CLINICAL SCIENCE

Serum homocysteine level is increased and correlated with endothelin-1 and nitric oxide in Behçet’s disease

H Er, C Evereklioglu, T Cumurcu, Y Türköz, E Özerol, K Şahin, S Doganay

Background/aims: Behçet’s disease (BD) is a systemic inflammatory vasculitis of young adults with unknown aetiology, characterised by endothelial dysfunction and occlusion in both deep venous and retinal circulation. Ocular involvement occurs in 70% of cases and is characterised by periphlebitis, periarthritis, vascular occlusion, and thrombosis leading to blindness despite vigorous treatment. Endothelin-1 (ET-1) is a vasoconstricting peptide while nitric oxide (NO) is a relaxing molecule and both are released by endothelial cells for blood flow regulation. Homocysteinaemia is a newly defined term connected to the increased risk of atherothrombotic and atherosclerotic systemic and retinal vascular occlusive diseases, and its role in the course of BD has not been previously described. The authors aimed to detect serum total homocysteine (tHcy), ET-1, and NO in BD and to assess if tHcy, ET-1, and NO are associated with ocular BD or disease activity.

Methods: 43 consecutive patients with ocular (n = 27) or non-ocular (n = 16) BD (36.95 (SD 9.80) years, 22 male, 21 female) satisfying international criteria and 25 age and sex matched healthy control subjects (37.88 (8.73) years, 13 male, 12 female) without a history of systemic or retinal venous thrombosis were included in this study. Patients were examined by two ophthalmologists with an interest in BD. Serum tHcy, ET-1, and NO concentrations were measured in both groups. Hyperhomocysteinaemia was defined as a tHcy level above the 95th percentile in the control group. Patients were divided into active and inactive period by acute phase reactants including C-reactive protein, erythrocyte sedimentation rate, and neutrophil count.

Results: The overall mean serum tHcy, ET-1, and NO levels were significantly higher in patients with BD than in control subjects (tHcy = 15.83 (4.44) v 7.96 (2.66) ng/ml, p < 0.001; ET-1 = 17.47 (4.33) v 5.74 (2.34) µmol/l, p < 0.001; NO = 37.60 (10.31) v 27.08 (7.76) µmol/l, p < 0.001). Serum tHcy, ET-1, and NO levels were significantly higher in active patients than in inactive patients and control subjects. In addition, among patients with ocular BD, the mean tHcy levels were significantly increased and correlated with ET-1 and NO levels when compared with non-ocular disease and control subjects. All acute phase reactant levels were significantly higher in active period than in inactive stage and controls.

Conclusions: Elevated tHcy may be responsible for the endothelial damage in BD and may be an additional risk factor for the development of retinal vascular occlusive disease, contributing to the poor visual outcome in these patients. Assessment of tHcy may be important in the investigation and management of patients with BD, especially with ocular disease.

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Behçet’s disease (BD), first described by a Turkish physician Hulusi Behçet,1 is an immunoinflammatory disorder of unknown aetiology. It is a multisystem disease affecting almost every organ without exception.2 It is characterised by retinal occlusive vasculitis and thrombosis, and anterior or posterior uveitis in association with oral aphthae, genital ulceration, and cutaneous lesions.3 Ocular inflammatory disease is generally bilateral and occurs in approximately 70% of cases. Although patients with predominantly anterior uveitis have a relatively good prognosis, recurrent obliterative retinal vasculitis and thrombosis occur in 30%–40% of patients and is the major cause of blindness despite vigorous treatment.4 Systemic venous occlusion also occurs in 40% of cases.5 However, the certain pathogenic mechanism and the relation between thrombogenic events and retinal or systemic vascular complications remain unclear. One of the major factors responsible for the increased frequency of thrombogenic is thought to be endothelial dysfunction, which is the characteristic feature of BD.6

