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Relationship between behçet's disease and oxidant and antioxidant markers

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Abstract

Behçet's disease is known as a chronic and inflammatory vasculitis with multiple system and organ involvement. In this study, we aimed to evaluate the relationship between BD and oxidative stress by evaluating the total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) in healthy control group and patients with Behçet's disease (BD). Materials and Methods: Study groups were composed of BD patients (n = 57) and healthy controls (n = 54). Serum total TAS, TOS, (OSI) and serum lipid levels were measured by photometric method. All measurements were made on Beckman Coulter AU5800 Series (Japan). OSI was determined by the TOS / TAS ratio. Serum TAS levels in BD were lower than the healthy controls (p = 0.039). Serum levels of TOS, OSI and lipids did not differ significantly in BD patients compared to healthy controls. Also, the sensitivity of TAS for BD was high (0.825). Low TAS levels can play an important role in the etiopathology of BD. Increasing serum TAS levels may be beneficial for the clinical process. More studies are needed in this regard.

Keywords: Behçet's disease, TAS, TOS, HDL, LDL

Introduction

Behçet's disease (BD) is a disease characterized by recurrent oral ulcer, genital ulcer, skin, joint and eye involvement [1]. BD is a common systemic disease in the Eastern Mediterranean and Middle East regions. The etiology of BD has not been fully clarified [2]. It is a complex disease that can affect many systems and may have a wide range of phenotypic findings [3]. BD is a disease that significantly affects the quality of life. It can affect every organ in the body, and often the cause of symptoms is vasculitis [2]. High levels of low-density lipoproteins (LDL) increase the risk of atherosclerosis. Low levels of seem to be an independent risk factor for atherosclerosis [4]. It is thought that the balance between antioxidant systems and oxidant systems is responsible for tissue damage in BD. Oxidant systems disrupt antioxidant systems and reduce the protective effects of antioxidants[1,5]. Diffuse oxidative stress may cause vasculitis by endothelial damage [6, 7]. It has been reported that inflammation in BD is caused by free oxygen radicals [8] The production and removal of oxidant substances from the body in normal conditions are in balance. Failure of any of the systems that maintain this balance can cause oxidative damage. Oxidative damage may play a role in the etiology of various diseases by increasing cell damage [9]. Total antioxidant status (TAS) shows all the effects of various antioxidant systems in all body fluids and tissues. Total oxidant status (TOS) reflects the sum of the effects of oxidant systems. Measurements can be made separately for both systems [9]. In the current study, we planned to investigate the relationship between TAS, TOS and oxidative stress index (OSI) with BD by measuring total oxidant and antioxidant systems in healthy controls and BD patients.

Material and Methods

Ethics committee approval numbered 2020/144 was obtained for this study. The patients included in the study have no known chronic disease history, smoking, alcohol use and acute infection history in the last two weeks. The control group was consisted of individuals who admitted to our hospital for general health screening without any disease. The study was carried out with 57 patients and 54 healthy individuals. The ages and demographic characteristics of the patient and control groups were similar. The diagnosis of BD was made with the presence of at least two other organ and system findings in addition to the oral ulcer. Behçet's Syndrome Activity Score (BSAS) [10] was used in the BD evaluation. After 10-12 hours of fasting blood samples were taken from the antecubital area in a sitting position through the vacutainer needle into the plain gel tubes. The blood in gel tubes was kept at room temperature and coagulated. After coagulating, it was centrifuged at 4000rpm for 10 minutes. Routine

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examinations of the patients were studied after centrifugation. The remaining serum samples were separated into small volume portions and kept at -80°C. Then, the portioned samples were thawed and analyzed.

Analysis

Application of Rel Assay Diagnostics (Turkey) commercial kits for TAS and TOS analysis was performed on Beckman Coulter AU5800 Series (Japan). After the application process, analyzes were done by photometric method using Rel Assay Diagnostics (Turkey) kits. The ratio of TOS to TAS constitutes OSI. The unit of TAS was converted to µmol / L so that the units of TAS and TOS were similar. OSI = [(TOS, µmol / L) / (TAS, µmol Trolox equivalent / L)] [6].

