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Original Article

Evaluation of endothelial function in patients with Behçet's disease in remission: A cross-sectional study

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Abstract

Objective: Endothelial dysfunction is an initial stage of the atherogenic process, which can be evaluated by a noninvasive method (flow-mediated dilation - FMD) and has a well-established prognostic value for cardiovascular (CV) risk. Currently, there is no evidence of increased CV mortality in Behçet's disease (BD), although its association with endothelial dysfunction has been described. There are still doubts in the literature whether the presence of chronic vascular inflammation might trigger the development of atherosclerosis, despite BD remission, which is why this study was conducted.

Methods: We analyzed 24 subjects in this cross-sectional study (12 patients with BD in remission and 12 subjects matched by gender age). Endothelial function was analyzed via FMD.

Results: The lowest median for FMD was presented by the BD group (2.025% - interquartile range (IQR) 7.785 versus 5.46% - IQR 3.625, $P = .18$). The median total cholesterol in the BD group was lower than the controls (168 mg dL^{-1} - IQR 46 and 216.5 mg dL^{-1} - IQR 54, respectively, $P = .0193$). In the right carotid artery, the intima-media thickness was equal to 0.740 - IQR 0.16 for the patients and 0.740 - IQR 0.11 for the controls ($P = .9473$); on the left, 0.725 - IQR 0.13 and 0.745 - IQR 0.120 ($P = .4333$), respectively.

Conclusion: The lower median trend of FMD in patients with BD suggests endothelial dysfunction, despite clinical remission of the inflammatory disease, although our study is limited by the sample size and greater use of statins in BD group.

Keywords: Carotid intima-media thickness, atherosclerosis, cross-sectional studies, Behçet's disease

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Introduction

Behçet's disease (BD) is a systemic vasculitis of unknown etiology, characterized by episodes of aphthous stomatitis, genital ulcers, cutaneous, and ophthalmological lesions. Other systems can also be affected, such as the central nervous, gastrointestinal, and vascular (thrombosis and aneurysms in the arteries and veins of any caliber) systems.[1–3] Vascular involvement is a worse prognostic factor, affecting about 20-30% of patients, being more frequent and more severe in young men.[4] The highest prevalence of the disease is in the Middle East and Mediterranean. In the past, BD was believed to predominate in the male gender. Nevertheless, more recent data have revealed similar involvement between men and women.[5]

Atherosclerosis is a chronic inflammatory disease of multifactorial origin that occurs in response to endothelial aggression, mainly affecting the intima layer of medium and large caliber arteries. From this aggression, endothelial dysfunction increases the permeability of the intima to plasma lipoproteins, favoring their retention in the subendothelial space. The deposit of lipoproteins in the arterial wall is a key process at the beginning of atherogenesis. Thus, endothelial dysfunction is considered the initial lesion in the development of atherosclerosis.[6] Although it has been described that there is no higher cardiovascular (CV) mortality in BD,[7] data from the meta-analysis of Merashli et al.[8] revealed an impairment of flow-mediated dilation (FMD) in patients with this vasculitis, to a greater degree in those with active disease, as well as an increase in intima-media thickness (IMT), and a higher prevalence of carotid plaques compared to healthy controls.

This study aimed to evaluate the endothelial function of patients with BD in remission, and to compare it with a paired population by sex and age, using the technique of FMD of the brachial artery. Blood inflammatory markers, lipid profile, and anthropometric data for metabolic syndrome were also analyzed, allowing a more accurate evaluation of the CV risk of these patients during remission of the disease.

Methods

Patients

Twelve patients older than 18 years with BD according to the International Study Group on Behcet's disease criteria[9] attended at the Rheumatology Outpatient Clinic of the Pedro Ernesto University Hospital (HUPE) between July 2016 and July 2018, in remission for at least 1 month, according to BR-BDCAF.[10] The control group was composed of 12 HUPE-UERJ employees with no evidence of autoimmune disease, matched by age and sex. All subjects signed an informed consent to be included in the study, which was presented to the HUPE Research Ethics Committee. Individuals who presented acute coronary syndrome in the last 3 months or with uncontrolled arterial hypertension (systolic blood pressure $\geq$ 160 mmHg or diastolic blood pressure $\geq$ 110 mmHg) were excluded. The sample was calculated in the OpenEpi program, version 3, open source statistics calculator for public health, available at http://www.openepi.com.