Homocysteine (Hcy) is an intermediary amino acid formed during the conversion of methionine to cysteine. Hyperhomocysteinaemia refers to mild to moderate elevation of Hcy in blood or serum. High levels of Hcy causes lipid peroxidation, vascular endothelial injury, impaired vasomotor regulation, prothrombotic surface, and therefore atherothrombogenesis.7 Furthermore, raised Hcy levels have recently been suggested as a risk factor for non-arteritic anterior ischaemic optic neuropathy8 and retinal vascular occlusive disease with thromboembolism.9 Two recently identified cellular mediators endothelin-1 (ET-1) and nitric oxide (NO) are released from endothelium. ET-1 induces vasoconstriction and contributes to ocular pathological manifestations, promoting retinal capillary non-perfusion and ischaemia.10 On the other hand, NO induces vasorelaxation and inhibits platelet adhesion.11 The combination of the paracrine effects of ET-1 along with release of NO are likely to have a relevant physiological role in the regulation of systemic and retinal blood flow.12

We have recently reported for the first time that some vasoregulatory molecules such adrenomedullin13 and NO14 are elevated in patients with BD. These findings led us to investigate the role of hyperhomocysteinaemia in the pathogenesis of BD. The results of this study confirmed the previous observations and suggested that hyperhomocysteinaemia is a contributing factor to the development of retinal vascular occlusive disease in patients with BD.

Abbreviations: BD, Behçet’s disease; CV, coefficients of variance; EUSA, enzyme linked immunosorbent assay; ESR, erythrocyte sedimentation rate; ET-1, endothelin-1; Hcy, homocysteine; HPLC, high performance liquid chromatography; LDH, lactate dehydrogenase; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; tHcy, total homocysteine.
might participate in the reparatory vessel endothelium mechanisms during the course of BD. Furthermore, our results demonstrated that adrenomedullin was correlated with disease chronicity whereas NO was correlated with disease activity, suggesting NO as a possible new activity marker. Since homocysteinaemia participates in thromboembolic events and retinal vascular occlusive disease by direct toxic effect on endothelial cells, we considered it as an interesting target of investigation, and its role in the aetiopathogenesis of BD has not been previously investigated.

In addition, we assessed whether the Hcy level is associated with ocular disease and disease activity. We also evaluated if the Hcy level is correlated with the two endothelium derived ET-1 and NO levels during the course of the disease. To our knowledge, this is the first report on Hcy levels during the course of BD.

**MATERIALS AND METHODS**

**Patients**

A total of 43 consecutive patients with ocular (n = 27) or non-ocular (n = 16) BD (36.95 (SD 9.80) years (range 17–57), 22 male and 21 female) attended our Behçet’s disease clinic and 25 age and sex matched healthy control subjects (37.88 (SD 8.73) years (19–57), 13 male and 12 female) from a similar ethnic background were included in the present study. All BD patients fulfilled the criteria of the International Study Group for Behçet’s Disease.

Since there was no clinically acceptable scoring system and laboratory screening profile to define the severity of BD, clinical and laboratory findings were used to classify the patients as active or inactive. Erythrocyte sedimentation rate (ESR), neutrophil count, and acute phase reactants (α1 antitrypsin and α1 macroglobulin) were determined and constituted the laboratory findings as described before. In clinical evaluation, worsening of clinical symptoms at the time of study with having at least three of the major findings (retinal vascular occlusive disorder or anterior/posterior or panuveitis; aphthous stomatitis; genital ulcers; papulopustular or pseudofollicular cutaneous lesions; pathergy test positivity) were considered to be in the active stage of the disease. The diagnosis of uveitis was made according to the International Uveitis Study Group.

Patients’ details were obtained from case notes and ocular examinations were performed by two experienced ophthalmologists using a standard procedure. In particular, a history of systemic thrombosis and evidence for retinal vascular occlusion was sought. Where the posterior segment could not be visualised, patients with an end stage ocular disease (phthisical or completely blind) were assumed to have suffered vaso-occlusive disease of the retina.

