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A Cross-Sectional Measurement of Endogenous Oxidative Stress Marker Levels in Obsessive Compulsive Disorder

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ABSTRACT

Background: There is a correlation between the increase in reactive oxygen radicals and the presence of specific mental illnesses. In this context, the objective of this study is to investigate the relationship between obsessive-compulsive disorder and the variations in the levels of several endogenous oxidative stress markers.

Methods: Thirty obsessive-compulsive disorder patients were included in the study as the patient group, and 30 healthy volunteers of matching demographic characteristics were included in the study as the control group. Accordingly, the patient group consisted of 10 females and 20 males with a mean age of 29.5 ± 6.1 years, and the control group consisted of 15 females and 15 males with a mean age of 31.9±5.6 years. The serum nicotinamide adenine dinucleotide phosphate oxidase-2, nicotinamide adenine dinucleotide phosphate oxidase-4, and malondialdehyde levels of the 2 groups were compared using the independent samples *t*-test. The relationships between the serum nicotinamide adenine dinucleotide phosphate oxidase-2, nicotinamide adenine dinucleotide phosphate oxidase-4, and malondialdehyde levels of the 2 groups were analyzed using the Pearson's correlation coefficient.

Results: The serum nicotinamide adenine dinucleotide phosphate oxidase-2, nicotinamide adenine dinucleotide phosphate oxidase-4, and malondialdehyde levels of the patient group were statistically significantly higher than those of the control group ($P < .001$). Statistically significant positive correlations were detected between the serum nicotinamide adenine dinucleotide phosphate oxidase-2 and nicotinamide adenine dinucleotide phosphate oxidase-4 levels ($r=0.692$, $P=.001$) and between the serum nicotinamide adenine dinucleotide phosphate oxidase-2 and malondialdehyde levels ($r=0.563$, $P=.001$).

Conclusion: The results of this study indicated that oxidative stress and lipid peroxidation levels were higher in obsessive-compulsive disorder patients. Based on this finding, NOX-2 and NOX-4 levels can be used as indicators of endogenous oxidative stress in obsessive-compulsive disorder patients.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) consists of obsessions and compulsions outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. Obsessions are repetitive and persistent thoughts, impulses, or images that are experienced involuntarily and intrusively. Compulsions, on the other hand, are repetitive behaviors and mental acts generally exhibited in response to an obsession or a rule that must be strictly adhered to.[1] Obsessive-compulsive disorder is a chronic neuropsychiatric disease that affects approximately 1%-3% of the general population. Obsessive-compulsive disorder can cause significant destruction and loss of workforce and reduce quality of life.[1]

To date, the etiopathogenesis of OCD has not yet been fully elucidated. Nevertheless, it has been estimated that genetic, environmental, biochemical factors, for example, neurotransmitter disorders, stress caused by various traumatic experiences, and immunological factors, play a role in its etiology.[2,3] In addition, there is increasing evidence that systemic dysregulation of inflammation and oxidative stress play a role in OCD, as well.[4]

The immune system and the oxidative system are closely related. Immune reactions generate numerous free radicals, and immune system cells are very sensitive to oxidative damage. Additionally, oxidative stress causes aging and triggers diseases of the immune system.[4]

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In a healthy organism, oxidative stress reactions are in balance. Free radicals are produced in normal metabolic pathways and removed by means of antioxidant defense mechanisms. This balance is disrupted in the event of certain conditions or diseases, and free radicals begin to accumulate in the organism.[5] The disruption of the oxidative balance in favor of free radicals may damage the lipids found in the structure of the cell membrane, thereby negatively affecting the proteins and nucleic acids found in the structures inside the cell.[6] This phenomenon is called oxidative stress. Oxidative stress affects almost all organs in the organism, among them the brain tissue, which has the highest oxygenation compared to body mass, is the most affected organ.[5]

It has been reported in several studies on psychiatric diseases that oxidative stress plays a role in diseases such as schizophrenia, mood disorders, anxiety disorders, and autism.[4,7] As a matter of fact, oxidative stress seems to be a common feature in the pathologies of psychiatric diseases, and OCD is no exception.[4,6,8-10]

Numerous biomarkers have been used to determine oxidative damage. One of these biomarkers is malondialdehyde (MDA), an oxidation marker, which is used as an indicator of the lipid peroxidation caused by oxidative stress. There are findings reported in the literature which indicate that the serum concentrations of oxidative stress markers including MDA significantly increase in individuals with OCD.[4,6]

Malondialdehyde levels of OCD patients were reported to be higher than those of healthy control subjects in several studies.[6,8-10] In parallel, Shrivastava et al[11] did not find a significant difference between the MDA levels of the first-degree relatives of OCD patients and those of healthy control subjects. These findings suggest that high MDA levels are associated with OCD.

