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Childhood depression and oxidative stress

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Abstract

Background: Oxidative stress is a contributing factor in the etiopathogenesis of major depressive disorder (MDD). Pediatric studies regarding MDD-oxidative stress relationship are insufficient. In this study, we aimed to compare oxidative stress parameters of pediatric MDD patients with those of the control group and to examine factors affecting these parameters.

Results: Total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), malondialdehyde (MDA) and superoxide dismutase (SOD) activities of 42 patients with MDD and 38 healthy controls were evaluated. Children depression inventory (CDI) was applied to all participants. In the MDD group, serum levels of TOS, OSI and MDA were higher, while TAS and SOD levels were lower ($p < 0.001$). When all participants were examined, oxidative stress increased as the CDI score increased, but in the MDD group, SOD increased as the CDI score increased. Increase in body mass index (BMI) percentile increased the oxidative stress in the MDD group. When factors affecting the presence of MDD were analyzed by binary logistic regression analysis, a one-unit increase in SOD decreased depression by 0.190 times.

Conclusions: This study showed that oxidative stress increases in children and adolescents with MDD, and the increase in the severity of depression further increases oxidative stress, but when the depression becomes very severe, level of SOD increases compensatorily. It has been observed that high BMI in MDD patients creates an additional burden on oxidative stress. The role of oxidative stress in the etiopathogenesis of MDD in children and adolescents should be evaluated more comprehensively.

Keywords: Child psychiatry, Biomarkers, Oxidative stress, Depression

Background

Major depressive disorder (MDD) is a chronic, recurrent psychiatric disorder with a high mortality rate and a lifetime prevalence of 3.6–8.5% [1, 2]. Along with environmental and genetic factors, irregularities between neurotransmitters and neuroendocrine dysregulation are important in its etiology [3]. It is known that oxidative stress is also effective in the pathophysiology of MDD [4]. Under physiological conditions, there is a balance between oxidative and antioxidative systems in the organism. Disruption of this balance causes many neuropsychiatric diseases, including MDD. Oxidative stress negatively affects neuronal signal transmission, cellular flexibility and neuronal plasticity, and causes disruptions in critical brain circuits that regulate temperament and motor behavior. These factors are thought to be involved in the development of symptoms related to depression [5, 6].

It has been shown that oxidation metabolites are high and antioxidation metabolite levels are low in adults with MDD [7]. In patients with depressive episodes, total oxidant status (TOS) and oxidative stress index (OSI) were found to be high, while the total antioxidant status (TAS) levels were low [8]. Malondialdehyde (MDA), one of the lipid peroxidation products, has been investigated as an index of oxidative damage in adult MDD [9]. Levels of superoxide dismutase (SOD), one of the antioxidant defense system enzymes, were shown to be low in adults with MDD [10]. Adolescents with unipolar depression

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were reported to have higher TOS, OSI, and MDA values, and lower TAS than their healthy peers [11].

The recurrent nature of MDD and its consequences that may lead to suicide in adolescents show the necessity of early detection of this disease and importance of monitoring the treatment response. Therefore, we need biomarkers that may be predictors for MDD. There are very few studies investigating oxidative stress parameters in pediatric and adolescent MDD patients. In this study, our primary aim was to compare the oxidative stress parameters of children and adolescents with MDD with those of healthy children. Our secondary aim was to determine the relationship between oxidative stress parameters and clinical variables such as gender, height, weight, body mass index (BMI), blood pressure, and depressive symptom severity.

Methods

The study was designed as a case–control study and conducted at outpatient clinic of Department of Child and Adolescent Psychiatry at Yozgat Bozok University, Faculty of Medicine. All study procedures were performed in accordance with the Declaration of Helsinki. The participation was voluntary. Participants and their parents were informed about the study and parents gave written informed consent. We also sought consent from children and adolescents participating in the study. The university's Medical Ethics Board of Medical School approved the study (Approval number: 2017-KAEK-189_2021.03.10_07).

