Decreased Total Antioxidant Response and Increased Oxidative Stress in Behcet’s Disease

AHMET ISIK,1 SULEYMAN SERDAR KOCA,1 BILAL USTUNDAG2 and SAHABETTIN SELEK3

1Department of Rheumatology, Firat University, Faculty of Medicine, Elazig, Turkey
2Department of Biochemistry, Firat University, Faculty of Medicine, Elazig, Turkey
3Department of Biochemistry, Harran University, Faculty of Medicine, Sanliurfa, Turkey

ISIK, A., KOCA, S.S., USTUNDAG, B. and SELEK, S. Decreased Total Antioxidant Response and Increased Oxidative Stress in Behcet’s Disease. Tohoku J. Exp. Med., 2007, 212 (2), 133-141 —— Behcet’s disease (BD) is a chronic systemic inflammatory disease. Inflammatory reactions trigger the oxidative stress and oxidants decrease the level of antioxidants. In the present study, we aimed to determine serum oxidative/antioxidative status in patients with BD. Serum antioxidative status was evaluated by measuring total antioxidant capacity (TAC), paraoxonase 1, arylesterase, sulfhydryl groups and ceruloplasmin in patients with BD and in healthy controls. Serum oxidative status was evaluated by measuring total peroxide (TP), lipid hydroperoxides and oxidative stress index (OSI). OSI was calculated by percent ratio of TP to TAC. Serum levels of TAC, sulfhydryl groups and activities of paraoxonase 1, arylesterase, and ceruloplasmin were significantly lower in patients than in controls (p < 0.001 for all). In contrast, TP, lipid hydroperoxides and OSI values were significantly higher in patients than in controls (p < 0.001 for all). Further, the level of TAC was negatively correlated with the levels of TP, lipid hydroperoxides and OSI both in the BD (r = −0.578, p < 0.01; r = −0.559, p < 0.01 and r = −0.552, p < 0.01, respectively) and the control groups (r = −0.469, p < 0.05; r = −0.351, p < 0.05 and r = −0.391, p < 0.05, respectively). These results indicate that the oxidant parameters increased and antioxidant parameters decreased in patients with BD; therefore, these patients might have been exposed to oxidative stress. We suggest that impaired oxidant/antioxidant balance should be taken into consideration in the follow-up of patients with BD. ——— Behcet’s disease; total antioxidant response

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Activated neutrophils lead to the production of reactive oxygen species (ROS), such as hydrogen peroxide (H₂O₂), hydroxyl radical, and superoxide radical and of nitrogen-involving radicals (Niwa et al. 1982; Weiss 1989; Orem et al. 1997, 2002). Polymorphonuclear leukocytes increase the production of hypochlorous acid (HOCI) from H₂O₂ via myeloperoxidase enzyme (Weiss 1989; Orem et al. 2002). HOCI, which leads to sulfhydryl oxidation and protein decarboxylation, takes part in tissue damage through oxidative modification of tissue macromolecules (Weiss 1989). ROS cause peroxidation of cell membrane double-chain fatty acids and then cellular injury, and also increase oxidative stress (Niwa et al. 1982; Weiss 1989). Oxidants damage the antioxidant system.
and decrease antioxidant levels; on the other hand, antioxidant defense system can protect cells against potentially detrimental effects of oxidant agents (Weiss 1989; Young and Woodside 2001).

Behcet’s disease (BD) is a chronic relapsing inflammatory disease. It is characterized by recurrent oral aphthous ulcer, genital ulcer/scar, ocular inflammation, and skin and joint signs. It has been reported that the impaired oxidant/antioxidant balance is responsible for tissue injury in BD (Niwa et al. 1982). Increased ROS production and decreased levels of antioxidants in patients with BD have been demonstrated (Niwa et al. 1982; Kose et al. 1995; Orem et al. 1997, 2002; Bekpinar et al. 2005).

Blood contains many antioxidant molecules which prevent and/or inhibit harmful free radical reactions (Young and Woodside 2001). Paraoxonase (PON) and arylesterase (ARE), located on high-density lipoprotein (HDL), are among the antioxidants and calcium dependent esterase enzymes. Glutathione, one of the main components of the antioxidant system, detoxifies oxidants with sulfhydryl (SH) groups. Level of SH and activities of PON and ARE have been shown to decrease in patients with BD (Kose et al. 1995; Karakucuk et al. 2004; Bekpinar et al. 2005). Ceruloplasmin (CP) produced by hepatocytes is an acute phase protein and has antioxidant characteristics (Gutteridge et al. 1985). It has been reported that the activity of CP increases in patients with BD (Kose et al. 1995; Taysi et al. 2002).