Clinical and laboratory evaluation

We evaluated endothelial function using FMD, a noninvasive method, initially described by Celermajer et al.[11] This protocol is established and validated by the literature for the assessment of endothelial function,[12] based on ultrasound images and measurements of the brachial artery.[11,13,14] It shows prognostic relevance,[15] being a predictor of CV events. According to the meta-analysis of Inaba et al.,[16] each 1% increase in FMD yields a 13% decrease in the risk of CV events. The methodology used was the same as that described in the Guideline of the American College of Cardiology, published in 2002.[17] There is no traditional percentage value that suggests the preservation of endothelial function, but this guideline defined that the minimum absolute difference of 1.5%-2% in FMD would be statistically significant after interventions, considering the minimum sample size of 20-30 individuals in cross-sectional studies.[17]

Main Points

- The endothelial dysfunction in the BD population, even during remission, possibly determines a higher risk of atherosclerosis.
- Even BD patients in remission are at risk for long-term arterial damage.
- This reinforces the need for control of traditional cardiovascular risk factors to retard the development of additional cardiovascular disease.

An initial measurement of the arterial diameter was performed, followed by a new measurement 60 seconds after deflation of the cuff. These values were used to calculate the percentage variation of the diameter (FMD%). The cuff was positioned in the forearm, distally to the transducer located in the brachial artery, and inflated to 200 mm Hg for 5 minutes, inducing ischemia. The images were obtained and recorded through a 10 MHz linear transducer (MyLab 60 - Esaote, Italy) and evaluated later. All examinations were performed by the same experienced cardiologist, blind to the clinical condition of the individuals.[18]

In addition to FMD evaluation, blood samples were collected to determine erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid profile, and glycemia after 12-hour fasting. A clinical evaluation was also performed by calculating body mass index, blood pressure, and abdominal circumference, as well as the objective evaluation of the inflammatory activity of BD through BR-BDCAF.[19] This is the Brazilian version of the original protocol in English, BDCAF,[9] transculturally adapted into Portuguese.

The IMT was evaluated in all patients, consisting of the ultrasonographic measurement of the distance between the middle and intima layers, in the distal centimeter of each common carotid artery, through a linear 11 MHz transducer (MyLab 60 - Esaote, Italy). IMT greater than or equal to the 75th percentile is considered to be indicative of increased CV risk.[20]

Statistical analysis

Values are presented as medians unless otherwise noted. For the bivariate analysis, Fisher's exact test was used for the comparison of categorical variables, and the Mann–Whitney test for the comparison of medians of numerical variables with non-normal distribution between two groups. The level of significance of all hypothesis tests of the bivariate analysis was defined as 95% ($P < .05$). The STATA software version 11.1 (StataCorp, College Station, TX) was used for the calculations.

Results

The baseline characteristics of patients and controls, including age, sex, body mass index, waist circumference, and CV risk factors (except for statins use and total cholesterol), were comparable (Table 1).

Lower FMD was observed in the BD group (FMD (%): BD patients in remission, 2.025 - interquartile range (IQR) 7.785 and controls, 5.46 - IQR 3.625). FMD (%) was compared using the Mann–Whitney test, with no statistical difference ($P = .184$). Upon comparison of the absolute values of FMD, in millimeters, and their medians, we found $P = .271$. Figure 1 highlights the difference between the medians of the flow-mediated dilatation of each group. The median basal diameter of the brachial artery for the control group was 3.565 - IQR 0.735. For the BD group, it was 3.7 - IQR 1.05. There was no statistical significance in comparing basal diameters ($P = .452$). Table 2 describes the baseline diameters and FMD measurements of control subjects. These data are described in Table 3 for the patient group.

The intima–media thickness of the patients was similar to that found for the control group. In the right carotid artery, we observed a median thickness of 0.740 - IQR 0.16 for the patients and 0.740 - IQR 0.11 for the controls. On the left, 0.725 - IQR 0.13 and 0.745 - IQR 0.120 for patients and controls, respectively.

When we explored the results of body mass index in the study group, we found two patients (16.66%) classified as normal, six (50%) overweight, and four (33.33%) considered obese. The same was analyzed in the control group, which showed four normal (33.33%), four (33.33%) overweight, and four (33.33%) obese individuals.

The individuals included used medications continuously, which were kept unchanged in their dosages during the study. Drugs relevant to the analysis of endothelial function in the BD group were as follows: eight (66.66%) were corticosteroid users; nine (75.0%) used azathioprine daily; six (50.0%) used colchicin; three (25.0%) controlled blood pressure with angiotensin-converter enzyme inhibitor (ACEI) or angiotensin-1 receptor blockers (ARB). When analyzing the control group, we observed the following: no individuals using corticosteroids, azathioprine, or colchicin; pressure control with ACEI or ARB in three patients (25.0%).

We observed a higher median of the inflammatory tests in the study group (CRP: 5.15 mg dL^{-1} - IQR 6; ESR: 26.5 mm h^{-1} - IQR 23.5) compared to the control group (CRP: 2.7 mg dL^{-1} - IQR 4.95; ESR: 23 mm h^{-1} - IQR 19.5), but there was no statistical significance ($P = .4881$ and .8622 for CRP and ESR, respectively).