The study included 42 children and adolescents that were diagnosed with MDD according to the diagnostic criteria of DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th Edition) [12]. A detailed DSM-5-based psychiatric diagnosis interview was conducted by a child and adolescent psychiatrist to screen for comorbid psychiatric diagnoses in the patient group and to exclude presence of any psychiatric diagnosis in the control group. Those with comorbid psychiatric diagnoses other than MDD, those who use psychotropic drugs, and those with chronic systemic diseases were excluded from the study. Any medical or psychiatric illness and drug use were also exclusion criteria for the control group. All participants' medical disorders were evaluated using family anamnesis, imaging reports, if any, and epicrisis records. Three patients with subthreshold depressive symptoms were excluded from the study. Seven patients with generalized anxiety disorder and attention deficit hyperactivity disorder and 5 patients who did not want to give blood samples were excluded from the study. A total of 42 patients participated in the study. All 38 participants in the control group participated in the study voluntarily and willingly. The control group consisted of children who came to the general pediatric outpatient clinic for routine check-up.

The Children's Depression Inventory (CDI) was used to assess the severity of depressive symptoms in all participants. CDI is a self-report depression scale modeled after Adult Beck Depression Inventory [13], which is used to assess depressive symptoms. Twenty-seven multiple-choice items evaluate the severity of depressive symptoms during the previous 2 weeks. The scale is widely used and has demonstrated good concurrent validity and reliability in Turkish children and adolescents (applicable to children aged 7–17) [14]. The scale is scored between 0–2 with the maximum score of 54. High score indicates the severity of the depression level. The cut-off value for Turkish patients was 19 [14]. BMI was evaluated according to height and weight, and the BMI percentiles of all the participants were within the normal range for age according to World Health Organization parameters (https://www.who.int/growthref/who2007_bmi_for_age/en/, accessed on September 09, 2018). Blood pressure was measured for each participant.

Following a 12-h overnight fast, 3–5 ml venous blood was drawn and transferred into a biochemistry tube. The sera were separated with centrifugation at 4000 rpm for 10 min. All samples were stored at − 80 °C until analysis. Serum TAS and TOS were determined with commercial kits (Rel Assay Diagnostics kit; Mega Tıp, Gaziantep, Turkey) developed by Erel and OSI values were calculated. Serum TAS was measured by generation of 2,2′-azino-di-3-ethylbenzthiazoline sulphonate radical cation using the commercial kit according to the manufacturer's manual. TOS was measured as described by the manufacturer's protocol. In this method, the oxidants present in the sample oxidized the ferrous ion–*o*-dianisidine complex to ferric ion. Ferric ion produces a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide and the results were expressed in terms of μmol H_2O_2 equivalent/L of serum. The TOS:TAS ratio was used as the OSI, and was calculated as follows: OSI (arbitrary units) = [(TOS, μmol H_2O_2/L)/(TAS, mmol Trolox equiv./L)]. Total SOD activity was determined using the SOD Activity Assay kit (Rel Assay Diagnostics kit; Mega Tıp, Gaziantep, Turkey), according to the manufacturer's instructions. MDA levels were measured using a colorimetric kit (Cayman Chemical, MI, USA).

Statistical analyses were performed with SPSS version 25.0 program 2017 software package for Windows (SPSS Inc., Chicago, IL, USA). The conformity of the variables to normal distribution was examined by histogram graphics and the Kolmogorov–Smirnov test. Mean,

standard deviation, and median values were used when presenting descriptive analyses. Categorical variables were compared with the Pearson Chi-square test. The Mann–Whitney *U* test was used when evaluating non-normally distributed (nonparametric) variables between two groups. Spearman correlation test was used in the analysis of the measurement data with each other. In diagnosing depression, cut-offs of CDI, MDA, SOD, TAS, TOS, and OSI values were determined with the help of receiver operating characteristics (ROC) analysis. Linear regression analysis was used while examining the factors affecting CDI, MDA, SOD, TAS, TOS and OSI values. Binary logistic regression analysis was utilized when determining the factors affecting the presence of MDD diagnosis. Cases where the p value was below 0.05 were considered as statistically significant results.

Results

While CDI, MDA, TOS and OSI values were significantly higher in the MDD group compared to the control group ($p<0.001$); weight percentile, SOD and TAS values were lower ($p=0.042$ for weight percentile; $p<0.001$ for SOD and TAS). There was no significant difference between the two groups in terms of age, gender, height, BMI percentile and blood pressure ($p=0.276$, $p=0.430$, $p=0.305$, $p=0.168$, $p=0.808$, $p=0.531$, respectively) (Table 1).

