Received: 17.10.2014 - Accepted: 19.12.2014

ANTIOXIDANT DEFENSE SYSTEM IN BEHCET'S DISEASE

Mustafa Şahin[1], Mert Kahraman Maraşlı[1], Elif Sitre Koç[2], İdil Memiş[2]

[1] Erciyes University School of Medicine, Kayseri, TURKEY
[2] Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Behcet's disease (BD), first described by the Turkish dermatologist Hulusi Behcet in 1937, is characterized by triad of symptoms that include oral aphthous lesions, genital ulcerations and iritis with hypopyon. The etiopathogenesis is not yet fully explained, although reactive oxygen species produced (ROS) by the hyperfunction of neutrophils which are significant for the immune response are thought to play a role. Antioxidant defense system protects the body against the harmful effects of reactive oxygen species. Normally, there is a balance between reactive oxygen species and antioxidant defense system but as levels of reactive oxygen species are above the body's neutralization and elimination ability disrupts the balance. With the imbalance, increased levels of reactive oxygen species disrupt biomolecules such as lipids, proteins, nucleic acids and cause cell, tissue and organ damage. Studies with parameters associated with antioxidant defense system are included in our study. When viewed as whole, most of the studies support that imbalance between oxidants/antioxidants plays a role in etiopathogenesis of Behcet's disease but it should not be forgotten that there are studies show otherwise. Reactive oxygen species affect patients with active disease more than patients with inactive disease. In conclusion, studies classified in detail with larger group of patients on Behcet's disease are needed. If patients' clinical findings and levels of oxidants and antioxidants are interpreted together in the studies, they can be used to monitor the disease and success of the therapy.

Key Words: Behcet's disease, antioxidants, oxidative stress, lipid peroxidation

INTRODUCTION

Behcet's disease (BD), first described by the Turkish dermatologist Hulusi Behcet in 1937, is characterized by triad of symptoms that include oral aphthous lesions, genital ulcerations and iritis with hypopyon (1). Along with the triad of symptoms, mucocutaneous, cardiovascular, neurological, pulmonary, gastrointestinal, rheumatologic, musculoskeletal and genitourinary tract related symptoms may accompany (2). BD shows itself with one or more symptoms and other symptoms may present later. It is characterized by self-limiting recurrent episodes of acute inflammation except for ocular system. Main histopathological finding is vasculitis in arteries and veins of various sizes (3). The etiology of the disease has yet not been fully explained although genetic predisposition, triggering infections and dysregulation of the immune system are thought to play a role (4-7). Prevalence of Behcet's disease (BD) is 20-420/100.000 in Turkey, whereas it is 2.1-19.5/100.000 in Asia, 1.5-15.9/100.000 in Southern Europe, 0.3-4.9/100.000 in Northern Europe.

The etiopathogenesis is not yet fully explained, although reactive oxygen species produced (ROS) by the hyperfunction of neutrophils which are significant for the immune response are thought to play a role. Recent study results support this (8-12). Reactive oxygen species (ROT) produced during the reactions for energy production and metabolism in biological systems are superoxide radicals (O2.–), hydrogen peroxide (H2O2) and hydroxyl radicals (OH•). Normally, there is a balance between reactive oxygen species and antioxidant defense system but as levels of reactive oxygen species are above the body's neutralization and elimination ability disrupts the balance. The result of this is expressed as "oxidative stress" (13). Inflammation, radiation, aging, above-normal partial oxygen pressures, chemicals and drugs increase ROS production When elimination is not sufficient, they disrupt biomolecules such as lipids, proteins, nucleic acids and cause cell, tissue and organ damage due to their high reactivity (12, 14-16). Antioxidant defense system that protects body against harmful effects of ROSs can be both endogen and exogen. Enzymes such as superoxide dismutase (SOD), catalase (CAT), glu-

Adress for Correspondence: Mustafa Şahin, Erciyes University Faculty of Medicine, Edirne, Turkey - e-mail: mustafasahin.md@gmail.com

tathione peroxidase (GPx), glutathione S-transferase (GST), and glutathione reductase (GSSG-R) form enzymatic system. These enzymes and albumin, uric acid, ceruloplasmin, transferrin, ferritin, lactoferrin, vitamin E, vitamin C, glutathione (GSH), ubiquinol and flavonoids are among the antioxidants that are a part of cellular and non-cellular defense mechanisms. Trace elements such as copper (Cu), zinc (Zn) and selenium (Se) are necessary for the function of these enzymes and also a part of this antioxidant defense system (17).