**Control subjects**

Twenty five hospital based healthy control subjects from a similar ethnic background were age and sex matched and had no history or clinical evidence of any systemic or ocular disease. Exclusion criteria were hepatic and renal diseases (chronic renal failure), thyroid disease, diabetes, essential hypertension, congestive heart disease, psychiatric illness, and pregnancies. Since drugs (fibates, carbamazepine, phenytoin, methotrexate, corticosteroids, cytotoxics, non-steriodals, etc.) could affect the levels of measured parameters, detailed histories of medication were obtained in both groups and such patients were not included in the study. None of the subjects had nutritional deficiency or took vitamin supplementation.

All participants in both groups gave their written informed consent and approval of the hospital’s institutional ethics review board was obtained. The laboratory personnel were maintained masked to the clinical diagnosis and group of the subjects, matching each blood sample by letter coding, and so were the clinicians to subsequent Hcy, ET-1, and NO level determinations until the end of the study.

**Blood samples**

Whole blood samples (totally 10 ml) were drawn using a 25 gauge needle from a peripheral vein, avoiding haemolysis, into plain tubes in the morning hours (08:00–10:00) after an overnight fast and 30 minutes of supine rest. None of the patients and controls had received any topical or systemic medication at least 2 weeks before blood collection. Following an immediate centrifugation of the first three quarters of the blood samples (7.5 ml) at 800 g for 10 minutes at 4°C, serum was collected and kept at −70°C until use.

**Serum Hcy analysis**

Since the concentration of Hcy in serum increases artificially over time if blood is stored uncooled and uncentrifuged immediately after sampling, owing to the time and temperature dependent release of Hcy from erythrocytes, the blood samples were cooled and centrifuged immediately after collection and the erythrocytes removed. Serum total homocysteine (tHcy) levels were determined by enzyme linked immunosorbent assay (ELISA) kit (Homocysteine Enzyme Immunoassay Kit, Bio-Rad Lab, Oslo, Norway). It is an easy to use immunoassay for the assessment of tHcy levels in serum. The tHcy enzyme immunoassay has highly specific enzymatic sample pretreatment, convenient microplate format, standardised immunoassay procedure, parallel sample processing, and wide dynamic range. Test results correlate well with reference high performance liquid chromatography (HPLC) at a level of at least 0.98.

In addition to the total mean serum levels for Hcy, hyperhomocysteinaemia was defined as a serum tHcy level above the 95th percentile in the control group as described before.

**Serum ET-1 analysis**

Duplicate serum samples from each subject were assayed for ET-1 by a commercially available ELISA kit (Endothelin-1 Enzyme Immunoassay Kit, Cayman Chem, Ann Arbor, MI, USA). It is a sandwich enzyme immunoassay that permits ET-1 measurements with a detection limit of ~1.5 pmol/ml. The intra-assay and interassay coefficients of variance (CV) were both less than 10%. The assay allows sensitive and specific (100%) analysis of ET-1 in serum.

**Serum total nitrite (NO2− + NO3−) analysis**

NO is a labile compound with a brief half life and is rapidly converted to the stable end products nitrate (NO3−) and nitrite (NO2−) in typical oxygenated aqueous solutions, and is subsequently excreted into urine. Because an excellent and sensitive colorimetric reagent (the Griess reagent) exists for the determination of NO3−, it is a common practice to use enzymatic or chemical reduction to convert all NO3− to NO2−. This is made by continuation of the incubation of 5 µl of substrate buffer (imidazole 0.1 mol/l, reduced NADP (NADPH) 210 µmol/l, flavine adenine dinucleotide, 3.8 µmol/l; pH 7.6) in the presence of nitrate reductase (Aspergillus niger, Sigma) for 45 minutes to convert NO3− to NO2−. Excess reduced NADPH, which interferes with the chemical detection of NO2−, was oxidised by continuation of the incubation of 5 µg

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Er, Evereklioglu, Cumurcu, et al

