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Elevated Monocyte to High-Density Lipoprotein Cholesterol Ratio and Endothelial Dysfunction in Behçet Disease

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Abstract

Behçet disease (BD) is a multisystemic disorder characterized by endothelial dysfunction and inflammation. Monocyte to high-density lipoprotein cholesterol ratio (MHR) is a recently emerged indicator of inflammation and oxidative stress. Sixty patients with BD and 50 control individuals were included to investigate the relationship between MHR and endothelial dysfunction. Endothelial function was assessed by flow- and nitroglycerin-mediated dilatation technique (FMD and NMD, respectively). Serum high-sensitivity C-reactive protein (hsCRP) levels were measured in all study participants. The MHR and hsCRP levels were significantly higher in patients with active BD than in controls. Brachial artery FMD was significantly lower in patients with active BD than in controls. Brachial artery NMD was similar between groups. There was a strong inverse correlation between MHR and FMD and a strong positive correlation between MHR and serum hsCRP levels. Thus, elevated MHR may be a useful marker reflecting impaired endothelial function and systemic inflammation in patients with BD.

Keywords

biomarkers, endothelial dysfunction, flow-mediated dilation, C-reactive protein, inflammation

Introduction

Behçet disease (BD) is a multisystem inflammatory disorder characterized by relapsing episodes of recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions.[1] Behçet disease may affect the cardiovascular system leading to pericarditis, myocarditis, endocarditis, endomyocardial fibrosis, intracardiac thrombus, and myocardial infarction. In addition, vascular involvement is a major clinical feature in approximately up to one-third of the patients with BD.[2,3] The exact pathogenic mechanism underlying the vascular involvement in BD is unclear. However, endothelial dysfunction due to vasculitis is thought to play a key role in the vascular involvement.[4-6] High-sensitivity C-reactive protein (hsCRP) is an acute-phase reactant of hepatic origin that reflects systemic inflammation. It has also been shown that serum hsCRP concentration is related to endothelial dysfunction.[7] Brachial artery flow-mediated dilation (FMD) has been also established as a noninvasive technique which reveals indirect evidence of endothelial dysfunction.[8,9]

Macrophages and monocytes are the most important cell types for secretion of proinflammatory and prooxidant cytokines at the site of inflammation.[10] High-density lipoprotein cholesterol (HDL-C) has been shown to defend endothelial cells against the unfavorable effects of low-density lipoprotein cholesterol (LDL-C) and to inhibit oxidation of LDL molecules.[11-13] Therefore, it was believed that HDL-C exhibits anti-inflammatory and antioxidant actions. Recently, the monocyte count to HDL-C ratio (MHR) has been reported as a new prognostic marker.[14-16] It has been shown that increased monocyte count and decreased HDL-C levels may be related to inflammation and oxidative stress. Also, several studies have revealed that oxidative and inflammatory events contribute to endothelial dysfunction in BD.[17-19] However, no studies up to date investigated MHR in patients with BD. In this context, we aimed to assess the relationship between MHR and endothelial function using FMD and between MHR and hsCRP levels in patients with newly diagnosed and untreated patients with BD and to assess whether MHR may be a surrogate marker of inflammation in BD.

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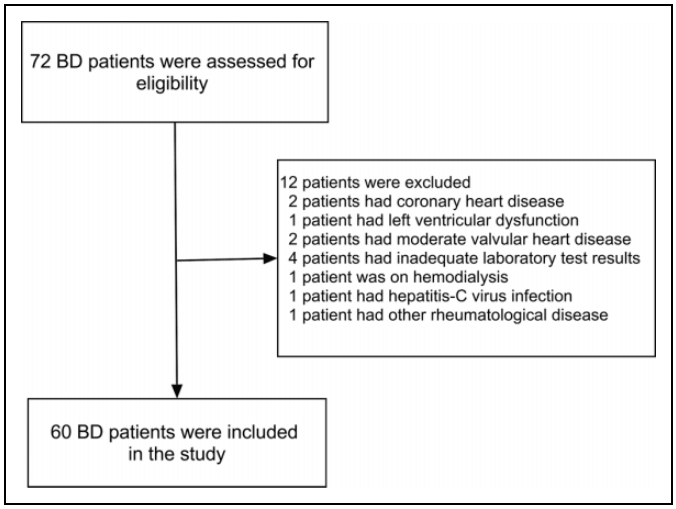

Figure 1. Flowchart of the patients for screening and eligibility.