In this study, "Behcet's disease, antioxidants, lipid peroxidation" key words are used in the PubMed database. From libraries of Trakya University and Erciyes University, international English publications in PubMed database have been analyzed. Parameters associated with the antioxidant defense system in the studies were included in our study. As far as we know, there are no review papers on the antioxidant defense system in Behcet's disease in literature. Our study is original in that respect. After analyzing research studies in literature, parameters about antioxidant defense system are given in Table 1.

PARAMETERS

Malondialdehyde (MDA): Lipids are biomolecules that are susceptible to effects of ROS. Impairment in antioxidant defense system results in oxidative breakdown of olyunsaturated fatty acids which cause lipid peroxidation. Correspondingly, permeability is observed in cytoplasm, mitochondria, nucleus and membrane of endoplasmic reticulum. One of the end products of in vivo peroxidation of polyunsaturated fatty acids is MDA. MDA assay is the most commonly used test for determining the level of lipid peroxidation. It is available in blood and urine. It is not a specific or quantitative indicator of lipid peroxidation but there is a correlation between them. For this reason, malondialdehyde level in biologic materials is an indicator of level of lipid peroxide (18-21).

Superoxide Dismutase (SOD): Superoxide dismutase is the antioxidant enzyme that catalyses the conversion of molecular oxygen(O2) and hydrogen peroxide (H2O2) from superoxide free radical (O2.–). SOD prevents oxidative damage by clearing superoxides from the body and preventing the formation of peroxynitrite. Two isomer types of SOD are available. These are Cu-Zn SOD which is in dimeric structure and Mn SOD which is found intetrameric structure in mitochondria. Generally, the most abundant type is cytosolic Cu-Zn SOD. It is available in high concentrations in liver, brain and testicular tissue; in low concentrations in erythrocyte, lungs and pancreas. Mn SOD present in high concentrations in heart, liver and kidneys. Cu-Zn SOD can be inhibited by cyanide while Mn SOD cannot (22-24).

Catalase (CAT): Catalase protects the organism from known harmful effects of H2O2 such as aging, inflammation and cancer by conversing hydrogen peroxide into molecular oxygen and water. CAT present in high concentrations in blood, bone marrow, mucous membranes, liver and kidneys (25).

Glutathione peroxidase (GSH-Px): GSH-Px is the most important enzyme that is responsible for the reduction of large molecular lipid hydroperoxide and the protection of lipids from peroxidation in intracellular matrix. It uses GSH as the hydrogen donor for detoxification of H_2O_2 (17, 26, 27).

Glutathione reductase (GRD): Glutathione reductase catalyses the conversion of reduced glutathione (GSH) from oxidized glutathione (GSSG) which formed by the reduction of hydroperoxide by GSH-Px (28).

Glutathione S-Transferase (GST): Glutathione S-Transferase (GST) family is a major group of key enzymes which has a role in phase 2 metabolism of many genotoxic compounds. Glutathione S-Transferase M1 (GSTM1) and T1 (GSTT1) are two major subtypes of this family which has a role in detoxification of products of lipid peroxidation and reactive oxygen species.

Glutathione (GSH): GSh is an important intracellular antioxidant and it presents in very low concentrations in extracellular matrix. It is a tripeptide consisting of three amino acids which are glutamic acid, cysteine and glycine. It protects cells against oxidative damage by reacting with free radicals and peroxides (30).

Selenium (Se): It is a compound of some subtypes of GSH-Px family. Selenium is biologically important because it is the cofactor of these enzymes. It protects cell membrane by reacting with vitamin E from oxidative damage caused by peroxides which are formed as a result of lipid metabolism (31, 32).

Vitamin E: Vitamin E has 4 main forms which are biologically active. These are alpha, beta, gamma and delta tocopherols. The most effective form that prevents

lipid peroxidation is alpha-tocopherol (33, 34).

Vitamin C: Ascorbic acid is a strong antioxidant due to its strong reducing capasity. It reacts with superoxide (O2.–) and hydroxyl radical (OH•) and helps removing them.

Vitamin A: Vitamin A balances the harmful effects of oxidative stress not only by removing free oxygen radicals but also by regulating activity of antioxidant enzymes (36, 37).

Beta-carotene: β-carotene which is a precursor of vitamin A has been found to has a role as an antioxidant by quenching singlet oxygen, removing superoxide radical and interacting directly with peroxide radicals (38).