The ability of SOD, TAS, TOS, and OSI values to predict the diagnosis of MDD was examined and cut-off values for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) rates were determined (Table 2). Increased CDI score, TOS, OSI and MDA values and decreased TAS and SOD values were found to be strong predictive biomarkers for diagnosing MDD (Fig. 1). In total, MDA, SOD, TAS, TOS, OSI values were compared in terms of gender in both groups, and it was determined that in the control group, male patients' SOD values were higher than those of the female patients. In the MDD group, no significant difference was found in terms of oxidative stress parameters (Table 3).

Factors affecting total MDA, SOD, TAS, TOS and OSI values were examined. Accordingly, one standard deviation (SD) increase in the CDI score increased the MDA SD value by 0.358. One SD increase in the CDI score decreased the SOD by 0.524 SDs. One SD increase in the diastolic blood pressure (DBP) increased the TAS value by 0.298 SD, while one SD increase in the CDI score decreased TAS by 0.441 SDs. One SD increase in the CDI increased the TOS value by 0.450 SDs and the OSI value by 0.569 SDs (Table 4).

The correlation between CDI score and other measured values in all participants was examined and it was seen that there was a direct correlation between CDI

Table 1 Comparison of MDD and control groups in terms of clinical variables and oxidative stress parameters

	MDD						p^1
	Absent (Control)			Present (MDD)			
	Mean	S.D	Median	Mean	S.D	Median	
Gender							
Male	14	(36.84)		12	(28.57)		0.430[2]
Female	24	(63.16)		30	(71.43)		
Age	14.42	±2.99	15.00	15.48	±1.58	16.00	0.276
Weight percentile	64.08	±32.17	75.00	49.12	±31.97	50.00	**0.042**
Height percentile	62.58	±33.52	75.00	58.52	±26.82	50.00	0.305
BMI percentile	60.21	±30.40	50.00	50.90	±33.12	50.00	0.168
Systolic blood pressure	105.39	±13.07	100.00	103.69	±9.04	100.00	0.808
Diastolic blood pressure	65.39	±7.20	60.00	64.76	±8.04	60.00	0.531
CDI	10.66	±4.58	11.00	27.95	±7.16	27.00	**<0.001**
MDA	0.29	±0.03	0.28	0.33	±0.04	0.32	**<0.001**
SOD	18.29	±1.02	18.57	16.18	±1.03	16.34	**<0.001**
TAS	0.71	±0.07	0.70	0.62	±0.10	0.61	**<0.001**
TOS	7.58	±0.86	7.38	9.94	±1.86	9.63	**<0.001**
OSI	1.07	±0.11	1.08	1.64	±0.36	1.62	**<0.001**

Bold indicates p-value ≤ 0.05 is statistically significant

MDD major depressive disorder, *BMI* body mass index, *CDI* children depression inventory, *MDA* malondialdehyde, *SOD* superoxide dismutase, *TAS* total antioxidant status, *TOS* total oxidant status, *OSI* oxidative stress index

[1] Mann–Whitney *U* test

[2] Chi-square test

Table 2 Cut-off values of CDI, MDA, SOD, TAS, TOS, OSI and sensitivity, specificity, PPV and NPV rates in diagnosing MDD

	AUC	Std. error	*p*	95% confidence interval		Cut-off	Sensitivity	Specificity	PPV	NPV
				Lower bound	Upper bound					
CDI	0.998	0.002	**< 0.001**	0.994	1.000	> 18.5	(100.00)	(97.37)	(97.67)	(100.00)
MDA	0.832	0.049	**< 0.001**	0.735	0.928	> 0.285	(92.86)	(68.42)	(76.47)	(89.66)
SOD	0.930	0.029	**< 0.001**	0.872	0.987	< 17.66	(95.24)	(78.95)	(83.33)	(93.75)
TAS	0.769	0.054	**< 0.001**	0.664	0.875	< 0.635	(59.52)	(89.47)	(86.21)	(66.67)
TOS	0.921	0.029	**< 0.001**	0.863	0.978	> 8.235	(83.33)	(86.84)	(87.50)	(82.50)
OSI	0.958	0.019	**< 0.001**	0.920	0.995	> 1.30	(80.95)	(100.00)	(100.00)	(82.61)

Bold indicates *p*-value ≤ 0.05 is statistically significant

ROC analysis

CDI children depression inventory, *MDA* malondialdehyde, *SOD* superoxide dismutase, *TAS* total antioxidant status, *TOS* total oxidant status, *OSI* oxidative stress index, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under curve

