Serum Interleukin-6 and Adiponectin Levels in Patients with Active or Inactive Behçet's Disease

Aktif ya da İnaktif Behçet Hastalığı Bulunan Hastaların Serum İnterlökin-6 ve Adiponektin Seviyeleri

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ABSTRACT Objective: Behçet's disease (BD) is a chronic systemic inflammatory disease and its etiopathogenesis still remains unknown. Cytokines play a role in immune response and inflammatory reactions. The aim of this study is to determine the levels of proinflammatory cytokine interleukin-6 (IL-6) and anti-inflammatory cytokine adiponectin in the sera of patients with BD and to assess their importance as biological markers for disease activity. **Material and Methods:** Forty-four BD patients [19 males, 25 females, age: 35.65 ± 10.84 yrs (mean ± standart deviation) (SD)] and 25 healthy controls (10 males, 15 females, age: 29.80 ± 8.20 yrs) were included in the study. Patients were divided into active or inactive groups according to their clinical and laboratory findings (active, n= 21; inactive, n= 23). We determined serum IL-6 levels using the chemiluminescence method, and serum adiponectin levels by ELISA method. Results were expressed as mean ± standard error (SE). **Results:** Serum levels of IL-6 and adiponectin in BD patients (n= 44) (5.24 ± 0.84 pg/mL; 22.31 ± 1.71 μg/mL, respectively) were similar to the control group (n= 25) (4.59 ± 1.01 pg/mL; 21.68 ± 1.91 μg/mL, respectively). No significant difference was found in IL-6 and adiponectin levels between the active (n= 21), inactive (n= 23) and control (n= 25) groups. **Conclusion:** In parallel with the presence of inflammation and increased CRP, erythrocyte sedimentation rate and white blood cell count, higher IL-6 and lower adiponectin levels were expected in active BD patients compared to the controls. However, they were found to be similar in all groups. We conclude that ongoing anti-inflammatory treatment should be taken into consideration while interpreting the cytokine levels in these patients.

Key Words: Behcet's syndrome; adipokines; interleukin-6

ÖZET Amaç: Behçet hastalığı (BH), kronik sistemik inflamatuar bir hastalık olup etiyopatogenezi henüz bilinmemektedir. İmmun cevap ve inflamatuvar süreç ilişkisinde sitokinler rol oynamaktadırlar. Bu çalışmanın amacı, BH'lı hastaların serumlarında pro-inflamatuar bir sitokin olan IL-6 ile anti-inflamatuar sitokin olan adiponektinin seviyelerini ölçerek, bunların hastalığın aktivitesinde biyolojik belirteç olarak etkilerini belirlemektir. **Gereç ve Yöntemler:** Çalışmaya 44 BH'lı hasta (19 erkek, 25 kadın, yaş ortalaması 35.65 ± 10 yıl) ve kontrol grubu olarak da 25 sağlıklı kişi (10 erkek, 15 kadın, yaş ortalaması 29.80 ± 8.20 yıl) alınmıştır. Hastalar klinik ve laboratuvar bulgularına göre aktif (n: 21) ve inaktif (n: 23) gruba ayrıldılar. Serum IL-6 seviyesi kemiluminesens metod ile, serum adiponektin seviyesi ise ELISA yöntemi ile ölçülmüştür. Sonuçlar aritmetik ortalama ± standart hata olarak belirtilmiştir. **Bulgular:** Tüm BH'lı hastaların serum IL-6 ve adiponektin seviyeleri sırasıyla 5.24 ± 0.84 pg/mL ve 22.31 ± 1.71 μg/mL: sağlıklı kontrol grubunda ise 4.59 ± 1.01 pg/mL ve 21.68 ± 1.91 μg/mL olarak benzer bulunmuştur. Serum IL-6 ve adiponektin seviyeleri aktif ve inaktif BH'lı hastalar ve sağlıklı kontrol grubu arasında karşılaştırıldığında aradaki fark istatistik olarak anlamlı bulunmamıştır. **Sonuç:** İnflamasyon varlığı, artmış C reaktif protein seviyesi, eritrosit sedimentasyon hızı ve lökosit sayısına paralel olarak serum IL-6 seviyesinin yükselmiş, adiponektinin ise düşük bulunması beklenmesine rağmen bunlar tüm gruplarda benzer seviyelerde bulunmuştur. BH'lı hastalarda serum sitokin seviyelerini değerlendirirken anti-inflamatuar tedavinin durumunu da ele almak gerektiği sonucuna varmış bulunmaktayız.