Discussion

Endothelial dysfunction is a marker of vascular damage observable before the development of atherosclerotic plaques.[21] As described by Chambers et al.,[22] the FMD of the brachial artery is reduced in patients with active BD, which evidence endothelial dysfunction, a key event in atherogenesis.[23] Despite this fact, there is no evidence that CV complications,

Table 1. Baseline characteristics of study groups.

Variables	BD Patients	Controls	P
Age, years	46.5 - 8	50.5 - 11	.7942
Female gender, n (%)	7 (58.33)	9 (75)	.667
Years since disease onset	15 - 6	Not applicable	–
BD vascular involvement	7 (58.33)	Not applicable	–
Statin use, n (%)	9 (75)	1 (8.33)	.003
Diabetes mellitus, n (%)	2 (16.66)	1 (8.33)	1.000
SAH, n (%)	4 (18.18)	3 (25)	1.000
CAD - fam. history, n (%)	6 (50)	9 (75)	.400
Active smokers, n (%)	1 (8.33)	0 (0)	.400
Ex-smoker, n (%)	5 (41.66)	3 (25)	.400
Systolic AP (mm Hg)	109 - 17	115 - 12.5	.2565
Diastolic AP (mm Hg)	76.5 - 8	72 - 10	.3355
BMI (kg m^{-2})	27.2 - 4.825	28.8 - 8.77	.9310
Abdominal circumf. (cm)	95.5 - 8.5	90.5 - 14	.5055
Total cholesterol (mg dL^{-1})	168 - 46	216.5 - 54	.0193
LDL (mg dL^{-1})	91 - 22.3	106.6 - 52.8	.1330
HDL (mg dL^{-1})	50.5 - 10.75	52.95 - 15.2	.5438
Triglycerides (mg dL^{-1})	101 - 70	126 - 84.5	.5635
Glycemia (mg dL^{-1})	91 - 18.4	93.95 - 12.85	.4356
CRP (mg L^{-1})	5.15 - 6	2.7 - 4.95	.4881
ESR (mm h^{-1})	26.5 - 23.5	23 - 19.5	.8622

Note: Data presented in medians - IQR (interquartile range), except when indicated (%).
BD, Behçet's disease; n, number; SAH, systemic arterial hypertension; CAD, coronary artery disease; AP, arterial pressure; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

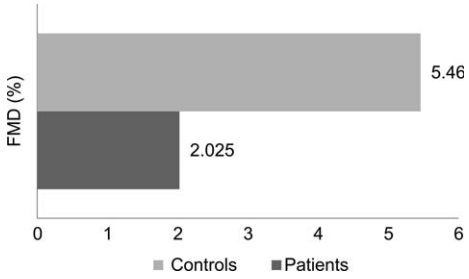

Figure 1. FMD (%): median of the percent flow-mediated dilation. FMD: flow-mediated dilation.

such as coronary artery disease or congestive heart failure, are important causes of death in BD patients.[7]

This study aimed to determine the behavior of endothelial homeostasis in a group of patients with BD in remission, as well as to describe the data found with inflammatory markers, lipid profile, and anthropometric data for the metabolic syndrome. In order to document disease activity, we used BR-BDCAF. In this instrument, scoring is based on the history of new clinical features present over the preceding 4 weeks prior to assessment. Since BD is a vasculitis, its activity could compromise the assessment of endothelial function. Therefore, it was necessary to evaluate the patients during remission based on BR-BDCAF to minimize vasculitis activity and its direct effect over this method. We observed a difference in flow-mediated dilatation between the groups, revealing a trend toward lower brachial artery dilation in the BD population, including some patients with a negative variation of FMD, suggesting endothelial dysfunction in this population, even during remission. However, the difference between the groups did not present statistical significance, which may be due to the sample size and greater use of statins among BD patients.[24] These data are consistent with those observed in the systematic review by Merashli et al.,[8] who found that FMD was compromised in patients with an inactive disease status with moderate statistical heterogeneity. Caliskan et al.[25] also described lower FMD in patients with BD in remission compared to healthy controls, in addition to greater arterial dilation compared to active patients. This suggests that BD carriers are at risk for long-term arterial damage, although they are in remission, which corroborates the independent predictive value of flow-mediated dilatation on CV risk.[6]

Table 2. Baseline diameter and FMD measurement-control group.

