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CONCISE COMMUNICATION

Serum leptin concentration is increased in patients with Behçet's syndrome and is correlated with disease activity

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Summary

Background Behçet's syndrome is a systemic, relapsing immuno-inflammatory disease with a generalized vasculitis of the microvasculature endothelial dysfunction. Leptin, a recently discovered neuroendocrine hormone, is a metabolic peptide that appears to be involved. Serum proinflammatory cytokines upregulate leptin levels and leptin itself directly induces nitric oxide production from endothelial cells with its specific receptors.

Objectives To detect changes of serum leptin concentrations in patients with Behçet's syndrome compared with age- and sex-matched healthy volunteers by using enzyme-linked immunosorbent assay. We also investigated whether disease activity or the duration of Behçet's syndrome correlates with leptin concentration.

Methods Thirty-five consecutive patients with Behçet's syndrome (41·2 ± 8·4 years, 16 male, 19 female) and 20 age- and sex-matched healthy control subjects (40·4 ± 10·91 years, nine male, 11 female) were included in this study. The body mass index (BMI) [weight (kg) height^{-1} (m^2)] was calculated for subjects at study enrolment. We measured serum leptin with a leptin enzyme immunoassay kit, and acute-phase reactants, including erythrocyte sedimentation rate, α_1-antitrypsin, α_2-macroglobulin and neutrophil count. The Mann–Whitney *U*-test was used for statistical analysis and $P < 0{\cdot}05$ was considered significant. Values were expressed as mean ± SD.

Results The gender ratio, age and BMI were not substantially different among Behçet's patients and controls. The mean serum leptin concentrations in patients with Behçet's syndrome (16·8 ± 7·49 ng mL^{-1}) were significantly ($P < 0{\cdot}001$) higher than in healthy control volunteers (7·5 ± 2·77 ng mL^{-1}). Active Behçet's patients had significantly ($P = 0{\cdot}001$) higher leptin concentrations (20·5 ± 7·99 ng mL^{-1}) when compared with patients in inactive periods (12·8 ± 4·43 ng mL^{-1}). In addition, patients with longer disease duration (mean, 20·1 ± 5·15 years) had also significantly ($P = 0{\cdot}013$) higher leptin concentrations (20·2 ± 8·52 ng mL^{-1}) than those with shorter disease duration (13·4 ± 4·52 ng mL^{-1}) (mean, 7·4 ± 3·29 years). All acute-phase reaction parameters were found to be significantly (for each, $P < 0{\cdot}01$) increased in active disease.

Conclusions Leptin may have a role in modulating endothelial function and may be involved in mechanisms for vessel endothelium repair, during an exacerbation as well as in chronic disease.

Key words: Behçet's syndrome, chronicity, disease activity, leptin

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Behçet's syndrome is a chronic, systemic, inflammatory disorder affecting multiple organs with a generalized vasculitis of arteries and veins.[1] It was first described by the Turkish dermatologist Hulusi Behçet in 1937 and is a rare form of vasculitis of unknown aetiology.[2] The classical triad of signs is recurrent oral aphthae and genital ulcers with ocular involvement. But today it is well known that the disease may affect any organ system in an unpredictable manner. Its aetiology is not clear but is presumed to be multifactorial, implicating immune system dysregulation, cellular and humoral immune defects, genetic predisposition and endothelial cell dysfunction.[3]

Leptin is a 167-amino acid large vasoactive protein originally discovered at the end of 1994 during research directed at identifying the molecular defect in obesity.[4] Although leptin is seen as an adipocyte-derived signalling molecule, recent studies have demonstrated that it is expressed in human vasculature and in primary cultures of human endothelial cells.[5] It is known that leptin is influenced by proinflammatory cytokines; patients with an acute-phase response have significantly higher serum leptin levels.[6] It has also been demonstrated that leptin directly induces the release of nitric oxide from endothelial cells.[5] Furthermore, we have more recently reported that the serum nitric oxide level is increased in patients with Behçet's syndrome and is correlated with disease activity.[7]

Because of its endothelial cell implications, we considered leptin as an interesting target for investigation and hypothesize that leptin could be important in modulating vasoregulatory function in Behçet's syndrome. Therefore, the purposes of this study were: (i) to investigate the association of serum leptin concentrations in patients with Behçet's syndrome; (ii) to evaluate whether disease activity has an effect on the blood leptin concentration; and (iii) to explore the effect of disease chronicity on serum leptin levels. To our knowledge this is the first report on serum leptin concentrations in Behçet's syndrome.

