Original Article

Carotid artery stiffness in Behçet's disease

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Abstract

Objective: Increased carotid arterial stiffness (CAS) is a predictor of subclinical early atherosclerosis as well as carotid intima-media thickness (cIMT). We aimed to determine CAS and cIMT in Behçet's disease (BD).

Material and Methods: BD (n=49) and rheumatoid arthritis (RA) (n=64) patients and healthy controls (HC) (n=40) were included in the study. cIMT was measured. CAS indices, including arterial compliance (AC), arterial distensibility (AD), Young's elastic modulus (YEM), Peterson's elastic modulus (Ep), and β stiffness index (βSI) were measured based on the diameter-pressure relationship.

Results: When compared to the HC group, the mean cIMT was significantly higher in the RA group (p=0.033), but it was not higher in the BD group. The CAS indices, including AD, AC, Ep, and βSI were not significantly different among the study groups. Moreover, the cIMT and CAS indices were not significantly different between active (n=20) and inactive BD patients, and these indices were not correlated with the scores of disease activity. AD, AC and Ep were significantly lower in the BD patients with a positive pathergy reaction than in those with a negative reaction.

Conclusion: These results suggest that BD does not directly lead to arterial stiffness or to an increase in cIMT.

Keywords: Behçet's disease, arterial stiffness, intima-media thickness

Introduction

Behçet's disease (BD) is a chronic inflammatory disease that leads to recurrent genital ulcers, oral aphthae, skin lesions, uveitis, and vascular involvement (1). The etiology of BD is not fully known, but it has been demonstrated that vasculitis affecting the small and large vessels of the venous and arterial systems is the predominant lesion. Vascular involvement in BD consists of vein thrombosis, arterial thrombosis, and arterial aneurysm (2). Venous system involvement is observed in roughly one-third of all patients, but arterial involvement is usually seen in fewer than 5%. In BD, when vascular involvement is seen at any site, it is known that the risk of vascular involvement and progressive multifocal vascular complications even in different regions is increased (3).

Increased and accelerated atherosclerosis is found in several rheumatic inflammatory diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), but this increase is not observed in BD (4). Both structural and functional changes can influence arterial stiffness. Endothelium-derived nitric oxide (NO) and other local and/or circulating vasoactive agents affect the stiffness of arteries. Endothelial dysfunction leads to the proliferation of smooth muscle cells and increased structural proteins, especially collagen, in the extracellular matrix. Increased inflammatory mediators in the circulation can stimulate the infiltration of leukocytes into the artery wall, and the occurrence of these structural and functional changes can also initiate changes in the vessel wall (5).

Measurement of carotid arterial stiffness (CAS) is a simple, inexpensive, non-invasive, and repeatable method for showing vascular involvement. CAS is an independent predictive marker of cardiovascular events as well as carotid intima-media thickness (cIMT) (6, 7). Abnormalities in CAS have been shown in several inflammatory rheumatic diseases, and CAS has been demonstrated to be increased in RA, antiphospholipid antibody syndrome, systemic sclerosis, spondyloarthritis, and SLE (5, 8-12).

Carotid arterial stiffness has been evaluated in a few studies with small numbers of BD patients, and controversial results have been obtained from these studies (13-15). Therefore, we aimed to evaluate cIMT and CAS in a cohort of patients with BD.

Material and Methods

Participants

A total of 49 patients with BD, 64 patients with RA, and 40 healthy controls (HC) were included in this cross-sectional study. The patients met established criteria that are used for diagnosis and classification in routine practice (16, 17).

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The exclusion criteria of the study were younger than 18 years, older than 80 years, evidence of infection, and pregnancy. The study protocol was approved by the local Ethics Committee of Fırat University. All participants signed an informed consent form. They were questioned for detailed medical histories, and their systemic and rheumatologic examinations were performed. The clinical progress of the participants and their treatment protocols were also recorded.

Disease activity and severity scoring

Behçet syndrome activity score (BSAS) and disease activity score (DAS) - 28 were calculated in the BD and RA groups, respectively (18, 19). BD patients were considered as active when a patient had a BSAS score ≥2 with the following clinical involvements: skin lesions, genital ulcers, active arthritis, recent vascular involvement, recent eye involvement, recent neurological involvement, a positive pathergy test in addition to oral ulcer, as well as high C-reactive protein (CRP) and/or high erythrocyte sedimentation rate (ESR).

