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- **Title:** The Effect of Drug Use, Body Mass Index and Blood Pressure on Oxidative Stress Levels in Children and Adolescents with Attention Deficit and Hyperactivity Disorder
- **Running Title:** Oxidative Stress, Attention Deficit and Hyperactivity Disorder
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- **KeyWords:** Attention deficit hyperactivity disorder, Oxidative stress, Total oxidant status, Total antioxidant status, Malondialdehyde, Superoxide dismutase

## ABSTRACT

**Objective:** The aim of this study was to determine the correlation between clinical variables such as body mass index, blood pressure, drug use and oxidative stress level in children and adolescents with attention deficit and hyperactivity disorder (ADHD).

**Methods:** Total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), malondialdehyde (MDA) and superoxide dismutase (SOD) activity were measured in the serum of 51 patients (38 male, 13 female) diagnosed with ADHD according to DSM-5 diagnostic criteria and 32 control subjects (12 male, 20 female). The Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version was applied to all participants.

**Results:** The mean TOS, OSI, MDA values were determined to be significantly higher ( $p < 0.001$ ) and the mean SOD value was lower in the ADHD group ( $p < 0.001$ ). Multivariate regression analysis indicated significantly lower SOD and diastolic blood pressure values and significantly higher MDA in the ADHD group compared to the control group ( $p < 0.01$ ). Low SOD (sensitivity 90.2%, specificity 78.0%) and high MDA (sensitivity 86.3%, specificity 81.2%) were determined to be predictive parameters for diagnosing ADHD. In univariate analysis, the mean TOS, OSI and SOD values were higher in ADHD patients under medication, while the mean TAS was higher in patients not using medication ( $p < 0.01$ ). Only TOS was significant in multivariate logistic regression analysis ( $p < 0.01$ ).

**Conclusion:** The results of this study demonstrate that impaired oxidative balance may play a role in the etiology of ADHD.

**KEY WORDS:** Attention deficit hyperactivity disorder; Oxidative stress; Total oxidant status; Total antioxidant status; Malondialdehyde; Superoxide dismutase.

## INTRODUCTION

ADHD is the most common neurodevelopmental disorder with an early childhood onset prevalence of 5–10% [1]. It is more common in boys than girls and is associated with symptoms of impulsiveness, difficulty concentrating, and hyperactivity [2]. Although the interaction of various neurobiological factors is thought to play a role in the etiology of ADHD, the mechanisms underlying this disorder are still largely unknown [3]. One of the areas investigated in studies on ADHD etiology is oxidative stress. Free radicals that are produced by the reduction reactions are highly toxic and can cause cell damage or even death by affecting the basic structures of cells [4].

Increase in free radicals such as nitric oxide (NO) and MDA, and a decrease in antioxidant molecules such as glutathione peroxidase and SOD have been observed in many psychiatric diseases such as schizophrenia, bipolar affective disorder, depression, autism spectrum disorders and ADHD. Thus, disturbance in the balance between the production of free radicals and antioxidant defences is involved. It has been hypothesized that the effect of oxidative stress arises from the reaction of oxidants with cell membrane proteins. This may lead to deterioration in neuronal cell membrane structure, which may also affect the neuronal receptors, thus causing deterioration of neuron functions. Disruptions in neuronal cell membranes may cause adverse effects on neurotransmitters, especially norepinephrine and dopamine [5-9]. At the same time, inflammation in the brain occurs as a result of the production of reactive oxygen radicals. Neuroinflammation is known to have a significant role in the pathophysiology of ADHD [10]. Therefore, in the neuroinflammation developing associated with the increase in oxidative stress in ADHD, another pathophysiological hypothesis has emerged between ADHD and oxidative stress [11]. ADHD is a neurodevelopmental disorder, in which genetic and environmental factors together with exposure to toxins play a role in the etiology. Genetic and environmental factors and risk factors in pregnancy may contribute to an increase in oxidative stress in ADHD [12,13]. However, the reports of studies on oxidative stress and ADHD are conflicting and inconsistent.

In adult ADHD patients, TAS, TOS and oxidative stress index (TOS / TAS) have been found to be higher than in the control group, but despite this increase in TAS, the oxidant-antioxidant balance was still disturbed. The increase in TAS level might be related to the attempt to balance the increased oxidative load [14]. The level of MDA, a marker of lipid peroxidation,

has been shown to be high in some studies and low in others in both adult and adolescent ADHD groups [8, 15–18].

One of the most common causes of obesity is nutritional obesity, which increases oxidative stress by leading to lipid peroxidation associated with dietary intake of free fatty acid exceeding the antioxidant capacity [19]. There is a high risk of obesity in individuals with ADHD, and it is assumed that together with obesity, oxidative stress, which plays a role in the etiopathogenesis of ADHD, will increase further [20]. Free oxygen radicals and oxidative stress are also known to increase blood pressure [21]. As a result of the accumulation in the body of the drugs used for several different diseases, free radicals form and oxidative stress increases [22]. Therefore, the aim of this study was to evaluate these parameters that affect oxidative stress.

To the best of our knowledge, there is no study in the literature that has examined the correlation between oxidative stress and BMI, blood pressure, and drug use in children and adolescent ADHD patients. The primary goal of this study was to investigate the relationship between BMI, blood pressure and the oxidant-antioxidant balance in children and adolescents with ADHD, and the secondary goal was to determine the factors affecting oxidative stress parameters.