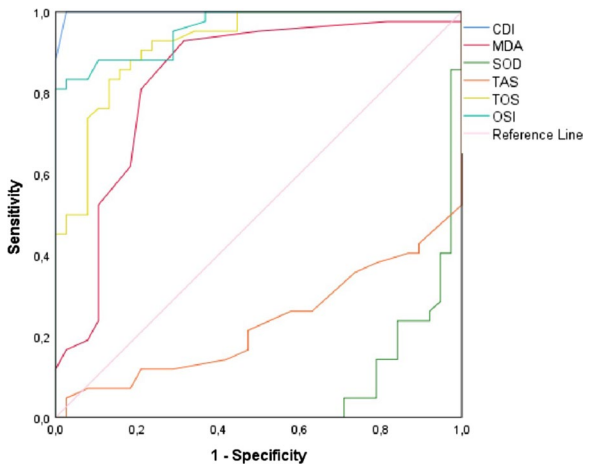

Fig. 1 Receiver operating characteristic (ROC) curve analysis to predict serum oxidative stress biomarkers for diagnosing MDD

score and age, MDA, TOS and OSI, and an inverse correlation between CDI score and weight percentile, SOD and TAS. In the control group, there was a direct correlation between CDI score, age, and diastolic blood pressure. In the MDD group, there was a direct correlation between CDI score, height percentile and SOD (Table 5).

The factors affecting MDA, SOD, TAS, TOS and OSI values in the MDD group were examined. Accordingly, one SD increase in BMI percentile value increased the MDA value by 0.341 SDs. One SD increase in age decreased the TAS value by 0.326 SDs, while one SD increase in DBP increased the TAS value by 0.384 SDs. One SD increase in the BMI percentile increased the TOS value by 0.397 SDs, while one SD increase in the DBP increased TOS value by 0.315 SDs. Moreover, one SD increase in BMI percentile increased the OSI value by 0.392 SDs (Table 6).

The factors affecting the presence of MDD were examined and it was observed that a one-unit increase in the SOD value leads to 0.190 time reduction in depression (Table 7).

Discussion

In our study, the levels of oxidative stress parameters such as TOS, OSI and MDA were high enough to be predictive for MDD in children and adolescents. We also found that levels of antioxidant parameters such as SOD and TAS were low. We did not find a significant difference in oxidative stress parameters between males and females with MDD. In addition, based on all participants, we found that oxidative stress increased as the severity of depressive symptoms increased. In the MDD group, the increase in severity of depression was correlated with the increase in SOD enzyme activity. We also found that in the MDD group, oxidative stress increased as the BMI increased. We did not find any relationship between BMI and oxidative stress in the control group. On examining the factors affecting the presence of MDD diagnosis, we found that high SOD enzyme activity significantly reduced depression.

Similar to our study, some studies have shown that in MDD, oxidative stress parameters increase and in severe depressive symptoms antioxidant capacity decreases [4]. In a study conducted with adolescents with unipolar depression, TOS, OSI and MDA values were higher while the TAS values were lower compared to their healthy peers [11]. However, in a study comparing TAS levels and cognitive functions in patients with recurrent depression and healthy controls, it was shown that high TAS levels were associated with depression severity both before and after treatment and reflected cognitive deterioration [15]. However, it has been shown that antidepressant treatments can mediate the improvement of antioxidant function and reduce oxidative stress [16]. In our study, all MDD patients were patients with first episode unipolar

Table 3 Comparison of oxidative stress parameters of MDD and control groups in terms of gender

	Total						*p*	Control						*p*	MDD						*p*
	Male			Female				Male			Female				Male			Female			
	Mean	SD	Median	Mean	SD	Median		Mean	SD	Median	Mean	SD	Median		Mean	SD	Median	Mean	SD	Median	
MDA	0.31	±0.04	0.30	0.31	±0.04	0.30	0.922	0.29	±0.03	0.28	0.28	±0.03	0.28	0.853	0.33	±0.03	0.34	0.32	±0.05	0.32	0.341
SOD	17.52	±1.65	17.99	17.02	±1.37	16.77	0.081	18.69	±0.72	18.81	18.06	±1.11	18.40	**0.022**	16.15	±1.33	16.18	16.19	±0.91	16.34	0.989
TAS	0.67	±0.09	0.68	0.66	±0.11	0.68	0.738	0.71	±0.06	0.71	0.71	±0.07	0.70	0.891	0.62	±0.09	0.61	0.62	±0.11	0.60	0.749
TOS	8.90	±2.38	7.93	8.78	±1.61	8.40	0.498	7.41	±0.56	7.46	7.68	±0.99	7.36	0.515	10.63	±2.53	9.81	9.66	±1.48	9.63	0.351
OSI	1.36	±0.43	1.19	1.37	±0.38	1.21	0.648	1.06	±0.13	1.08	1.08	±0.09	1.07	0.660	1.72	±0.39	1.59	1.61	±0.35	1.65	0.568