Subjects and methods

Patients and controls

This multicentre study included 35 consecutive patients with Behçet's syndrome aged from 26 to 56 years and 20 healthy hospital staff volunteers aged 23–58 years. The diagnosis of patients with Behçet's syndrome was made according to the criteria of the International Study Group for Behçet's Disease.[8] Subjects in both groups with a history of medications, eating disorders, acute or chronic neurological disorder, hypertension, ischaemic heart disease, diabetes or amenorrhoea were not included in the present study.[9–11] In addition, all subjects were non-smokers. Subjects were matched for age, sex and adiposity.

Both clinical and laboratory findings were used for the diagnosis of active and inactive Behçet's patients. Clinically, patients with worsening of clinical symptoms at the time of study with at least three of the major findings (aphthous stomatitis; genital ulcers; anterior iridocyclitis or posterior vasculitis or panuveitis; cutaneous findings; pathergy test positivity[12]) were considered to be in the active stage of the disease. The criteria of the International Uveitis Study Group were used for the diagnosis of uveitis.[13] Laboratory findings included erythrocyte sedimentation rate, neutrophil count, and the acute-phase reactants α_1-antitrypsin and α_2-macroglobulin. All patients with Behçet's syndrome were further divided into two groups according to the duration of the disease to investigate the association of serum leptin concentrations and the clinical course.

After informed consent had been obtained from all subjects in both groups, antecubital whole blood samples (5 mL) were drawn using a 25-gauge needle, avoiding haemolysis, into plain tubes in the morning hours (0900–1100) after an overnight fast and 30 min of supine rest. None of the subjects in either group had received any topical or systemic medication for at least 2 weeks prior to blood collection. Following centrifugation of half of the blood sample (2·5 mL) at 800 ***g*** for 10 min, serum was collected and kept at −70 °C until use. In addition, the body mass index [BMI; weight (kg) height^{-1} (m^2)] was calculated for subjects at study enrolment.

Serum leptin analysis

Duplicate serum samples were assayed for leptin using enzyme-linked immunosorbent assay (ELISA; Leptin Enzyme Immunoassay Kit, Cayman Chemical Co., Ann Arbor, MI, U.S.A.). It is an immunometric sandwich enzyme immunoassay that permits leptin measurements within the range of 1–50 ng mL^{-1} with a limit of detection of 1 ng mL^{-1}. Inter- and intra-assay coefficients of variance (CV) were both less than 9%. The assay allows sensitive and specific analysis of leptin in serum.

Table 1. Neutrophil count, erythrocyte sedimentation rate (ESR) and acute-phase reactants (α_1-antitrypsin, α_2-macroglobulin) in patients with active or inactive Behçet's syndrome and the comparison with healthy control subjects

	Active patients ($n = 18$) Mean ± SD	Inactive patients ($n = 17$) Mean ± SD	Healthy controls ($n = 20$) Mean ± SD
Neutrophils (10^3 mL^{-1})	5·9 ± 1·54[a,b]	3·5 ± 0·53[b]	2·51 ± 0·3
ESR (mm h^{-1})	31·9 ± 6·82[a,b]	16·8 ± 4·59[b]	7·92 ± 1·6
α_1-antitrypsin (mg dL^{-1})	231·6 ± 38·59[a,b]	161·6 ± 21·24[b]	119·31 ± 11·9
α_2-macroglobulin (mg dL^{-1})	272·6 ± 24·52[a,b]	211·3 ± 26·11[b]	161·93 ± 21·8

[a] Significantly different from the inactive stage by Mann–Whitney *U*-test (for each, $P < 0·01$). [b] Significantly different from the controls by analysis of variance (for each, $P < 0·01$).

Analysis of sedimentation rate, neutrophil count and acute-phase reactants

The other half of the blood samples (2·5 mL) with ethylenediamine tetraacetic acid (1 mg mL^{-1}) anticoagulant was used for neutrophil counting with an automated blood counter (Coulter-STKS, Luton, U.K.). The erythrocyte sedimentation rate was determined by the classical Westergren method. Serum α_1-antitrypsin and α_2-macroglobulin levels were measured by a Behring nephelometer 100 analyser.

Statistical analysis

The Mann–Whitney *U*-test and analysis of variance were used for the statistical analysis and the results were expressed as mean ± SD. $P < 0·05$ was considered significant.

