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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Relationship between serum homocysteine levels and structural-functional carotid arterial abnormalities in inactive Behçet's disease

Ramazan Ozdemir[1], Julide Yagmur[2], Nusret Acikgoz[2], Mehmet Cansel[2], Yelda Karincaoglu[3], Necip Ermis[2], Hasan Pekdemir[2], A. Kadir Arslan[3]

[1]Department of Cardiology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey
[2]Department of Cardiology, Faculty of Medicine, Inonu University, Malatya, Turkey
[3]Department of Dermatology, Faculty of Medicine, Inonu University, Malatya, Turkey
[4]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Malatya, Turkey

Abstract

Background: Behçet's disease (BD) is a chronic autoimmune disorder with symptoms manifesting from an underlying vasculitis. Since the disease activity is correlated with characteristic vascular endothelial dysfunction, BD places individuals at increased risk of cardiovascular diseases, such as atherosclerosis. Hyperhomocysteinaemia is an independent risk factor for arteriosclerotic vascular diseases.

Aim: This study was designed to investigate how plasma homocysteine (Hcy) affects the structural and functional properties of the carotid artery in humans.

Methods: Sixty-eight BD patients with subclinical atherosclerosis and 40 healthy controls underwent carotid sonography and Doppler ultrasound to measure carotid artery intima–media thickness (C-IMT) and carotid stiffness and distensibility (indicating elasticity). Total Hcy level was determined by enzyme-linked immunosorbent assay. For analysis, the BD patients were sub-grouped according to hyperhomocysteinaemia (> 15 μmol/L).

Results: The patients with BD were found to have increased C-IMT and beta stiffness and decreased distensibility. In addition, hyperhomocysteinaemia was significantly correlated with these detrimental changes in the carotid artery, possibly raising the risk of these patients developing atherosclerosis.

Conclusions: These findings suggest a potential mechanism of atherosclerosis in BD and highlight the processes that future research should focus on to address identification and prophylactic treatment of BD patients at risk of cardiovascular disease.

Key words: Behçet's disease, arterial distensibility, homocysteine

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INTRODUCTION

Behçet's disease (BD) is a chronic autoimmune disorder of unknown aetiology. Its clinical presentation is characterised by a triad of recurrent ulcerations involving the mouth, genitals, and eye [1]. The symptoms are a manifestation of an underlying vasculitis, and effects have been noted in a wide range of systems, including circulatory, respiratory, cardiac, and gastrointestinal. As such, recent research has focused on vascular endothelial function in BD and found marked impairment that correlates with disease activity [2], as well as association with increased cardiovascular risk in younger patients with advanced BD [3, 4].

The molecular mechanisms underlying the pathogenic vascular endothelial dysfunction in BD remain largely unknown, but will provide insights into the relationship of atherosclerosis and BD [5]. Diagnosis of atherosclerosis, even when at the preclinical stage, is routine in clinical practice and uses well-established measurements made by widely available technologies, such as of arterial stiffness, carotid artery intima–media thickness (C-IMT), and flow-mediated vasodila-

Address for correspondence:
Ramazan Ozdemir, Professor, MD, Bezmialem Vakif University Faculty of Medicine, Department of Cardiology, Vatan Street, Fatih, Istanbul, Turkey, tel: +90 212 4531700, fax: +90 2126318551, e-mail: drramazan_ozdemir@hotmail.com
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tation. It has been reported that BD patients show increased measurements for each of these three parameters [6–8], but other studies have reported contradictory findings [5, 9].

Appropriate artery wall stiffness is key to proper vascular function; for example, increased stiffness decreases distensibility, which can disrupt local and systemic homeostasis. Moreover, decreased distensibility has been implicated as a contributing factor to cardiovascular diseases (CVD) [10, 11]. Functional-structural impairments of the arterial wall are hallmarks of atherosclerosis, and the former (functional) can be detected before the latter (structural) in CVD and even before manifestation of clinical symptoms [9].