Superoxide, which takes part in immunological reactions, is one of the more important free radicals. Nicotinamide adenine dinucleotide phosphate (NADPH) takes part in the formation of superoxide. Nicotinamide adenine dinucleotide phosphate works as an electron carrier on biological membranes. Nicotinamide adenine dinucleotide phosphate oxidase (NOX) enzymes catalyze the oxidation of NADPH.[12] It has been well-established in the last 10 years that oxidative damage, which originates from the NOX enzyme family, affects cell nucleus, proteins, and amino acids, and plays a role in lipid peroxidation and in the oxidation of heavy metals.[13,14] Accordingly, increases in serum NOX levels have been used as an indicator of endogenous oxidative reactions.[15] The 2 most important and most studied members of the NOX enzyme family are NOX-2 and NOX-4 enzymes.[12] Some NOX enzymes have high affinity for tissue type and organ. In neurons, it has been reported that NOX 1-2-3-4 have been induced in pathological conditions such as oxidative stress.[13] Nicotinamide adenine dinucleotide phosphate oxidase-2 has been the most studied NOX enzyme in the context of etiopathogenesis of neuropsychiatric diseases, yet the findings on NOX-1 and NOX-4 in the said context have also begun to increase.[13]

The increase in the serum levels of NOX-2 and NOX-4 associated with various diseases has been demonstrated in several previously conducted studies, and this increase was said to be of endogenous origin.[13,16] Hernandes et al[17] reported that NOX-induced oxidative damage plays a role in the pathogenesis of neurodegenerative disorders in Alzheimer's and Parkinson's diseases. In addition, it was reported in other studies that NOX-induced oxidative stress damage plays a role in the pathogeneses of bipolar disorder, anxiety disorder, and autism spectrum disorder.[18,19] It was suggested that antidepressant drugs' mechanism of action may include improving the oxidative stress/antioxidant function.[20]

In another study, it was reported that NOX can be activated by various infectious agents, resulting in overproduction of free oxygen radicals and that this can lead to the death of the infected cells and trigger inflammatory response.[21] Furthermore, in another study, a relationship was found between the increase in NOX-2 induced by bacterial products and the obsessive-compulsive symptoms seen in children with PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).[22] Nevertheless, to the best of authors' knowledge, there is no study available in the literature that addressed the NOX-2 and NOX-4 levels in OCD patients.

In view of the foregoing, it was hypothesized in this study that the oxidative balance would be impaired in OCD patients, that the NOX-2 and NOX-4 levels in OCD patients would be higher than those of controls, and that the NOX-2 and NOX-4 levels would be correlated with the MDA levels indicating oxidative damage. Based on this hypothesis, this study was carried out to investigate any relationship between OCD and the increase in the biomarkers of endogenous oxidative stress. Accordingly, first, the blood samples of OCD patients and healthy control subjects were studied for endogenous NOX-2 and NOX-4 enzymes, which have a role in oxidative pathways, and MDA, and secondly, any correlation between the NOX-2, NOX-4, and MDA levels was investigated based on the results obtained.

MAIN POINTS

- The levels of NOX-2 and NOX-4 enzymes, the endogenous oxidative stress sources, are higher in OCD patients than in healthy control subjects.
- The levels of NOX-2 and NOX-4 enzymes are positively correlated with the levels of MDA, an oxidative stress marker.
- NOX induced oxidative stress damage may be playing a role etiopathogenesis of OCD.

MATERIAL AND METHODS

The study protocol was approved by the Institutional Ethics Committee of the Faculty of Medicine Ethics with the decision numbered 08 and dated January 29, 2020. Informed written consent forms were obtained from all study participants. The study was conducted with 60 participants, of whom 30 were OCD patients and 30 were healthy control subjects, during the period of February 1, 2020, and August 30, 2020. Inclusion criteria were determined as having been diagnosed with OCD and aged between 18 and 65, whereas the exclusion criteria were determined as having additional neuropsychiatric diseases and having chronic diseases.