Table 1: A list of studies on Behcet Disease arranged chronologically

Investigate Parameter	Studied Sample	Writers and Publishing Year	Number of Patients and Control Group				Results			
			NTP	NPNS	NPID	NCG	THG X CG	APGX CG	APG X IPG	IPG X CG
MDA	Neutrophil	Nazıroğlu et al.(2014)[39]	7	7	0	7	↑	↑	x	x
MDA	Serum	Sezer et al.(2012)[40]	60	33	27	46	↑	x	NS	x
MDA	Neutrophil	Korkmaz et al. (2011)[41]	12	6	6	6	x	↑	↑	↓
MDA	Serum	Korkmaz et al. (2011)[41]	12	6	6	6	x	↑	↑	NS
MDA	Plasma	Harzallah et al.(2008)[42]	40	x	x	40	↑	x	x	x
MDA	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	↑	x	x	x
MDA	Plasma	Buldanlıoğlu et al.(2005)[44]	49	26	23	26	↑	↑	↑	↓
MDA	Plasma	Bekpınar et al. (2005)[45]	24	x	x	25	↑	x	x	x
MDA	Serum	Karaküçük et al.(2004)[46]	16	16	0	15	↑	↑	x	X
MDA	Plasma	Sandıkçı et al. (2003)[47]	45	15	30	20	↑	↑	↑	↑
MDA	Serum	Noyan et al.(2003)[35]	20	11	9	20	x	↑	↑	↑
MDA	Plasma	Kökçam et al. (2002)[16]	25	25	0	25	↑	↑	x	x
MDA	Erythrocyte	Kökçam et al. (2002)[16]	25	25	0	25	↑	↑	x	x
MDA	Erythrocyte	Köse et al.(2002)[12]	22	0	22	30	↑	x	x	↑
MDA	Plasma	Köse et al.(2002)[12]	22	0	22	30	↑	x	x	↑
MDA	Erythrocyte	Köse et al.(1997)[48]	20	20	0	20	↑	↑	x	x
MDA	Plasma	Köse et al. (1995)[49]	24	24	0	30	↑	↑	x	X
SOD	Erythrocyte	Harzallah et al.(2008)[42]	40	x	x	40	↓	x	x	x
Cu-Zn SOD	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	↑	x	x	x
CuZn SOD	Plasma	Bekpınar et al. (2005)[45]	24	x	x	25	NS	x	x	x

Investigate Parameter	Studied Sample	Writers and Publishing Year	Number of Patients and Control Group				Results			
			NTP	NPNS	NPID	NCG	THG X CG	APGX CG	APG X IPG	IPG X CG
SOD	Erythrocyte	Buldanlıoğlu et al.(2005)[44]	49	26	23	26	NS	NS	NS	NS
SOD	Plasma	Erkılıç et al. (2003)[50]	35	17	18	20	x	↓	↓	↓
SOD	Erythrocyte	Erkılıç et al. (2003)[50]	35	17	18	20	x	↓	↓	↓
SOD	Plasma	Sandıkçı et al. (2003)[47]	45	15	30	20	NS	NS	NS	NS
SOD	Erythrocyte	Örem et al. (2002)[51]	25	x	x	25	↓	x	x	x
CuZn SOD	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	↓	x	↓	NS
SOD	Erythrocyte	Dinçer et al. (2002)[52]	26	26	0	21	↑	↑	x	x
SOD	Erythrocyte	Köse et al.(2002)[12]	22	0	22	30	↑	x	x	↑
SOD	Serum	Kiraz et al. (2001)[14]	25	11	14	15	x	NS	↓	↑
SOD	Serum	Tüzün et al.(1998)[53]	33	11	22	37	↓	NS	NS	NS
CAT	Erythrocyte	Harzallah et al.(2008)[42]	40	x	x	40	↑	x	x	x
CAT	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	↓	x	x	x
CAT	Erythrocyte	Erkılıç et al. (2003)[50]	35	17	18	20	x	↓	NS	↓
CAT	Plasma	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
CAT	Erythrocyte	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
CAT	Erythrocyte	Örem et al. (2002)[51]	25	x	x	25	↓	x	x	x
GSH-Px	Neutrophil	Nazıroğlu et al.(2014)[39]	7	7	0	7	↓	↓	x	x
GSH-Px	Neutrophil	Korkmaz et al. (2011)[41]	12	6	6	6	x	NS	NS	NS
GSH-Px	Serum	Korkmaz et al. (2011)[41]	12	6	6	6	x	NS	NS	NS
GSH-Px	Erythrocyte	Harzallah et al.(2008)[42]	40	x	x	40	NS	x	x	x

