Evaluation of epicardial adipose tissue thickness and carotid-media thickness in children with Behçet's disease

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Abstract

Objective

Behçet's disease (BD) is a systemic vasculitis affecting all sizes of arteries and veins. Approximately 5–10% of patients with BD are present during childhood. The chronic nature of the disease may lead to serious cardiovascular complications over time including early atherosclerosis. Increased levels of epicardial adipose tissue (EAT) and carotid intima-media thickness (CIMT) are considered early signs of subclinical atherosclerosis. Ongoing chronic inflammation may cause to increase in both EAT and CIMT. In this study, we aimed to evaluate CIMT and EAT in children with BD and determine their relationship with the clinical manifestations and course of the disease.

Methods

This cross-sectional study evaluated 30 patients with juvenile-onset BD and age-sex-matched 20 healthy controls. The CIMT and EAT thickness were measured by the same paediatric cardiologist. The association between clinical features, baseline disease activity, disease duration, EAT thickness and CIMT was also evaluated.

Results

Thirty children with BD and 20 age-sex-matched healthy volunteers enrolled in the study. The most common BD-related feature was oral aphthous (n=30), followed by mucocutaneous findings (n=22). Uveitis was observed in 5 patients, vascular involvement in 4, neurological involvement in 4, and gastrointestinal involvement in 2. All patients were inactive at the time of evaluation. The EAT thickness was significantly higher in patients while CIMT levels revealed no significant differences. However, there was no correlation between disease duration, baseline disease activity, and EAT thickness.

Conclusion

Increased EAT thickness may be a risk factor for early atherosclerosis in patients with BD. The EAT thickness was found to be significantly higher in paediatric BD patients. Confirmation of results in larger series may provide better insight into early screening for risk factors in these patients.

Key words

Behçet's disease, cardiovascular involvement, epicardial adipose tissue thickness, carotid intima-media thickness

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Introduction

Behçet's disease (BD), also known as the Silk Road Disease, is a variable vessel vasculitis characterised mainly by recurrent oral and genital aphthous lesions. The disease may exhibit a variety of symptoms including gastrointestinal, ocular, neurologic, cardiovascular, and musculoskeletal manifestations (1, 2). Although the disease mostly affects individuals between the 2nd and 4th decades of life, 5-10% of the patients present in childhood (2). The prevalence of cardiac involvement, morbidity, and mortality are higher in adult BD patients. Cardiac involvements in BD include the coronary arteries, pericardium, myocardium, endocardium, and the great vessels. Coronary artery aneurysm and stenosis, aortitis and aortic valve insufficiency, mitral valve prolapse and mitral insufficiency, intracardiac thrombosis and pulmonary-cerebral embolism, conduction diseases and arrhythmias may be seen in the course of the disease. Adult studies showed that patients with BD are at risk for endothelial dysfunction and early atherosclerosis as well (3, 4). Atherosclerosis is considered a form of chronic inflammation resulting from the interaction between modified lipoproteins, monocyte-derived macrophages, T cells, and the cellular elements of the arterial wall (5). Ongoing inflammation in rheumatic diseases may cause endothelial dysfunction and predispose to early atherosclerosis (6). Juvenile BD patients might be more likely to experience such long-term complications since it is a lifelong disease.

Epicardial adipose tissue (EAT) is a kind of visceral fat tissue. It is located between the myocardium and visceral pericardium and surrounds atrioventricular grooves and great coronary vessels. EAT is not separated by connective tissue from the myocardium and major coronary vessels. Unlike other visceral adipose tissues, it is an extraordinarily active paracrine tissue secreting many pro-inflammatory and anti-inflammatory mediators (7, 8). The paracrine properties of EAT and the close proximity to the coronary arteries and myocardium could have significant impact on the cardiovascular health and diseases. Carotid intima-media thickness (CIMT) is an ultrasound-based evaluation measuring the distance between the interface lumen-intima and the interface media-adventitia. Increased CIMT is considered as an early manifestation of subclinical atherosclerosis. Obesity and metabolic syndrome, sickle cell disease, inflammatory bowel disease, juvenile idiopathic arthritis, non-alcoholic fatty disease, familial hypercholesterolaemia can cause over time increased CIMT in children (9). Herein, we aimed to evaluate the EAT thickness and CIMT in children with BD.

