

Yeni tanı konulan ankilozan spondilitli hastalarda epikardiyal yağ dokusu kalınlığı hastalık ciddiyeti ile ilişkisi

Epicardial adipose tissue thickness is associated with disease severity in patients with newly- diagnosed ankylosing spondylitis

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ÖZ

GİRİŞ ve AMAÇ: İnflamatuvar hastalıklarda kardiyovasküler hastalıkların eşlik ettiği daha önceki çalışmalarda tanımlanmıştır. Geleneksel risk faktörlerinin yanı sıra epikardiyal yağ dokusu koroner ateroskleroz gelişim ve ilerlemesine katkıda bulunur. Bu çalışmada yeni tanı konulan ankilozan spondilitli (AS) hastalarda transtorasik ekokardiyografi ile ölçülen epikardiyal yağ dokusu kalınlığı ile hastalık ciddiyeti arasındaki ilişkiyi araştırmayı amaçladık.

YÖNTEM ve GEREÇLER: Bu retrospektif çalışmada yeni tanı konulan ankilozan spondilitli hastaların transtorasik ekokardiyografi raporları tarandı. Ayrıca katılım kriterlerini sağlayan yaş ve cinsiyet eşlenik bireyler kontrol grubu olarak çalışmaya dahil edildi.

BULGULAR: 100 birey [40.00 (34.25- 48.00) yıl, 65% erkek] çalışmaya dahil edildi. Epikardiyal yağ dokusu kalınlığı AS'li hastalarda kontrol grubuna göre artmıştı ($p<0.001$). Spearman'ın korelasyon analizinde epikardiyal yağ dokusu kalınlığı ile AS hastalık aktivite skoru koreleydi ($r=0.652$, $p<0.001$). Ayrıca lineer regresyon analizinde epikardiyal yağ dokusu kalınlığı, AS hastalık aktivite skoru ile bağımsız olarak ilişkiliydi ($p=0.001$).

TARTIŞMA ve SONUÇ: AS hastalık aktivite skoru, yeni tanı konmuş AS'li hastalarda epikardiyal yağ dokusu kalınlığı ile bağımsız olarak ilişkilidir. İlk tanıda AS hastalık aktivite skoru hastaların kardiyovasküler risk ve primer koruma stratejisi için yol gösterebilir.

Anahtar Kelimeler: ankilozan spondilit, epikardiyal yağ dokusu, kardiyovasküler hastalık

ABSTRACT

INTRODUCTION: Cardiovascular (CV) disease is a well-described co-morbidity in patients with inflammatory arthritis. Epicardial adipose tissue (EAT) contributes to the development and progression of coronary atherosclerosis independent of traditional CV risk factors. In this study, we aimed to investigate whether EAT thickness determined by transthoracic echocardiography (TTE) in newly-diagnosed ankylosing spondylitis (AS) patients is associated with AS severity.

METHODS: In this retrospective study, TTE reports of newly-diagnosed AS patients were reviewed. Age- and gender-matched control subjects who fulfilled the inclusion criteria were also included in the study.

RESULTS: 100 subjects [40.00 (34.25- 48.00) years, 65% male] were included in the study. EAT thickness was significantly increased in AS patients when compared to the controls ($p<0.001$). In Spearman's correlation analysis, EAT thickness in AS patients was found to be positively correlated with the Ankylosing Spondylitis Disease Activity Score (ASDAS) ($r=0.652$, $p<0.001$). In the linear regression analysis, EAT thickness was found to be independently associated with ASDAS ($p=0.001$).

DISCUSSION AND CONCLUSION: Our results indicates that ASDAS is independently associated with EAT thickness in newly- diagnosed AS patients. ASDAS at the first diagnosis may guide the patient's CV risk and primary prevention strategies.

Keywords: ankylosing spondylitis, epicardial adipose tissue, cardiovascular disease

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INTRODUCTION

Cardiovascular (CV) disease is a well-described co-morbidity in patients with inflammatory arthritis. Although the relationship between rheumatoid arthritis (RA) and CV morbidity and mortality is primarily investigated in previous studies(1-4), an association also exists between the wide spectrum of CV disease (CVD) and axial spondylo arthritis including ankylosing spondylitis (AS), psoriatic arthritis, and gouty arthritis(5, 6).