Investigate Parameter	Studied Sample	Writers and Publishing Year	Number of Patients and Control Group				Results			
			NTP	NPNS	NPID	NCG	THG X CG	APGX CG	APG X IPG	IPG X CG
GSH-Px	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	↓	x	x	x
GSH-Px	Full Blood	Buldanlıoğlu et al.(2005)[44]	49	26	23	26	↓	↓	x	↓
GSH-Px	Plasma	Erkılıç et al. (2003)[50]	35	17	18	20	x	↓	↓	↓
GSH-Px	Erythrocyte	Erkılıç et al. (2003)[50]	35	17	18	20	x	↓	↓	↓
GSH-Px	Plasma	Sandıkçı et al. (2003)[47]	45	15	30	20	NS	NS	↓	NS
GSH-Px	Plasma	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
GSH-Px	Erythrocyte	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
GSH-Px	Erythrocyte	Örem et al. (2002)[51]	25	x	x	25	NS	x	x	x
GSH-Px	Plasma	Örem et al. (2002)[51]	25	x	x	25	↓	x	x	x
GSH-Px	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	↓	x	↓	NS
GSH-Px	Plasma	Sağlam et al. (2002)[20]	50	26	24	30	NS	x	NS	NS
GSH-Px	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	↓	x	↓	NS
GSH-Px	Plasma	Sağlam et al. (2002)[20]	50	26	24	30	NS	x	NS	NS
GSH-Px	Erythrocyte	Köse et al.(2002)[12]	22	0	22	30	↓	x	x	↓
GSH-Px	Erythrocyte	Dinçer et al. (2002)[52]	26	26	0	21	↓	↓	x	x
GSH-Px	Serum	Tüzün et al.(1998)[53]	33	11	22	37	NS	NS	NS	NS
GSH-Px	Plasma	Köse et al. (1995)[49]	24	24	0	30	↓	↓	x	x
GSH	Neutrophil	Nazıroğlu et al.(2014)[39]	7	7	0	7	↓	↓	x	x

Investigate Parameter	Studied Sample	Writers and Publishing Year	Number of Patients and Control Group				Results			
			NTP	NPNS	NPID	NCG	THG X CG	APGX CG	APG X IPG	IPG X CG
GSH	Neutrophil	Korkmaz et al. (2011)[41]	12	6	6	6	x	↓	NS	↓
GSH	Serum	Korkmaz et al. (2011)[41]	12	6	6	6	x	↓	NS	↓
GSH	Plasma	Harzallah et al.(2008)[42]	40	x	x	40	↓	x	x	x
GSH	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	↓	x	x	x
GSH	Plasma	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
GSH	Erythrocyte	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
GSH	Erythrocyte	Dinçer et al. (2002)[52]	26	26	0	21	↓	↓	x	x
GSH/GSSG	Plasma	Harzallah et al.(2008)[42]	40	x	x	40	↓	x	x	x
GSSG	Plasma	Harzallah et al.(2008)[42]	40	x	x	40	↑	x	x	x
GRD	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	↑	x	x	x
GRD	Erythrocyte	Örem et al. (2002)[51]	25	x	x	25	NS	x	x	x
GRD	Plasma	Örem et al. (2002)[51]	25	x	x	25	NS	x	x	x
GRD	Erythrocyte	Dinçer et al. (2002)[52]	26	26	0	21	↓	↓	x	x
GST	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	NS	x	x	x
GST	Erythrocyte	Dinçer et al. (2002)[52]	26	26	0	21	NS	NS	x	x
Se	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	↓	x	NS	↓
Se	Plasma	Sağlam et al. (2002)[20]	50	26	24	30	NS	x	NS	NS
Se	Serum	Tüzün et al.(1998)[53]	33	9	24	32	↑	NS	Ad	↑

