

Investigation of Thiol/Disulfide Balance and Oxidative DNA Damage in Patients Experiencing Avalanche Disaster and with a Diagnosis of Post-Traumatic Stress Disorder

ABSTRACT

Objective: There are few studies on oxidative stress in patients with post-traumatic stress disorder (PTSD). The thiol/disulfide homeostasis is a new marker of oxidative stress. This study aimed to examine the oxidative DNA damage and thiol/disulfide homeostasis after 6 months in patients who developed PTSD after an avalanche disaster and to compare them with healthy controls.

Methods: A total of 31 patients who developed PTSD after 2 consecutive avalanche disasters that occurred in Van on February 4 and 5, 2020, resulting in 42 deaths, and 33 healthy volunteers were included in the study. The patients were followed up by a psychiatrist within the framework of psychosocial intervention during their admission to Yüzüncü Yıl University Medical Faculty Emergency Service. The patients monitored for a long time were diagnosed according to DSM-5 diagnostic criteria. The clinical follow-up was evaluated with the post-traumatic stress disorder self-assessment (PTSD-KD) and the impact of events scale. To determine oxidative DNA damage, 8-hydroxy-2-deoxyguanosine (8-OHdG) and deoxyguanosine (dG) levels were determined by isolating leukocyte DNA. Oxidative DNA damage was given as a ratio of 8-OHdG/106dG. Total thiol/native thiol levels were also determined. Disulfide levels were calculated by subtracting native thiol results from the total thiol results and dividing them by 2.

Results: It was determined that total thiol and native thiol levels in patients with PTSD were statistically significantly lower than in the healthy control group ($P = .001$), and the disulfide levels were higher in the PTSD group compared with that in the healthy control group ($P = .001$). In addition, 8-OHdG, an indicator of DNA damage, was found to be significantly lower in the control group than in the patient group ($P = .001$).

Conclusion: In our study, thiol/disulfide homeostasis was observed to shift toward disulfide in patients with PTSD when compared with healthy controls. The level of 8-OHdG, the indicator of DNA damage, was observed to increase in patients with PTSD. This result indicates that thiol/disulfide homeostasis can be significant in the pathophysiology of oxidative stress in these patients.

Keywords: Avalanche, DNA damage, post-traumatic stress disorder

Introduction

Disasters are reported nearly every day around the world, and millions of people are affected each year.^{1,2} Studies have reported that 10%-19% of adults experience at least 1 disaster in their lifetime.² Disasters are basically cumulative, time-limited, and have an acute onset.³ Post-traumatic stress disorder (PTSD) is a psychiatric disorder that occurs after witnessing or experiencing a life-threatening traumatic event. PTSD is a condition characterized by avoidance of stimuli reminiscent of the trauma occurring after the event, excessive arousal, and repetition of the traumatic event.⁴

It has been stated that being traumatized increases oxidative stress levels, especially in individuals with chronic stress, and the oxidative balance is disrupted in the body.⁵ With chronic stress, increased oxidative stress markers in the blood have been found to be associated with increased damage in RNA and lipid cells.⁶ Most studies conducted on PTSD show that it is associated with bodily complaints.⁷ Although the etiology of PTSD is suggested to be influenced by changes in various biochemical parameters, its etiopathogenesis is not clear.⁸



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Some studies have shown that oxidative stress and free radicals play a role in PTSD as well as in many psychiatric disorders.⁹⁻¹² Free radicals are formed as intermediates during cell metabolism, and there is a balance between the rate at which free oxygen or nitrogen radicals are formed and their elimination rate. This is called oxidant/antioxidant balance.¹³ Excessive free oxygen radicals can cause cell injury, lipid peroxidation, DNA damage, apoptosis, and protein carboxylation.¹⁴⁻¹⁵ Brain tissue is more susceptible to oxidative damage, and the body has an antioxidative mechanism against this oxidative damage.¹⁶ Enzymes or proteins such as superoxide dismutase, catalase, and glutathione peroxidase are involved in endogenous antioxidant mechanisms.¹⁷

Thiol groups in the structure of proteins can undergo oxidation by forming disulfide bonds with the effect of free radicals and can be reduced back to thiol groups in the presence of antioxidants. With these properties, thiol groups make an important contribution to the oxidant/antioxidant balance, and the disulfide/thiol ratio plays an important role in the evaluation of oxidative stress.¹⁸