The target sample size was determined as 60, half of which would be OCD patients and the other half control subjects. When the number determined during the study process was reached, the recruitment of participants was stopped. Individuals who were not suitable for the study due to various reasons were excluded from the study without sampling. This number is not recorded. Accordingly, the first 30 patients, who were diagnosed with OCD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria by a psychiatrist, admitted to the psychiatry outpatient clinic of the Van Yüzüncü Yıl University, School of Medicine hospital during the period of the study, and met the inclusion criteria were included in the study. Diagnostic and clinical features of the patients included in the study were reviewed by a psychiatrist. Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to rate disease severity. Accordingly, the disease severity of 3 patients was assessed as mild, 11 patients as moderate, 12 patients as severe, 2 patients as very severe, and 2 patients as subclinical. The mean disease duration in the patient group was calculated as 10.3 ± 8.71 years. The OCD patients included in the patient group significantly differed in terms of the type of treatment they received for OCD, that is, while some received certain types of medications or therapies, others were treatment-naive. Given the relatively small sample size, no differentiation could be made between the patients on the basis of symptom clusters and insight characteristics.

The control group consisted of hospital staff who were determined not to have a history of neuropsychiatric disease or any additional chronic disease based on a clinical interview conducted by a psychiatrist and who had sociodemographic characteristics that match the OCD patients included in the study. Accordingly, the first 30 healthy individuals from among the hospital staff that met the inclusion criteria were included in the control group. All participants were in the age group of 18 and 60 years old.

Those who were below 18 or above 60 years old, who have been receiving antioxidant therapy or vitamin supplementation, smoking, were pregnant or in the puerperal period, obese [body mass index (BMI) $\geq$ 30], had a history of psychiatric disease, alcohol-substance use disorders, neurological diseases, metabolic and endocrinological diseases, fever or infectious diseases, or other comorbid physical diseases, at the time of the study were not included in the study. While choosing the control group, psychiatric disorders and other chronic diseases were excluded by a clinical interview by a psychiatrist, and completely healthy individuals were included in the study.

Blood samples of the participants in both the patient and control groups were taken for biochemical analyses. Accordingly, 5 mL blood samples were taken from each participant through the brachial veins, placed in sterile tubes with dry gel, and centrifuged at $3000 \times g$ for 10 minutes. Serum samples were stored at -80°C during the period of study until used for tests. Malondialdehyde, NOX-2, and NOX-4 levels were measured using the prepurchased enzyme-linked immunoassay kits (Rel Assay Diagnostics, Gaziantep, Turkey) in accordance with the guidelines set by the manufacturer.

Statistical Analysis

We used the G-power 3.1.9.2 program to calculate the pre-study sample size. Jacob Cohen made suggestions as small, medium, and large for effect size in power analysis. The effect size for the sample size required for the 2 independent groups in the prior study power analysis is small 0.20, medium 0.50, and large 0.80. In our study, we took the effect size as 0.80 when calculating the sample size. The minimum power in the study was 0.80, in our study it was 0.85. The alpha value was 0.05. In this case, the minimum sample size for each group was determined as 30.

The research data were analyzed using the SPSS 20 (Statistical Package for Social Sciences for Windows, Version 20.0, IBM Corp., Armonk, NY, USA, 2011) software package. Shapiro-Wilks test was used to check whether the measured data conformed to the normal distribution. Independent samples *t*-test and Pearson's chi squared test were used to compare the data groups. Descriptive statistics pertaining to the data were presented in terms of numbers (n) and percentage values (%) and mean $\pm$ standard deviation (SD) in case of variables that conform to normal distribution. Pearson's correlation coefficient was used to analyze any correlations. The OCD group was divided into 5 groups according to the Y-BOCS scoring, and the comparison of the parameters was made with the Kruskal-Wallis test. Evaluation of the difference between the 2 groups was done with the Bonferroni test. Probability (*P*) values of $<.05$ were deemed to indicate statistical significance.