Investigate Parameter	Studied Sample	Writers and Publishing Year	Number of Patients and Control Group				Results			
			NTP	NPNS	NPID	NCG	THG X CG	APGX CG	APG X IPG	IPG X CG
Se	Plasma	Köse et al. (1995)[49]	24	24	0	30	↓	↓	x	x
Se	Serum	Doğan et al. (1993)[54]	40	40	x	12	↓	x	↓	x
Cu	Serum	Taysi et al.(2007)[43]	20	x	x	20	↑	x	x	x
Cu	Plasma	Sağlam et al. (2002)[20]	50	26	24	30	↑	x	↑	NS
Cu	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	NS	x	NS	NS
Cu	Serum	Tüzün et al.(1998)[53]	33	9	24	32	NS	NS	NS	NS
Cu	Plasma	Köse et al. (1995)[49]	24	24	0	30	↑	↑	x	x
Cu	Serum	Doğan et al. (1993)[54]	40	40	x	12	↑	x	↑	x
Zn	Serum	Taysi et al.(2007)[43]	20	x	x	20	↓	x	x	x
Zn	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	↑	x	NS	↑
Zn	Plasma	Sağlam et al. (2002)[20]	50	26	24	30	↓	x	NS	↓
Zn	Serum	Tüzün et al.(1998)[53]	33	9	24	32	↑	NS	NS	↑
Zn	Serum	Doğan et al. (1993)[54]	40	40	x	12	↓	x	↓	x
Mn	Serum	Taysi et al.(2007)[43]	20	x	x	20	NS	x	x	x
Mn	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	↑	x	NS	↑
Mn	Plasma	Sağlam et al. (2002)[20]	50	26	24	30	↓	x	NS	↓
Fe	Erythrocyte	Sağlam et al. (2002)[20]	50	26	24	30	NS	x	NS	NS

Investigate Parameter	Studied Sample	Writers and Publishing Year	Number of Patients and Control Group				Results			
			NTP	NPNS	NPID	NCG	THG X CG	APGX CG	APG X IPG	IPG X CG
Fe	Plasma	Sağlam et al. (2002)[20]	50	26	24	30	↓	x	NS	↓
Vit. E	Serum	Korkmaz et al. (2011)[41]	12	6	6	6	x	↓	↓	↓
Vit. E	Plasma	Bekpınar et al. (2005)[45]	20	x	x	18	NS	x	x	x
Vit. E	Plasma	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
Vit. C	Plasma	Bekpınar et al. (2005)[45]	21	x	x	23	NS	x	x	x
Vit. C	Serum	Noyan et al.(2003)[35]	20	11	9	20	x	↓	NS	↓
Vit. A	Plasma	Sezer et al.(2012)[40]	60	33	27	46	NS	NS	NS	NS
Vit. A	Serum	Korkmaz et al. (2011)[41]	12	6	6	6	x	↓	NS	↓
Vit. A	Plasma	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
β-Carotene	Serum	Korkmaz et al. (2011)[41]	12	6	6	6	x	↓	↓	↓
β-Carotene	Plasma	Kökçam et al. (2002)[16]	25	25	0	25	↓	↓	x	x
AOP	Erythrocyte	Taysi et al.(2007)[43]	20	x	x	20	↓	x	x	x
TAS	Plasma	Buldanlıoğlu et al.(2005)[44]	49	26	23	26	↓	↓	NS	↓
TAA	Plasma	Bekpınar et al. (2005)[45]	19	x	x	13	NS	x	x	x
TAS	Plasma	Sandıkçı et al. (2003)[47]	45	15	30	20	↓	↓	NS	↓
TAS	Plasma	Örem et al. (2002)[51]	25	x	x	25	↓	x	x	x
Albumin	Plasma	Sandıkçı et al. (2003)[47]	45	15	30	20	↓	↓	NS	↓
Uric Acit	Plasma	Sandıkçı et al. (2003)[47]	45	15	30	20	NS	NS	NS	NS
Transferrin	Plasma	Köse et al. (1995)[49]	24	24	0	30	↓	↓	x	x
Ceruloplasmin	Plasma	Köse et al. (1995)[49]	24	24	0	30	↑	↑	x	x

TPG x CG:Comparision of total patient group and control group, APG x CG:Comparision of group of patients with active disease and control group, APG x IPG:Comparision of groups of patients with active disease and inactive disease, IPG x CG:Comparision of group of patients with inactive disease and control group, NTP:Number of total patients, NPAD:Number of patients with active disease, NPID:Number of patients with inactive disease:Significantly lower results:Significantly higher results, NS:No statistically significant difference was found, x:Not studied, MDA:Malondialdehyde, SOD:Superoxide Dismutase, Cu-Zn SOD:Copper-Zinc Superoxide Dismutase, CAT:Catalase, GSH-Px:Glutathione Peroxidase, GSH:Glutathione, GSSG:Oxidized Glutathione, GRD:Glutathione Reductase, GST:Glutathione S-Transferase, Se:Selenium, Cu:Copper, Zn:Zinc, Mn:Manganese, Fe:Iron, Vit. A:Vitamin A, Vit C:Vitamin C, Vit E:Vitamin E, AOP:Antioxidant Potential, TAS:Total Antioxidant Status, TAA:Total Antioxidant Activity

RESULTS

When viewed as whole, most of the studies support that imbalance between oxidants/antioxidants plays a role in etiopathogenesis of Behcet's disease but it should not be forgotten that there are studies show otherwise.