Concentrations of these antioxidants in the serum (or plasma) can be measured one by one, but this procedure is time-consuming, labor-intensive and costly, and requires complicated techniques (Erel 2004). On the other hand, total antioxidant response (TAR) whose measurement method has been recently specified and developed can reflect the total antioxidant status of the plasma (Erel 2004). In this method, TAR of the plasma, which acts especially against potent free radical reactions strongly leading to oxidative damage of biomolecules such as lipids, proteins and DNA, is measured.

In this study, we aimed to measure both the levels of some conventional antioxidants and the total antioxidant capacity (TAC) levels in serum samples from patients with BD to evaluate their antioxidant status using a novel automated method (Erel 2004). As a reciprocal measure, the lipid hydroperoxides (LOOHs) and total peroxide (TP) levels in the same serum samples were also measured to evaluate oxidant status. The ratio of the serum TP level to the TAR level was regarded as the oxidative stress index (OSI) (Harma et al. 2005).

**Participants and Methods**

The study included 21 BD cases whose mean disease duration was 3.7 ± 2.9 years, and 23 healthy controls. The diagnosis of BD was made according to the International Study Group’s criteria for BD (ISG 1992). The patients were divided into two groups, as active and inactive, depending on the activity of their disease identified under the light of clinical and laboratory findings. The patients were considered as active if those with oral ulcer had at least two of the following pathologies; genital ulcer, skin lesion, recent ocular involvement, recent vascular involvement, recent neurological involvement, active arthritis, positive pathergy test and with high erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) (Yazici et al. 2004). Histories of all individuals participated to the study were obtained, and physical examinations were performed. The pathergy test was performed on all the patients, and 24-48 hours later, the patients were evaluated in terms of papulopustular lesions. All patients were assessed by an ophthalmologist for eye involvement.

Approval of the ethics committee of Firat University and informed consents of the patients and healthy individuals were obtained. The participants with dyslipidemia, cardiovascular diseases, diabetes mellitus, renal failure, chronic infection, alcohol abuse, and participants who used antilipidemic and antioxidant drugs were excluded from the study.

Fasting blood samples were withdrawn at 08:00-09:00 a.m. and their sera were separated with centrifugation at 1,500 × g for 10 min. Serum samples for specific parameters were stored at −20°C until the day of analysis shorter than one month.

**Measurement of the total antioxidant status**

The total antioxidant status of the serum was measured using a novel automated colorimetric method...
developed by Erel (2004). In this method, the hydroxyl radical, the most potent one, is produced by Fenton reaction, and reacts with the colorless substrate O-dianisidine to produce the dianisyl radical, which is bright yellowish-brown in color. Upon the addition of a serum sample, the oxidative reactions initiated by the hydroxyl radicals present in the reaction mix are suppressed by the antioxidant components of the serum, preventing the color change and thereby providing an effective measure of the TAC of the serum. The assay results are expressed as mmol Trolox equivalent/l.

**Measurement of SH level**

Free SH of serum samples were assayed according to the modified method of Elman (Hu et al. 1993). Briefly, 1 ml of buffer containing 0.1 M Tris, 10 mM EDTA, pH 8.2, and 50 μl serum was added to cuvettes, followed by 50 μl 10 mM 5,5′-dithiobis-(2-nitrobenzoate) (DTNB) in methanol. Blanks were run for each sample as a test, but there was no DTNB in the methanol. Following incubation for 15 min at room temperature, sample absorbance was read at 412 nm on a Cecil 3,000 spectrophotometer. Sample and reagent blanks were subtracted. The concentration of SH was calculated using reduced glutathione as free SH standard.

**Measurement of SH level**

Paraoxonase-1 (PON1) activity was determined using paraoxon as a substrate and measured by increases in the absorbance at 412 nm due to the formation of 4-nitrophenol, as already described (La Du and Eckerson 1984). Briefly, the activity was measured, at 25°C, by adding 50 μl of serum to 1 ml Tris/HCl buffer (100 mM, pH 8) containing 2 mM CaCl₂ and 5.5 mM of paraoxon. The rate of generation of 4-nitrophenol was determined at 412 nm. Enzymatic activity was calculated using the molar extinction coefficient 17,100 M⁻¹ cm⁻¹.