Bold indicates *p*-value $\leq$ 0.05 is statistically significant

MDA malondialdehyde, *SOD* superoxide dismutase, *TAS* total antioxidant status, *TOS* total oxidant status, *OSI* oxidative stress index

Mann–Whitney *U* test

Table 4 Investigation of factors affecting oxidative stress parameters in all participants

Dependent	Independent	Unstandardized coefficients		Standardized coefficients	*t*	Sig	95.0% confidence interval for *B*	
		B	Std. error	Beta			Lower bound	Upper bound
MDA	(Constant)	0.279	0.009		29.411	< 0.001	0.260	0.297
	CDI	0.001	0.000	0.358	3.384	**0.001**	0.001	0.002
SOD	(Constant)	18.618	0.300		62.001	< 0.001	18.020	19.216
	CDI	− 0.073	0.013	− 0.524	− 5.427	**< 0.001**	− 0.100	− 0.046
TAS	(Constant)	0.491	0.084		5.816	< 0.001	0.323	0.659
	Diastolic blood pressure	0.004	0.001	0.298	3.009	**0.004**	0.001	0.006
	CDI	− 0.004	0.001	− 0.441	− 4.458	**< 0.001**	− 0.006	− 0.002
TOS	(Constant)	7.241	0.402		18.021	< 0.001	6.441	8.041
	CDI	0.080	0.018	0.450	4.450	**< 0.001**	0.044	0.116
OSI	(Constant)	0.952	0.078		12.279	< 0.001	0.798	1.107
	CDI	0.021	0.003	0.569	6.106	**< 0.001**	0.014	0.028

Bold indicates *p*-value ≤ 0.05 is statistically significant

Linear regression analysis

CDI children depression inventory, *MDA* malondialdehyde, *SOD* superoxide dismutase, *TAS* total antioxidant status, *TOS* total oxidant status, *OSI* oxidative stress index

Table 5 Correlation between CDI score, clinical variables, and oxidative stress parameters in all participants

	CDI score (Total)		CDI score (Depression present)		CDI score (Depression absent)	
	r	*p*	*r*	*p*	*r*	*p*
Age	0.326	**0.003**	0.729	**< 0.001**	0.168	0.287
Weight percentile	− 0.226	**0.044**	0.037	0.824	− 0.147	0.354
Height percentile	0.026	0.816	0.177	0.287	0.323	**0.037**
BMI percentile	− 0.205	0.068	− 0.036	0.831	− 0.232	0.139
Systolic blood pressure	0.089	0.431	0.161	0.333	0.282	0.070
Diastolic blood pressure	0.093	0.410	0.405	**0.012**	0.230	0.143
MDA	0.486	**< 0.001**	0.062	0.712	− 0.112	0.481
SOD	− 0.586	**< 0.001**	− 0.072	0.666	0.338	**0.029**
TAS	− 0.398	**< 0.001**	0.146	0.383	− 0.153	0.335
TOS	0.633	**< 0.001**	0.073	0.661	− 0.117	0.460
OSI	0.674	**< 0.001**	− 0.029	0.864	− 0.022	0.888

Bold indicates *p*-value ≤ 0.05 is statistically significant

Spearman correlation test

BMI body mass index, *CDI* children depression inventory, *MDA* malondialdehyde, *SOD* superoxide dismutase, *TAS* total antioxidant status, *TOS* total oxidant status, *OSI* oxidative stress index

depression and did not use any psychotropic drugs. Therefore, we could not evaluate the effect of drug therapy on oxidative stress.

We did not find any significant relationship between MDD patients and oxidative stress parameters in terms of genders. Estrogen is known to be a neuroprotective agent with antioxidant properties that limit the disruption of the blood–brain barrier [17]. However, similar to our findings, Wiener et colleagues showed that despite the antioxidant properties of female sex hormones, TOS and OSI values were higher in depressed women, just as in depressed men. This has been explained by the view that increased oxidative stress in MDD patients negatively affects the integrity of the blood–brain barrier, rendering estrogen's protection ineffective [18, 19].