MDA levels in different samples support increased lipid peroxidation. Furthermore, the results show patients with active disease are exposed to oxidative stress more than patients with inactive disease. According to results of the studies Korkmaz et al. (41) and Buldanlıoglu et al. (44) carried, MDA levels are lower in the group of patient with inactive disease than control group. On contrary, there are studies that show high levels of MDA in patients with inactive disease which suggests different factors such as performance status and treatment have effects on lipid peroxidation.

There are studies with variety of results on enzymatic system, non-enzymatic system and trace elements that are a part of antioxidant defense system. There also are studies with results of high, normal or low parameters in patients with Behcet's disease. Patients with active disease are exposed to oxidative stress more than the patients with inactive disease. Contradictions between the results may be linked with the time of admission and severity of the symptoms at that time. In the early days of flare-up of the disease, substances working in antioxidant system may increase as a reaction but overuse of antioxidants due to high ROS levels may decrease antioxidant levels and weaken antioxidant defense system as the disease progresses. There are studies that link low GSH-Px levels with decreased levels of GSH which are used as substrate of GSH-Px. However, studies have shown that even very low levels of GSH is enough for GSH-Px activity. Therefore, those results are not reliable. As a result, studies classified in detail with larger group of patients on Behcet's disease are needed. If patients' clinical findings and levels of oxidants and antioxidants are interpreted together in the studies, they can be used to monitor the disease and success of the therapy.

Acknowledgement

We thank Asst. Prof. Dr. Serpil Taheri, Asst. Prof. Dr. Elif Funda Sener, Asst. Prof. Dr. Demet Kartal and Demet Kartal for their contributions.

Ethics Committee Approval: Not applicable
Informed Consent: Not applicable
Conflict of Interest: The authors declared no conflict of interest.
Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Behcet H. Uber rezidiverende aphthose, durch ein Virus ver ursachte Geschwure am Mund, am Auge and an den Genitalien. Dermatol Wochenschr 1937;105:1152-7.

2. Chajek T, Fainaru ML. Behcet's disease: Report of 41 cases and a review of the literature. Medicine (Baltimore) 1975;54:179-96.

3. Saleh Z, Arayssi T. Update on the therapy of Behçet disease. Therapeutic Advances in Chronic Disease 2014;5(3):112-34.

4. Jorizzo JL. Behcet's disease. In: Freedberg IM, Eisen AZ, Wolf K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's Dermatology in General Medicine. 5th ed. McGraw-Hill, New York; 1999.p.2161–5.

5. Sepici-Dincel A, Ozkan Y, Yardim-Akaydin S, Kaymak-Karatas G, Onder M, Simsek B. The association between total antioxidant status and oxidative stress in Behcet's disease. Rheumatology International

2006;26(11):1005–9.

6. Ghate JV, Jorizzo JL. Behcets disease and complex aphthosis. The Journal of The American Academy of Dermatology 1999;40:1–18.

7. Zouboulis CC. Epidemiology of Adamantiades–Behcets Disease. Annales de Medecine Interne 1999;150:488–98.

8. Niwa Y, Miyake S, Sakane T, Shingu M,Yokoyama M. Auto-oxidative damage in Behcet's disease-endothelial cell damage following the elevated oxygen radicals generated by stimulated neutrophils. Clinical and Experimental Immunology 1982;49:247–55.

9. Pronai L, Ichikawa Y, Nakazawa H, Arimori S. Enhanced superoxide generation and the decreased superoxide scavenging activity of peripheral blood leucocytes in Behcet's disease: effects of colchicine. Clinical and Experimental Rheumatology 1991;9:227–33.

10. 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 Behcet's disease: a comparative study with familial Mediterranean fever and healthy subjects. The Journal of Rheumatology 1993;20:1544–9.

11. Yapislar H, Aydogan S, Borlu M, Ascioglu O. Decreased nitric oxide and increased platelet aggregation levels in patients with Behcet's disease. Thrombosis Research 2007;119:461-5.

12. Köse K, Yazıcı C, Çambay N, Aşçıoğlu Ö, Doğan P. Lipid peroxidation and erythrocyte antioxidant enzymes in patients with Behçet's disease. The Tohoku Journal of Experimental Medicine 2002;197:9-16.