Materials and Methods

Study Groups

The present study was carried out retrospectively in the Inonu University Hospital between June 2012 and September 2016. Sixty patients with BD fulfilling the inclusion criteria (29 males and 31 females; mean age 44.1 $\pm$ 8.3 years) and 50 healthy control individuals (27 males and 33 females; mean age 45.4 $\pm$ 7.4 years) were included in the present study. The diagnosis of BD was carried out according to the criteria of International Study Group, which was at least 2 of the following clinical findings: oral ulcers, genital ulcers, eye lesions, skin lesions, arthritis, and thrombophlebitis.[20] Patients with BD were comprised newly diagnosed untreated patients and all were in a clinically active state.

The exclusion criteria were heart failure, coronary artery disease, moderate to severe valvular heart disease, renal and hepatic failure, active hepatobiliary disease, active infectious disease, hematological diseases, malignancy, and immunological disease (Figure 1). All patients with BD undergo complete cardiovascular physical examination, 12-lead electrocardiography, transthoracic echocardiography, and exercise stress tests if necessary as part of a routine clinical workup of this patient group to exclude any cardiac involvement. The study was approved by the institutional ethics committee.

Flow-Mediated and Nitroglycerin-Induced Dilatation

Endothelium-dependent FMD in response to reactive hyperemia and endothelium-independent nitroglycerin-induced vasodilatation (NMD) of the brachial artery were evaluated using a high-resolution B-mode ultrasonographic system (HDI 5000; ATL Ultrasound, Bothell, Washington, USA) with a 7-MHz linear transducer as previously described.[8] All patients were evaluated between 09:00 and 11:00 am after abstaining from alcohol, caffeine, tobacco, and fasting for 12 hours. All measurements were performed in a quiet clinical laboratory maintained at a temperature of 21°C to 23°C. Systolic blood pressure and diastolic blood pressure of all patients were measured after a resting period of 10 minutes. In FMD measurements, scans were taken at rest during reactive hyperemia (endothelial-dependent stimulus to vasodilation), again at rest, and after sublingual nitroglycerin (endothelium-independent vasodilation). Briefly, each patient was requested to rest in supine position for 10 minutes before the first scan was obtained. The brachial artery was scanned longitudinally 3 to 5 cm above the antecubital fossa and the skin was marked where the clearest image was available. The arm was kept immobile throughout the study. Following this stage, a pneumatic tourniquet placed around the forearm was inflated up to a pressure of 300 mm Hg for 5 minutes. The second scan was then obtained 30 seconds before and 90 seconds after cuff deflation (FMD). Endothelium-independent vasodilation was evaluated 15 minutes after reactive hyperemia testing which was actually an allowance for maintaining the baseline conditions and so the third scan was recorded at rest. Sublingual nitroglycerin (400 μg) was then administered and 3 to 4 minutes later the last scan was performed (NMD). The brachial artery diameter (BAD) was measured in the longitudinal plane as the distance between the anterior and posterior intima. All measurements were obtained at end diastole gated with electrocardiogram R waves. The FMD and NMD were expressed as the percentage change in diameter compared with baseline. All measurements were performed by 2 observers who were blinded to the study. The inter- and intraobserver variabilities for repeated measurements in our clinic were found to be <2%, both for FMD and for NMD.