Epicardial adipose tissue (EAT) is the visceral adipose tissue of the heart, that is known to cover 80% of the heart's surface(7). Due to its numerous metabolic and endocrine functions, increased thickness of EAT has been suggested to contribute to risk of developing CVD and metabolic syndrome in various studies(8-10). EAT thickness has also been associated with the presence and severity of coronary artery disease (CAD)(11-15). These studies have demonstrated that EAT thickness contribute to the development and progression of coronary atherosclerosis independent of traditional CV risk factors(11-15).

In this study, we aimed to investigate whether EAT thickness determined by transthoracic echocardiography in patients with newly- diagnosed AS is associated with AS severity, reflected with Ankylosing Spondylitis Disease Activity Score (ASDAS), which may guide the primary prevention strategies from CVD in AS patients.

MATERIALS AND METHODS

Study population

Patients who were newly- diagnosed with AS in Department of Physical Medicine and Rehabilitation were included in the study. Patients with a prior history of hypertension, hyperlipidemia, diabetes mellitus, smoking; concomitant infectious and inflammatory diseases; known or suspected cardiovascular diseases and/ or malignancy were excluded. Age and gender- matched control subjects who fulfilled the inclusion criteria were recruited from outpatient clinics of Department of Cardiology. Detailed medical history, laboratory and physical examination findings and transthoracic echocardiography (TTE) reports were reviewed for all subjects. In the patient group, diagnosis of AS was made using the modified New York criteria(16).

ASDAS was used to determine disease activity in AS patients(17). A previous study(18) has developed and validated an Assessment of SpondyloArthritis international Society (ASAS)- endorsed ASDAS consisting of total back pain, duration of morning stiffness, the BASDAI question on peripheral joints, patient global assessment of disease activity and CRP, whereas ESR for the acute phase reactant could be used in cases when CRP is not available.

Measurement of EAT thickness

All patients underwent a comprehensive transthoracic echocardiographic (TTE) examination during sinus rhythm. PhilipsEpiq 7® Ultrasound Machine with a 3.6 MHz probe was used. Echocardiographic measurements were acquired from three consecutive beats. Epicardial fat was identified as the echo-free space between the outer wall of the myocardium and the visceral layer of pericardium. EAT thickness was measured perpendicularly on the free wall of the right ventricle at end-systole in three cardiac cycles on Standard parasternal views. Maximum EAT thickness was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus, used as anatomical landmark for this view. The average value of three cardiac cycles from each echocardiographic view was taken into account.

Statistical analysis

Normally distributed parameters were presented as mean± standard deviation and skewed parameters were expressed as median (interquartile range defined as 25-75th percentiles). Descriptive data were presented as frequencies (number and percentage) and compared using chi-square test. Univariate analyses were performed on continuous variables with the use of the independent student's t-test for normally distributed variables and the Mann-Whitney U test for non- normally distributed data. Spearman correlation analysis was used to demonstrate the correlation between EAT thickness and baseline characteristics. Linear regression analysis was used for identifying factors that were independently correlated with EAT thickness. Statistical analyses were performed using SPSS statistical software (version 21.0; SPSS Inc., Chicago, Illinois, USA). A two- tailed $p < 0.05$ was considered statistically significant.

RESULTS

100 subjects [40.00 (34.25- 48.00) years, 65% male] were included in the study. Baseline characteristics of the study population are shown in Table 1. Age and gender did not differ among patient

and control groups. EAT thickness was significantly increased in AS patients when compared to the controls. Furthermore, serum C- reactive protein levels (CRP) and erythrocyte sedimentation rate (ESR) were significantly increased in AS patients when compared to the controls (**Table 1**).

Table 1. Baseline characteristics of the study population (n= 100).