Material methods

This is a cross-sectional study which was conducted between June 2022 and December 2022. Patients who were followed with a diagnosis of juvenile-onset BD and fulfilled the paediatric BD (PEDBD) classification criteria were enrolled in the study (1). Juvenile-onset BD was defined as the disease that fully appeared and was diagnosed in patients before the age of 16 years. The control group consisted of 20 age- and gender-matched healthy children and adolescents. Patients with a concomitant disease or obesity were excluded. Demographic data, clinical and laboratory features, treatment schedules, and disease outcomes were collected by a standard form. Patients were divided into subgroups according to the system involvement; 1. mucocutaneus involvement, 2. ocular involvement, 3. vascular involvement, and 4. neurological involvement.

Standard deviation score (SDS)s of weight, height, WC and BMI were computed using the least mean squares (LMS) method and the references for Turkish children (10).

All patients underwent echocardiography by a paediatric cardiologist (G.A.) (Canon Aplio i900). B-Mode, M-Mode images and pulsed Doppler measurements were obtained. The CIMT and EAT thickness were measured by the same paediatric cardiologist (G.A.). CIMT was measured by using a 7.5 mHz transducer in a patient with supine position and the neck slightly hyperextended. The average of three manual measurements in the right carotid artery was obtained for each patient, 1-2 cm

proximal to the bifurcation (11). Subsequently, CIMT-SDS was calculated using the LMS method and height-specific normative values (Fig. 1) (12). The EAT thickness was measured on the free wall of the right ventricle in both parasternal long- and short-axis views at end diastole by using 3.5-5 mHz transducer. Three measurements, each comprising 3 cardiac cycles were recorded and then their average values were calculated (Fig. 2) (13).

Hemogram, biochemistry, homocysteine and Von Willebrand Factor (vWF) levels were collected in the morning after a 12-hour fasting. All blood parameters were analysed using routine laboratory methods.

The disease activity was assessed by the Iranian BD dynamic activity measure (IBDDAM) and by the physician global assessment (PGA) scale (14).

The study protocol was approved by the local ethics committee. Informed consent was obtained from all participants before the study.

Statistical analysis

The statistical analysis was performed by using SPSS v. 21.0 (SPSS, Inc., Chicago, Illinois). The variables were evaluated using visual (histogram, probability plots) and analytic methods (Kolmogrov-Smirnov/Shapiro-Wilk's test) to determine whether they are normally distributed. Descriptive analyses were shown as proportion, mean, standard deviation (SD) median, and minimum-maximum whichever were appropriate. The Chi-square test or Fisher's exact test was used to examine the associations between two categorical variables whichever was appropriate. Comparisons of numeric variables between groups were carried out using independent samples T-test/Mann-Whitney U-test, whichever was appropriate. The Pearson test was used to evaluate the associations between variables. The significance was tested at the 5% level and differences were considered statistically significant at $p \leq 0.05$.

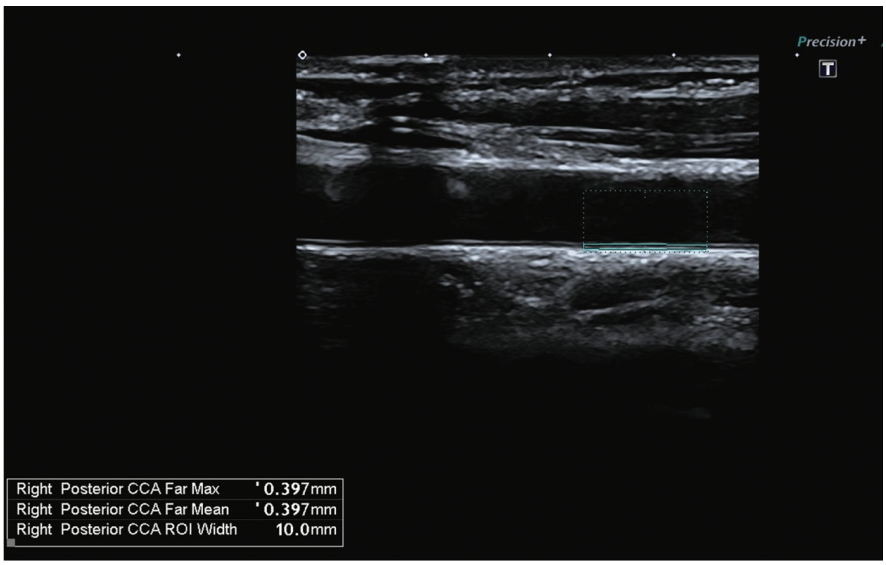

Fig. 1. Measurement of carotid intima-media thickness (CIMT).