Arylesterase activity was measured spectrophotometrically. The assay contained 1 mM phenylacetate in 20 mM Tris/HCl, pH 8. The reaction started by the addition of serum and the increase in absorbance was recorded at 270 nm, as already described (La Du and Eckerson 1984). Blanks were included to correct for the spontaneous hydrolysis of phenylacetate. Enzyme activity was calculated using the molar extinction coefficient of 1,310 M⁻¹ cm⁻¹.

**Measurement of CP activity**

Ceruloplasmin activity was assessed by measuring its oxidase activity using p-phenylenediamine as substrate (Sunderman and Nomoto 1970).

**Measurement of LOOHs level**

Triiodide complex formed as a result of the reaction between LOOH and iodine was evaluated by spectrophotometer at 365 nm wavelengths. The results were calculated using the extinction coefficient of triiodide (C = 2.46 × 10⁻⁴ M⁻¹ cm⁻¹) (Gorog et al. 1991).

**Measurement of TP concentration**

The total serum peroxide concentrations were determined using the FOX2 method (Miyazawa et al. 1989) with minor modifications (Cao and Prior 1998). The FOX2 test system is based on the oxidation of ferrous iron to ferric iron by various types of peroxides contained in the serum samples, in the presence of xylenol orange which produces a colored ferric-xylenol orange complex whose absorbance can be measured. The FOX2 reagent was prepared by dissolving ammonium ferrous sulphate (9.8 mg) in 250 mM H₂SO₄ (10 ml), to give a final concentration of 250 μM ferrous iron in acid. This solution was then added to 90 ml of HPLC-grade methanol containing 79.2 mg butylated hydroxytoluene (BHT). Finally, 7.6 mg xylenol orange was added with stirring to make the final working reagent (250 μM ammonium ferrous sulphate, 100 μM xylenol orange, 25 mM H₂SO₄, and 4 mM BHT in 90% v/v methanol in a final volume of 100 ml). The blank reagent contained all the components of the solutions except ferrous sulphate.

Aliquots (200 μl) of serum samples were mixed with 1.8 ml FOX2 reagent. After incubation at room temperature for 30 min, the vials were centrifuged at 12,000 g for 10 min. Absorbance of the supernatant was then determined at 560 nm. The total peroxide content of the serum samples was determined as a function of the difference in absorbance between the test and the blank samples using a solution of H₂O₂ as standard. The coefficient of variation for individual serum samples was less than 5%.

**Oxidative stress index (OSI)**

The ratio of the TP to the total antioxidant potential gave the OSI, an indicator of the degree of oxidative stress (Harma et al. 2005).

**Statistical analysis**

All results were expressed as means ± S.D. Student’s t-test and Spearman’s correlation analysis were per-
formed using SPSS for Windows Release 11.0 (SPSS Inc., Chicago, IL, USA). The p value less than 0.05 was considered to be significant.

**RESULTS**

Demographical characteristics and laboratory data involving blood biochemistry of the BD and the control groups are presented in the Table 1. There was no significant difference between the patient group and the control group with regard to individual antioxidants, which are albumin, bilirubin and uric acid (Table 1). The levels of TP, LOOHs and OSI were significantly higher, while the levels of TAR and SH and the activities of PON1, ARE and CP were significantly lower, in the BD group than those in the control subjects (Table 1).

The activity of ARE correlated with the level of LOOHs \((r = -0.46, p < 0.05)\), and the activity of CP correlated with the levels of SH and CRP \((r = 0.46, p < 0.05, r = -0.47, p < 0.05\), respectively) in the BD group. The level of TAR positively correlated with CP activity in the BD group, and the level of SH in the control group \((r = 0.449, p < 0.05 \text{ and } r = -0.432, p < 0.05\), respectively, Fig. 1). The level of TAR negatively correlated with TP, LOOHs and OSI levels both in the BD \((r = -0.559, p < 0.01; r = -0.578, p < 0.01 \text{ and } r = -0.552, p < 0.01\), respectively, Fig. 2) and the control groups \((r = -0.351, p < 0.05; r = -0.469\).