Measurement of CAS indexes and cIMT

Arteria carotis cominis (ACC) ultrasonography (USG) was performed on all participants. USG evaluations were performed a with high-resolution model USG device My Lab70 6-18 MHz B-mode USG device (Esaote; Genoa, Italy). Participants were examined in the supine position with the neck rotated 45 degrees in the direction opposite the site being examined. cIMT was measured on the far wall at 5 mm, 10 mm, and 15 mm proximal to the carotid bifurcation, over both the right and left ACC. The IMT was defined as the distance from the first echogenic line to the second echogenic line. For statistical evaluations, the average of six measures was accepted as the participant's IMT (20). The mean IMT was defined as the mean of the six measurements (three for each side).

Based on the pressure-diameter relationship, the CAS indexes of arterial compliance (AC), arterial distensibility (AD), Young's elastic module (YEM), Peterson's elastic module (Ep), and β stiffness index (βSI) were calculated. The following formulas were used for measurement of the CAS. Carotid AC = [systolic diameter (Ds) - diastolic diameter (Dd)] / [systolic pressure (Ps) - Diastolic pressure (Pd)]; carotid strain = (Ds - Dd) / Dd; βSI = ln (Ps / Pd) / carotid strain; AD = diameter difference (ΔD) / pressure difference (ΔP) × diameter; AC = ΔD / ΔP; Elastic Modulus = ΔP x volume / volume difference × wall thickness (7).

Laboratory analysis

Blood samples were taken between 08:00 and 10:00 in the morning after 8-12 hours of fasting. All of the routine laboratory tests of the participants, complete blood counts, ESR, CRP, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting blood glucose, and creatinine were analyzed on the same day by standard methods.

Statistical analysis

Data were analyzed using the Statistical Packages for the Social Sciences (SPSS) version 21 software (IBM Corp.; Armonk, NY, USA). Data were expressed as mean±SD. The *Kolmogorov*-Smirnov test was used to evaluate whether variables had a normal distribution. Parametric data were analyzed with analysis of variance (ANOVA) and post-hoc Tukey test. Non-parametric data were analyzed with the Mann-Whitney U test. Analysis of covariance (ANCOVA) was also used to adjust variables for sex and age because the gender distribution and mean age were significantly different among the groups. Categorical data were analyzed by the Chi-squared test. Pearson's correlation analysis was used to determine the relationships among the data. A p-value <0.05 was accepted as statistically significant.

Results

The demographic and clinical data are summarized in Table 1. The mean disease durations were 7.0±6.0 and 8.7±8.8 years in the BD and RA groups, respectively (p=0.247).

The BSAS was 14.8±17.2 in the BD group, and 20 patients with BD were active. All of the BD patients (n=49) had oral ulcers, while 43 patients had genital ulcers. Moreover, 18 patients had erythema nodosum-like lesions, 42 patients had acneiform lesions, 6 patients had neurological involvement, and 11 patients had vascular involvement. Also, the pathergy test was positive in 15 BD patients. In the BD group, 10 patients were taking corticosteroids, 38 patients were taking colchicine, 25 patients were taking azathioprine, 3 patients were taking cyclosporine, 2 patients were taking cyclosporine, 11 patients were taking acetylsalicylic acid, and 2 patients were taking warfarin.

In the RA group, the mean DAS-28-ESR was 3.1±1.5, and 35 patients had active disease. Rheumatoid factor was positive in 32 patients, and anti-cyclic citrullinated peptide antibody was positive in 38 patients in the RA group. Of the patients with RA, 46 of them were taking corticosteroids, 30 were taking methotrexate, 15 were taking leflunomide, 14 were taking sulfasalazine, 24 were taking hydroxychloroquine, and 4 were taking biological drugs.

The mean cIMT was significantly higher in the RA group (p=0.033), but not in the BD