In our control group, the SOD level of males was significantly higher than that of the females. It is suggested that SOD activity, which is one of the antioxidant defense system enzymes, decreases with age [20]. While the mean age of the females in the control group was 13.54, it was

Table 6 Investigation of factors affecting oxidative stress parameters in MDD group

Dependent	Independent	Unstandardized coefficients		Standardized coefficients	*t*	Sig	95,0% confidence interval for *B*	
		B	Std. error	Beta			Lower bound	Upper bound
MDA	(Constant)	0.304	0.012		26.396	< 0.001	0.281	0.328
	BMI percentile	0.000	0.000	0.341	2.296	**0.027**	0.000	0.001
SOD	(Constant)	15.057	0.630		23.900	< 0.001	13.783	16.330
	CDI	0.040	0.022	0.278	1.833	0.074	− 0.004	0.084
TAS	(Constant)	0.628	0.185		3.400	0.002	0.254	1.001
	Age	− 0.021	0.009	− 0.326	− 2.368	**0.023**	− 0.040	− 0.003
	DBP	0.005	0.002	0.384	2.788	**0.008**	0.001	0.009
TOS	(Constant)	4.091	2.067		1.979	0.055	− 0.090	8.273
	BMI percentile	0.022	0.008	0.397	2.902	**0.006**	0.007	0.038
	DBP	0.073	0.032	0.315	2.305	**0.027**	0.009	0.137
OSI	(Constant)	1.421	0.097		14.717	< 0.001	1.226	1.616
	BMI percentile	0.004	0.002	0.392	2.695	**0.010**	0.001	0.008

Bold indicates *p*-value ≤ 0.05 is statistically significant

Linear Regression Analysis

BMI body mass index, *CDI* children depression inventory, *MDA* malondialdehyde, *SOD* superoxide dismutase, *TAS* total antioxidant status, *TOS* total oxidant status, *OSI* oxidative stress index, *DBP* diastolic blood pressure

Table 7 Factors affecting the presence of MDD

	B	S.E	*p*	Exp (Bg)	95% C.I. for Exp (*B*)	
					Lower bound	Upper bound
SOD	− 1.660	0.380	**< 0.001**	0.190	0.090	0.400
TAS	− 7.262	4.355	0.095	0.001	0.001	3.577
Constant	33.610	6.937	< 0.001	3.952E+14		

Bold indicates *p*-value ≤ 0.05 is statistically significant

Binary Logistic Regression

SOD superoxide dismutase, *TAS* total antioxidant status

10.30 for males. We think that the higher mean age of the females may have affected the results.

When all participants were taken into account, we found that the CDI score increased in correlation with oxidative stress. While TOS, OSI and MDA were correlated in the same direction with the CDI score; TAS and SOD were negatively correlated. However, in the MDD group, CDI score and SOD were directly correlated. Some studies have shown that there is a decrease in antioxidant status in severe depressive symptoms [4]. In a study evaluating the severity of depressive symptoms with the CDI, depressed children had a significant decrease in the severity of depression after 3-month (2.4 g/day) treatment with an antioxidant omega-3 fatty acid [21]. However, in a study evaluating antioxidant capacity by performing glutathione (GSH) analysis with MRI spectroscopy, it was shown that the GSH level in adolescent patients with depression was significantly lower than in controls, but this was not associated with the severity of depression [22]. Another study has shown a significant positive correlation between the severity of depression and serum TOS and OSI, and a negative correlation with TAS [16]. The mean CDI score of all participants in our study was 19.30. The mean CDI score of the MDD group was 27.95. We can conclude that SOD enzyme activity is low in mild depression, but increases as the severity of depression increases in order to compensate the response of balancing the oxidative stress. As a matter of fact, it has been shown that SOD is the first-step enzyme in response to superoxide radical formation, and some studies have shown that the level of SOD increases in order to suppress the increased oxidative stress in MDD patients. In a study in which MDD patients were evaluated with the Hamilton Depression

Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS), SOD enzyme activity showed a positive correlation with HDRS and HARS scores, as was the case with the CDI score in our study [15]. At the same time, it was thought that in recurrent depression, high TAS levels both before and after treatment was associated with the severity of depression, and this situation could also be associated with SOD levels, since SOD is the main component of TAS [15]. A meta-analysis of 17 studies evaluating many of the lipid peroxidation markers, such as MDA, concluded that these markers are both high in depression and are associated with the severity of depression [23].