Parameters	Study population (n= 100)	Control group (n= 50)	Ankylosing spondylitis patients (n= 50)	p value
Age (years)	40.00 (34.25- 48.00)	40.00 (34.00- 46.00)	39.00 (35.00- 45.00)	0.786
Gender: male n (%)	65 (65.00)	32(64.00)	33 (66.00)	0.904
Body mass index (kg/m ²)	25.12± 4.17	25.66± 4.41	24.22± 3.11	0.119
Left ventricular end-diastolic diameter (mm)	45.53± 3.73	45.46± 3.80	45.59± 3.71	0.883
Left ventricular ejection fraction (%)	62.65± 4.54	62.00± 5.01	62.68± 4.10	0.947
Left atrial diameter (mm)	35.66± 3.81	35.90± 2.97	36.90± 3.81	0.193
Epicardial adipose tissue thickness (mm)	4.00 (3.25- 5.10)	3.50 (3.10- 4.00)	4.75 (3.80- 6.05)	<0.001*
C- reactive protein (mg/dL)	10.30 (3.33- 32.55)	9.00 (6.00- 13.00)	10.30 (3.33- 32.55)	0.025*
Erythrocyte sedimentation rate (mm/ hr)	37.00 (16.00- 50.50)	27.00 (21.00- 32.00)	37.00 (16.00- 50.00)	0.009*
White blood cell count (x10 ³ /µL)	7.20 (6.30- 9.05)	6.90 (6.00- 8.80)	7.30 (6.40- 9.20)	0.206
High density lipoprotein-cholesterol (mg/dL)	48.00 (40.75- 55.25)	50.50 (42.25- 57.75)	46.00 (40.00- 54.00)	0.643
Low density lipoprotein-cholesterol (mg/dL)	130.50 (107.25- 152.00)	121.50 (98.75- 156.50)	138.50 (110.00- 150.00)	0.356
Triglyceride (mg/dL)	116.50 (87.00- 170.75)	111.00 (86.50- 172.25)	132.50 (87.00- 170.50)	0.552
Total cholesterol (mg/dL)	200.50 (177.75- 225.50)	194.00 (160.25- 230.75)	208.00 (184.00- 224.00)	0.335
Fasting blood glucose (mg/dL)	96.50 (86.00- 107.25)	96.50 (89.50- 105.75)	97.50 (85.75- 108.50)	0.126

* denotes statistical significance.

Of 50 patients, 24 had high (2.1- 3.5) or very high (>3.5) disease activity, where 26 of them had inactive disease (<1.3) or low (1.3- 2.1) disease activity according to ASDAS scores. EAT thickness was significantly higher in patients with high or very high disease activity, when compared to patients with inactive disease or low disease activity [0.54 (0.47- 0.72) vs. 0.40 (0.31- 0.46) cm, p<0.001]. In Spearman's correlation analysis, EAT thickness in AS patients was found to be positively correlated

with ASDAS (r=0.652, p<0.001) (**Table 2**). In the linear regression analysis, EAT thickness was found to be independently associated with ASDAS and thereby with the disease activity in the newly-diagnosed AS patients (**Table 3**).

Table 2. Correlation of epicardial adipose tissue thickness and baseline characteristics in patients with ankylosing spondylitis (n= 50)

		Epicardial adipose tissue thickness	
Spearman's rho	Age (years)	Correlation coefficient	,167
		P value	,251
	Body mass index (kg/m ²)	Correlation coefficient	,084
		P value	,560
	Left ventricular ejection fraction (%)	Correlation coefficient	-,039
		pvalue	,808
	Left ventricular end- diastolic diameter (mm)	Correlation coefficient	,136
		P value	,397
	Left atrial diameter (mm)	Correlation coefficient	,093
		P value	,563
ASDAS		Correlation coefficient	,652
		P value	<0,001*
C- reactive protein (mg/dL)		Correlation coefficient	,228
		P value	,151
Erythrocyte sedimentation rate (mm/ hr)		Correlation coefficient	,117
		P value	,465
White blood cell count (x10 ³ /µL)		Correlation coefficient	,023
		P value	,879
High- density lipoprotein- cholesterol (mg/dL)		Correlation coefficient	,023
		P value	,884
Low- density lipoprotein- cholesterol (mg/dL)		Correlation coefficient	,152
		P value	,338
Triglyceride (mg/dL)		Correlation coefficient	,125
		P value	,429
Total cholesterol (mg/dL)		Correlation coefficient	,204
		P value	,195
Fasting blood glucose (mg/dL)		Correlation coefficient	,082
		P value	,646

ASDAS ankylosing spondylitis disease activity score.

Table 3. Linear regression analysis to determine independent associates of epicardial adipose tissue thickness in patients with ankylosing spondylitis (n= 50).