Unfortunately, no biomarker has yet been identified that reflects the risk of developing vascular lesions in BD. Plasma homocysteine (Hcy), a well-known risk factor of heart disease, may represent such a biomarker. Not only do BD patients show increased levels of Hcy but this amino acid has also been shown to directly cause endothelial dysfunction in BD [12]. In addition, elevated Hcy is reported to be associated with the subclinical atherosclerosis in BD [12, 13].

Hence, the present study was designed to investigate the effects of Hcy on structural and functional properties of vessels in patients with BD and subclinical atherosclerosis.

METHODS

This prospective study involved patients who were treated at the Dermatology Department between January 2013 and December 2016. Study enrolment was offered to patients diagnosed with BD based on the criteria published by the International Study Group for BD [2]. Study participation was denied to patients with acute phase BD or according to the presence of any one of the following: circulatory disorders of coronary artery disease, peripheral vascular disease, systemic hypertension (defined as blood pressure > 140/90 mmHg, or taking of antihypertensive medications), congestive heart failure, valvular heart disease, hypertrophic, restrictive and dilated cardiomyopathies or left ventricular hypertrophy, or treatment with vasoactive medications; metabolic disorders including diabetes (defined as fasting plasma glucose ≥ 110 mg/dL) or hyperlipidaemia (defined as total cholesterol > 200 mg/dL, or taking of lipid-lowering medications); pulmonary, renal, or haematological disorders; or the use of any medications known to alter plasma Hcy level (such as vitamin B_{12} or folate antagonist) or corticosteroids.

The BD patient group included 68 individuals (42 males and 26 females; mean age 42.1 ± 8.9 years), with mean duration of BD of 142 ± 47 months. A control group was recruited from the hospital staff and included 40 individuals (25 males and 15 females; mean age of 41.3. ± 8.2 years) with no clinically overt disease and not taking any medication. All study participants (cases and healthy controls) gave informed consent.

The patient records were reviewed for relevant clinical history, including findings from physical examinations, biochemical analyses, and imaging studies (i.e. resting electrocardiogram and echocardiography). All selected patients had chronic BD and were under treatment with colchicine, which was halted for three weeks upon study enrolment and before initiation of any of the study procedures. Patients who presented with enhanced BD symptoms during this period of non-treatment were excluded from the study (one male and three females).

The BD patients were divided into two groups according to Hcy levels at study baseline: group 1, Hcy > 15 μmol/L (n = 28, 18 males and 10 females); group 2, Hcy < 15 μmol/L (n = 40, 24 males and 16 females).

All participants underwent carotid sonography, which was performed by a single examiner who was not involved in the study, and using an HDI5000 system (ATL/Philips, Borhell, WA, USA) equipped with a 5–12.5 MHz linear array imaging probe [14]. The sonographic measurements were made in a dark, quiet room with the subjects in supine position, with head tilt at 45° in the direction opposite to the carotid artery. Anterolateral, posterolateral, and mediolateral directions of the left and right common carotid arteries were imaged as previously described [14]. The C-IMT was measured as previously described [6]. To determine the extent of intra-observer variability of the C-IMT measures, 10 volunteers were assessed at one month prior to initiation of the study, and the mean value was compared to the mean value of the measure obtained in the study.

Blood pressure was measured in the appropriate arm (MEC 1000 semi-automated patient monitor; Mindray, Shenzhen, China) during the examination of the common carotid arteries. M-mode presentation was used to assess the end-diastolic and peak systolic luminal diameters and end-diastolic inter-adventitial diameter, as previously described [15]. The extra-cranial carotid arteries were evaluated for lesions by using Doppler ultrasound (pulsed wave and colour) as previously described [14]. Beta index was determined as a marker for carotid stiffness and distensibility (indicating elasticity); intra-observer variabilities for these measures were determined as described above (i.e. comparison of pre-study values for 10 volunteers).