Number	Baseline Diameter (mm)	FMD (mm)	FMD (%)
1	3.00	0.13	4.33
2	4.30	0.36	8.37
3	3.53	0.04	1.13
4	3.60	0.03	0.83
5	4.10	0.23	5.61
6	3.50	0.20	5.71
7	3.43	0.27	7.87
8	4.33	0.29	5.31
9	3.23	0.14	4.66
10	3.93	0.20	5.09
11	4.07	0.43	10.57
12	3.27	0.36	11.00
Medians (IQR)	3.565 (0.735)	0.215 (0.19)	5.46 (3.625)

FMD, flow-mediated dilation; IQR, interquartile range.

The increase in the intima-media thickness develops as a result of the proliferation of

Table 3. Baseline diameter and FMD measurement-study group.

Number	Baseline Diameter (mm)	FMD (mm)	FMD (%)
1	4.50	–0.07	–1.55
2	4.30	0.07	1.62
3	3.50	–0.20	–5.71
4	3.23	0.03	0.40
5	3.40	0.07	2.05
6	3.50	0.07	2.00
7	3.40	0.30	8.82
8	3.33	–0.13	–3.90
9	5.33	0.43	8.00
10	4.53	0.23	5.08
11	3.90	0.27	6.42
12	4.40	0.57	12.95
Medians (IQR)	3.7 (1.05)	0.07 (0.305)	2.025 (7.785)

FMD, flow-mediated dilation; IQR, interquartile range.

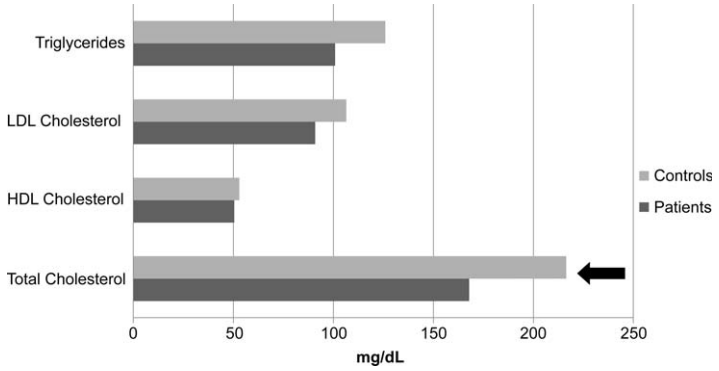

Figure 2. Lipid profile. Left facing arrow: statistically significant ($P < .05$). LDL, low-density lipoprotein; HDL, high-density lipoprotein. *Note*: data presented in medians.

smooth muscle cells of the intima and accumulation of atherogenic particles and can be used for the diagnosis of subclinical atherosclerosis.[26] Most of the patients in the present study had enough time to accumulate arterial damage expressed by a greater thickness of the intima-media in comparison with the controls, although traditional risk factors were disregarded, similar to what was found in the study by Öztürk et al.[23] The intima-media thickness develops independently of traditional risk factors, such as hypertension and dyslipidemia in patients with BD.[23] However, in our sample size, we found similar thicknesses between the groups, which may also have been influenced by the lower median of cholesterol (Figure 2).

Several markers can be used to evaluate endothelial function in patients with BD, in addition to FMD, such as CRP,[27] homocysteine, asymmetric dimethylarginine, soluble thrombomodulin, e-selectin, vascular endothelial growth factor, and the levels of endocan.[28] In this study, despite remission of BD, we observed a higher median of inflammatory markers (CRP and ESR) in the study group, when compared to controls. These data suggest a subclinical inflammatory activity, which could justify the possible endothelial dysfunction observed in these individuals. The relationship between inflammation and endothelial dysfunction is well described, as well as the improvement of endothelial function after controlling the inflammatory process.[18] In general, treatments that reduce systemic inflammatory parameters appear to minimize complications related to atherosclerosis.[29]

The tendency to lower FMD values found in BD patients suggests endothelial dysfunction even during periods of remission, which determines a higher risk of atherosclerosis; however, we are presenting a cross-sectional study. Future prospective studies with serial FMD and evaluation of intima-media thickness are needed to elucidate which subgroups of patients with Behçet are at greater risk of atherosclerosis and, consequently, greater cardiovascular risk.

Ethics Committee Approval: Ethical committee approval was received from the HUPE Research Ethics Committee (approval no.: 51323715.3.0000.5259).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.M.R., A.B.B., B.C.B., M.L.G.O., R.A.L.; Design - F.M.R., A.B.B., M.L.G.O., R.A.L.; Supervision - A.B.B., M.L.G.O., R.A.L.; Resources - R.A.L.; Data Collection and/or Processing - F.M.R., A.B.B., B.C.B., M.L.G.O.; Analysis and/or Interpretation - F.M.R., A.B.B., B.C.B., M.L.G.O.; Literature Review - F.M.R.; Writing - F.M.R.; Critical Review - A.B.B., B.C.B., M.L.G.O., R.A.L.

Declaration of Interests: The authors have no conflicts of interest to declare.

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