| Table 1. Demographical characteristics, some laboratory and serum indicators of oxidative stress in the Behcet’s disease and the control groups. |
|---|---|---|
| Behcet’s disease \((n = 21)\) | Controls \((n = 23)\) | \(p\) |
| Age (years) | 34.40 ± 7.40 | 36.70 ± 4.20 | 0.202 |
| Sex (M/F) | 13/8 | 14/9 | 0.892 |
| BMI (Kg/m\(^2\)) | 24.20 ± 3.40 | 24.10 ± 3.10 | 0.941 |
| Hemoglobin (gr/dl) | 14.20 ± 1.10 | 15.10 ± 1.80 | 0.854 |
| WBC (mm\(^3\)) | 8,376 ± 3,497 | 7,890 ± 4,215 | 0.675 |
| ESR (mm/hr) | 19.70 ± 11.40 | 12.50 ± 8.90 | 0.452 |
| CRP (mg/l) | 21.50 ± 23.20 | 3.20 ± 2.30 | \(0.022\) |
| Glucose (mg/dl) | 91.90 ± 9.60 | 91.60 ± 9.70 | 0.892 |
| Total Protein (gr/dl) | 7.36 ± 0.03 | 6.95 ± 0.60 | \(0.027\) |
| Albumin (gr/dl) | 4.28 ± 0.30 | 4.38 ± 0.40 | 0.393 |
| Uric Acid (mg/dl) | 4.40 ± 0.96 | 4.70 ± 1.20 | 0.675 |
| Total Bilirubin (mg/dl) | 0.82 ± 0.34 | 0.86 ± 0.31 | 0.651 |
| Direct Bilirubin (mg/dl) | 0.11 ± 0.08 | 0.10 ± 0.04 | 0.202 |
| TAR (mmol Trolox equivalent/l) | 1.04 ± 0.07 | 1.16 ± 0.08 | \(<0.001\) |
| PON1 activity (U/l) | 91.80 ± 20.10 | 149.10 ± 21.30 | \(<0.001\) |
| ARE activity (U/l) | 337.80 ± 48.80 | 393.60 ± 42.30 | \(<0.001\) |
| SH (mmol/l) | 0.33 ± 0.02 | 0.43 ± 0.01 | \(<0.001\) |
| CP activity (U/l) | 172 ± 27.20 | 211.10 ± 29.70 | \(<0.001\) |
| TP (μmol H\(_2\)O\(_2\)/l) | 13.40 ± 4.50 | 7.72 ± 1.86 | \(<0.001\) |
| LOOHs (μmol H\(_2\)O\(_2\) equivalent/l) | 9.93 ± 3.25 | 5.99 ± 1.01 | \(<0.001\) |
| OSI (Arbitrary unit) | 1.45 ± 0.52 | 0.67 ± 0.18 | \(<0.001\) |

M, male; F, female; BMI, body mass index; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TAR, total antioxidant response; PON1, Paraoxonase 1; ARE, arylesterase; SH, sulfhydryl groups; CP, ceruloplasmin; TP, total peroxide; LOOHs, lipid hydroperoxides; OSI, oxidative stress index.
Fig. 1. The level of serum TAR was positively correlated with the activity of serum CP in the Behcet’s disease group (a), and the level of serum SH in the control group (b).

TAR, total antioxidant response; CP, ceruloplasmin; SH, sulfhydryl groups.

Fig. 2. The level of serum TAR was negatively correlated with the levels of serum TP (a) and LOOHs (b) both in the Behcet’s disease and the control groups.

BD, Behcet’s disease; TAR, total antioxidant response; TP, total peroxide; LOOHs, lipid hydroperoxides.
The level of LOOHs correlated with TP and OSI levels of the control group \( (r = 0.798, p < 0.001 \) and \( r = 0.829, p < 0.001, \) respectively). Clinical characteristics of the BD group were oral ulcer \( (100\%) \), genital ulcer/scar \( (57.1\%) \), other skin lesions \( (90.4\%) \), ocular findings \( (28.5\%) \) and neurological involvement \( (4.7\%) \). Comparisons between the patients with and without positive pathergy test (pathergy test positivity was \( 42.8\% \)) and patients with and without ocular lesions in the BD group did not show a significant difference in terms of the parameters concerned. In seven out of the BD group \( (33.3\%) \), diagnoses had been made recently and they did not use any drugs. The remaining 14 cases \( (66.7\%) \) had been diagnosed previously and among these patients, 6 cases were using colchicine, 4 cases azothioprine, corticosteroid and colchicine combination, 2 cases infliximab and methotrexate, 1 case sulfasalazine and colchicine, and the last case was using interferon \( \alpha 2b \) alone. There was no significant difference between recently diagnosed and previously diagnosed BD cases in terms of the parameters involved.