Each study participant provided 12-h fasting blood samples. Glucose and creatinine levels, and lipid profiles were determined by standard biochemical methods. High-sensitivity C-reactive protein (hs-CRP) level was determined using an automated Behring Nephelometer Analyser (Seimens, Marburg, Germany). Total Hcy level was determined by the Axis® Homocysteine EIA enzyme-linked immunosorbent assay (Axis-Shield, Dundee, Scotland). Because the normal range of total Hcy for adult males and females is 5–15 μmol/L, hyperhomocysteinaemia was signified by a level of > 15 μmol/L [16].

Table 1. Baseline characteristics of patients and controls

	Behçet's disease group (n = 68)	Controls group (n = 40)	P
Age [year]	42.1 ± 8.9	41.3. ± 8.2	NS
Male/female	42/26	25/15	NS
Body mass index [kg/m^2]	24.2 ± 4.1	25.3 ± 3.6	NS
Smoker	18%	21%	NS
Plasma glucose [mg/dL]	91.6 ± 12.3	92.1 ± 13.6	NS
Total cholesterol [mg/dL]	179.1 ± 29.6	185,2 ± 27.2	NS
Creatinine [mg/dL]	0.85 ± 0.2	0.83± 0.1	NS
Hcy level [μmol/L]	16.4 ± 4.2	8.3 ± 3.2	< 0.0001
Hcy > 15 μmol/L	28 (41%)		
hs-CRP [mg/L]	7.7 ± 2.8	3.14 ± 2.5	< 0.001
Folic acid [ng/mL]	9.6 ± 2.2	10.7 ± 2.1	< 0.05
Vitamin B_{12} [pg/mL]	351 ± 84.9	391 ± 105	< 0.05
Disease duration [months]	142 ± 47	–	–
Heart rate [/min]	64.9 ± 4.9	65.2 ± 4.3	NS
Systolic BP [mmHg]	109.0 + 8.4	111.2 + 8.1	NS
Diastolic BP [mmHg]	72.1 + 6.5	71.4 + 5.7	NS

Values are given as mean ± standard deviation or number (percentage); BP — blood pressure; Hcy — homocysteine; hs-CRP — highly sensitive C-reactive protein; NS — not significant

Table 2. Comparison of three groups according to carotid artery structural and functional value

	Group 1 (n = 28); BD pts: Hcy > 15 μmol/L	Group 2 (n = 40); BD pts: Hcy < 15 μmol/L	Controls (n = 40)	p 1 vs. 2	p 1 vs. 3	p 2 vs. 3
Distensibility [$10^{-3} \times kPa^{-1}$]	20.71 ± 2.99	24.75 ± 1.92	28.84 ± 3.2	0.02	< 0.001	0.01
Beta-stiffness index	3.73 ± 0.45	3.33 ± 0.24	3.07 ± 0.17	< 0.001	< 0.001	< 0.001
C-IMT [mm]	0.77 ± 0.7	0.63 ± 0.7	0.59 ± 0.1	0.780	< 0.001	< 0.01

Values are given as mean ± standard deviation; BD — Behçet disease; Hcy — homocysteine; C-IMT — carotid artery intima-media thickness; pts — patients

Vitamin B_{12} and folic acid levels were determined by the Immulite® immunoassay automated analyser and reagents (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistical analysis

All statistical analyses were carried out with the SPSS statistical software, version 23.0 (IBM Corporation, Armonk, NY, USA). Variables are presented as mean ± standard deviation. Test of normality was conducted by the Kolmogrov-Smirnov/Shapiro-Wilk test. Non-normally distributed variables were assessed by the Kruskal-Wallis H test followed by the Bonferroni corrected Mann-Whitney U test (multiple comparisons). Normally distributed variables were assessed by the independent samples t-test followed by one-way ANOVA and post-hoc Tukey or Tamhane's T2 tests. Homogeneity of variances was assessed by Levene's test. Correlations between non-normally and normally distributed variables were assessed by Spearman's rank and Pearson's coefficient. All two-tailed p values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study population are shown in Table 1. There were no significant differences between the BD patient group and the healthy control group with respect to sex, age, body mass index, blood pressure, total cholesterol, high-density and low-density cholesterols, and triglycerides. Findings of physical examination were normal for all.