Anahtar Kelimeler: Behçet sendromu; adipokinler; interlökin-6

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Multisystemic involvement in BD was introduced by the studies performed after it had been defined by Prof. Dr. Hulusi Behçet in 1937, as a disease characterized by uveitis with hypopyon, oral and genital ulcerations.[1] The etiopathogenesis of BD, which is considered as an immunoinflammatory disorder,[2] has not yet been completely defined in detail. Genetic factors, infection, immunoglobulins, immune-complexes, antibodies and oxidative stress have been alleged as the causes of BD.[3-5] Evereklioglu et al and Buldanlioglu et al, pointed out that nitric oxide levels were increased in BD patients and this increase was associated to activation of the disease.[6,7]

Cytokines are low-molecular-weight bioactive polypeptides functioning in intercellular communications.[8] In inflammatory diseases, it is considered that there is a relationship between cytokines, T cells and oxidative stress.[8] It has been been known that proinflammatory cytokines aggravate oxidative stress by increasing the secretion of nitric oxide from endothelial cells. In the same way, homocysteine stimulates the expression of chemoattractants by increasing the synthesis of nitric oxide in the endothelial cells, and it is significantly related to cytokines.[9,10] Studies on cytokine profile in BD have yielded conflicting results.[8,11-20]

Adiponectin is an adipocytokine which was defined first and it is the major protein produced by the adipocytes. It is a central regulatory protein controlling lipid and carbohydrate metabolism in many physiologic pathways and it mediates various vascular processes. Adiponectin exhibits both anti-inflammatory and anti-atherogenic properties.[21] In contrary to other adipocytokines, adiponectin levels decrease paradoxically in cases with insulin resistance including obesity, metabolic syndrome, hypertension and coronary arterial diseases.

In literature, there is only one study in which serum adiponectin levels were measured, performed by Oguz et al.[22] This study reported that no statistically significant difference was found between the BD group and the healthy volunteers in terms of serum adiponectin levels.

In our study in order to understand the etiopathogenesis of BD better by measuring the levels of IL-6, which is a proinflammatory cytokine and anti-inflammatory cytokine adiponectin, we aimed to investigate the relationships of these two cytokines with the activity of the disease.

MATERIAL AND METHODS

Forty-four patients (19 males, 25 females; mean age 35 years; range 16-60) with BD and twenty-five healthy control subjects (10 males, 15 females; mean age 29 years; range 19-45) from a similar ethnic background were included in the study. Subjects with systemic disorder such as renal or hepatic diseases, diabetes pregnant patients and patients on antioxidant therapy were excluded from the study. The diagnosis of BD was made according to the criteria of the International Study Group for BD.[23] The ethic committee of our hospital approved the protocol and informed consent was obtained from all participants.

Active (n= 21) and inactive (n= 23) BD patients were determined by clinical and laboratory findings. In clinical evaluation, having at least three of the major symptoms at the time of study (oral ulcers, genital ulcers, skin lesions, uveitis, positive pathergy test) were considered to indicate the active period of the disease. Patients in remission, lacking these activity symptoms were evaluated as inactive patients. In the laboratory investigations, the serum C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR) and white blood cell count (WBC) were determined.

Of 44 BD patients, 25 (56.8%) were on colchicine treatment, five 5 (11.36%) were on colchicine+steroid treatment, two (4.54%) were on colchicine+non steroid anti-iflammatory drug treatment, one (2.27%) was on colchicine+azothiopurine treatment, one (2.27%) was on interferon-α-2a and one (2.27%) was receiving cyclosporine treatment.