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accurately measure as little as 1 µmol/l. Other acute phase reactant (ESR was determined by the classic Westergren method. The automated blood counter (Coulter-STKS, Luton, UK). The mg/ml) anticoagulant was used for the neutrophil counting by the other part of the blood samples (2.5 ml) with EDTA (1 µmol/l) pyruvate (Sigma), and 79 ml of water. Total nitrite was then analysed by reacting the samples with Griess reagent (1% sulphanilamide, 0.1% N-(1-naphthyl)-ethylenediamine dihydrochloride in 5% H3PO4 spectroquant: Merck, Darmstadt, Germany). 15 ml of lactate dehydrogenase (LDH, Sigma), 0.2 mmol/l (120 µl) pyruvate (Sigma), and 79 ml of water. Total nitrite was then analysed by reacting the samples with Griess reagent (1% sulphanilamide, 0.1% N-(1-naphthyl)-ethylenediamine dihydrochloride in 5% H3PO4 spectroquant: Merck, Darmstadt, Germany). Reacted samples were treated with 500 µl of trichloroacetic acid (20%), centrifuged for 15 minutes at 8000 g, and the absorbance at 548 nm was compared with that of NaNO2 standard (0–100 µmol/l). This method can be used to accurately measure as little as 1 µmol of NO2-(final concentration in the assay). Very little of the sample is required (5–85 µl for most samples).

**Neutrophil count, ESR, and acute phase reactants analysis**

The other part of the blood samples (2.5 ml) with EDTA (1 mg/ml) anticoagulant was used for the neutrophil counting by an automated blood counter (Coulter-STKS, Luton, UK). The ESR was determined by the classic Westergren method. The other acute phase reactant (α1 antitrypsin and α2 macroglobulin) in patients with active or inactive Behçet’s disease and controls

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Serum homocysteine, endothelin-1, and nitric oxide levels in patients with Behçet’s disease and controls with statistical comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>All BD  (n=43)</td>
<td>Active BD (n=20)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>tHcy (ng/ml)</td>
<td>36.95 (9.80)</td>
</tr>
<tr>
<td>EF1 (µmol/ml)</td>
<td>15.83 (4.44)†</td>
</tr>
<tr>
<td>NO (µmol/l)</td>
<td>37.60 (10.31)†</td>
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</tbody>
</table>

**Table 2** | Neutrophil count, erythrocyte sedimentation rate, and acute phase reactants (α1 antitrypsin, α2 macroglobulin) in patients with active or inactive Behçet’s disease and controls |
<table>
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</thead>
<tbody>
<tr>
<td>Active BD (n=20)</td>
<td>Inactive BD (n=23)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Neutrophils (103/ml)</td>
<td>6.64 (1.41)†</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>32.88 (8.36)†</td>
</tr>
<tr>
<td>α1 antitrypsin (mg/dl)</td>
<td>219.34 (39.42)†</td>
</tr>
<tr>
<td>α2 macroglobulin (mg/dl)</td>
<td>269.52 (31.58)†</td>
</tr>
</tbody>
</table>

ESR, erythrocyte sedimentation rate.

†Significantly different from the inactive stage by Wilcoxon test (for each, p<0.01).

‡Significantly different from the controls by Mann-Whitney U test (for each, p<0.001).

*The mean age between the groups was comparable (p>0.05).

§Significantly different from the non-ocular patients (Wilcoxon test; for each, p<0.01) and controls (Mann-Whitney U test; for each, p<0.001).

†Significantly different from the controls by Mann-Whitney U test (for each, p<0.01).

*The mean age between the groups was comparable (p>0.05).

§Significantly different from the non-ocular patients (Wilcoxon test; for each, p<0.01) and controls (Mann-Whitney U test; for each, p<0.001).

Alpha2 macroglobulin (mg/dl) 269.52 (31.58)† 201.89 (28.54)‡ 165.11 (23.91)
nitric oxide levels in BD patients and control subjects were 37.60
(10.31) and 27.08 (7.76) μmol/l respectively and the difference was
significant (p < 0.001). Serum total nitrite levels for Behçet’s patients in active and inactive period were 41.15
(7.96) and 34.52 (10.76) μmol/l respectively and the difference was
significant (p = 0.029). Ocular BD patients had also significa-
cantly (p = 0.004) higher total nitrite levels (42.00 (10.62)
μmol/l) than non-ocular patients (33.40 (7.48) μmol/l).

The measured acute phase reactants α, antitrypsin and α, macroglobulin, ESR and neutrophil count were increased sig-
ificantly in active patients when compared with inactive patients and control subjects (Table 2).