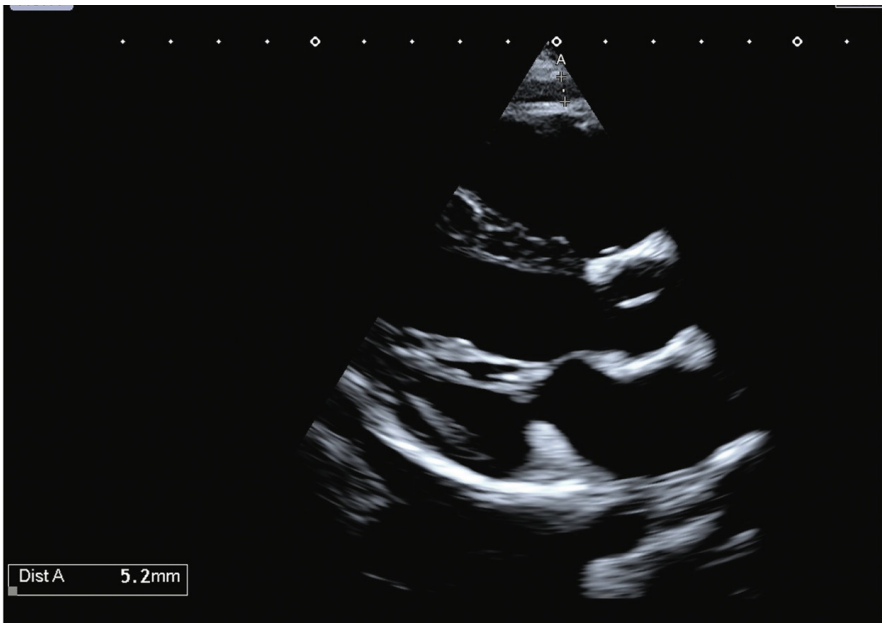

Fig. 2. Measurement of epicardial adipose tissue (EAT) thickness.

Results

Baseline clinical findings of patients

This cross-sectional study included 30 patients with juvenile onset BD and age-sex matched 20 healthy controls (Table I). Among 30 juvenile-onset BD, 18 (60%) were female, 12 (40%) were male. The median age of diagnosis was 156 (108-190) months. The median time between the onset of symptoms and diagnosis was 6 (6-12) months. All patients suffered from oral aphthous ulceration. Other mucocutaneus features accompanying the disease were as follows: genital ulcers (n=22, 73.3%), pseudofollicutis (n=19, 63.3%), erythema nodosum (n=9, 30%). Arthralgia was present in 22 (73.3%) patients and arthritis was detected in 9 (30%). Five (16.7%) patients presented with uveitis. Four (13.3%) patients had vascular involvement. Neurological and gastrointestinal involvements were observed in 4 (13.3%) and 2 (6.7%) patients, respectively. Pathergy test was positive in 5 (16.7%) patients and HLA-B51 was positive in 24 (80%) patients. Nine (30%) patients had a family history of BD. The median IBDDAM and PGA were 3 (3-8) and 4 (3-8), respectively.

Treatments and outcomes of patients

All patients were given colchicine. Fifteen patients were also treated with az-

athioprine. Five patients were receiving biologic drugs (adalimumab = 3 and infliximab = 2) due to uveitis (n=3) and vascular involvement (n=2). All patients were clinically inactive and none of them were treated with corticosteroids at the time of evaluation.

At the time of cardiac evaluation

The median age of patients was 16.5 (13-18) years at the time of cardiac evaluation. The median time of disease duration was 33 (18–78) months. As shown in Table II, the median SDS of CIMT (0.43 *vs*. 0.44, *p*=0.559) was similar to healthy control while EAT thickness (6.89 *vs*. 4.6, *p*=0.003) was significantly higher in BD patients compared to healthy individuals. There were no significant differences in terms of CIMT, CIMT-SDS and EAT thickness between subgroups of BD regarding mucocutaneous, ocular, vascular, and neurological involvements (*p*>0.05). Furthermore, there was no correlation between disease duration, baseline disease activity and EAT thickness (*p*>0.05). Baseline cardiovascular findings were also depicted in Table II. There were no differences between patient and control group in terms of hemogram and biochemistry parameters, homocysteine and vWF levels (Table III).