Table 1. Demographics and laboratory characteristics in the study groups

	HC (n=40)	RA (n=64)	BD (n=49)	p
Sex (F/M)	11/29	13/51	21/28	0.001[b]
Age (years)	43.5±13.5	50.3±15.1*	37.3±11.2[†††]	<0.001[a]
BMI (kg /m²)	26.8±4.9	27.2±5.5	26.5±4.4	0.764[a]
ESR (mm/h)	16.3±10.9	33.8±23.7***	23.1±21.8[†]	<0.001[a]
CRP (mg/dL)	0.31±0.32	2.46±3.65**	1.37±2.23	0.002[a]
WBC (10³/μL)	6.5±1.5	7.3±2.3	7.2±2.2	0.174[a]
Hb (g/dL)	13.8±1.4	12.3±1.7***	13.4±1.5[††]	<0.001[a]
PLT (10³/μL)	266.8±68.7	294.3±9.8	260.4±77.3	0.083[a]
Total cholesterol (mg/dL)	190.7±53.2	168.9±35.2	173.3±51.8	0.059[a]
Triglycerides (mg/dL)	147.5±90.1	99.9±47.8*	145.4±125.7[†]	0.008[a]
LDL (mg/dL)	136.8±46.2	110.2±31.1**	113.0±47.2[†]	0.004[a]
HDL (mg/dL)	50.2±14.0	50.4±13.5	50.6±17.2	0.994[a]
Smoking, n (%)	10 (25)	21 (32)	8 (16)	0.670[b]
HT, n (%)	8 (20)	21 (32)	8 (16)	0.029[b]
DM, n (%)	1 (2)	9 (14)	1 (2)	0.018[b]
CAD, n (%)	0	2 (4)	1 (2)	0.425[b]

HC: healthy control; RA: rheumatoid arthritis; BD: Behçet's disease; F: female; M: male; BMI: Body Mass Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol: HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease

Data were expressed as mean±standard deviation.

[a]ANOVA and [b]chi-square p-values.

When compared to the HC group; *p<0.05, **p<0.01, ***p<0.001.

When compared to the RA group; [†]p<0.05, [††]p<0.01, [†††]p<0.001.

group, compared to the HC group. However, there was no significant difference in terms of CAS indices, including AD, AC, Ep, and βSI, among the study groups (Table 2). Even after adjustments for age and gender, arterial stiffness indexes were not significantly different in the study groups (ANCOVA p>0.05 for all). Moreover, there were no significant differences in terms of cIMT and these CAS indices between active (n=20) and inactive BD patients (p>0.05 for all), and these indices were not correlated with disease activity score (p>0.05 for all).

There were no significant differences in cIMT and CAS indexes between BD patients with vascular involvement (n=11) and BD patients without vascular involvement, (p>0.05 for all). Also, there were no differences in cIMT and CAS indexes between patients with neurobehçet (n=6) and patients without neurobehçet (p>0.05 for all).

In pathergy test-positive BD patients compared to negative BD patients, carotid AD (4.6±1.7 vs. 6.7±3.2 cm^2·dyn^{-1}·10^{-3}, p=0.040) and carotid AC (1.3±0.4 vs. 1.9±0.7 mm^2/kPa, p=0.011) were significantly lower. Conversely, Ep was signifi-

cantly higher in pathergy test-positive BD patients than pathergy test-negative BD patients (612±578 vs. 352±89 kPa, p=0.032). However, in pathergy test-positive and negative BD patients, there were no significant differences in terms of cIMT or other CAS indexes (p>0.05 for all).

There were no significant differences between smoking (n=10) and non-smoking BD patients in terms of cIMT or CAS indexes (p>0.05 for all). BD patients with hypertension (HT) had significantly higher Ep (526.9±107.9 vs. 464.3±364.1 kPa, p=0.04) and cIMT (0.71±0.10 vs. 0.61±0.09 mm, p=0.04) compared to BD patients without HT. However, carotid AD was significantly lower (4.1±0.8 vs. 5.6±2.5 cm^2·dyn^{-1}·10^{-3}, p=0.044) in the hypertensive BD patients.

The mean dose of corticosteroid was higher in the BD (n=10) group compared to the RA (n=46) group (8.8±5.5 vs. 4.6±4.0 mg/day, p=0.008). In the BD group, there were no significant differences in terms of IMT or CAS indexes between patients who were taking and who were not taking corticosteroids, azathioprine, or acetylsalicylic acid (p>0.05 for all). Similarly, ESR and CRP levels were not associated with cIMT or CAS indexes in BD patients (p>0.05 for all).

Carotid intima-medis thickness was positively correlated with diastolic arterial blood pressure, body mass index (BMI), total-cholesterol, and triglyceride levels in the BD group. However, carotid AD was negatively correlated with BMI and with duration of the disease (Table 3).