The thiol/disulfide ratio has a critical role in detoxification, antioxidant protection, signal transduction, regulation of enzymatic activity, apoptosis, and cellular signaling mechanisms.^{19,20} The thiol/disulfide index has recently been used as an important indicator of oxidative stress. Determination of dynamic thiol disulfide homeostasis can provide important information about normal or abnormal biochemical processes because it has been reported that the balance is disturbed in diseases such as migraine and epilepsy, including abnormal thiol disulfide homeostasis state, schizophrenia, autistic spectrum disorders, as well as neurological disorders.^{21,22} Only methods that measure thiol values can provide information about the state of the antioxidant buffer system. Thiol disulfide homeostasis, which is the dynamic redox system of the organism,²³ requires measuring both thiol and disulfide to evaluate the thiol/disulfide balance globally.²⁴ The first target of the reactive oxygen species (ROS) in proteins is the cysteine SH group in the protein structure. It turns into disulfide by oxidizing and causes loss of protein function.

Thiol-containing compounds, such as glutathione (GSH), are an important part of the organism's antioxidant defense system. In addition, thiol-containing compounds are important in the stabilization of apoptosis and proteins.

Free radicals damage cell structure and extracellular matrix components and disrupt genetic structure through DNA damage,²⁵ and

8-hydroxy-2-deoxyguanosine (8-OHdG) is a determinant of oxidative stress, mitochondrial dysfunction, and impaired metabolism.²⁶ After oxidation, the damaged DNA is cellular and is repaired by mechanisms, and 8-OHdG is excreted from body fluids. As a result, endogenous 8-OHdG levels can be determined in blood and urine and associated with DNA damage. Therefore, it has been used as a marker in various disorders.²⁷ Total thiol and native thiol concentrations are important parameters reflecting the state of the antioxidant system. A shift of dynamyl thiol/disulfide homeostasis toward disulfide may also mean that an increase in oxidative damage. However, the increase in oxidative stress does not mean that the DNA in a section that is protected against oxidative damage in the cell nucleus will undergo oxidative damage. Therefore, determination of dynamic thiol/disulfide homeostasis together with 8-OHdG, which is an oxidative DNA damage marker, will give us more information about the possible level of oxidative damage in these patients to better understand the extent of oxidative damage.

This study was conducted with 31 survivors of PTSD who survived 2 consecutive avalanche disasters that occurred in Van between February 4 and 5, 2020 and resulted in the death of 42 people. Although many studies have been conducted regarding the development of PTSD after natural disasters, such as earthquakes, floods, storms, and tornadoes, PTSD and oxidant/antioxidant status after an avalanche disaster have not yet been adequately studied. This study aimed to examine thiol/disulfide homeostasis and oxidative DNA damage in patients who developed PTSD after an avalanche and compare it with that of the patients with PTSD in the control group.

Methods

A total of 31 patients diagnosed with PTSD by a psychiatrist according to the DSM-5 diagnostic criteria in Yüzüncü Yıl University Psychiatry Clinic and 33 healthy volunteers as the control group were included. The PTSD group consisted of rescuers who went to the region to search and rescue after the first avalanche on Van-Bahçeşaray highway and volunteers who were relatives of the ones caught in the first avalanche. The patients were followed up by the psychosocial support team of our hospital to provide psychosocial support as part of the emergency treatment applied in the Emergency Department. All of patients in the PTSD group participating in our study stated that they were buried beneath the avalanche. Blood samples were taken from the patients in the 6th month of the disaster. This was an open-label cross-sectional study conducted between April and August 2020.

Individuals who were exposed to at least either of the 2 avalanches and developed PTSD were included in the study. The control group was determined randomly from healthy volunteers having no PTSD or other psychiatric diseases. In addition, height, weight, and body mass index measurements were carried out for individuals in both groups.

The exclusion criteria included metabolic diseases, diabetes mellitus and other endocrinologic diseases, pregnancy, smoking, obesity, alcohol and substance use disorders, other psychiatric pathologies, mental retardation, psychosis, schizophrenia, mood disorders, patients who are receiving ECT treatment and vitamin supplement, neurological diseases, and finally the history of antioxidant agent use.

MAIN POINTS

- Total thiol and native thiol levels in individuals who developed PTSD after an avalanche were lower than in the healthy control group and the disulfide level was higher than in the healthy controls.
- Thiol/disulfide homeostasis shifts toward disulfide in patients who were diagnosed with PTSD after the avalanche.
- Determining the direction in which the thiol/disulfide homeostasis shifts indicates the information about the oxidative state of the organism.
- 8-OHdG/106dG, an indicator of oxidative DNA damage, was found to be higher in patients with PTSD compared with that in the control group.