Seven mililiters of whole blood samples were obtained by venipuncture from a peripheral vein and put into a plain tube for lipid profile, CRP, IL-6 and adiponectin; 1.5 mL blood was put into a K_3-ethylenediamine tetraacetic acid (EDTA)-contai-

ning tube for WBC and 1.6 mL blood was put into a sodium citrate (3.2%; 0.4 mL) containing tube for ESR. Blood samples were obtained in during resting position between 08.00-10.00 a.m. hours. The plain tube was centrifuged at 1500 x g for 10 minutes. Serum was separated and kept at -80° C until the time of IL-6 and adiponectin analysis. IL-6 and adiponectin levels were detected within 6 months. ESR, WBC and concentrations of serum total cholesterol (Tot-C), triglyceride (TG), HDL-cholesterol (HDL-C) and CRP were determined on the same day. The blood samples were taken in both active and inactive periods of eight patients with BD.

The ESR was determined by Eriline AR automated analyzer (Linear Chemicals, I.L., Barcelona, Spain). WBC was counted by Advia 120 hematology system (Siemens, Germany). The concentrations of Tot-C, TG and HDL-C in serum were measured by Modular DP autoanalyser (Roche Diagnostics, Frankfurt, Germany). LDL-C was calculated by Friedewald formula. The CRP concentration was measured in the serum by a BN-II automated nephelometer (Siemens-Dade Behring, West Sacramento, U.S.A.).

IL-6 analysis was performed according to the Immulite 2000 chemiluminescent enzyme immunometric assay (Siemens-Diagnostic Products Corporation, Los Angeles, U.S.A.). Serum adiponectin levels were measured by AssayMax ELISA Kit (St Charles, MO, U.S.A.).

STATISTICAL ANALYSIS

Results were analyzed statistically by using one way ANOVA for the descriptive analysis and Tukey HSD for the multiple comparisons among the three groups. The values of all BD patients and the control group were compared using Student's t and Mann-Whitney U tests. $P< 0.05$ was considered significant. Wilcoxon test was performed for comparing the results of the same patient during active and inactive periods. Pearson test was used for correlation analysis. The SPSS Inc.Package Program (Chicago, IL, U.S.A.) was used for all statistical analyses.

TABLE 1: Clinical manifestations in active BD patients (n= 21).

Patient No	Pathergy (48 hours)	Oral aphthous ulcers	Genital aphthous ulcers	Skin involvement	Ocular involvement	Neurological involvement	Articular involvement
1	+	+	-	+	+	-	-
2	+	+	-	+	+	-	-
3	+	+	+	-	-	-	-
4	+	+	-	-	+	-	-
5	+	+	+	+	-	-	-
6	+	+	+	+	-	+	-
7	+	+	-	+	+	-	+
8	+	-	+	+	-	-	-
9	+	+	-	-	+	-	+
10	-	+	-	-	+	+	+
11	+	+	-	-	-	-	+
12	+	+	+	-	-	-	-
13	-	+	+	-	-	-	+
14	-	+	+	-	+	+	-
15	-	+	+	-	+	-	+
16	+	+	-	-	-	-	+
17	+	+	+	-	-	-	-
18	+	+	+	-	-	-	-
19	+	+	-	-	-	-	+
20	+	+	+	-	+	+	-
21	+	+	+	+	-	-	-

TABLE 2: Clinical manifestation in inactive BD patients (n= 23).

Patient No	Pathergy 48 hours	Oral aphthous ulcers	Genital aphthous ulcers	Skin involvement	Ocular involvement	Neurological involvement	Articular involvement
1	-	-	-	-	+	-	-
2	-	-	-	-	-	-	-
3	-	-	-	-	-	-	+
4	-	-	-	-	-	-	-
5	-	-	-	-	-	-	+
6	-	-	-	-	-		+
7	-	-	-	-	-	-	+
8	-	+	-	-	-	+	-
9	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-
12	-	-	-	-	-	-	-
13	-	-	-	-	-	-	+
14	-	-	-	-	-	-	-
15	-	-	-	-	+	-	+
16	-	-	-	-	-	-	-
17	-	-	-	-	-	+	+
18	-	+	-	+	-	-	-
19	-	-	-	-	-	+	+
20	-	-	-	-	-	+	+
21	-	-	-	-	-	+	+
22	-	-	-	-	-	-	-
23	-	-	-	+	-	-	-

TABLE 3: Demographic and laboratory findings of the groups.