RESULTS

The conformity of the parameters to the normal distribution was examined using the Shapiro-Wilks test. As

Table 1. Sociodemographic Characteristics of the Study Participants

		Control Group n = 30	Patient Group n = 30	χ^2 value	*P*
Gender (n, %)	Female	15 (50%)	10 (33.3%)	1.341	.190
	Male	15 (50%)	20 (66.7%)		
				***t* value**	
Age (mean ± SD)		29.53 ± 6.06	31.94 ± 5.57	1.604	.125
BMI (mean ± SD)		23.7 ± 2.34	24.13 ± 2.16	0.74	.511

BMI, body mass index; SD, standard deviation.

Table 2. Comparison of MDA, NOX-4, and NOX-2 Levels Between the Groups

	Patient Group	Control Group	*t* Value	*P*	95 % CI	
					Lower	Upper
MDA (μM)	6.34 ± 1.63	3.25 ± 1.54	7.053	<.001	2.21	3.97
NOX-4 (ng/mL)	12.4 ± 3.06	7.12 ± 1.89	7.393	<.001	3.85	6.73
NOX-2 (ng/mL)	54.9 ± 10.62	25.7 ± 5.71	11.909	<.001	24.3	34.1

MDA, malondialdehyde; NOX-2, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2; NOX-4, NADPH oxidase 4.

a result of the Shapiro-Wilk normality test, the *P* value for MDA was determined as .386, .427 for NOX4, and .991 for NOX2, indicating that these three parameters are normally distributed.

There was no statistically significant difference between the patient and control groups in sociodemographic characteristics. In other words, the groups were of matching characteristics in terms of gender, age, and BMI. Sociodemographic characteristics of the groups are shown in Table 1.

Nicotinamide adenine dinucleotide phosphate oxidase-2, NOX-4, and MDA levels of the OCD patients were significantly higher than those of the healthy control subjects ($P < .001$) (Table 2).

The analysis of the relationships between the levels of NOX enzymes and MDA using Pearson's correlation coefficient revealed a statistically significant correlation in the positive direction between the NOX-2 and NOX-4 levels and the MDA levels. These relations are shown in Table 3.

A scatter plot representation of the correlation between NOX-2 and NOX-4 levels for all participants is shown in Figure 1.

Table 3. Relations Between MDA, NOX-4, and NOX-2 Levels

n = 60		MDA	NOX-4	NOX-2
MDA	*r*	1	0.365*	0.563*
	P		.007	.001
NOX-4	*r*	0.365*	1	.692*
	P	.007		.001
NOX-2	*r*	0.563*	0.692*	1
	P	.001	.001	

r, Pearson's correlation coefficient; n, number of subjects; MDA, malondialdehyde; NOX-2, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2; NOX-4, NADPH oxidase 4.
*Correlation is significant at the $P = .01$ level (two-tailed).

DISCUSSION

As a result of the study, NOX2 and NOX4 levels, which are members of the NOX enzyme family, which is the source of endogenous oxidative stress, were found to be higher in OCD patients than in the control group. At the same time, MDA level, which indicates oxidative stress, was found to be higher in OCD patients than in the control group. Malondialdehyde level was positively correlated with both NOX2 and NOX4. These findings support that oxidative stress may contribute to the etiopathogenesis of OCD.

To the best of our knowledge, this is the first study to date, in which the levels of NOX-2 and NOX-4 enzymes, which are endogenous sources of oxidative stress, and the correlation of these levels with the levels of MDA, which is an indicator of lipid peroxidation, were comparatively investigated in OCD patients and healthy control subjects with matching demographic characteristics. The findings of this study provide further evidence for the relationship between oxidative stress, oxidative damage, and OCD and suggest that NOX-related oxidants may have a role in the oxidative damage in OCD. The findings of this study are consistent with the findings of other studies, which suggest a relationship between oxidative stress and other psychiatric diseases. Taken together with the findings of other relevant studies available in the literature, the results of this study support the hypothesis that there is a relation between endogenous oxidative stress and OCD and offer new horizons for the development of novel treatment options. Preliminary evidence has suggested that antidepressant treatment results in increased antioxidant capacity and a decrease in circulating free radicals, enhances neuroplasticity mechanisms and adult neurogenesis in brain.[23,24] Studies have also supported that adjunctive antioxidant drugs like N-acetylcysteine, an antioxidant precursor to glutathione, may reduce symptoms of OCD.[25]