Complete blood count, blood lipids, fasting blood glucose, C reactive protein (CRP) insulin measurements, and other laboratory tests were performed on all the participants. Approval was obtained from the Yüzüncü Yıl University clinical research ethics committee (decision #14, dated March 4, 2020). All practices which were carried out with the consent of all individuals participating in the study were made in accordance with the ethical standards of the institutional and national research committee and the 1964 Helsinki Declaration and its subsequent revisions or comparable ethical standards.

Equipment

In the study, sociodemographic data forms were filled out for both the groups. The post-traumatic stress disorder symptom scale self-assessment (PTSD-CD) and perceived stress scale (PSS) scales were also applied to the PTSD group.

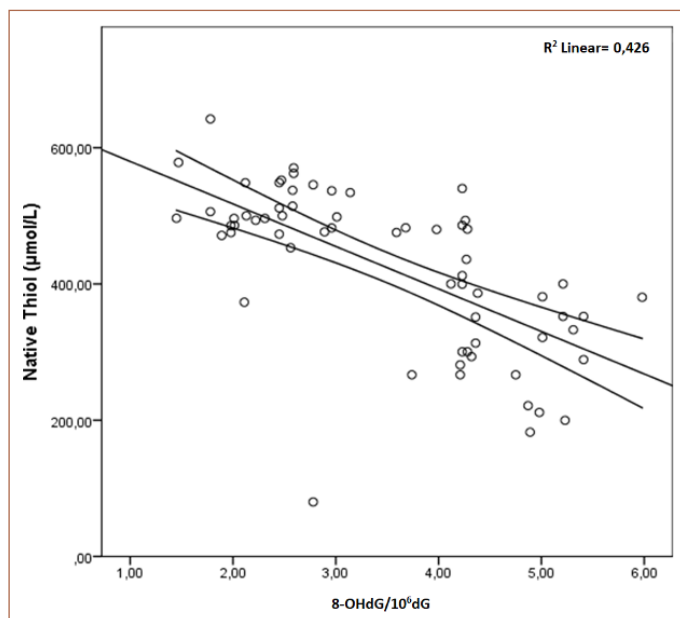


Figure 1. Correlation Distribution Between Oxidative DNA Damage and Native Thiol/Point Presentation

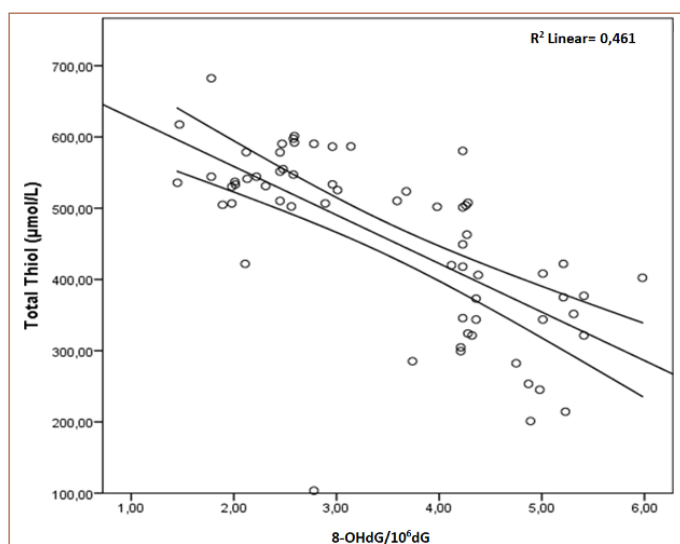


Figure 2. Correlation Distribution Between Oxidative DNA Damage and Total Thiol/Point Presentation

PTSD-CD: It is a 17-item Likert-type self-assessment scale scored between 0 and 3 designed to evaluate PTSD symptoms, developed by Foa et al.²⁸ Scores of 13 or higher indicate the possibility of PTSD. Its Turkish validity and reliability were demonstrated by Aydın et al.²⁹

Impact of event scale-revised (IES-R): This is a 5-point Likert-type scale developed by Weiss and Marmar in 1997 to examine possible post-traumatic stress disorders. It includes 3 subcomponents; re-experiencing, avoidance, and overstimulation. Its Turkish validity and reliability study was conducted by Çorapçıoğlu et al.³⁰