	Active Group (n= 21)	Inactive Group (n= 23)	Control Group (n= 25)	Total BD Group (n= 44)
Age (yrs; mean ± SD)	34.71 ± 12.51	36.52 ± 9.27	29.80 ± 8.20	35.65 ± 10.84
Male/Female (n, %)	7 (33.3)/14 (66.6)	12 (52.1)/11 (47.9)	10 (40)/15 (50)	19 (43.1)/25 (56.9)
BMI (mean ± SD)	24.40±0.94	34.04±7.87	22.76 ± 0.50	29.44 ± 4.16
Tot-C. (mg/dL; mean ± SD)	167 ± 37	173 ± 39	152 ± 29	170 ± 38
TG (mg/dL; (mean ± SD)	94 ± 44*,$^{\Phi}$	156 ± 116$^{\#\#}$	70 ± 25	126 ± 93$^{\&}$
HDL-C. (mg/dL; mean ± SD)	45 ± 13**	42 ± 10$^{\#\#}$	56 ± 16	44 ± 11$^{\&\&}$
LDL-C. (mg/dL; mean ± SD)	99 ± 28	100 ± 33$^{\#}$	83 ± 23	99 ± 31$^{\&}$
ESR (mm/hour) (mean ± SD)	30.85 ± 26.20**	18.60±12.70$^{\#}$	7.48±4.20	24.45 ± 20.90$^{\&\&}$
WBC (10^3/mm^3) (mean ± SD)	8.24 ± 2.90*	7.74±2.40	6.85±2.90	7.98 ± 2.69$^{\&}$
CRP (mg/L; mean ± SE)	11.22 ± 3.20**	4.75 ± 1.01$^{\#}$	3.20 ± 0.01	8.50 ± 1.79$^{\&}$
IL-6 (pg/mL; mean ± SE)	4.53 ± 1.15	5.88 ± 1.24	4.59 ± 1.01	5.24 ± 0.84
Adiponectin (mg/mL; mean ± SE)	20.6 ± 1.83	23.87 ± 2.83	21.68 ± 1.91	22.31 ± 1.71

BMI: Body mass index

*p< 0.05 (active vs. control);**p< 0.01 (active vs. control); $^{\Phi}$p< 0.05 (active vs. inactive)

$^{\&}$p< 0.05 (total vs.control); $^{\&\&}$p< 0.01 (total vs. control); $^{\&\&\&}$p< 0.001 (total vs. control);

$^{\#}$p< 0.05 (inactive vs. control), $^{\#\#}$p< 0.001 (inactive vs. control).

TABLE 4: The comparisons of the parameters in to the active and inactive periods of 8 patients with BD.

	Active Period	Inactive Period
Tot-C (mg/dL; mean ± SD)	155 ± 16	164 ± 31
TG (mg/dL; mean ± SD	109 ± 54	111 ± 50
HDL-C (mg/dL; mean ± SD)	39 ± 7	41 ± 8
LDL-C (mg/d; mean ± SD)	93 ± 21	100 ± 32
ESR (mm/hour; mean ± SD))	27.87±24.11*	12.12 ± 6.93
WBC (10^3/mm^3; mean ± SD)	8.17±1.55	7.35 ± 2.35
CRP (mg/L;mean ± SE)	12.3 ± 8.7	7.79 ± 12.29
IL-6 (pg/mL;mean ± SE)	6.35 ± 8.35	5.57 ± 5.07
Adiponectin (mg/mL;mean ± SE)	16.86 ± 3.98	17.81 ± 7.14

*p< 0.05.

RESULTS

Table 1 and 2 show the clinical manifestations of total, active and inactive BD patients, respectively.

Table 3 shows the demographic and laboratory findings of the groups.

Table 4 shows the comparisons of the parameters related to the active and inactive periods of 8 patients with BD.