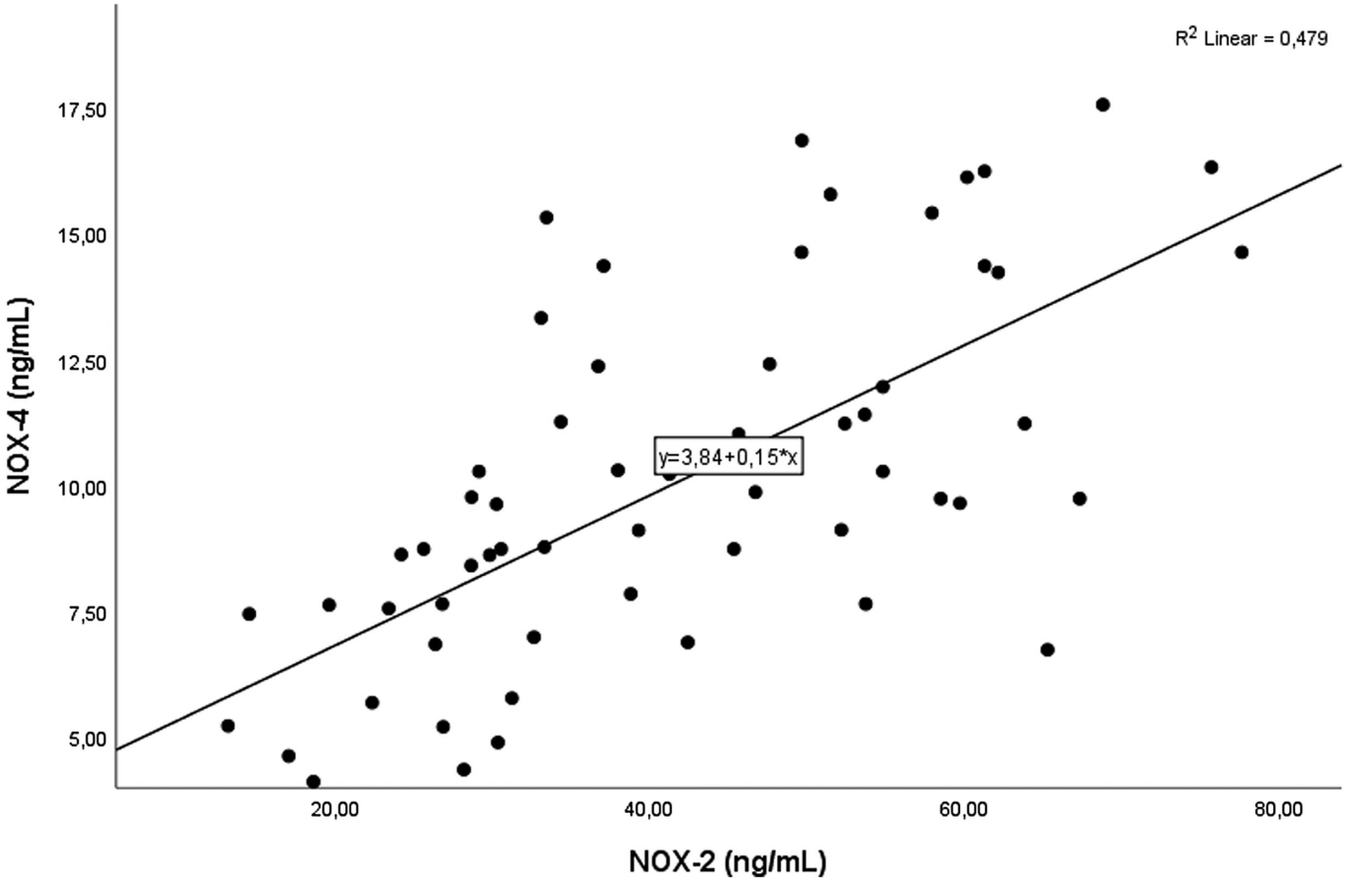

Figure 1. Scatter plot representation of the correlation between NOX-2 and NOX-4 levels (n = 60). NOX, nicotinamide adenine dinucleotide phosphate oxidase.