Thiol/disulfide homeostasis: The total thiol/native thiol levels were determined by commercial kits using a newly developed colorimetric method (Rel Assay diagnostic, Turkey). Determination of total thiol and natural thiol levels was carried out according to the protocols of the commercially available kits. First, 10 µL of serum sample or standard and 10 µL of reagent 1 were added to the total thiol test and mixed in a glass tube. After incubating for 100 seconds at room temperature (21 degrees Celsius), we added 110 µL of reagent 2 and incubated at room temperature for 200 seconds. At the end of incubation, we determined the initial absorbance at 415 nm wavelength. We then added 10 µL of reagent 3 to the mixture and incubated for 300 seconds at room temperature. We determined the final absorbance at a wavelength of 415 nm. Total thiol concentration was calculated according to the standard curve created. A total of 10 µL of sample or standard was placed in a native thiol glass inspection tube, and 100 µL of reagent 1 was added to it and incubated for 300 seconds at room temperature. At the end of incubation, the first absorbance at 415 nm wavelength was detected. Then, 10 µL of reagent 2 was added to the mixture and incubated for 300 seconds at room temperature. At the end of incubation, the final absorbance was determined at 415 nm wavelength. Native thiol concentrations were calculated according to the standard curve created after the total thiol/native thiol levels were determined. The amount of disulfide was determined by subtracting the native thiol results from the total thiol and dividing them by 2. Disulfide/total thiol, disulfide/native thiol, and native thiol/total thiol ratios were calculated, and the results were given as percentages.¹⁰

Oxidative DNA damage analysis: To determine oxidative DNA damage, leukocyte DNA was isolated, and 8-OHdG and deoxyguanosine levels were determined. Oxidative DNA damage was indicated as 8-OHdG/10⁶dG. First, the DNA samples were isolated from whole blood samples taken from patient and healthy control volunteers by using commercially available DNA isolation kits (Nucleo Spin Blood DNA, RNA and Protein Preparation, Macherey-Nagel from Germany). The isolated DNA samples were hydrolyzed with formic acid as previously described by Kaur and Halliwell.³¹ The 8-OHdG and dG concentrations of the hydrolyzed DNA samples were determined by using the electrochemical detector (ECD) and variable wavelength detector (UV) high pressure liquid chromatography (HPLC) method.³² Prior to analysis by HPLC, hydrolyzed DNA samples were dissolved in HPLC eluent (final volume 1 mL). A total of 20 µL of the final lysate was analyzed by HPLC-ECD. A reverse phase-C18 analytical column was used (250 mm × 4.6 mm × 4.0 µm, Phenomenex, California, United States). The mobile phase contained 0.05 M potassium phosphate buffer, pH 5.5 and acetonitrile (97:3, v/v) and the flow rate was 1 mL/min. DG concentration was monitored based on absorption at 245 nm, and the 8-OHdG level was determined based on the ECD reading (600 mV). DG and 8-OHdG levels were measured using dG and 8-OHdG

Table 1. Thiol/disulfide Homeostasis in PTSD and Healthy Control Groups

	PTSD group, N=31, Mean (SD)	Healthy control group, N=33, Mean (SD)	95% CI		P
			Lower	Upper	
Total thiol (μmol/L)	365.4 (85.5) ^a	537.9 (46.7)	-206.2	-137.4	.001
Native thiol (μmol/L)	336.9 (86.3) ^a	515.9 (49.8)	-214.4	-143.7	.001
Disulfide (μmol/L)	14.4 (2.66) ^a	10.9 (3.42)	1.89	5.02	.001
Disulfide/native thiol (%)	4.61 (1.66) ^a	2.17 (0.95)	1.75	3.12	.001
Disulfide/total thiol (%)	4.18 (1.98) ^a	2.06 (0.83)	1.54	2.68	.001
Native thiol/total thiol (%)	91.6 (2.74) ^a	95.86 (1.67)	-5.38	-3.08	.001
8-OHdG/106dG	4.57 (0.62) ^a	2.47 (0.61)	1.78	2.41	.001

^aP: significance compared with healthy control group.

Abbreviations: PTSD, post-traumatic stress disorder; 95% CI, 95% confidence interval difference interval.