Laboratory Assessment

In our hospital, blood samples were routinely drawn from the antecubital vein at 08.00 to 10.00 am after an overnight fasting period. Blood samples were collected in dipotassium ethylenediaminetetraacetic acid containing tubes. Complete blood count was measured by using Beckman Coulter LH 780 Hematology Analyzer (Beckman Coulter, Miami, FL, USA). The hsCRP measurements were performed by a nephelometric method (BN II nephelometer; Dade Behring Holding GmbH, Liederbach, Germany). The other biochemical analyses were determined by standard methods.

Statistical Analysis

Statistical analysis was performed by using the SPSS for windows 22.0 software (Chicago, Illinois). All continuous variables are expressed as mean (SD), and categorical variables are expressed as numbers. Continuous variables were compared using a Student *t* test. Categorical variables were compared using a χ^2 test. Correlation analysis for MHR, FMD, hsCRP, and other variables was evaluated by the Pearson rank correlation tests where appropriate. Linear regression analysis was used to examine the effect of laboratory parameters on BD. The presence of BD was entered into model as a dependent variable. Sedimentation, hsCRP, MHR, FMD, and monocyte count were entered as independent variables. Results were

Table 1. Comparison of Baseline Clinical Characteristics and Laboratory Parameters of the Study Groups.

	Patients With Behcet Disease (n = 60)	Controls (n =50)	P
Age (years)	44.1 + 8.3	45.4 + 7.4	.397
Male/female	29/31	27/33	.689
BMI, kg/m^2	23.0 + 1.6	22.9 + 1.5	.799
Diabetes mellitus, n (%)	4 (6.6)	3 (6)	.887
Hypertension, n (%)	7 (11.6)	6 (12)	.957
Smokers, n (%)	14 (23.3)	15 (30)	.429
Lipid-lowering agent use, n (%)	4 (6.6)	1 (2)	.242
Oral ulcerations, n (%)	60 (100)	–	
Genital ulcerations, n (%)	52 (86.6)	–	
Skin lesions, n (%)	41 (68.3)	–	
Eye involvement, n (%)	22 (36.6)	–	
Arthritis, n (%)	43 (71.6)	–	
Thrombophlebitis, n (%)	11 (18.3)	–	
Neurological involvement, n (%)	34 (56.6)	–	
Positive pathergy test, n (%)	15 (25)	–	
Disease duration, months	6.2 ± 3.9	–	
Glucose (mg/dL)	91 + 12	92 + 13	.691
Creatinine (mg/dL)	0.84 + 0.19	0.83 + 0.17	.894
Hemoglobin (g/dL)	13.4 + 1.5	13.3 + 1.4	.956
WBC ($\times 10^9$/L)	8.5 ± 1.8	7.3 ± 1.6	.001
Neutrophil ($\times 10^9$/L)	5.2 + 1.4	4.6 + 1.3	.032
Lymphocyte count ($\times 10^9$/L)	2.5 + 0.7	2.1 + 0.7	.011
Monocyte count ($\times 10^9$/L)	0.68 + 0.15	0.53 + 0.15	<.001
Total platelet count ($\times 10^9$/L)	260 ± 60	261 ± 63	.929
Total cholesterol (mg/dL)	180 + 30	185 + 27	.394
LDL-C (mg/dL)	110 + 26	113 + 24	.235
HDL-C (mg/dL)	42 + 7	44 + 7	.573
Triglyceride (mg/dL)	142 + 56	143 + 50	.917
ESR (mm/h)	24 ± 22	7 ± 3	<.001
hsCRP (mg/dL)	8.8 ± 3.2	1.3 ± 1.6	<.001

Abbreviations: BMI, body mass index; WBC, white blood cell; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein.

presented as β coefficients and 95% confidence intervals. All P values were 2 tailed and a P <.05 was considered significant.