13. Sies H. Biochemstry of oxidative stres. Angewandte Chemie International Edition in English 1986;25:1058-71.

14. Kiraz S, Ertenli I, Çalgüneri M, Ozturk MA, Haznedaroglu IC, Altun B et al. Interactions of nitric oxide and superoxide dismutase in Behçet's disease. Clinical and Experimental Rheumatology 2001;19:25-9.

15. Accardo-Palumbo A, Triolo G, Carbone MC, Ferrante A, Ciccia F, Giardina E et al. Polymorphonuclear leukocyte myeloperoxidase levels in patients with Behçet's disease. Clinical and Experimental Rheumatology 2000;18:495-8.

16. Kökçam I, Nazıroğlu M. Effects of vitamin E supplementation on blood antioxidants levels in patients with Behçet's disease. Clinical Biochemistry 2002;35:633-9.

17. Frei B. Reactive oxgen species and antioxidant vitamins: Mechanisms of Action. The American Journal of Medicine 1994:26;97:5-13.

18. Taysi S, Kocer I, Memisogullari R, Kiziltunc A. Serum oxidant/antioxidant status in serum of patients with Behçet's disease. Annals of Clinical & Laboratory Science 2002;32:377–82.

19.Aydin E, Sogut S, Ozyurt H, Ozugurlu F, Akyol A. Comparison of serum nitric oxide, malondialdehyde levels, and antioxidant enzyme activities in Behçet's disease with and without ocular disease. Ophthalmic Research 2004;36:177–82.

20. Saglam K, Serce AF, Yilmaz MI, Bulucu F, Aydin A, Akay C et al. Trace elements and antioxidant enzymes in Behçet's disease. Rheumatology International 2002;22:93–96.

21. Ho E, Karimi Galougahi K, Liu CC, Bhindi R, Figtree GA. Biological markers of oxidative stress: Applications to cardiovascular research and practice. Redox Biology 2013;8:483-91.

22. Halliwell B. Antioxidants in human health and disease. The Annual Review of Nutrition 1996;16:33-50.

23. Kuhn MA. Oxygen free radicals and antioxidants. American Journal of Nursing 2003;103(4):58-62.

24. Nakao K, Isashiki Y, Sonoda S, Uchino E, Shimonagano Y, Sakamoto T. Nitric oxide synthase and superoxide dismutase gene polymorphisms in Behçet disease. Archives of Ophthalmology 2007;125(2):246-51.

25. Lisanti MP, Martinez-Outschoorn UE, Lin Z, Pavlides S, Whitaker-Menezes D, Pestell RG et al. Hydrogen peroxide fuels aging, inflammation, cancer metabolism and metastasis: the seed and soil also needs "fertilizer". Cell Cycle 2011;10(15):2440-9.

26. Margis R, Dunand C, Teixeira F.K, Margis-Pinheiro M. Glutathione peroxidase family—an evolutionary overview. FEBS Journal 2008;275:3959–70.

27. Cheeseman KH, Slater TF. An introduction to free radical biochemistry. Br Med Bull 1993;49(3):481-93.

28. Gill SS, Anjum NA, Hasanuzzaman M, Gill R, Trivedi DK, Ahmad I et al. Glutathione and glutathione reductase: a boon in disguise for plant abiotic stress defense operations. Plant Physiology and Biochemistry 2013;70:204-12.

29. Ding B, Sun W, Han S, Cai Y, Ren M. Polymorphisms of glutathione S-transferase M1 (GSTM1) and T1 (GSTT1) and endometriosis risk: a meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology 2014;183:114-20.

30. Schwenke DC. Antioksidants and atherogenesis. The Journal of Nutritional Biochemistry 1998;9:424-45.

31. Gebre-Medhin M, Ewald U. Platin L. Elevated serum selenium in diabetic children. Acta Pediatrica Scandinavica 1984;73:109-14.

32. Kaur S, Bansal MP. Protective role of dietary-supplemented selenium and vitamin E in heat-induced apoptosis and oxidative stress in mice testes. Andrologia 2014.

33. Padmaja K, Somasekharaiah BV, Prasad AR. Selenium induced lipid peroxidation in heart tissues of chick embryos. The Bulletin of Environmental Contamination and Toxicology 1993;51(3):401-8.

34. Squires EJ, Valdes EV, Wu J, Leeson S. Research note: utility of the thiobarbituric acid test in the determination of the quality of fats and oils in feeds. Poultry Science 1991;70(1):180-3.