DISCUSSION

The most prominent feature of BD is systemic and retinal vas-
culitis with endothelial dysfunction.7 The mechanism for vas-
cular involvement includes arterial and venous thrombosis.8 9
Although the prevalence of deep venous thrombosis is not higher
in ocular than in non-ocular patients, venous occlusions are more common than arterial thrombus and pro-
tein S deficiency has been suggested as the pathogenesis for
thrombogenesis.10 Although many hypotheses have been sug-
gested as the cause of obliterative retinal vasculitis and
thrombosis, the exact aetiology is still unknown.

Hyperhomocysteinaemia refers to mild to moderate eleva-
tion of tHcy in blood or serum. Although the Hcy theory was
proposed 25 years ago, only in the last few years has extensive
research linked homocysteinaemia with systemic and retinal
vascular occlusive disease and thrombogenesis during the
course of systemic diseases.30 31 32 Hcy generates superoxide and
dehydrogen peroxide, both of which have been linked to
endothelial damage. It changes coagulation factor levels so as
to encourage blood clot formation with aggregated platelets.33
Elevated tHcy level has been shown to be a risk factor for
myocardial infarction34 and stroke.35 Some limited studies
showed that elevated tHcy may increase the risk of retinal
vascular diseases such as retinal artery and retinal vein
thrombosis and occlusion.36 37 38 Hcy induced vascular prob-
lems may be multifactorial, including direct Hcy damage to
the endothelium, enhanced LDL peroxidation, and increased
platelet aggregation by the effects on the coagulation system.39

The present study demonstrated an association between serum tHcy and BD over control subjects. Higher serum tHcy
levels were observed in active patients when compared with
inactive subjects. To the best of our knowledge, this investiga-
tion is the first to demonstrate higher serum tHcy concentra-
tions in BD. Compared with both non-ocular patients and
normal control subjects, ocular patients had significantly higher tHcy concentrations. This increase in tHcy was associ-
ated and correlated with the increase in serum ET-1 and NO
levels (data not shown). Since it is well known that endothelial
damage, venous stasis or occlusion, and thrombogenesis have
been extensively documented in the course of BD,11 12 13 these
findings raise the intriguing possibility that hyperoxia,
venous stasis and thrombogenesis may have had an additive
effect for enhanced tHcy and ET-1 production, and perhaps
account for the differences observed between the clinically
distinct subgroups. Therefore, our results support the sugges-
tion that tHcy may be a risk factor for BD but also identify it
as a risk factor for the development of ocular disease. Further-
more, serum tHcy levels among ocular patients with observed
retinal vaso-occlusion were significantly higher than ocular
patients without such occlusion, suggesting thrombogenic
 tendency for Hcy that is the main feature when present in
excess.14 This supports the hypothesis that Hcy is a risk factor
for the development of ocular vaso-occlusive diseases in BD
patients, especially in the exacerbation period.

We found that both ET-1 and NO are higher in active
disease. In our previous study, we have demonstrated that
serum NO levels are increased in BD and correlated with dis-
ease activity.20 The results of this study for NO confirm our
previous findings. Our present findings imply further that
NO levels may be another indicator for ocular disease. The levels
of ET-1 were also significantly higher among patients with
ocular disease in the active stage, and among patients with
vaso-occlusive disease compared with non-ocular patients.
Whether retinal vascular occlusion in patients with BD is
mainly caused by an obliterative periaphebitis, thrombosis, or
both, remains to be specified.