Results

Baseline clinical characteristics, disease features, and laboratory parameters of the study population are shown in Table 1. There was no statistically significant difference between the study groups in terms of age, sex, body mass index, glucose, creatinine, hemoglobin, total platelet count, total cholesterol, HDL-C, LDL-C, and triglyceride levels. White blood cell count, neutrophil, lymphocyte, and monocyte levels weresignificantly higher in patients with BD than in controls (8.5 ± 1.8 vs 7.3 ± 1.6 × 10^9/L, P = .001; 5.2 + 1.4 vs 4.6 + 1.3 × 10^9/L, P = .032; 2.5 + 0.7 vs 2.1 + 0.7 × 10^9/L, P = .011; and 0.68 + 0.15 vs 0.53 + 0.15 × 10^9/L, P = .001, respectively).

Table 2. Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR) Values According to Clinical Features of Patients With Behçet Disease (BD).

	Present	Absent	P
Overall	16.3 ± 2.8	12.4 ± 3.5	<.001
Genital involvement	16.2 ± 3.1	16.7 ± 2.3	.59
Skin involvement	17.0 ± 2.7	14.7 ± 2.3	.003
Eye involvement	16.9 ± 2.5	15.9 ± 2.8	.15
Arthritis	16.0 ± 2.9	16.8 ± 2.4	.33
Thrombophlebitis	16.1 ± 2.9	16.3 ± 2.7	.82
Neurological involvement	16.6 ± 2.8	15.8 ± 2.7	.31
Pathergy test positiveness	17.5 ± 2.5	15.9 ± 2.8	.06

The hsCRP levels and erythrocyte sedimentation rate (ESR) were also significantly higher in patients with BD than in controls (8.8 ± 13.2 vs 1.3 ± 1.6 mg/dL, P < .001; and 29.1 ± 30.5 vs 7.3 ± 3.1 mm/h, P < .001, respectively). In addition, MHR increased significantly in patients with BD when compared with controls (16.3 ± 2.8 vs 12.4 ± 3.5, P < .001). When MHR values were assessed across the clinical features of the patients with BD, only those with skin involvement had elevated MHR values compared with those without skin involvement (17.0 ± 2.7 vs 14.7 ± 2.3, P = .003; Table 2). There were positive correlations between MHR and hsCRP and also between MHR and sedimentation rate in patients with BD (r = .732, P < .0001; r = .523, P < .0001, respectively; Figure 2).

The comparison of brachial FMD, NMD, and BAD values of the study groups is shown in Table 3. The FMD value was significantly lower in patients with BD than in controls (5.9% + 1.8% vs 15.9% + 1.7%, P < .001). The BAD and NMD values were similar between the study groups. In correlation analysis, MHR were found to be inversely correlated with FMD (r = −.770, P < .001) in patients with BD (Figure 2). In linear regression analysis, MHR, hsCRP, and FMD were independently correlated with BD (Table 4).

Discussion

We found that vascular endothelial function was impaired and MHR and CRP levels were significantly higher in patients with BD than in controls. In addition, MHR and hsCRP levels were inversely correlated with FMD in patients with BD. To our knowledge, this is the first study showing that elevated MHR was significantly associated with impaired endothelial function and systemic inflammation in patients with BD.

Behçet disease is a multisystemic vasculitis. Although the underlying exact pathogenic mechanisms have not been precisely elucidated, it is widely believed that an underlying vasculitic process leads to endothelial dysfunction.[6] Also, BD has been associated with both oxidative stress and inflammation. Several studies have reported elevated levels of oxidative stress and inflammation markers such as E-selectin, vascular