Results

The gender ratio, age and BMI were not substantially different among patients with Behçet's syndrome (16 male, 19 female; ages 41·2 ± 8·4 years; BMI: 23·4 ± 1·28) and healthy volunteers (nine male, 11 female; ages 40·4 ± 10·9 years; BMI: 23·3 ± 1·2). There were 18 patients in the exacerbation stage (42·8 ± 8·2 years, eight male, 10 female) and 17 patients in the inactive stage (39·5 ± 8·5 years, eight male, nine female). Indicators for acute inflammation, including erythrocyte sedimentation rate, neutrophil count, α_1-antitrypsin and α_2-macroglobulin were reported to be increased in the exacerbation period of Behçet's syndrome.[14] In the present study, mean concentrations for α_1-antitrypsin, α_2-macroglobulin, neutrophil count and the erythrocyte sedimentation rate were found to be significantly higher (for each, $P < 0·01$) among the patients with active Behçet's syndrome when compared with those in an inactive period and with healthy control subjects (Table 1).

Recurrent aphthous stomatitis was present in all Behçet's patients. Skin lesions were present in 33 (94·2%), recurrent genital aphthae in 31 (88·5%) and ocular lesions in 18 (51·4%) patients. Seventeen patients showed pathergy test positivity (48·5%). In addition, articular symptoms and signs were present in 22 patients (62·8%) and gastrointestinal symptoms in 11 patients (31·4%). Migraine or migraine-like headache was present in eight patients (22·8%) (Table 2).

The mean serum leptin concentration was significantly higher ($P < 0·001$) in patients with Behçet's syndrome (16·8 ± 7·49 ng mL^{-1}) when compared with that in healthy control subjects (7·5 ± 2·77 ng mL^{-1}) (Table 3). Behçet's patients in the active stage had significantly ($P = 0·001$) higher serum leptin concentrations (20·5 ± 7·99 ng mL^{-1}) than those in an inactive period (12·8 ± 4·43 ng mL^{-1}). Behçet's patients with longer disease duration, over 13·6 years (mean duration, 20·1 ± 5·15 years), had significantly ($P = 0·013$) higher serum leptin levels (20·2 ± 8·52 ng mL^{-1}) when compared with patients with shorter (below 13·6 years) duration of disease (mean duration, 7·4 ± 3·29 years) (13·4 ± 4·52 ng mL^{-1}). The median disease duration across all Behçet's patients was 13·6 years.

Discussion

Behçet's syndrome is a multisystem disorder affecting every organ in the body with no exceptions.[1,3,15–17] The male to female ratio varies between 2 and 1 and the syndrome occurs in high prevalence in Mediterranean, Middle Eastern countries, Turkey and Japan and in low prevalence in northern Europe, the United States and the United Kingdom.[18] The onset of the disease is usually between the second and fourth decades of life (range 0–72 years). The aetiology is unknown but viral infections, immune disorders, genetic predisposition and environmental factors have been implicated in

Table 2. Clinical findings of active and inactive patients with Behçet's disease (International Study Group criteria for the diagnosis of Behçet's disease[a])[8]

