels of total cholesterol, LDL, and triglycerides were higher in the sarcoidosis group ($p<0.05$). Furthermore, these findings correlated positively with EAT thickness. Though the lipoprotein levels were higher in the sarcoidosis group, the total cholesterol, LDL, HDL, and triglyceride levels were similar in both groups. Increased EAT thickness in patients with sarcoidosis may be explained by a high blood level of non-HDL cholesterol. Non-HDL cholesterol elevation may be associated with chronic inflammation.

CRP is a marker of immune system activation. The CRP level is known to increase in all clinical situations that trigger the inflammatory circle. It has also been demonstrated that the level of CRP was increased in cases of coronary heart disease, unstable angina pectoris, and myocardial infarction with complication. In addition, the CRP level has a prognostic value in coronary artery disease.[21] In this study, the CRP level was higher in the sarcoidosis group than in the healthy controls and a positive correlation between EAT thickness and CRP level was observed. Açıksarı et al.[22] investigated endothelial dysfunction in patients with sarcoidosis and found that the CRP level was higher in the sarcoidosis group. Similar results were obtained from studies of rheumatologic diseases, such as psoriasis vulgaris, systemic amyloidosis, and ankylosing spondylitis.[23–25] It may be related to the chronic inflammatory process of sarcoidosis. There was a positive correlation between the ESR and CRP. The ESR was slightly higher in the sarcoidosis group and there was no discrepancy between the groups ($p>0.05$). It may have been due to the fact that the disease was not in the active phase.

The primary limitations of this study are the small sample size and retrospective design. Some demographic data such as body mass index, weight, height were not available. Due to the small number of sarcoidosis patients, no comparison was made between patients with and without hyperlipidemia in terms of TCACS. Also, EAT thickness was not measured using transthoracic echocardiography.

Sarcoidosis is a chronic inflammatory disease. Greater EAT thickness is a marker of atherosclerosis. The results of this study using thorax CT demonstrated that EAT thickness was greater in patients with sarcoidosis. Also, we found that there was correlation between EAT thickness and total cholesterol, LDL, HDL, triglycerides and CRP level. Increased EAT thickness may be a predictive marker of cardiovascular involvement in patients with sarcoidosis.

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Ethical statement: The study design was approved by the İstanbul Training and Research Hospital Ethics Committee (date: 29.03.2019, no: 1762).

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Keywords: Atherosclerosis; epicardial adipose tissue thickness; sarcoidosis; total coronary calcium score.

Anahtar sözcükler: Eteroskleroz; epikardiyal adipöz doku kalınlığı; sarkoidoz; koroner arter kalsiyum skoru.