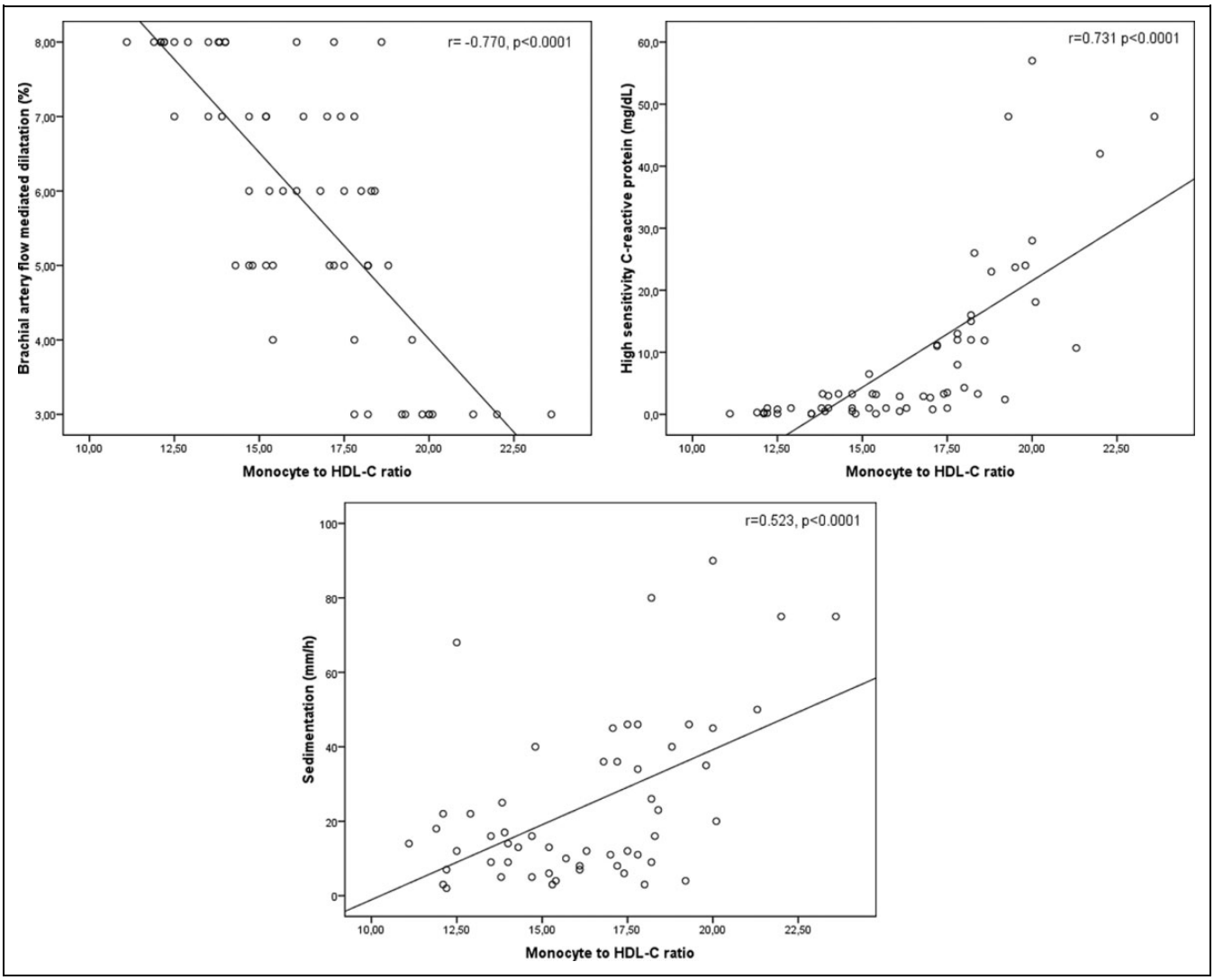

Figure 2. Correlations between monocyte to HDL-C ratio and brachial artery flow-mediated dilatation, hsCRP, and sedimentation rate. HDL-C indicates high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.

Table 3. Comparison of Brachial Artery Flow-Mediated Dilation (FMD), Nitroglycerin-Induced Vasodilatation (NMD), and Brachial Artery Diameter (BAD) Measurements of the Study Population.

	Patients With BD (n = 60)	Controls (n = 50)	*P*
FMD (%)	5.9 + 1.8	15.9 + 1.7	<.001
NMD (%)	17.5 + 1.0	17.7 + 1.5	.431
BAD (mm)	21.7 ± 28.9	2.5 ± 1.1	.799

Abbreviation: BD, Behçet disease.