The main factor responsible for the increased frequency of
thrombosis is thought to be endothelial dysfunction in BD.4
Vascular endothelial regulation vascular tone by the roles of
both vasocostructor and vasodilator molecules. In subjects
with endothelial dysfunction, vasodilator responses are lost,
exacerbating the vasoconstrictor response. ET-1 is a potent
vasoconstrictor peptide produced by vascular endothelial
and participates in inflammation, cellular injury, and vascular
events.5 It has been demonstrated that many cytokines and
chemokines induce ET-1 release by endothelium.32 In addition,
elevated ET-1 levels are a well known marker of vascular
endothelial dysfunction and contribute to ocular pathological
manifestations, promoting retinal capillary closure and
ischaemia.31 32 In this respect, Iannaccone et al40 have recently
demonstrated that increased circulating ET-1 levels in patients
with retinal vein occlusion may be a marker of the occlusive
event. They suggested that ET-1 homeostasis might be relevant
to retinal vein occlusion pathogenesis and retinal ischaemic
manifestations. Our findings clearly demonstrated that serum
ET-1 levels were higher in BD, especially in the active period.
In addition, ocular BD patients had significantly higher ET-1 lev-
els than non-ocular subjects. Furthermore, serum tHcy levels
were correlated with ET-1 levels at all comparisons. Therefore,
these findings suggest that ET-1 and tHcy may be interrelated
in endothelial cell activities in BD. On the other hand, NO,
synthesised mainly by the endothelium, is a very important
molecule for the vascular system. Two important functions of
NO are platelet adhesion inhibition and endothelial vasorelaxation.35 Since large amounts of NO are released as a
response to systemic immunoinflammatory diseases, we think
that the increased NO levels found in our BD patients are a
result of inflammatory stimuli, which are the characteristic
feature of the disease. Some cytokines known to be involved in
the upregulation of endothelial cells may be responsible for
the increased NO production. It is possible that increased ET-1
levels could directly favour vascular retinal occlusions. In this
process, synthesised ET-1 may outweigh the amount of NO.
This observation was possibly caused not only by endothelial
cells, but also by polymorphonuclear leucocytes and macro-
phages found in inflammation since these cells are also known
to be involved in the pathogenesis of BD.6 In addition, since
increased tHcy and ET-1 have vasocostricting properties with
atherothrombogenic activity, NO may be increased to compen-
sate for these effects with its vasodilatory and adhesion
inhibitory properties.

The mechanism of Hcy associated vascular thrombosis and
endothelial toxicity is not fully understood. Possible mecha-
nisms include promotion of platelet activation and atherogene-
sis by oxidative injury, increased adhesiveness, enhanced
coaugulability and vascular matrix damage.6 Important in this
respect is the prominent features of BD including obliterative
retinal vasculitis and thrombosis, the major cause of
blindness. Likewise, systemic venous occlusion occurs in
30–40% of all patients.7 It has been demonstrated that
coagulation indices including fibrinogen, von Willebrand fac-
tor, and plasminogen activator activity are increased in BD,27
but the underlying cause of this thrombotic state and the
to which it may promote endothelial damage and periavascu-
litis remain unknown. Furthermore, the association of factor V Leiden, an important mediator in this pathology,
has more recently been demonstrated in BD, especially in
ocular disease.27 A prevailing hypothesis is that Hcy promotes the
Homocysteine, endothelin-1, and nitric oxide in Behçet’s disease

clothing cascade via several actions—inactivation of protein C, activation of coagulation factor V, increased vascular smooth muscle cell proliferation, and inhibition of thrombomodulin. Therefore, it is plausible that there may be an association between serum tHcy and BD and our results are consistent with these hypotheses. The high percentage of patients with bilateral vaso-occlusive disease who manifested hyperhomocysteinemia will have to be confirmed by other studies. As a result, tHcy may be another risk factor for the development of vascular disease in BD patients, especially in retinal vascular occlusive disease.

In conclusion, we demonstrated for the first time that serum tHcy levels are increased in BD and correlated with disease activity. Likewise, tHcy levels were higher among patients with ocular disease compared with non-ocular disease and healthy control subjects. In addition, serum tHcy levels are positively correlated with serum ET-1 and NO levels at all comparisons. If thrombogenetic events do indeed contribute to retinal or systemic vaso-occlusion in BD, and if higher tHcy levels are responsible for this, anticoagulant therapy and the role of some vitamins, known to affect tHcy levels, may warrant investigation. The clinical inference is that measurement, treatment, and monitoring of tHcy levels may be valuable in the management of patients with BD, not only in active stage but also in those with ocular disease.

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