Variable	Univariate model					Multivariate model				
	Unstandardized		Sig.	95% Confidence		Unstandardized		Sig.	95% Confidence Interval	
	Coefficients			Interval for B		Coefficients			for B	
	B	Std. Error	Lower	Upper	B	Std. Error	Lower Bound	Upper Bound		
ASDAS	0.196	0.034	<0.001*	0.127	0.265	0.162	0.044	0.001*	0.072	0.252
C- reactive protein (mg/ dL)	0.001	0.001	0.142	0.000	0.002	0.000	0.001	0.821	-0.002	0.003
Total cholesterol (mg/ dL)	0.001	0.000	0.181	0.000	0.002	0.000	0.001	0.509	-0.001	0.002

ASDAS ankylosing spondylitis disease activity score.

* denotes statistical significance.

DISCUSSION

Findings of our study are unique for demonstrating the significant association between ASDAS and EAT thickness, as a surrogate marker of CVD risk, in newly- diagnosed AS patients.

Although an association between AS and CVD other than coronary artery disease, such as hypertension(19) and left ventricular diastolic dysfunction(20), has been documented, due to the young age of AS patients at the time of diagnosis, evaluation of ischemic CVD risk in AS has been relatively hard and studies that have been performed have led to inconsistent results. A meta analysis published in 2011 has shown that AS patients did not have increased risk of cardiovascular events when compared to healthy controls (21). However, a population- based study that was not included to the meta- analysis has shown an increased prevalence of CVA, ischemic heart disease, and peripheral vascular disease in 8.616 AS subjects(22). Another population- based study has also reported an increased standardized morbidity rate ratio of ischemic heart disease (IHD) in 935 AS subjects(23). Despite a negative association for CV and cerebrovascular events in 1.686 AS subjects and 1.206.621 controls in Wales(24), an increased hazard ratio (HR) for incident IHD in AS subjects compared to non-AS controls have been reported in a Taiwanese population(25).

There are currently no studies in the literature evaluating the associates of CVD risk in newly-diagnosed AS patients. A previous study has shown that EAT thickness was higher in AS patients when compared to the controls and there was a significant correlation between carotid intima-media thickness and EAT thickness in AS patients(26). However both were also significantly correlated with duration of disease(26). Our study demonstrates that EAT thickness is significantly higher in newly- diagnosed AS patients when compared to controls and that EAT thickness is significantly correlated to disease severity. Considering the previously documented link between EAT thickness and CVD, EAT thickness in newly- diagnosed AS patients may suggest the association between AS and CVD. ASDAS at first diagnosis is positively correlated with EAT thickness; therefore ASDAS at first

diagnosis may be an indirect determinant of future CVD risk in these patients.

Echocardiography, computed tomography (CT) and magnetic resonance imaging (MRI) may be used to evaluate EAT thickness. Echocardiography allows quick and adequate assessment of EAT in most clinical situations. It provides reliable data, since echocardiographic measurement of EAT thickness have been shown to be correlated with MRI measurements ($r = 0.91$, $p = 0.001$)(9). Echocardiography is performed with low cost, is not time- consuming, and does not require any special software for analysis of data. Points under debate for the use of echocardiography include the location of measurement and determination of most suitable time in the cardiac cycle (since some recommends the measurement during systole to prevent possible deformation by compression during diastole(27) and others in diastole, to coincide with other imaging modalities)(28).

Role of CT and MRI is increasing due to high spatial resolution and the possibility of volumetric assessment. MRI is considered the gold standard for the assessment of total body fat, and also the detection and quantification of EAT(9). The interobserver reproducibility of EAT volume measurement has been reported to be superior to the EAT thickness measurement; however, it is technically more difficult. The measurement of maximum EAT thickness is more feasible, without significant accuracy decrease (29, 30). For EAT measurements by CT, there is no need to use contrast (unless obtained from CT angiography); however, radiation exposure occurs at a predetermined phase of the cardiac cycle (65-85% of RR interval). EAT thickness, volume and total area can be accurately measured by CT. The difficulty in standardizing measurement locations limits the determination of EAT thickness reference values by CT. Similar to echocardiography, EAT thickness assessment by CT is susceptible to interobserver variability, however may be minimized by EAT volume measurement (31, 32).

There are several limitations of this study. First, this is a retrospective study, and reveals only an association. Second, our sample size is relatively small. Third, subclinical atherosclerosis markers, other than EAT have not been assessed.

CONCLUSION

Our results indicates that ASDAS is independently associated with EAT thickness in newly- diagnosed AS patients. ASDAS at the first diagnosis may guide the patient's CV risk in newly-diagnosed AS patients without major CVD risk factors.

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DECLARATION OF CONFLICT OF INTEREST

All authors declare no conflict of interest.

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