Lipid parameters were analyzed by using Beckman Coulter original commercial kits on Beckman Coulter AU5800 Series (Japan) device from serum samples.

Statistics

Descriptive statistics are given as minimum-maximum, mean, median, standard deviation and percentage value. The homogeneity of variances was checked for parametric tests with Levene test. Normality was tested by Shapiro-Wilk test. Student t test and Mann Whitney-U test were performed to compare the differences between the two groups. The performance of any test is determined by the diagnostic capability of that test or its ability to accurately divide events into subgroups (TAS, TOS). Breakpoints of the tests were evaluated by ROC analysis. Sensitivity, selectivity, and AUC value were found. Data were analyzed with SPPS 20 (IBM Corp. 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). The significance levels were taken as $p < 0.05$ and $p < 0.01$.

Results

This study was conducted with 57 patients and 54 healthy individuals. HDL cholesterol was higher in the control group. Other lipid parameters were higher in the patient group. However, these differences in lipid parameters were not significant. TAS levels were significantly lower in patients. TOS and OSI, on the other hand, were not significant, although they were higher in patients (Table 1).

Only TAS was found statistically significant. TAS sensitivity was considered to be high for BD. The area under the ROC curve was not found too high (Figure 1). Values below 1.1 mmol / L for TAS can be diagnostic (Table 2).

Table 1. The biochemical test paramaters of patients with Behçet's disease (BD) and the control group

Number of Patient	Behçet's Patient (n=57) Mean±SD Median(Min-Max)	Healthy Control (n=54) Mean±SD Median(Min-Max)	p
TAS (mmol Trolox/L)	1.295±0.205 1.260 (0.770-1.780)	1.4±0.236 1.345 (01.06-1.96)	0.039€*
TOS(µmol H2O2 Equiv/L)	5.7±6.88 3.26 (0.10-43.85)	4.32±5.45 2 (0.30-22.59)	0.173€
OSI [arbitrary unit (AU)]	0.406±0.605 0.232 (0.087-3.380)	0.301±0.348 0.151 (0.019-1.345)	0.118€
TC (mg/dL)	215.86±58.77 209 (115-424)	215.28±45.38 208 (133-319)	0.775€
TG (mg/dL)	144.54±78.1 128 (48-390)	129.61±64.3 118 (43-310)	0.47€
HDL(mg/dL)	49.11±14.2 44 (26-83)	52.37±10.34 52 (34-81)	0.069€
LDL (mg/dL)	137.82±51.9 132 (66-345)	136.39±38.6 133 (72-223)	0.782€

*p<05: statistically significant
€ Mann Whitney-U test
TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative citres index

Table 2. AUC, sensitivity and selectivity values for total antioxidant status (TAS)

Area Under the Curve								
				Asymptotic 95% Confidence Interval				
Test	**Area**	**Std. Errora**	**p**	**Lower Bound**	**Upper Bound**	**Cut-Off Point**	**Sensitivity**	**Spesificity**
TAS	0.386	0.054	0.039*	0.282	0.491	1.105	0.825	0.037