No.	Sex	Age (years)	Course (years)	AS	GA	Pathergy[c]	Cutaneous lesions	Ocular lesions	Others
1[b]	M	52	29	+	+	+	Papulopustular eruptions, erythema nodosum-like lesions	–	Oligoarticular arthritis, appendicitis-like pain
2	F	42	12	+	+	–	Acneiform nodules, papulopustular eruptions, palpable purpuric lesions of necrotizing vasculitis	Anterior iridocyclitis (B)	Oligoarticular arthritis, appendicitis-like pain
3[b]	F	46	25	+	+	+	Acneiform nodules, papulopustular eruptions	–	Oligoarticular arthritis
4	M	50	15	+	+	–	Acneiform nodules, papulopustular eruptions, palpable purpuric lesions of necrotizing vasculitis	Panuveitis (L)	Migraine-like headache
5[b]	F	51	29	+	+	–	Papulopustular eruptions, palpable purpuric lesions of necrotizing vasculitis, erythema nodosum-like lesions, acneiform nodules	Anterior iridocyclitis (R)	Oligoarticular arthritis
6	F	35	8	+	+	+	Papulopustular eruptions	–	Migraine-like headache, oligoarticular arthritis
7[b]	M	26	3	+	+	–	Papulopustular eruptions	Posterior vasculitis (L)	Migraine-like headache
8	F	35	4	+	+	–	Acneiform nodules, papulopustular eruptions	Posterior vasculitis (B)	Oligoarticular arthritis, appendicitis-like pain
9[b]	M	38	16	+	+	–	Papulopustular eruptions, erythema nodosum-like lesions	–	Oligoarticular arthritis appendicitis–like pain
10	M	30	5	+	+	+	Papulopustular eruptions	–	–
11[b]	F	39	19	+	+	–	Papulopustular eruptions	Anterior iridocyclitis (R)	Oligoarticular arthritis
12	F	55	22	+	+	–	Papulopustular eruptions	Posterior vasculitis (L)	Migraine-like headache
13[b]	F	33	11	+	–	+	Papulopustular eruptions, erythema nodosum-like lesions	Anterior iridocyclitis (B)	Oligoarticular arthritis
14	M	32	1	+	+	+	Acneiform nodules, papulopustular eruptions	–	Migraine-like headache, oligoarticular arthritis
15[b]	M	45	15	+	+	–	Papulopustular eruptions, palpable purpuric lesions of necrotizing vasculitis	–	Appendicitis-like pain
16	F	56	10	+	+	+	Acneiform nodules, papulopustular eruptions, palpable purpuric lesions of necrotizing vasculitis	Posterior vasculitis (L)	–
17[b]	F	46	25	+	+	+	–	–	Migraine-like headache, oligoarticular arthritis, melaena
18	M	45	11	+	+	+	Acneiform nodules, papulopustular eruptions	–	Migraine-like headache, oligoarticular arthritis
19[b]	M	45	19	+	+	+	Papulopustular eruptions	–	Oligoarticular arthritis
20	F	35	7	+	+	–	Acneiform nodules, papulopustular eruptions	–	Oligoarticular arthritis
21[b]	M	54	22	+	–	–	Papulopustular eruptions	Anterior iridocyclitis (R)	–
22	F	29	8	+	+	–	Acneiform nodules, papulopustular eruptions	Anterior iridocyclitis (R)	Appendicitis-like pain
23[b]	M	37	14	+	+	+	Papulopustular eruptions	–	Oligoarticular arthritis
24	F	39	6	+	+	–	Papulopustular eruptions	Posterior vasculitis (B)	Appendicitis-like pain
25[b]	M	41	18	+	+	–	Acneiform nodules, papulopustular eruptions, erythema nodosum-like lesions	Panuveitis (L)	Migraine-like headache, oligoarticular arthritis
26	M	45	10	+	–	+	Papulopustular eruptions, erythemanodosum-like lesions	Anterior iridocyclitis (R)	Oligoarticular arthritis
27[b]	F	56	22	+	+	+	Acneiform nodules, papulopustular eruptions	–	Melaena
28	M	34	11	+	+	–	Papulopustular eruptions, palpable purpuric lesions of necrotizing vasculitis	Posterior vasculitis (L)	–

Table 2. Continued

No.	Sex	Age (years)	Course (years)	AS	GA	Pathergy[c]	Cutaneous lesions	Ocular lesions	Others
29[b]	F	51	25	+	+	+	Papulopustular eruptions	–	Oligoarticular arthritis, appendicitis-like pain
30	F	40	15	+	+	+	Papulopustular eruptions	–	Oligoarticular arthritis
31[b]	F	41	9	+	+	–	–	Anterior iridocyclitis (B)	–
32	M	29	3	+	+	+	Papulopustular eruptions	–	Oligoarticular arthritis
33[b]	F	34	14	+	+	–	Papulopustular eruptions	Posterior vasculitis (L)	Appendicitis-like pain
34	M	40	5	+	–	+	Papulopustular eruptions	–	Oligoarticular arthritis
35[b]	F	35	9	+	+	–	Papulopustular eruptions, palpable purpuric lesions of necrotizing vasculitis	Uveitis (R)	Oligoarticular arthritis

AS; aphthous stomatitis, GA; recurrent genital aphthae, B; bilateral, R; right, L; left. [a] AS plus two of the following criteria (ocular lesions, cutaneous lesions, genital aphthae, positive pathergy test). [b] Active patients with Behçet's syndrome. [c] Observation of a pustular lesion by a physician at 24–48 h after a needle-stick injury to the forearm.