DISCUSSION

In studies it has been observed that enzymatic and nonenzymatic antioxidant molecules decreased and indicators for oxidative stress increased in the sera of BD patients.[5,24-26]

Being a multifunctional proinflammatory cytokine regulating immune response, IL-6 is produced by monocytes, epithelial cells and fibroblasts and it causes polyclonal B cell activation, hypergammaglobulinemia and T cell activated autoantibody production.[27,28] It was pointed out that the secretion of acute phase reactants enhances the proliferation and differantiation of the cells.[29] It was detected that overproduction of IL-6 was observed in some autoimmune diseases and chronic inflammatory reactions.[30]

A collagen like protein named adiponectin which is secreted from adipose tissue is emphasized to be an important anti-atherogenic, antidiabetic and anti-inflammatory protein in recent studies.[31] When the endothelial barrier is damaged, being susceptible to mechanical stress and chemical compounds such as oxidized LDL, adiponectin binds subendothelial collagen accumulated in the subendothelial space of vascular walls where it manifests its anti-atherogenic properties.[32] Adiponectin inhibits expressions of adhesion molecules by inhibiting activation of NF-κ-B. Thus adiponectin prevents monocytes from adhering to vascular endothelial cells.[33] Adiponectin also impairs the vascular smooth muscle cellular proliferation induced by growth factor inhibition of mitogen activated protein kinase.[34]

In the light of this information, we investigated the levels of Tot-C, TG, HDL-C, LDL-C, CRP, ESR, WBC, IL-6 and adinopectin in 44 BD patients, in active and inactive periods of 8 patients with BD, and investigated their relationships with disease activation.

We observed that the serum TG levels of active, inactive and total patient groups were significantly higher and HDL-C levels were significantly lower in comparison to the control group. We detected that the LDL-C levels of inactive, active and total patient groups were significantly higher in comparison to those of the control group. Our findings on lipid levels are compatible with that of Sandikci,[5] Mitamura,[35] Orem[24,36,37] and Chambers[38] et al. In BD, as a result of an increase in TG and LDL-C levels, lipids and lipoproteins exposed to oxidative stress develop lipid peroxidation products. Therefore, this may be the responsible factor of endothelial dysfunction in BD. Our findings on lipids and lipoproteins support that oxidative stress plays a role in vascular inflammatory incidents in etiopathogenesis of BD.

In our study, when we compared IL-6 and adinopectin levels in active, inactive and total patient groups, we could not find any significant differences between the groups. Studies on cytokine profile in BD hawe shown conflicting results . Many in vivo studies have demonstrated that TNF-α, IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, G-CSF and IFN-γ were all important components of the proinflammatory response in BD.[8,11-18] Mege et al. found that the spontaneous secretion of TNF-α,

IL-6 and IL-8 by monocytes was significantly increased in patients with active BD.[11] Turan et al. reported that IL-10 and IL-12 were increased in BD and IL-12 had a correlation with activation.[12] Yamakawa et al. examined the levels of IL-6 in plasma and supernatants of peripheral blood mononuclear cells (PBMC) from BD patients and healthy controls using a sensitive ELISA.[13] The IL-6 concentrations in culture supernatants of patients with active BD were significantly high when compared to patients with inactive disease and the controls. They reported that IL-6 might play a role in the pathogenesis of BD. Nawata et al. speculated that the repeated febrile episodes might have been manifestations of neutrophil hyperfunction induced by increased blood levels of inflammatory cytokines, including IL-6, IL-8 and G-CSF, in association with rare complications of BD.[14]

Hamzaoui et al. reported higher IL-6 levels in active and inactive patient groups in comparison to the control group.[15] Evereklioglu et al. reported that IL-6 was a key activator of acute phase response and the increase might be responsible for the increase in the synthesis of acute phase reactants in the liver, and thus IL-6 had an important role in the course of BD.[8] They detected significantly higher levels of acute phase reactants; neutrophil count, ESR, α-1-antitripsin and α-2-macroglobulin in the active patient group in comparison to the inactive and the control groups. They also detected significantly higher levels of these parameters in the inactive patient group in comparison to the control group. Bardak et al. detected significantly higher serum levels of IL-6, IL-8 ve TNF-α in BD patients with active uvetis in comparison to the remission period of the same patient group and healthy individuals.[16] Adam et al. found significantly higher levels of CRP and IL-6 in the active BD patient group in comparison to the control group.[17] Akdeniz et al. found significantly higher serum levels of IL-6, IL-8 and TNF-α in BD in comparison to the control group.[18]