Although the results of this cross-sectional study revealed the relationship between OCD and increased markers of oxidative stress, the role of oxidative stress in etiopathogenesis or causality of OCD remains unclear. Thus, further studies are needed to elucidate the causality of the relationship between OCD and oxidative stress.

Oxidative stress levels and inflammatory pathways are closely related. Pro-inflammatory cytokines are released in response to oxidative stress, but they also complicate the inflammatory cycle.[26] It has been emphasized that inflammatory disorders in OCD patients may originate from the cortico-adreno-medullary circuit and that there may be an increase in oxidative stress markers due to the overworking of this circuit.[27] Additionally, it has been suggested that the oxidative balance would be impaired in favor of oxidants in the event of excessive activation of the hypothalomo-pituitary-adrenal axis and sympatho-adrenal-medullary systems.[28,29]

The role of NOX enzymes and NADPH in increasing oxidative stress is noteworthy. Bacterial products and inflammatory cytokines are known to induce NOX enzymes and cause cell death (including bacteria) via reactive oxygen radicals (ROS). It has been demonstrated that the increase in NOX-2 induced by bacterial products, as shown in children with PANDAS, and the increase in interleukin (IL)-6-related NOX in ketamine-related psychosis, as shown in mouse experiments, may contribute to the pathogenesis by causing oxidative stress.[13,22]

When it comes to OCD, it is known that OCD patients have a high rate of comorbid autoimmune diseases. Additionally, it is also known that serum levels of pro-inflammatory cytokines and IL-6 are increased in OCD patients and that certain types of antineuronal antibodies are associated with OCD symptoms.[27] All these suggest the increase in NOX activity and oxidative stress, which may be triggered by autoimmune inflammation, as a possible mechanism for the etiopathogenesis of OCD.

It has been speculated that OCD is mainly caused by an imbalance in the cortico-striato-thalamo-cortical circuit, between direct and indirect pathways, leading to hyperactivation in the orbitofrontal cortex and thalamus, and recent studies have shown that functional changes in certain brain regions may also contribute to the development of OCD.[31] Further studies are needed to determine whether NOX-2, NADPH, and ROS, which reportedly have roles in neuronal signaling, and perhaps NOX-4, are associated with changes in serotonin and dopamine signaling in OCD.

Another possible mechanism suggested for the increase in NOX-2, NOX-4, and oxidative stress in OCD is based on the effect of medication and lifestyle. As a matter of fact, increased levels of oxidative stress were reported in treatment-naive patients in the literature.[32] Moreover, the high rates of comorbid systemic diseases, for example, metabolic syndrome and autoimmune diseases, other psychiatric diseases, and substance use disorders, in OCD patients suggest that lifestyle and physical characteristics may also play a role in increasing the oxidative stress.[4,30] It is also possible that OCD and comorbidities have common predisposition factors and share a common etiopathogenesis and that increased oxidative stress may contribute to this common etiopathogenesis.

In summary, the increased levels of oxidative stress markers and NOX enzymes stand out as valuable biomarkers for the diagnosis, prognosis, and follow-up of OCD, regardless of the mechanism. Furthermore, the use of these biomarkers may help develop new treatment options such as antioxidant therapies.

Apart from its strengths mentioned throughout the text, there were also some limitations to this study. The cross-sectional nature of the study and its relatively small sample size prevent generalization of the results to all OCD patients. The evaluation of the patient group and the control group was made with an unstructured psychiatric interview, and the fact that a structured interview tool was not used is a limitation of the study. The fact that the participants in the patient group were taking medication was another limitation to this study due to the possible antioxidant effects of antidepressant drugs. It was not possible to overcome this limitation simply by categorizing the patients based on the types of medication they have been using since the medications used were very diverse and the sample size was not large enough. Another limitation to this study was that the relations between MDA levels, levels of NOX enzymes, symptom clusters, and insight characteristics could not be examined because the sample size was not large enough. In this study, it could not be examined whether MDA, NOX-2, and NOX-4 levels changed according to the severity of obsessive-compulsive symptoms because of the small sample size. Testing the relations between oxidative damage marker levels and OCD disease severity in studies with larger sample sizes will make an important contribution to illuminating this area. Lastly, other factors that might have affected the oxidative stress levels such as dietary patterns, status of doing exercise, sleep patterns, working conditions, familial histories, and menstrual status, where appropriate, could not be excluded.