Table 2. Relationship Between Oxidative DNA Damage and Thiol/Disulfide Homeostasis

		8-OHdG/10 ⁶ dG
Total thiol (μmol/L)	r	-0.679 ^a
	P	.000
	N	64
Native thiol (μmol/L)	r	-0.653 ^a
	P	.000
	N	64
Disulfide	r	-0.619 ^a
	P	.000
	N	64
Disulfide/native thiol (%)	r	-0.069
	P	.591
	N	64
Disulfide/total thiol (%)	r	-0.074
	P	.563
	N	64
Native thiol/total thiol (%)	r	0.074
	P	.562
	N	64
8-OHdG/10 ⁶ dG	r	1
	P	
	N	64

^aP < .001, r: Pearson's correlation coefficient.

Abbreviation: N, number of individuals.

standards purchased from Sigma. The 8-OHdG level was indicated as 8-OHdG molecules per 106 dG.

Statistical Analysis

The data obtained were analyzed using SPSS version 20 software program (IBM Corp.; Armonk, NY, USA). The normal distribution of our data was checked by Shapiro-Wilks. Independent sample-t test and chi-square tests were used for comparison between groups. Data were expressed as mean (SD) deviation. Statistical significance was accepted as $P < .05$ value.

Results

Totally; 31 PTSD patients with a mean age of 31.6 (SD = 5.53) years (range = 25-46) and 33 healthy volunteers (control group) with a mean age of 33.6 (SD = 5.21) years (range = 18-42) participated. There was no statistical difference in terms of sociodemographic characteristics. Both groups were matched in terms of age and gender. The

average duration of illness in the patient group was six months. There was no difference between the groups in terms of body mass index.

In the evaluation made with Post-Traumatic Stress Disorder Self-Assessment and the Impact of Events Scale in the patient group at the sixth month, it was found that PTSD-KD was 16.83 (SD = 9.29), IES avoidance was 8.34 (SD = 4.69), IES increased arousal was 9.37 (SD = 5.42), IES re-experiencing was 10.54 (SD = 6.70), and IES was 28.09 (SD = 15.69) in total. It was found that the total thiol and native thiol levels in PTSD patients were statistically significantly lower than the healthy control group ($P = .001$). Besides, disulfide levels were found to be higher in PTSD patients than healthy controls ($P = .001$). Likewise, disulfide/total thiol and disulfide/native thiol ratios were significantly higher in PTSD patients than in the control group. Native/total thiol ratio was higher in the control group ($P = .001$). Oxidative DNA damage was also found to be statistically higher in PTSD patients compared to the control group ($P = .001$) (Table 1). In addition, we determined that 8-OHdG/106dG values were negatively correlated with total thiol and native thiol values as a result of correlation analysis. This indicates that oxidative DNA damage increases with the decrease in total thiol and native thiol values (Table 2).

Discussion

Our study found that total thiol and native thiol levels in individuals who developed PTSD after an avalanche were statistically significantly lower than in the healthy control group and that the disulfide level was higher than in the healthy controls. According to these results, we can hypothesize that thiol/disulfide homeostasis shifts toward disulfide in patients who were diagnosed with PTSD after the avalanche. Determining the direction in which the thiol/disulfide homeostasis shifts gives us information about the oxidative state of the organism. Studies on this subject found that the shifting of balance toward to disulfide is associated with important pathological conditions, such as cardiovascular diseases and diabetes.^{33,34}

Oxidative stress plays a role in the pathogenesis of neurological disorders such as Alzheimer's, migraine, and epilepsy as well as stressful traumatic life events.^{6,35-37} Various approaches have been used to explain the etiology of oxidative stress in the brain.³⁸ There is increasing evidence of a link between the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenal-medullary system and oxidative stress.³⁹ An alternative explanation of the mechanisms underlying oxidative stress is the activation of the HPA axis, which causes corticosterone release along with catecholamines and sympatho-adrenal-medullary system.⁴⁰

It has been stated that neuronal damage associated with oxidative stress plays a role in the development of many neuropsychiatric disorders, including psychiatric disorders such as schizophrenia, depression, and anxiety.^{10,22,41} It has been shown that the balance shifts toward disulfide in major psychiatric disorders such as schizophrenia, bipolar disorder, and depressive disorder.^{10,41-42} Similarly, it has been reported that thiol/disulfide homeostasis shifts toward disulfide in neurological diseases, such as migraine and epilepsy.^{43,44} In a study conducted with patients with generalized anxiety disorder, it was reported that the total thiol and native thiol levels of the patients were higher than in the control group.⁴⁵ Few studies have focused on the relationship between PTSD and oxidative stress.¹² In individuals who survived the avalanche and developed PTSD, it was observed that the oxidative balance shifted toward disulfide significantly 6 months later compared with that in the control group. At this juncture, an alternative view can be propounded that serum thiol/disulfide homeostasis, which is accepted as a new biomarker in determining the level of oxidative stress in patients with PTSD, could contribute to the determination of the level of oxidative stress in these patients.