On the other hand, al-Dalaan et al. reported that serum levels of IL-6, TNF-α and IFN-γ were not significantly elevated in patients with BD.[19] Sayinalp et al. simiarly found that serum levels of IL-1 beta, IL-2 and IL-6 in the patients with BD were similar to the control group, but serum levels of sIL-2R and TNF-α were higher in patients with BD compared to controls.[20] Our findings on serum IL-6 levels are inconsistent with those of Mege, Turan, Yamakawa, Nawata, Hamzaoui, Evereklioglu, Bardak, Adam, Akdeniz et al., however they are consistent with those of al-Dalaan, and Sayinalp et al.[8,11-20]

The only study in literature in which serum adinopectin level is investigated in BD was performed by Oguz et al.[22] In this study, serum adinopectin levels were not significantly different in BD in comparison to the healthy control group. Their patient group manifested similarities to our patients because 86.8% of the patients used colchicine, 2.6% used steroid and 5.3% used immunosupressives. Our findings on adinopectin levels overlap with those of Oguz et al.[22]

We suppose that the reason of conflicting results in terms of IL-6 levels emanates from the variation of measurement methods and/or drug/medication used in patients included in the study, as well as the duration of the therapy. Evereklioglu et al. reported that they excluded the patients using glucocorticoids and immunosupressives that decreased the transcription of proinflammatory cytokines.[8] Because of the medical conditions of our patients it was not possible for them to stop their anti-inflammatory/immunosuppressive medications. Thus, we only excluded the patients on antioxidant medications. Of the 44 BD patients, 25 (56.8%) were on colchicine treatment, five (11.36%) were on colchicine+steroid treatment, two (4.54%) were on colchicine+non steroid anti-inflammatory drug treatment, one (2.27%) was on colchicine+azothiopurine treatment, one (2.27%) was on interferon-α-2a and one (2.27%) was receiving cyclosporine treatment. It has been known that colchicine inhibits fibronectin and alveolar macrophage derived growth factor secretion from alveolar macrophages; it inhibits cellular replication by binding tubuline and it manifests an antifibrotic effect by inhibiting cytokine release from polimorphonuclear leukocytes. It was concluded that, because of colchicine and other anti-inflam-

matory/immunosupressive drugs used by both active and inactive patients, serum IL-6 and adinopectin levels were depressed and due to that, there were no differences between the groups in terms of cytokines.

Although 79.5% of the patients used steroid–non steroid anti-inflammatory/immunusupressive medication, ESR, WBC and CRP levels were measured to differentiate the active BD patients from the inactive BD patients. The levels of these parameters were significantly higher in the active and total patient groups when compared to the control group. In the active patient group, only ESR was significantly higher when compared to inactive patient group. We concluded that, in contrary to IL-6 and adiponectin, these acute phase reactants, in spite of drug or medications, yielded true information to differentiate BD patients from healthy individuals, and only ESR can be used to differentiate the active phase of the disease from the inactive phase. Although IL-6 is known as a key activator of acute phase response, in our study, IL-6 did not increase in serum of the patients with BD. Thus, factors other than cytokine inducing ESR increase should be considered in BD.

We could not find any statistically significant differences in the blood samples obtained during active and inactive periods of eight patients with BD in terms of lipids, acute phase reactants or cytokine levels. We concluded that this result emanated from the effects of the drugs on serum levels of these parameters.

In conclusion, anti-inflammatory and immunosupressive drugs used in BD patients depress pro-inflammatory and anti-inflammatory cytokine levels. Therefore we conclude that it is convenient to evaluate the importance of pro-inflammatory and anti-inflammatory cytokines in active or inactive phases by measuring the cytokines in newly diagnosed BD patients who are not on any medication.