Table 3. Serum leptin concentration in patients with Behçet's syndrome and healthy controls

	n	Age, years (mean ± SD)	P^a =	Serum leptin (ng mL^{-1}) (mean ± SD)	P^a =	Course (median; 13·6 years)[b] (mean ± SD)	P^a =
Behçet's subjects	35	41·2 ± 8·37	0·752	16·8 ± 7·49	< 0·001		
Controls	20	40·4 ± 10·91		7·5 ± 2·77			
Active Behçet's subjects	18	42·8 ± 8·20	0·197	20.5 ± 7.99	0·001		
Inactive Behçet's subjects	17	39·5 ± 8·47		12.8 ± 4.43			
Behçet's with longer duration[c]	17	45·9 ± 6·83	0·001	20·2 ± 8·52	0·013	20·1 ± 5·15	< 0·001
Behçet's with shorter duration[d]	18	36·7 ± 7·29		13·4 ± 4·52		7·4 ± 3·29	

[a] By Mann–Whitney *U*-test. [b] 13·6 is the median of disease duration across all Behçet's patients. [c] Behçet's patients with disease duration over 13·6 years. [d] Behçet's patients with disease duration below 13·6 years.

the aetiopathogenesis, although this is not proven yet.[18] The characteristic pathological feature is a multifocal necrotizing vasculitis with lymphocytic infiltration of the veins, capillaries and arteries, and up to 25% of patients suffer systemic venous thrombosis.[3,19] Endothelial dysfunction is the most prominent feature of Behçet's syndrome.[20] The intermittent nature of the disease and the lack of consistent response to therapy make the underlying aetiology difficult to define.

Leptin (*Ob* protein), the product of the newly cloned *ob* gene, is a recently discovered 16-kDa protein that plays a crucial role during inflammation.[21] Leptin achieves most of its effects by interacting with specific receptors located in the central nervous system and in peripheral tissues. The recent observation that leptin receptors are expressed on endothelial cells led us to hypothesize that leptin could be important in modulating vasoregulatory function in Behçet's syndrome. A recent study has demonstrated that impaired endothelial function is reversed after leptin replacement.[5] In addition, it has been demonstrated that leptin directly enhances the release of nitric oxide from endothelial cells. Furthermore, administration of cytokines to human volunteers has been followed by an increase in serum leptin levels.[22] Therefore, the primary role of cytokines in the induction of leptin and the induction effect of leptin on nitric oxide (cytokines–leptin–nitric oxide) from endothelial cells during inflammation suggest that some of the biological activities of these molecules may be specifically mediated by leptin. Indeed, our recent study has demonstrated for the first time that serum nitric oxide levels are significantly increased in patients with Behçet's syndrome and are correlated with disease activity.[7] Moreover, our further studies have also demonstrated that serum proinflammatory cytokines, including soluble interleukin 2 receptor, interleukins 6 and 8 and tumour necrosis factor α levels are increased in Behçet's patients and correlate with disease activity[23]. Therefore, it is highly plausible that leptin may play a part in the pathophysiology of Behçet's syndrome.

In the present study, we aimed to investigate serum leptin concentrations in patients with Behçet's syndrome and to evaluate the significance of disease activity or its duration. We have demonstrated: (i) an increased serum leptin concentration about 2·5-fold in patients with Behçet's syndrome; (ii) serum leptin levels correlated with disease activity; and (iii) an association between leptin levels and the duration of the disease. Based on these results, it is possible that leptin may participate in the pathophysiology of vascular lesions in Behçet's syndrome, although not having a disease-specific character. In this respect the recent focus on the role of the endothelium in inflammation and the increase in proinflammatory cytokines in patients with active Behçet's syndrome has been important.[3,23] As increased serum leptin concentrations in patients with Behçet's syndrome do correlate with the activity of the disease, an association of leptin with proinflammatory cytokines can be suggested.

In conclusion, the present study clearly demonstrated for the first time that serum leptin concentration is increased in Behçet's patients when compared with control subjects, suggesting an autocrine or paracrine modulator role for leptin in Behçet's syndrome. Leptin may be produced as a response to endothelial dysfunction during the course of inflammation and may act as a non-specific reparatory mechanism for the diseased endothelium in Behçet's syndrome. In addition, patients with active Behçet's had significantly higher serum leptin levels than controls. Furthermore, patients with longer disease duration also have significantly higher leptin concentrations. Therefore, circulating leptin might be related to the extent of activation of the immune system and might serve as a marker of severity and chronicity for patients with Behçet's syndrome. In addition, our working hypothesis for future research is that this alteration of serum leptin levels may tend to restore the altered endothelial function in Behçet's syndrome and opens the way to further studies evaluating interactions in the cytokine–leptin–nitric oxide cycle in such patients.

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