As shown in Table 2, the BD patient group showed significantly higher mean serum Hcy (16.4 ± 4.2 μmol/L vs. healthy control group: 8.3 ± 3.2 μmol/L, $p < 0.001$). Mean Hcy levels in the BD patient subgroups were 22.0 ± 8.4 μmol/L for group 1 and 12.4 ± 4.1 μmol/L for group 2, and both groups showed significantly higher levels than the healthy control group ($p < 0.001$ and $p < 0.01$, respectively). The BD patient group also showed significantly higher hs-CRP (5.7 ± 2.8 mg/L vs. healthy control group: 3.14 ± 2.5 mg/L, $p < 0.01$).

As shown in Table 2, both BD patient subgroups showed significantly higher mean C-IMT values than the healthy con-

Table 3. Bivariate correlation analysis of levels homocysteine and carotid artery structural and functional abnormalities

Parameters	Homocysteine	
	r	p
Distensibility [$10^{-3} \times kPa^{-1}$]	–0.634	< 0.001
C-IMT [mm]	0.565	< 0.001
Beta stiffness index	0.769	< 0.001
Disease duration [months]	0.601	< 0.001

C-IMT — carotid artery intima–media thickness

trols (group 1: 0.77 ± 0.7 mm and group 2: 0.63 ± 0.7 mm vs. healthy control group: 0.59 ± 0.1 mm, $p < 0.001$ and $p < 0.01$, respectively). The intra-observer variability of the C-IMT measures was insignificant (0.030 ± 0.022 mm). In addition, both BD patient subgroups showed significantly higher beta stiffness (group 1: 3.73 ± 0.45 and group 2: 3.33 ± 0.24 vs. healthy control group: 3.07 ± 0.17, $p < 0.001$, respectively). The intra-observer variability of the beta stiffness index measures was insignificant (0.95 ± 0.90). Distensibility was significantly decreased in both BD patient subgroups (group 1: 20.71 ± 2.99 $10^{-3} \times kPa^{-1}$ and group 2: 24.75 ± 1.92 $10^{-3} \times kPa^{-1}$ vs. healthy control group: 28.84 ± 3.2 $10^{-3} \times kPa^{-1}$, $p < 0.001$ and $p < 0.01$, respectively). The intra-observer variability of the distensibility measures was insignificant (0.55 ± 0.91 $10^{-3} \times kPa^{-1}$).

As shown in Table 3, Hcy level was positively correlated with carotid beta stiffness index ($r = 0.769$, $p < 0.001$), C-IMT ($r = 0.565$, $p < 0.001$) and disease duration ($r = 0.601$, $p < 0.001$) but inversely correlated with distensibility ($r = –0.634$, $p < 0.01$).

DISCUSSION

The main findings of our study were increased C-IMT and beta stiffness index and decreased distensibility in patients with BD, and that an Hcy level of > 15 μmol/L is significantly correlated with these detrimental changes in the carotid artery, possibly raising the risk of these patients for development of atherosclerosis.

Although patients with BD present with vascular endothelial dysfunction, the link between BD and CVD is still not fully understood. BD is an autoimmune disease causing lesions in multiple endothelial tissues, and atherosclerosis has a well-known underlying aetiology of chronic inflammation. Inflammation-related vascular endothelial dysfunction leads to arterial stiffness — affecting elasticity — which can progress to atherosclerotic lesions, a major cause of CVD [2]. Previous studies of premature atherosclerosis in adult BD patients have shown significantly increased C-IMT and arterial stiffness and decreased flow-mediated vasodilatation, supporting the existence of a link between BD and development of atherosclerosis [2, 6–8]. Moreover, these findings suggest that preclinical atherosclerosis may be more prevalent in BD patients than currently recognised.