REFERENCES

1. Behcet H. [Aphthous sequelae formed as a result of ulcers caused by a virus in oral, opthalmic and genital regions]. Dermatol Wochenschr 1937;105:1152-7.
2. Jorizzo JL, Hudson RD, Schmalstieg FC, Daniels JC, Apisarnthanarax P, Henry JC, et al. Behçet's syndrome: immune regulation, circulating immune complexes, neutrophil migration, and colchicine therapy. J Am Acad Dermatol 1984;10(2 Pt 1):205-14.
3. Erkiliç K, Evereklioglu C, Cekmen M, Ozkiris A, Duygulu F, Dogan H. Adenosine deaminase enzyme activity is increased and negatively correlates with catalase, superoxide dismutase and glutathione peroxidase in patients with Behçet's disease: original contributions/clinical and laboratory investigations. Mediators Inflamm 2003;12(2):107-16.
4. Ghate JV, Jorizzo JL. Behçet's disease and complex aphthosis. J Am Acad Dermatol. 1999;40(1):1-18; quiz 19-20.
5. Sandikci R, Türkmen S, Güvenen G, Ayabakan H, Gülcan P, Koldas M, et al. Lipid peroxidation and antioxidant defence system in patients with active or inactive Behçet's disease. Acta Derm Venereol 2003;83(5):342-6.
6. Evereklioglu C, Turkoz Y, Er H, Inaloz HS, Ozbek E, Cekmen M. Increased nitric oxide production in patients with Behçet's disease: is it a new activity marker? J Am Acad Dermatol 2002;46(1):50-4.
7. Buldanlioglu S, Turkmen S, Ayabakan HB, Yenice N, Vardar M, Dogan S, et al. Nitric oxide, lipid peroxidation and antioxidant defence system in patients with active or inactive Behçet's disease. Br J Dermatol 2005;153(3):526-30.
8. Evereklioglu C, Er H, Türköz Y, Cekmen M. Serum levels of TNF-alpha, sIL-2R, IL-6, and IL-8 are increased and associated with elevated lipid peroxidation in patients with Behçet's disease. Mediators Inflamm 2002;11(2):87-93.
9. Ikeda U, Ikeda M, Minota S, Shimada K. Homocysteine increases nitric oxide synthesis in cytokine-stimulated vascular smooth muscle cells. Circulation 1999;99(9):1230-5.
10. Sarican T, Ayabakan H, Turkmen S, Kalaslioglu V, Baran F, Yenice N. Homocysteine: an activity marker in Behçet's disease? J Dermatol Sci 2007;45(2):121-6.
11. Mege JL, Dilsen N, Sanguedolce V, Gul A, Bongrand P, Roux H, et al. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects. J Rheumatol 1993;20(9):1544-9.
12. Turan B, Gallati H, Erdi H, Gürler A, Michel BA, Villiger PM. Systemic levels of the T cell regulatory cytokines IL-10 and IL-12 in Bechçet's disease; soluble TNFR-75 as a biological marker of disease activity. J Rheumatol 1997;24(1):128-32.
13. Yamakawa Y, Sugita Y, Nagatani T, Takahashi S, Yamakawa T, Tanaka S, et al. Interleukin-6 (IL-6) in patients with Behçet's disease. J Dermatol Sci 1996;11(3):189-95.
14. Nawata R, Shinohara K, Takahashi T, Yamada T, Katsuki K. [Refractory anemia with trisomy-8 complicated by Behçet's disease with elevated levels of inflammatory cytokines]. Rinsho Ketsueki 1999;40(10):1100-4.
15. Hamzaoui K, Hamzaoui A, Guemira F, Bessioud M, Hamza M, Ayed K. Cytokine profile in Behçet's disease patients. Relationship with disease activity. Scand J Rheumatol 2002;31(4):205-10.
16. Bardak Y, Aridoğan BC. The demonstration of serum interleukin 6-8, tumor necrosis factor-alpha, complement, and immunoglobulin levels in Behçet's disease with ocular involvement. Ocul Immunol Inflamm 2004;12(1):53-8.