When we examined the relationship between BMI and oxidative stress in our study, we found that oxidative stress increased as BMI increased in the MDD group, but there was no such relationship in the control group. Increased oxygen consumption due to mechanical load and increased myocardial metabolism in obesity leads to an increase in mitochondrial respiration-induced superoxide, hydroxyl radical and hydrogen peroxide formation, thereby stimulating oxidative stress. Therefore, biomarkers showing oxidative damage were found to be higher in people with high body fat and BMI [24, 25]. However, in our study, we found that BMI was not associated with oxidative stress in healthy children, but was related in the MDD group, suggesting that weight gain in depressed individuals may be considered a more negative profile than weight gain in healthy individuals. Similarly, several studies have shown that weight loss has positive effects on improving depression [26, 27]. However, it is known that depression causes an increase in oxidized lipid levels by stimulating inflammatory pathways. Another hypothesis that may explain why depression causes lipid peroxidation is that depressed people are more prone to behaviors such as smoking, alcohol use or a sedentary lifestyle, which in turn increases oxidative stress [28]. Therefore, high BMI may have more devastating effects in individuals with MDD than in healthy individuals.

When the factors affecting the presence of MDD diagnosis were examined by binary logistic regression analysis, increase in SOD enzyme activity significantly reduced depression. In a study by Herken et colleagues, it was reported that SOD enzyme activities of patients with MDD were significantly lower at the time of the diagnosis compared to healthy controls, and there was a remarkable increase in SOD activities after 8 weeks of antidepressant treatment. It has even been suggested that SOD may play a role in the pathophysiology of MDD, predict the prognosis of MDD, and can be used as a biomarker in monitoring response to treatment [29]. Although low SOD enzyme activity level is an important indicator in diagnosing MDD and following treatment, if the severity of depression exceeds a certain threshold in MDD patients, it is possible that SOD enzyme activity will increase with a compensatory mechanism to suppress the increased oxidative stress.

There are many endogenous and exogenous factors affecting the oxidant–antioxidant balance in the organism. Diet, exercise, smoking, and sedentary/active life affect oxidative stress [30, 31]. Although we evaluated factors such as age, gender, BMI, blood pressure, and medication use, the fact that we did not question the above factors is a limitation of our study. In addition to the small sample size, other limitations are that we did not re-evaluate the patients who were started on drug therapy after the initial diagnosis in terms of oxidative stress parameters. Since drug-naive MDD patients were included in this study, the effect of drugs on oxidative stress was excluded. Seeing the effect of drug therapy on oxidative stress would have contributed significantly to the literature. Despite these limitations, this study is important because it evaluates oxidative stress in children and adolescents with MDD along with clinical variables such as BMI, height, weight, and blood pressure.

Conclusions

As a result, we concluded that oxidative stress is increased, while antioxidant capacity is decreased in children and adolescents with MDD. Moreover, high depressive symptom severity may increase oxidative stress even more, but SOD enzyme activity may increase compensatorily after a certain depressive symptom threshold is reached. We found that high BMI in MDD patients creates an additional burden on oxidative stress. In the light of these results, we can say that people with depression should be more sensitive in the fight against obesity. There is a need for larger-scale long-term studies in which areas such as the duration of depressive episodes, its recurrent nature, severity, treatment course and resistance to treatment are evaluated in more detail.

Abbreviations

MDD: Major depressive disorder; TOS: Total oxidant status; TAS: Total antioxidant status; OSI: Oxidative stress index; MDA: Malondialdehyde; SOD: Superoxide dismutase; CDI: Children depression inventory.

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Author contributions

DYM prepared the main idea, and was the main supervisor on editing the manuscript. DYM and AYG prepared the collected samples, questionnaire's data, analyzed and interpreted the patient data regarding the clinical data and psychometric tools and was a major contributor in writing the manuscript. AYG was the major contributor in interpreting labs data. All authors read and approved the final manuscript.

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Availability of data and materials
The data set of this work is available.

Declarations

Ethics approval and consent to participate
The university's Medical Ethics Board of Medical School approved the study (Approval number: 2017-KAEK-189_2021.03.10_07).
Contents of consent were clarified prior to participation. Informed written consent was obtained from all patients for participation and publication of this study.

Consent for publication
Not applicable.

Competing interests
There were no financial or non-financial conflict of interest.

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