In the BD group, 10 patients were in active and 11 patients were in inactive state of the disease. The increases in ESR and CRP in the active BD group were significant \( (p < 0.01 \) and \( p < 0.05, \) respectively) when compared with the inactive group. However, differences between active and inactive BD groups in terms of antioxidants and oxidants were not significant \( (\text{Table 2}) \).

### DISCUSSION

It has been reported that serum levels of malondialdehyde (MDA) \( \text{Karakucuk et al. 2004; Buldanlioglu et al. 2005} \), thiobarbituric acid reactive substance \( \text{Akar et al. 2003} \) and LOOHs \( \text{Orem et al. 2002} \), which are lipid peroxidation (LPO) products, increase in patients with BD. In the present study, the level of the LPO byproducts LOOHs, have also been found higher in the BD group. TP shows the sum of many peroxides like protein peroxide, lipid peroxide and \( \text{H}_2\text{O}_2 \) \( \text{Abuja and Albertini 2001} \). Although it is known that \( \text{H}_2\text{O}_2 \) and lipid peroxides increase \( \text{Orem et al. 1997} \), oxidative stress has not been evaluated through TP, in patients with BD. It was shown in the present study that TP level increased in the BD group. Possible reasons for this increase in TP might involve the increase of lipid peroxides and ROS including \( \text{H}_2\text{O}_2 \).

It has been reported that when compared

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<tr>
<th>Behcet’s Disease</th>
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<tr>
<td>Active ( n = 10 )</td>
<td>Inactive ( n = 11 )</td>
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<tr>
<td>ESR (mm/hr)</td>
<td>28.30 ± 22.50</td>
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<tr>
<td>CRP (mg/l)</td>
<td>40.30 ± 23.60</td>
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<tr>
<td>TAR (mmol Trolox equivalent/l)</td>
<td>1.04 ± 0.09</td>
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<tr>
<td>PON1 activity (U/l)</td>
<td>85.06 ± 20.40</td>
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<tr>
<td>ARE activity (U/l)</td>
<td>329.70 ± 55.50</td>
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<td>SH (mmol/l)</td>
<td>0.33 ± 0.02</td>
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<tr>
<td>CP activity (U/l)</td>
<td>162.20 ± 36.30</td>
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<tr>
<td>TP (μmol ( \text{H}_2\text{O}_2 )/l)</td>
<td>12.63 ± 4.30</td>
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<tr>
<td>LOOHs (μmol ( \text{H}_2\text{O}_2 ) equivalent/l)</td>
<td>10.48 ± 3.97</td>
</tr>
<tr>
<td>OSI (Arbitrary unit)</td>
<td>1.45 ± 0.64</td>
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ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PON1, Paraoxonase 1; TAR, total antioxidant response; ARE, arylesterase; SH, sulfhydryl groups; CP, ceruloplasmin; TP, total peroxide; LOOHs, lipid hydroperoxides; OSI, oxidative stress index.
with the healthy individuals, PON1 activity is decreased in BD (Karakucuk et al. 2004) and RA (Isik et al. 2007) cases, and the activity of ARE is also decreased along with PON1 in RA cases with amyloidosis complication (Maury et al. 1984). Activities of PON1 and ARE enzymes were also lower in the BD group in the present study. It has been demonstrated that LPO products bound to cysteine residues found on the 283rd position of PON1 which is responsible for activity, thereby inactivate PON1 and rehematoid arthritis (ARE) activities (Aviram et al. 1999). The negative correlation between the levels of LOOHs and ARE activity in our study might support the idea that LPO products are responsible for the decrease in the activities of PON and ARE, in BD cases.

It is noted that CP activity increases in BD and this is related with the acute phase response of CP (Kose et al. 1995; Bekpinar et al. 2005). In the present study, however, it has been found that CP activity is reduced in BD and that CP is negatively correlated with CRP, a marker of acute phase response, and positively correlated with SH which is known as an antioxidant. CP also has antioxidant properties (Gutteridge et al. 1985). It has been reported that ROS inhibit CP activity (Gutteridge et al. 1985). The decrease in CP activity along with other antioxidants in BD group may support this claim and it seems to be an expected result. However, it is also possible that increased oxidants may be responsible for the decrease in CP activity, as stated (Gutteridge et al. 1985).