The findings of this study should be reproduced and validated with studies to be conducted with larger samples and more homogeneous groups in terms of clinical characteristics and insight levels of OCD patients. Follow-up studies on the treatment-naive patients that will also include more comprehensive evaluations of the lifestyles, menstrual statuses, familial histories, and so on, of these patients, may offer clues in terms of elucidating cause–effect relationships.

In conclusion, the findings of this study revealed that the levels of NOX-2 and NOX-4 enzymes, the endogenous oxidative stress sources, were higher in OCD patients than in healthy control subjects, and were positively correlated with the levels of MDA, an oxidative stress marker. These markers may provide a better understanding of the OCD and may be valuable as clinically relevant biomarkers. The results of this study may serve as a guide for future studies on the relationship between oxidative stress and OCD. Accordingly, it is recommended that future studies on the relationship between oxidative stress and OCD should further categorize the OCD patients based on whether they receive medication or not and compare these groups both with each other and with the control group. In addition, further studies should also include pretreatment and posttreatment follow-up studies. In this way, levels of oxidative markers and NOX enzymes can be measured at different stages during the course of the disease, that is, acute, chronic, exacerbation, and remission phases. Findings of prospective studies using antioxidant drugs, like N-acetylcysteine, for augmentation of antidepressant drugs, will also contribute to the clinical practice.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Van Yüzüncü Yıl University (Approval No: 08).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association; 2013. [CrossRef]
2. Miller ML, Brock RL. The effect of trauma on the severity of obsessive-compulsive spectrum symptoms: a meta-analysis. *J Anxiety Disord*. 2017;47:29-44. [CrossRef]
3. Schrag A, Gilbert R, Giovannoni G, Robertson MM, Metcalfe C, Ben-Shlomo Y. Reply from the authors. *Neurology*. 2010;74(17):1398-1399. [CrossRef]
4. Maia A, Oliveira J, Lajnef M, et al. Oxidative and nitrosative stress markers in obsessive-compulsive