17. Adam B, Calikoglu E. Serum interleukin-6, procalcitonin and C-reactive protein levels in subjects with active Behçet's disease. J Eur Acad Dermatol Venereol 2004;18(3):318-20.
18. Akdeniz N, Esrefoglu M, Keleş MS, Karakuzu A, Atasoy M. Serum interleukin-2, interleukin-6, tumour necrosis factor-alpha and nitric oxide levels in patients with Behcet's disease. Ann Acad Med Singapore 2004;33(5):596-9.
19. al-Dalaan A, al-Sedairy S, al-Balaa S, al-Janadi M, Elramahi K, Bahabri S, et al. Enhanced interleukin 8 secretion in circulation of patients with Behçet's disease. J Rheumatol 1995;22(5):904-7.
20. Sayinalp N, Ozcebe OI, Ozdemir O, Haznedaroğlu IC, Dündar S, Kirazli S. Cytokines in Behçet's disease. J Rheumatol 1996;23(2):321-2.
21. Chandran M, Phillips SA, Ciaraldi T, Henry RR. Adiponectin: more than just another fat cell hormone? Diabetes Care 2003;26(8):2442-50.
22. Oguz A, Dogan EG, Uzunlulu M, Oguz FM. Insulin resistance and adiponectin levels in Behçet's syndrome. Clin Exp Rheumatol 2007;25(4 Suppl 45):S118-9.
23. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 1990;335(8697):1078-80.
24. Orem A, Yandi YE, Vanizor B, Cimşit G, Uydu HA, Malkoç M. The evaluation of autoantibodies against oxidatively modified low-density lipoprotein (LDL), susceptibility of LDL to oxidation, serum lipids and lipid hydroperoxide levels, total antioxidant status, antioxidant enzyme activities, and endothelial dysfunction in patients with Behçet's disease. Clin Biochem 2002;35(3):217-24.
25. Pronai L, Ichikawa Y, Nakazawa H, Arimori S. Enhanced superoxide generation and the decreased superoxide scavenging activity of peripheral blood leukocytes in Behçet's disease--effects of colchicine. Clin Exp Rheumatol 1991;9(3):227-33.
26. Köse K, Yazici C, Cambay N, Aşcioğlu O, Doğan P. Lipid peroxidation and erythrocyte antioxidant enzymes in patients with Behçet's disease. Tohoku J Exp Med 2002;197(1):9-16.
27. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J 1990;265(3):621-36.
28. Hirano T. Interleukin-6 and its relation to inflammation and disease. Clin Immunol Immunopathol 1992;62(1 Pt 2):S60-5.
29. Kapp A, Piskorski A, Schöpf E. Elevated levels of interleukin 2 receptor in sera of patients with atopic dermatitis and psoriasis. Br J Dermatol 1988;119(6):707-10.
30. Evans CA, Jellis J, Hughes SP, Remick DG, Friedland JS. Tumor necrosis factor-alpha, interleukin-6, and interleukin-8 secretion and the acute-phase response in patients with bacterial and tuberculous osteomyelitis. J Infect Dis 1998;177(6):1582-7.
31. Matsuzawa Y. Adipocytokines and metabolic syndrome. Semin Vasc Med 2005;5(1):34-9.
32. Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M, et al. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res 2000;32(2):47-50.
33. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation 2000;102(11):1296-301.
34. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002;105(24):2893-8.
35. Mitamura T, Ohno S, Ariga H, Ohsaka T, Iwasaki N, Matsuda H, et al. Lipoprotein cholesterol concentrations in patients with Behçet's disease. Clin Chim Acta 1988;175(3):277-83.
36. Orem A, Değer O, Memiş O, Bahadir S, Ovali E, Cimşit G. Lp(a) lipoprotein levels as a predictor of risk for thrombogenic events in patients with Behçet's disease. Ann Rheum Dis 1995;54(9):726-9.
37. Orem A, Efe H, Değer O, Cimşit G, Uydu HA, Vanizor B. Relationship between lipid peroxidation and disease activity in patients with Behçet's disease. J Dermatol Sci 1997;16(1):11-6.
38. Chambers JC, Haskard DO, Kooner JS. Vascular endothelial function and oxidative stress mechanisms in patients with Behçet's syndrome. J Am Coll Cardiol 2001;37(2):517-20.