Table I. Demographic and anthropometric findings of groups.

	Juvenile onset BD group (n=30)	Control group (n=20)	*p*-value
Age, years*	16.5 (13-18)	16 (13-18)	0.345
Female/Male**	12/18	8/12	1.000
BMI SDS*	0.45 (-1.78-1.34)	0.48 (-0.90-1.29)	0.966
Weight SDS*	0.46 (-1.93-1.20)	0.52 (-1.29-1.05)	0.666
Height SDS*	0.35 (-1.65-2.09)	0.36 (-1.04-1.66)	0.223

*Data presented as median (minimum-maximum) and Mann-Whitney U-test were used to compare two groups.
**Categorical variables were compared with the Chi-square test or Fisher's exact test where appropriate.
BD: Behçet's disease; BMI: body mass index.

Table II. Cardiovascular findings of groups.

	Juvenile onset BD group (n=30)	Control group (n=20)	*p*-value
EF (%)*	70 (58-79)	65 (58-71)	0.056
SF (%)*	39 (30-48)	35 (30-39)	0.109
IVSd (mm)*	8 (6-10)	8 (6-10)	0.541
LVDs (mm)*	27 (21-42)	28 (20-31)	0.802
LVDd (mm)*	44 (36-53)	43 (30-50)	0.407
LVPWd (mm)*	7 (6-10)	7 (5-9)	0.205
CIMT (mm)*	0.415 (0.290-0.546)	0.391 (0.376-0.658)	0.699
CIMT SDS*	0.43 (-1.34-3.89)	0.44 (-0.71-1.63)	0.559
EAT thickness (mm)*	6.89 (4-9.70)	4.6 (3.5-7.2)	**0.003**

*Data presented as median (minimum-maximum), and Mann-Whitney U-test were used to compare two groups.
BD: Behçet's disease; CIMT: carotid intima media thickness; EAT: epicardial adipose tissue; EF: ejection fraction; SF: shortening fraction; IVSd: interventricular septal thickness diastolic diameter; LVDd: left ventricular end-diastolic diameter; LVDs: left ventricular end-systolic diameter; LVPWd: left ventricular posterior wall thickness diastolic diameter.

Table III. Laboratory findings of patients and controls at the time of cardiac evaluation.

	Juvenile onset BD group (n=30)	Control group (n=20)	p-value
Leukocyte count, /mm^{3*}	7100 (4270-14900)	8625 (6200-14970)	0.100
Haemoglobin, gr/dL*	13.1 (10.3-14.6)	13.05 (11.7-14.2)	0.638
Platelet count, /mm^{3*}	271500 (184000-367000)	322000 (224000-365000)	0.519
MPV, fL*	10 (8.1-12.1)	9.7 (8.8-11.1)	0.589
Triglycerides, mg/dL*	68.9 (44-150)	58 (44-130)	0.403
Total cholesterol, mg/dL*	138.5 (110-180)	136 (112-144)	0.461
LDL cholesterol, mg/dL*	70.65 (49-129)	67 (49-70)	0.119
HDL cholesterol, mg/dL*	48.5 (26-70)	51 (26-63)	0.565
CRP, mg/dL*	2.65 (0.5-4.5)	3.14 (1.2-10.6)	0.336
Homocysteine level*, μmol/l	9.35 (5.06-15.4)	8.7 (5.1-13)	0.450
Vitamin B12 level, ng/L*	338 (221-1152)	356 (278-1152)	0.239
VW Factor level, %*	102.8 (27.4-194)	106.1 (55.9-194)	0.774

*Data presented as median (minimum-maximum) and Mann-Whitney U-test were used to compare two groups.
LDL: low-density lipoprotein; HDL: high-density lipoprotein; MPV: mean platelet volume; CRP: C reactive protein.

Discussion

To our best knowledge, this is the first study focusing on EAT thickness in juvenile onset BD. We found increased EAT thickness in BD patients while CIMT-SDS was not statistical different compared to healthy peers.