disorder: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2019;139(5):420-433. [CrossRef]
5. Ciobica A, Padurariu M, Dobrin I, Stefanescu C, Dobrin R. Oxidative stress in Schizophrenia-focusing on the main markers. *Psychiatr Danub*. 2011;23(3):237-245.
6. Ersan S, Bakir S, Erdal Ersan E, Dogan O. Examination of free radical metabolism and antioxidant defence system elements in patients with obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30(6): 1039-1042. [CrossRef]
7. Schiavone S, Trabace L. Pharmacological targeting of redox regulation systems as new therapeutic approach for psychiatric disorders: a literature overview. *Pharmacol Res*. 2016;107:195-204. [CrossRef]
8. Behl A, Swami G, Sircar SS, Bhatia MS, Banerjee BD. Relationship of possible stress-related biochemical markers to oxidative/antioxidative status in obsessive-compulsive disorder. *Neuropsychobiology*. 2010;61(4): 210-214. [CrossRef]
9. Ozdemir E, Cetinkaya S, Ersan S, Kucukosman S, Ersan EE. Serum selenium and plasma malondialdehyde levels and antioxidant enzyme activities in patients with obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(1):62-65. [CrossRef]
10. Fındıklı E, Camkurt MA, İzci F, et al. The diagnostic value of malondialdehyde, superoxide dismutase and catalase activity in drug naïve, first episode, non-smoker generalized anxiety disorder patients. *Clin Psychopharmacol Neurosci*. 2018;16(1):88-94. [CrossRef]
11. Shrivastava A, Kar SK, Sharma E, Mahdi AA, Dalal PK. A study of oxidative stress biomarkers in obsessive compulsive disorder. *J Obsessive Compuls Relat Disord*. 2017;15:52-56. [CrossRef]
12. Landry WD, Cotter TG. ROS signalling, NADPH oxidases and cancer. *Biochem Soc Trans*. 2014;42(4):934-938. [CrossRef]
13. Sorce S, Krause KH. NOX enzymes in the central nervous system: From signaling to disease. *Antioxid Redox Signal*. 2009;11(10):2481-2504. [CrossRef]
14. Belarbi K, Cuvelier E, Destée A, Gressier B, Chartier-Harlin MC. NADPH oxidases in Parkinson's disease: a systematic review. *Mol Neurodegener*. 2017;12(1):84. [CrossRef]
15. Muñoz M, López-Oliva ME, Rodríguez C, et al. Differential contribution of Nox1, Nox2 and Nox4 to kidney vascular oxidative stress and endothelial dysfunction in obesity. *Redox Biol*. 2020;28:101330. [CrossRef]
16. Avci V, Ayengin K, Alp HH. Oxidative DNA damage and NOX4 levels in children with undescended testes. *Eur J Pediatr Surg*. 2019;29(6):545-550. [CrossRef]
17. Hernandes MS, Britto LR. LNADPH oxidase and neurodegeneration. *Curr Neuropharmacol*. 2012;10(4): 321-327. [CrossRef]
18. Liu F, Havens J, Yu Q, et al. The link between angiotensin II-mediated anxiety and mood disorders with NADPH oxidase-induced oxidative stress. *Int J Physiol Pathophysiol Pharmacol*. 2012;4(1):28-35.
19. Nadeem A, Ahmad SF, Bakheet SA, et al. Toll-like receptor 4 signaling is associated with upregulated NADPH oxidase expression in peripheral T cells of children with autism. *Brain Behav Immun*. 2017;61:146-154. [CrossRef]
20. Jiménez-Fernández S, Gurpegui M, Díaz-Atienza F, Pérez-Costillas L, Gerstenberg M, Correll CU. Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: results from a meta-analysis. *J Clin Psychiatry*. 2015;76(12):1658-1667. [CrossRef]
21. Panday A, Sahoo MK, Osorio D, Batra S. NADPH oxidases: an overview from structure to innate immunity-associated pathologies. *Cell Mol Immunol*. 2015;12(1): 5-23. [CrossRef]
22. Loffredo L, Spalice A, Salvatori F, et al. Oxidative stress and gut-derived lipopolysaccharides in children affected by paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *BMC Pediatr*. 2020;20(1):127. [CrossRef]
23. Chang CC, Lee CT, Lan TH, Ju PC, Hsieh YH, Lai TJ. Effects of antidepressant treatment on total antioxidant capacity and free radical levels in patients with major depressive disorder. *Psychiatry Res*. 2015;230(2):575-580. [CrossRef]
24. Pompili M, Serafini G, Innamorati M, et al. Agomelatine, a novel intriguing antidepressant option enhancing neuroplasticity: a critical review. *World J Biol Psychiatry*. 2013;14(6):412-431. [CrossRef]
25. Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther*. 2016;41(2):214-219. [CrossRef]
26. Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BWJH. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. *Psychoneur oendocrinology*. 2015;51:164-175. [CrossRef]
27. Privitera AP, Distefano R, Wefer HA, Ferro A, Pulvirenti A, Giugno R. OCDB: a database collecting genes, miRNAs and drugs for obsessive-compulsive disorder. *Database (Oxford)*. 2015;2015:bav069. [CrossRef]
28. Haddad JJ, Saadé NE, Safieh-Garabedian B. Cytokines and neuro-immune-endocrine interactions: a role for the hypothalamic-pituitary-adrenal revolving axis. *J Neuroimmunol*. 2002;133(1-2):1-19. [CrossRef]
29. Terawaki H, Terada T, Ogura M, Era S, Hosoya T. The elevation of oxidative stress after the great East Japan earthquake. *Clin Exp Nephrol*. 2012;16(5):816-817. [CrossRef]
30. Gerentes M, Pelissolo A, Rajagopal K, Tamouza R, Hamdani N. Obsessive-compulsive disorder: autoimmunity and neuroinflammation. *Curr Psychiatry Rep*. 2019; 21(8):78. [CrossRef]
31. Hazari N, Narayanaswamy JC, Venkatasubramanian G. Neuroimaging findings in obsessive-compulsive disorder: a narrative review to elucidate neurobiological underpinnings. *Indian J Psychiatry*. 2019;61(Suppl 1):S9-S29. [CrossRef]
32. Şimşek Ş, Gençoğlan S, Yüksel T. DNA damage and antioxidants in treatment naïve children with obsessive-compulsive disorder. *Psychiatry Res*. 2016;237:133-137. [CrossRef]