Table 2. Intima-media thickness and arterial stiffness indexes in the study groups

	HC (n=40)	RA (n=64)	BD (n=49)	p
Mean carotid IMT (mm)	0.64±0.08	0.68±0.13	0.62±0.09†	0.035^a
Carotid AD (cm^2·dyn-1·10^{-3})	5±1	4.7±2.5	5.5±2.4	0.241^a
Carotid AC (mm^2/ kPa)	1.4±04	1.3±0.6	1.5±0.5	0.295^a
Ep (kPa)	467.4±146.2	600.1±486.1	471.9±343.1	0.113^a
YEM (kPa)	219.9±71.7	297.7±279.9	240.5±17.2	0.159^a
βSI	4.7±1.2	5.8±4.6	4.9±3.5	0.219^a
Carotid Strain (%)	9.9±3.1	9.3±4.2	10.8±4.4	0.173^a
Artery plaques, n (%)	1 (2)	4 (6)	2 (4)	0.648^b
Systolic BP (mmHg)	122.5±14.1	126.1±18.3	120.1±1.2	0.196^a
Diastolic BP (mmHg)	79.5±8.4	81.8±11.1	77.5±12.3	0.113^a

HC: healthy control; RA: rheumatoid arthritis; BD: Behçet's disease; IMT: intima-media thickness; AD: arterial distensibility; AC: arterial compliance; Ep: Peterson's elastic modulus; YEM: Young's elastic modulus; βSI: β Stiffness Index; BP: blood pressure.
Data were expressed as mean±standard deviation.
^{a}ANOVA and ^{b}chi-square p-values.
When compared to the RA group; †p<0.05.

Table 3. Correlation analysis of the data in the BD group

	Carotid IMT		Ep		YEM		βSI		Carotid AD		Carotid AC		Carotid strain	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Age	0.297	0.051	0.021	0.895	0.006	0.969	-0.077	0.619	-0.266	0.081	-0.230	0.133	-0.055	0.721
Disease duration	0.091	0.541	0.101	0.493	0.103	0.487	0.023	0.875	-0.356	0.013	-0.324	0.024	-0.183	0.213
Systolic BP	0.245	0.089	0.095	0.518	0.061	0.676	-0.102	0.485	-0.097	0.506	-0.085	0.563	0.248	0.086
Diastolic BP	0.294	0.041	0.088	0.549	0.046	0.755	-0.114	0.437	-0.036	0.807	-0.008	0.959	0.225	0.120
BMI	0.291	0.045	0.102	0.490	0.053	0.720	0.028	0.848	-0.285	0.049	-0.240	0.100	-0.136	0.355
BSAS	0.023	0.874	-0.174	0.232	-0.171	0.239	-0.108	0.460	0.058	0.692	0.098	0.502	-0.074	0.612
ESR	0.213	0.142	0.015	0.920	-0.019	0.898	0.025	0.866	-0.068	0.642	-0.057	0.698	-0.162	0.265
CRP	0.107	0.530	-0.028	0.870	-0.100	0.556	0.002	0.990	-0.086	0.614	-0.058	0.733	-0.143	0.399
TC	0.504	0.000	-0.066	0.664	-0.079	0.603	-0.134	0.376	0.063	0.677	0.173	0.251	0.120	0.427
TG	0.426	0.003	-0.087	0.567	-0.119	0.432	-0.122	0.420	-0.002	0.991	0.132	0.383	0.011	0.941
LDL	0.243	0.104	0.075	0.620	0.083	0.583	0.010	0.950	0.039	0.796	0.074	0.625	0.100	0.507
HDL	0.075	0.618	-0.078	0.607	-0.083	0.584	-0.092	0.543	0.132	0.382	0.123	0.417	0.146	0.331

IMT: intima-media thickness; Ep: Peterson's elastic modulus; YEM: Young's elastic modulus; βSI: β Stiffness Index; AD: arterial distensibility; AC: arterial compliance; BP: blood pressure; BMI: Body Mass Index; BSAS: Behçet's syndrome activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TC: total cholesterol; TG: triglycerides; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol

Discussion

In this study, we evaluated the parameters that are early indicators of vascular involvements such as CAS and IMT in BD and RA patients. There were no significant differences among the groups in terms of CAS indexes. Compared with the HC subjects, the average cIMT was higher in the RA group, but not higher in the BD group.

Behçet's disease is a vasculitis that can affect the arteries and veins of all sizes. Systemic inflammation is known to be associated with endothelial cell dysfunction, and endothelial dysfunction is accepted as the earliest evidence of vascular involvement and is known to cause arterial stiffness (5). In BD patients, 41% of mortality is caused by large-vessel disease and 12% by heart diseases (21). Thus early diagnosis and treatment of cardiovascular involvement is vital. The first signs of the involvement are deterioration in NO bioavailability, endothelial dysfunction, and increased arterial stiffness (22).