Studies have shown that ongoing inflammation is associated with endothelial dysfunction. BD has a chronic inflammatory background and may predispose to premature atherosclerosis. CIMT serves as a non-invasive tool for assessing endothelial health. Measurement of CIMT may be valuable for risk assessment of early atherosclerosis in patients with chronic inflammatory disease. A meta-analysis by Merashli *et al*. (15) showed a 2.85-fold increased risk of carotid plaques in adult BD patients with a pooled prevalence of 12%. However, studies focused on CIMT in BD patients revealed high statistical heterogeneity and conflicting results. For instance, some studies reported increased CIMT values in adult BD patients (16-20) while the others reported similar CIMT levels between adult BD patients and healthy controls (21-23). However, there was only one study that evaluated CIMT in juvenile-onset BD patients. Most recently, Demir *et al*. (24) reported that CIMT values were comparable between BD patients with and without vascular involvement. Nevertheless, they demonstrated that BD patients with vascular involvement exhibited increased aortic stiffness. However, the aforementioned study does not include a control group. Herein we showed

that CIMT-SDS levels were similar between BD patients and gender-matched healthy peers. Furthermore, there were no significant differences between subgroups of BD in terms of CIMT and CIMT-SDS. Increased CIMT as an early sign of atherosclerosis and a result of ongoing chronic endothelial damage from systemic inflammation seems to be associated with the disease duration and age. Chronic ongoing inflammation in juvenile BD patients may cause over time endothelial injury and increased CIMT with early atherosclerosis (16).

Epicardial adipose tissue is a part of visceral fat tissue and is a source of various pro-inflammatory and pro-atherogenic mediators (25). EAT is accumulated around the heart and reflects visceral adiposity. It is considered as a cardiometabolic risk factor (13). Yüksel *et al*. (3) evaluated 36 adults with ocular BD without overt vasculitis and 35 age and gender-matched healthy individuals. They reported that both EAT thickness and CIMT were significantly higher in BD than healthy controls. Furthermore, EAT thickness and CIMT values were positively correlated with disease duration. They also suggested that CIMT values greater than 0.45 mm predicted the presence of BD with 83% sensitivity and 84% specificity (3). Taşolar *et al*. (4) compared 35 adult BD patients with 35 healthy volunteers in terms of EAT thickness and flow-mediated, endothelium-dependent dilatation. They found that EAT thickness was significantly higher while flow-mediated, endothelium-dependent dilatation significantly lower in BD patients than in healthy controls. In the aforementioned study, EAT thickness was positively correlated with BD activity. In our study, EAT thickness was significantly higher in BD patients while there was not any association between disease duration, baseline disease activity and EAT thickness. EAT stores free fatty acids to protect coronary circulation and cardiomyocytes from excessive circulating lipids and releases free fatty acids as an immediate energy source for the myocardium. Therefore, a definite relationship between EAT thickness and obesity is present as expected (26). However, increased EAT thickness may be seen in non-obese individuals who have cardiovascular or chronic inflammatory diseases. In the presence of inflammation, EAT shows dense inflammatory infiltrates including macrophages, mast cells, T cells, B cells, and releases many pro-inflammatory mediators such as IL-1, IL-6, TNF-α (20). These dense inflammatory infiltrates and excessive paracrine/endocrine activity may be responsible for increased EAT thickness.

Many laboratory parameters have been utilized as a biomarker for assessing the risk of early atherosclerosis or endothelial dysfunction. Yücel *et al*. (27) showed that adult BD patients had higher levels of tumour necrosis factor-α, a high sensitive C-reactive protein (CRP), homocysteine, apoA1, apoB, high density lipoprotein (HDL), and erythrocyte sedimentation rate (ESR) than healthy controls. Çalık *et al*. (28) showed that higher pentraxin-3, homocysteine and CRP levels were correlated with impaired echocardiographic parameters in patients with BD. Özdemir *et al*. (29) demonstrated a correlation between elevated homocysteine levels and increased CIMT values in adult BD patients. Another adult study presented high levels of vWF in BD patients compared to healthy controls (30). Hypercoagulable state with endothelial cell activation was also shown in BD patients without vascular involvement (31). However, in our study, no differences were observed between patient and control groups in terms of laboratory parameters.

Single centre design and small sample size are limitations of our study. Another limitation of the study was the lack of a disease control group.

In conclusion, we demonstrated increased EAT thickness in juvenile onset BD patients. Controlling disease activity and prevention from long-term complications should be a part of disease management. Increased EAT thickness may indicate the possible risk of early atherosclerosis. Increasing knowledge of this issue may provide physicians to serve a better care. However, since ethnic and environmental factors play an important role in the course of the disease, the present results need to be confirmed by international multicentre studies.

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