*p<05: statistically significant

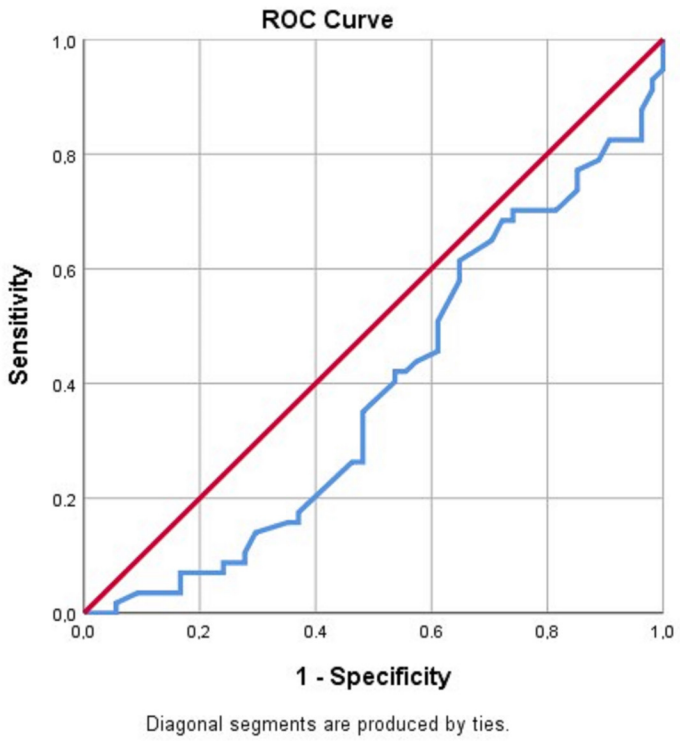

Figure 1. Total antioxidant status ROC curve

Discussion

The main purpose of this study is to determine the oxidative and antioxidative status in BD and to investigate the relationship between oxidative stress and BD. In this study, TAS was significantly lower in patients. Although TOS and OSI were high in patients, this highness was not significant. Also, no significant difference was observed between the patient and healthy control groups in terms of lipid parameters.

The etiology of BD is not fully elucidated. However, endothelial dysfunctions due to vascular disorders are accused as one of the important causes. Immune-mediated vasculitis, increased proinflammatory cytokine, and increased adhesion molecules and free oxygen radicals may be responsible for the formation of endothelial dysfunctions [11]. The increase of neutrophil-induced nicotinamide adenine dinucleotide phosphate (NADPH) plays an important role in the increase of reactive oxygen species (ROS) in BD [12]. ROS play a very important role especially in endothelial damage, endothelial dysfunction and inflammation [13].

In the study conducted by Emmi G. et al., plasma TAS levels were found to be significantly lower in BD than the control group. Also in this study, thiobarbituric acid reactive substances (TBARS) was found high in BD [12]. In the study conducted by Sepici Dinçel A. et al., plasma TAS levels were found to be significantly lower in BD with recurrent aphthous stomatitis than the control group. Also in this article, TOS was found higher in BD with recurrent aphthous stomatitis[14]. In another study, TAS was found to be low and TOS, OSI and malondialdehyde (MDA) were higher in BD patients [15]. Despite the uncertainties in BD etiology, ROS produced by leukocytes are mostly accused [16]. In another study conducted with BD patients, oxidative stress markers were found to be higher in patients, especially myeloperoxidase (MPO) [17]. In the study conducted in patients with recurrent aphthous ulcers, there was no significant difference in TAS and TOS between patients and controls, while OSI was significantly higher in patients [18]. It has been shown that there is a relationship between BD and oxidative stress. Despite this, a complete consensus of which oxidative stress markers are more effective has not been achieved. However, in recent years, it is emphasized that TAS is especially effective in BD. In BD, a decrease in TAS levels is also reported to be associated with leukocyte increase [12]. In our study, serum TAS levels decreased in the patient group. This result makes us think that antioxidant system and / or molecules are used excessively in BD.

In a study conducted on BD patients, HDL was decreased in patients, while other lipids were increased [19]. In another study, no significant difference was found in lipids [20]. In the study conducted by Yılmaz E. et al., IL-6 showed a significant increase compared to the controls, while there was no significant difference in insulin, homeostasis model assesment-insulin resistance (HOMA-IR), adiponectin and lipid parameters[21]. Although there are contradictions between studies on lipids in BD, no significant relationship was found between BD and lipids in most of the studies. There was no significant difference between our study groups in terms of lipids.

In this study, the limited number of patients, the low number of biomarkers investigated, the fact that patients were not grouped as active and inactive can be counted among the limitations of the study.

We think that keeping TAS levels above certain levels (1.1 mmol Trolox / L) may decrease the recurrence frequency of the disease. Likewise, we think that increasing TAS levels may be useful in the treatment of the disease. Antioxidant supplements can be used to

increase plasma TAS levels. These supplements can have positive effects in BD treatment. Further studies are needed to strengthen our hypothesis.

Conflict of interests

We declare that we have no conflict of interest.

Financial Disclosure

This study received no financial support.

Ethical approval

Ethics committee approval numbered 2020/144 was obtained for this study.

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