Coronary angiography is the standard method to determine symptomatic or significant cardiovascular involvements, and the coronary artery calcium score viewed by multidetector computed tomography angiography is a non-invasive method for determination of early coronary atherosclerosis. However, these approaches expose the patient to radiation, are expensive, and show only structural changes (23). Thus, recent studies have focused on methods using USG to evaluate the structural and functional changes, and such methods have the potential to detect pathology earlier.

Methods evaluating arterial stiffness reflect the risk of developing vascular events. Increased AD, AC, and carotid strain indexes are related to decreased risk of death due to cardiovascular causes, coronary ischemic events, and other vascular events, although increased Ep, YEM, and βSI have been shown to be related to an increase in these incidents (24).

Controversial results have been obtained in studies related to cIMT in patients with BD. cIMT has been reported to be high in some studies on BD (13, 25-28). However, this high value has not been detected in other studies (14, 29-31). In our study, the mean cIMT value of the BD group was no higher than the HC group. In the RA group, the cIMT value was significantly higher than in the BD and HC groups.

In our study, early and accelerated atherosclerosis was not observed in BD patients, which is in contrast to previous studies (32). A previous study showed increased cIMT values in BD patients with vascular involvement compared to those without vascular involvement (27). In another study, the cIMT values of BD patients with vascular involvement were found to be similar to the control group (33). Our study also showed no significant difference between cIMT values in cases with and without vascular involvement. Although BD is a vasculitis that can affect the arteries and veins of all sizes, it predominantly affects lower extremity veins and generally shows regional involvement. Therefore, it is possible that the structural and functional changes in the vessels are limited to the involved region.

The pathergy phenomenon is an exaggerated inflammatory response against any factor that disrupts the integrity of the tissue or a minor injury, and the release of abnormal cytokines occurs with minimal trauma (34). This leads to perivascular infiltration and excessive inflammatory response. Therefore, it has been suggested that the interaction of cell adhesion molecules might play a role in endothelial proliferation. In our study, BD patients with a positive pathergy test had significantly lower AD and AC values and higher Ep values compared to those with a negative test. This situation might be the result of an exaggerated response by the vascular endothelium to any factor that disrupts the tissue integrity in pathergy-positive BD patients. This result suggests that pathergy test positivity might be useful in identifying patients who are at risk for developing early arterial stiffness.

The results of several studies that have evaluated CAS are incompatible with each other with regards to BD patients (14, 30, 35-38). Some studies have shown increased arterial stiffness in BD patients (14, 30, 35-38). On the other hand, Kurum et al. (15) have shown that the pulse wave velocity (PWV) of BD patients is similar to the healthy controls. Moreover, in patients with BD, the AD value has been reported to be lower and to be similar to healthy controls (27, 30). In our study, there was no significant difference in arterial stiffness values between the BD and HC groups.

Behçet's disease patients with and without arterial involvement have been reported to have similar arterial distensibility (27, 30). In our study, BD patients with and without arterial involvement also had similar arterial distensibility. In another study, PWV was shown to be significantly higher in active BD patients (39).

However, in our study, the arterial stiffness indexes of active BD patients and BD patients in remission were not significantly different.

Behçet's disease affects the venous system rather than the arteries, and it can be expected that arterial stiffness indexes and cIMT values are unchanged in BD because they evaluate the arterial system. In addition, BD does not lead to accelerated atherosclerosis in contrast to other inflammatory diseases. It has been reported that atherosclerotic plaque formation is not increased in BD (40), and Seyahi et al. (31) have shown that plaque frequency and mean cIMT are not higher in BD patients compared to healthy controls.

Our study had some limitations. The numbers of patients might be inadequate to evaluate the different BD involvements. In addition, other arteries such as the aorta, femoral arteries, brachial artery, and innominate artery have a potential involvement risk and should be evaluated.

In conclusion, CAS and cIMT measurements in patients at high risk of cardiovascular diseases are simple, repeatable, and non-invasive techniques to detect the atherosclerotic risk. These indexes are obtained by USG and provide information about impaired endothelial function prior to the development of significant structural changes in the arterial wall. In the present study, there were no significant differences between BD and HC in terms of arterial stiffness indexes or cIMT values. These results suggest that there is no increase in atherosclerosis in BD patients in contrast to other inflammatory rheumatic diseases.

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