Several factors have been implicated in the vascular endothelial dysfunction in BD. These include the inflammatory and immunological factors expected from the autoimmune nature of the disease, but also include metabolic factors, such as Hcy [8, 17], CRP [17, 18], lipids [8, 18, 19], as well as reactive oxygen and reactive nitrogen species [19, 20]. The contributory role of Hcy in CVD involves its impact at the cellular level (i.e. vascular endothelial cells and smooth muscle cells), whereby arterial structure is altered with functional consequences (i.e. oxidative damage and weakened elasticity) [21]. Indeed, functional impairment may proceed structural impairment, even before the latter manifests clinical signs or symptoms detectable by current technologies [10]. Detection of the earliest changes can improve prognosis of patients at risk of CVD.

Concentrations of Hcy have been demonstrated as associated with arterial stiffness in the general population [21]. Arterial stiffness — the first or at least an early manifestation of structural and functional vascular changes — occurs before increased C-IMT. Several research groups have reported findings of significantly higher C-IMT in BD patients as compared to healthy controls [22, 23]; however, other groups have reported the opposite (i.e. no significant difference in C-IMT of BD patients and healthy controls) [5, 9, 24]. However, Merashli et al. [2] reported that the increased C-IMT observed in patients was statistically valid and the discrepant findings probably reflect the real-life clinical heterogeneity of BD.

On the other hand, no study in the publicly available literature reports on investigation into the relation between serum Hcy level and structural and functional carotid arterial abnormalities in inactive BD. To this end, our study showed that the patients with BD, who had Hcy levels > 15 μmol/L, also had increased C-IMT, compared with controls, while the BD patients with Hcy levels < 15 μmol/L had C-IMT, which was similar to that of the controls. Statistical analysis indicated a significant correlation between high Hcy levels and increased C-IMT. Thus, this is the first study to demonstrate the relation between Hcy levels and structural and functional abnormalities of carotid artery in BD. In addition, we found that the decrease in arterial distensibility and the increase in stiffness — the first manifestations of functional changes in the vessel wall — were followed by the elevation in C-IMT values; these results are similar those reported by Alan et al. [7].

Although the C-IMT in patients with BD and Hcy levels of < 15 μmol/L was not statistically different from that in the controls, arterial stiffness and distensibility in all BD patients irrespective of Hcy levels were significantly different from those in the controls. These findings support the idea that arterial stiffness is the first, or at least an early manifestation of, functional vascular changes that occur before the appearance of increased C-IMT. Therefore, we believe that different stages of vascular endothelial dysfunction during BD may explain the

different values of arterial stiffness, distensibility, and C-IMT that have been observed in the different studies. A graded increase in Hcy concentration may be related to this as well, paralleling the progression towards, and establishment of, vascular endothelial dysfunction. Further studies with large series of patients, particularly using a stratification schema to investigate the BD cases according to their clinical manifestations, are warranted.

Limitations of the study

When considering the findings of our study, some limitations inherent to the study design should be considered. First, the study population was small and taken from a single institute. Second, the data was prospective and no follow-up time period was included to assess correlation with prognosis or clinical end-points, such as treatment outcome or survival. Although enhanced Hcy can be reduced by the combination therapy of folic acid and vitamin B, results reported from clinical trials have yet to show definitive efficacy on related disease status [25]; for now, however, such a treatment remains an attractive potential approach for addressing hyperhomocysteinaemia in BD. Our study was too preliminary to justify any experimental treatment, including that with vitamins, but it will be interesting to see the results from future studies on the effects of vitamins on Hcy and long-term outcomes in BD patients.

CONCLUSIONS

In conclusion, the present study demonstrated functional and structural alterations in the carotid artery of patients with BD, particularly of those with high Hcy level. This finding suggests a potential mechanism of atherosclerosis in BD and highlights the processes that future research should focus on to address identification and prophylactic treatment of BD patients at risk of CVD.

Conflict of interest: *none declared*

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