Table 4. Linear Regression Analysis of the factors in Patients With Behçet Disease (BD).

Parameter	β	95% CI	*P*
hsCRP	.28	0.15 to 0.42	<.001
FMD	.31	0.13 to 0.38	<.001
MHR	.24	0.10 to 0.36	<.001
Sedimentation	.03	−0.03 to 0.18	.41

Abbreviations: CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; FMD, flow-mediated dilatation; MHR, monocyte to high-density lipoprotein cholesterol ratio.

endothelial growth factor, tumor necrosis factor α, interleukin 1b, interleukin 6, hsCRP, neutrophil–lymphocyte ratio, asymmetric dimethylarginine, soluble thrombomodulin, and total homocysteine in patients with BD.[9,17-19,21-23]

As previous studies have shown, oxidative stress and inflammation are well-known mechanisms for both initiation and progression of atherosclerosis.[24,25] Monocytes as a distinct subtype of leukocytes play a major role in this process.[10] Activated monocytes interact with damaged or activated endothelium, which lead to overexpression of some proinflammatory mediator molecules including monocyte chemotactic protein 1 ligand, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1.[26] Thereafter, monocytes differentiate

into the macrophages that eventually ingest oxidized LDL-C and form the initial foamy cells.[26] The HDL-C molecules counteract macrophage migration and remove cholesterol debris from those cells. Recent studies also indicate the role of HDL-C in modulating monocyte activation, adhesion, and also in controlling the proliferation of progenitor cells that differentiate to monocytes.[27-29] Besides its anti-inflammatory and antioxidative effects, HDL-C molecules also increase vasodilatation and endothelial nitric oxide synthase expression.[30,31] Therefore, monocytes exert a proinflammatory and prooxidant effects, but HDL-C functions as a reversal factor during these processes. Indeed, histopathologic feature of BD lesions shows perivascular infiltration of lymphocytes, monocytes, neutrophils, and surrounding tissue necrosis.[23]

The hsCRP is a valuable acute-phase reactant of hepatic origin with a high sensitivity revealing systemic inflammation. Recently, MHR is a novel and surrogate marker of inflammatory status. Kanbay et al reported that higher MHR has been associated with worse cardiovascular prognosis in chronic renal disease.[14] In an another study, Canpolat et al investigated this marker in atrial fibrillation (AF) population and reported increased preablation MHR values as a predictor of AF recurrence after catheter ablation.[15] Also, in a recent study, MHR has been demonstrated to be associated with the presence of slow coronary flow.[16] In addition, MHR has been determined to be a predictor of stent thrombosis and in-hospital MACE as well as mortality in patients with myocardial infarction.[32,33] In all studies, MHR has been postulated to have an association with systemic inflammation and endothelial dysfunction and attributed as a novel inflammation-based prognostic marker in cardiovascular diseases. Consistent with the above studies, in our study, we found impaired endothelial function by using the brachial artery FMD technique in patients with BD and that MHR, hsCRP levels, and ESR were significantly higher in patients with BD than in controls and also there was a good relationship between MHR and FMD, hsCRP, and ESR. Therefore, MHR may be used as a surrogate marker of inflammation in patients with BD.

Our study has several limitations. First, the number of patients included was relatively small. Second, we used a single MHR value for our analysis. Finally, we could not follow up the patients prospectively for adverse cardiovascular outcomes.

In conclusion, we observed higher MHR and CRP levels and also demonstrated impaired endothelial function (using FMD) in patients with BD. Additionally, we found that a strong inverse relationship between increased MHR and impaired endothelial function in these patients. We speculate that an elevated MHR is a marker of endothelial dysfunction and systemic inflammation as well as an early predictor of future vascular involvement in patients with BD.

Author Contribution

All authors contributed to (1) substantial contributions to conception and design or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Declaration of Conflicting Interests

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