Serum SH groups act as important cellular scavengers of peroxides and thus help to protect cells from damage by these molecules. In BD, decreased SH level (Kose et al. 1995; Bekpinar et al. 2005), which is negatively correlated with MDA and CRP levels (Bekpinar et al. 2005) has been reported. In our study, SH level was lower in the BD group than the healthy controls. The positive correlation between the SH level and the activity of CP can support the claim that LPO products reduce SH levels together with other antioxidants.

Many antioxidant molecules as mentioned above are found in the blood (Young and Woodside 2001). Individual antioxidants level or activity indicates the antioxidant characteristics of only one antioxidant, whereas TAC may represent the total antioxidant characteristics of all antioxidants found in the serum. TAR and total antioxidant status (TAS) are used synonymously with TAC (Ghiselli et al. 2000). It is doubtlessly more advantageous to evaluate TAR, instead of individual antioxidant level or activity. Many methods have been developed recently for this aim. Total radical trapping antioxidant parameter (TRAP), oxygen radical absorbance capacity (ORAC) and ferric reducing antioxidant power (FRAP) are colorimetric methods previously developed to assess TAC (Ghiselli et al. 2000; Erel 2004). The widely used methods for the measurement of plasma TAR are reported as inappropriate for routine usage (Janaszewska and Bartsz 2002; Schlesier et al. 2002). It has been reported that TAR is correlated with the data obtained by other methods, mentioned above (Erel 2004).

In BD, TAS levels have been reported to decrease (Orem et al. 2002; Sandikci et al. 2003; Buldanlioglu et al. 2005), except for one study (Bekpinar et al. 2005). Similarly, in the present study, TAR level was lower in the BD group, and it was correlated with the activity of CP and the level of SH. Correlation between TAR and SH levels has also been reported (Erel 2004). The increase in TP, LOOHs and OSI levels and the negative correlation between these increases and TAR level in the present study suggest the impaired oxidant/antioxidant balance might be the possible cause of the decrease in TAR level.

Albumin, uric acid and bilirubin which have been shown to correlate with the TAR level (Erel 2004) are known as major antioxidant components of plasma (Ghiselli et al. 2000; Erel 2004). Thiol groups on the surface of albumin are oxidized by oxidants (Sengupta et al. 2001). Thus, low level of albumin can cause oxidative stress (Sengupta et al. 2001). Uric acid is another well-known low molecular weight water-soluble plasma antioxidant (Erel 2004). However, uric acid concentrations are influenced by age, diet, heavy exercise, renal failure and some metabolic diseases (Puig et al. 1986; Ghiselli et al. 2000).
Therefore, uric acid level may not appropriately reflect the TAC. Moreover, it has been also reported that uric acid has not been a strong antioxidant and might not protect against free radicals (Smolenska et al. 1999). In the present study, there was no significant difference between the BD and the control groups in the levels of albumin, bilirubin and uric acid. It has also been reported that bilirubin is not correlated with TAR (Harma et al. 2005). In the present study, TAR level did not correlate with any of these antioxidants.

No significant difference was found between active and inactive patient groups with respect to oxidants and antioxidants. This might be explained by the activity criteria used to determine the disease activity state of BD. It is known that currently there are no agreed activity criteria for BD cases. It is also possible that the oxidant/antioxidant balance is impaired at the onset of the disease and continues thereafter. Our findings might support the above idea as no correlation between the disease duration and oxidant/antioxidant levels have been found.

Dietary habits and drugs may affect antioxidant capacity. Two groups of this present study include individuals who live in the same region and have similar economic status and dietary habits. Moreover, no difference was observed between cases with and without usage of medications with regard to oxidant and antioxidant levels. However, one limitation of our study might be that we did not evaluate the possible relationship between the levels of oxidants and the antioxidants with drugs used in our cases and levels of cytokines. The low number of participants of the groups might be another limitation of our study.

In conclusion, TAR level decreases in BD, and oxidant/antioxidant balance seems to be impaired at all stages of BD, and these patients might have been exposed to potent oxidative stress. We speculate that supplementation of the conventional treatment with powered antioxidants may be helpful for these patients.

References