In our study, 8-OHdG, an indicator of oxidative DNA damage, was found to be significantly higher in patients with PTSD compared with that in the control group. Previous studies have examined oxidative DNA damage in patients with PTSD.⁹ In our study, we determined 8-OHdG levels in DNA rather than 8-OHdG values in serum, plasma, or urine, using the HPLC method which is more precise. If the base modifications caused by ROS are not corrected by DNA repair genes, it causes mutations in DNA and the loss of the function of proteins synthesized by DNA. This can lead to serious complications. There is strong evidence that oxidative damage occurs permanently in cell membrane lipids, proteins, and DNA. In nuclear and mitochondrial DNA, 8-OHdG is one of the main forms reflecting oxidative damage caused by free radicals.²⁵ A study has reported that post-mortem levels of 8-OHdG in the hippocampus in patients with schizophrenia were 10 times higher than in controls without psychiatric disorders.⁴⁶ Patients with major depression are also reported to have higher levels of serum 8-OHdG than controls.⁴⁷ Furthermore, patients with recurrent depressive episodes have been shown to have more oxidative DNA damage than in patients with a depressive episode.⁴⁸

In our study, we found a negative correlation between oxidative DNA damage and total thiol and native thiol, and although total thiol and native thiol values decreased, 8-OHdG/106dG values increased. The decrease in antioxidative parameters indicates that it may cause damage in the DNA structure. In the literature, oxidative stress parameters have been studied in patients with schizophrenia, but no significant relationship was found between oxidative stress levels and DNA damage.⁴⁹ In another study investigating the relationship between oxidative stress and DNA damage in patients with depression, it was seen that they had increased oxidative DNA damage.⁵⁰

Another study on children and adolescents exposed to sexual abuse, patients with and without PTSD, investigated the relationship between oxidative stress levels and DNA damage, but found no difference between the 2 groups.⁹ Significantly high levels of oxidative stress and oxidative DNA damage in individuals who had suffered from an avalanche disaster and developed PTSD demonstrate that DNA damage caused by stress can accelerate aging in these patients. Pharmacological treatments, cognitive therapies, treatment of sleep problems, regular exercise, or natural antioxidants before developing

PTSD may help to regulate the thiol/disulfide balance and prevent oxidative DNA damage.

Our study had a number of limitations. Since our study was a cross-sectional study, it was difficult to make general inferences. Owing to the small number of patient groups, the patients could not be classified according to the severity of the disease. In addition, the inability to eliminate factors affecting oxidative stress such as the family history of the participants, diet, exercise status, sleep patterns, and working conditions were the other limitations of our study.

This study is the first study to examine thiol/disulfide homeostasis in individuals who developed PTSD after an avalanche and compare it with a control group. It shows that the thiol/disulfide balance in patients with PTSD shifts toward disulfide compared with that in healthy controls and that 8-OHdG levels, which are an indicator of DNA damage, are higher than in healthy controls. Our study showed that oxidative stress balance is seriously impaired in individuals with PTSD. Increasing evidence of a link between the hypothalamic-pituitary-adrenal axis and sympatho-adrenal-medullary systems and oxidative stress in patients with PTSD may be associated with increased levels of oxidative stress. Regulation of oxidative stress balance in patients with PTSD will be helpful in treatment and reducing morbidity. In the following studies, the relationship between the duration of the disease, the severity of symptoms, and oxidative stress levels in patients with PTSD can be examined and how the treatments administered to patients with PTSD affect oxidative stress levels can be measured. If we believe that treatments help regulate the oxidative balance and prevent oxidative DNA damage, antioxidant agents can be used in the future treatments of patients with PTSD. However, more extensive studies are needed to understand the relationship between oxidative stress and PTSD and whether the use of natural antioxidant substances can be beneficial in treatment and morbidity.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Yüzüncü Yıl University School of Medicine (Approval Date: March 4, 2020; Approval Number: 14).

Informed Consent: Informed consent was obtained from the individuals who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.K.; Design - F.K., H.H.A.; Supervision - F.K.; Resources - F.K.; Data Collection and Processing - F.K., H.H.A.; Analysis and/or Interpretation - F.K., H.H.A.; Literature Review - F.K.; Writing - F.K.; Critical Review - F.K., H.H.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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