35. Noyan T, Sahin I, Sekeroğlu MR, Dülger H. The serum vitamin C levels in Behçet's disease. Yonsei Medical Journal 2003;44(5):771-8.

36. Kandi B, Cicek D, Ilhan N. Vitamin levels in Behcet's disease. Journal of Dermatological Treatment 2007;18:69–75.

37. Alper G, Irer S, Duman E, Caglayan O, Yilmaz C. Effect of I-deprenyl and gliclazide on oxidant stress/antioxidant status and dna damage in a diabetic rat model. Endocrine Research 2005;31(3):199–212.

38. Kasperczyk S, Dobrakowski M, Kasperczyk J, Ostałowska A, Zalejska-Fiolka J, Birkner E. Beta-carotene reduces oxidative stress, improves glutathione metabolism and modifies antioxidant defense systems in lead-exposed workers. Toxicology and Applied Pharmacology 2014;280(1):36-41.

39. Nazıroğlu M, Sahin M, Ciğ B, Aykur M, Erturan I, Ugan Y. Hypericum perforatum modulates apoptosis and calcium mobilization through voltage-gated and TRPM2 calcium channels in neutrophil of patients with Behcet's disease. The Journal of Membrane Biology 2014;247(3):253-62.

40. Sezer ED, Aksu K, Caglayan O, Keser G, Karabulut G, Ercan G. DNA damage and its relationship with other oxidative stress parameters in Behcet's disease. Rheumatology International 2012;32:217–22 .

41. Korkmaz S, Erturan İ, Nazıroğlu M, Uğuz AC, Çiğ B, Övey İS. Colchicine modulates oxidative stress in serum and leucocytes of patients with Behcet's disease through regulation of Ca2+ release and antioxidant system. The Journal of Membrane Biology 2011;244:113–20.

42. Harzallah O, Kerkeni A, Baati T, Mahjoub S. Oxidative stress: Correlation with Behçet's disease duration, activity and severity. European Journal of Internal Medicine 2008;19:541–7.

43. Taysi S, Demircan B, Akdeniz N, Atasoy M, Sari RA. Oxidant/antioxidant status in men with Behçet's disease. Clinical Rheumatology 2007;26:418–22.

44. Buldanlioglu S, Türkmen 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. British Journal of Dermatology 2005;153:526–30.

45. Bekpinar S, Kilic N, Unlucerci Y, Akdag-Kose A, Azizlerli G, Ozbek-Kirt Z. Evaluation of nitrosive and oxidative stres in Behcet disease. Journal of The European Academy of Dermatology and Venereology 2005;19:167–71.

46. Karakucuk S, Baskol G, Oner AO, Baskol M, Mirza E, Ustdal M. Serum paraoxonase activity is decreased in the active stage of Behcet's disease. British Journal of Ophthalmology 2004;88:1256–8.

47. Sandikci R, Turkmen S, Guvenen G, Ayabakan H, Gulcan P, Koldas M et al. Lipid peroxidation and antioxidant defence system in patients with active or inactive Behcet's disease. Acta Dermato-Venereologica 2003;83:342–6.

48. Köse K, Doğan P, Aşçıoğlu M, Aşçıoğlu Ö. In vitro antioxidant effect of Ginkgo biloba extract (EGb 761) on lipoperoxidation induced by hydrogen peroxide in erythrocytes of Behcet's patients. The Japanese Journal of Pharmacology 1997;75:253– 8.

49. Kose K, Dogan P, Ascioglu M, Erkilic K, Ascioglu O. Oxidative stress and antioxidant defenses in plasma of patients with Behcet's disease. Tohoku Journal of Experimental Medicine 1995;176:239–48.

50. Erkilic 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 of Inflammation 2003;12:107-16.

51. Orem A, Yandi YE, Vanizor B, Cimşit G, Uydu HA, Malkoç M et al. 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 Behcet's disease. Clinical Biochemistry 2002;53:217–24.

52. Dincer Y, Alademir Z, Hamuryudan V, Fresko I, Akcay T. Superoxide dismutase activity and glutathione system in erythrocytes of men with Behcet's disease. The Tohoku Journal of Experimental Medicine 2002;198:191–5.

53. Tuzun A, Aydin A, Turan M. Erythrocyte antioxidant activity and trace element level in Behcet's disease. Biological Trace Element Research 1998;64:169–74.

54. Doğan P, Doğan M, Klockenkämper R. Determination of Trace Elements in Blood Serum of Patients with Behcet Disease by Total Reflection X-Ray Fluorescence. Clinical Chemistry Analysis 1993;39:1037-41.