## METHODS

The study included 51 children (7-18 years), who were diagnosed with ADHD according to the DSM-5 criteria (APA 2013) and semi-structured interviews (via K-SADS-PL-Turkish) and who gave verbal assent with parental written informed consent for participation. Patients were excluded from the study if they had any intellectual disability, autism spectrum disorder, medical comorbidity (with pediatric consultation), or comorbid psychopathology other than oppositional defiant disorder (ODD, via KSADS- PL). The diagnostic phase of the study was based on the Turgay Diagnostic and Statistical Manual of Mental Disorders (4th ed; DSM-IV) and Disruptive Behavior Disorders Rating Scale (T-DSM-IV-S) completed by the parents. The Wechsler Intelligence Scale for Children- Revised (WISC-R) was applied to all the participants to eliminate any patients with intellectual disability. 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/](https://www.who.int/growthref/who2007_bmi_for_age/en/), accessed on September 09, 2018).

Blood pressure was measured for each participant. A control group was formed of 32 mentally and physically healthy children and adolescents **in the age range of 7-18 years**, with similar sociodemographic characteristics. Written informed consent was obtained from the parents or legal guardians of all the participants. The research protocol was approved by the Research Ethics Committee of the University of Yozgat Bozok. All study procedures were conducted in accordance with the principles of the Declaration of Helsinki and local laws and regulations.

### **Instruments**

#### **Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL)-Turkish**

This semi-structured interview was developed by Kaufman et al. [23] to evaluate present and lifetime psychopathology in children and adolescents according to DSM-IV criteria. The reliability and validity study of the Turkish translation was conducted by Gökler et al. [24]. The K-SADS-PL-Turkish version was used in this study for the ADHD diagnoses and to exclude those with comorbid psychopathologies (except ODD).

#### **The Turgay DSM-IV-Based Child and Adolescent Disruptive Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S)**

This scale was developed by Turgay [25] to screen and rate disruptive behavior disorders. A validity and reliability study for the Turkish population was carried out by Ercan et al. [26].

#### **Wechsler Intelligence Scale for Children-Revised Short Form (WISC-R)**

The WISC-R scale measures the intelligence levels of children aged between 6 years and **16 years 11 months 30 days**. It was adapted to Turkish by Uluc et al. [27].

### **Blood collection and preparation**

Following a 12-hour 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.

### **Determination of total antioxidant status (TAS) and total oxidant status (TOS)**

Serum TAS and TOS were determined with commercial kits (Rel Assay Diagnostics kit; Mega Tıp, Gaziantep, Turkey) developed by Erel and Oxidative Stress Index (OSI) values were calculated.

Serum TAS was measured by generation of 2,2'-azino-di-(3-ethylbenzthiazoline sulphonate) (ATBS) 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  $\mu\text{mol H}_2\text{O}_2$  equivalent/L of serum.

#### **Calculation of oxidative stress index (OSI)**

The TOS:TAS ratio was used as the OSI, and was calculated as follows: OSI (arbitrary units) = [(TOS,  $\mu\text{mol H}_2\text{O}_2/\text{L}$ )/(TAS, mmol Trolox equiv./L)].

#### **Determination of superoxide dismutase (SOD) activity**

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.

#### **Determination of malondialdehyde (MDA)**

MDA levels were measured using a colorimetric kit (Cayman Chemical, MI, USA).

#### **Statistical analyses**

Data obtained in the study were analyzed using statistics software. Descriptive tables of the data were formed. The arithmetic means of the variables in the ADHD and control group were compared using the Independent Samples t-test. Non-parametric tests were used in the analysis of variables with non-homogeneous variance. The Chi-square test was applied in the comparisons of frequencies. Correlations between continuous variables were established using Spearman's correlation analysis since the weight percentile (WP), height percentile (HP) and body mass index

percentile (BMI-P) were ordinal data. The effects of systolic blood pressure (SBP), diastolic blood pressure (DBP), TAS, TOS, MDA, SOD markers, the presence of ADHD (dummy) and other variables were analyzed using the linear regression (LR) forward LR model. The presence of ADHD and gender, which are categorical variables, were set as dummy variables in the LR analysis. The factors affecting the probability of being in the ADHD group, being in the ADHD combined type and the probability of using ADHD drugs were analyzed using the binary logistic regression (BLR) forward model. Measurement units of continuous variables included in the BLR analysis were standardized by conversion to a Z score. In the BLR analysis, the goodness of fit was evaluated using the Hosmer and Lemeshow test and the effect size with the Nagelkerke R Square. Before the analysis, the homogeneity of the model was examined. The variables found to be significant in the analyses are shown in the tables.

## RESULTS

The rate of males was 74.5% (n=38) in the ADHD group and 37.5% (n=12) in the control group. The mean age in the control group ( $13.7 \pm 3.26$  years) was higher than in the ADHD group ( $10.1 \pm 2.72$  years). The weight, height, and BMI percentile, SBP and DBP values were also higher in the control group. The mean TAS, TOS, OSI and MDA values were higher, the mean SOD value was lower in the ADHD group compared to the control group. With the exception of TAS, these differences were statistically significant ( $p < 0.001$ ) (Table 1). A significant correlation was found between oxidative stress parameters (TAS, TOS, OSI, MDA and SOD) and age, height percentile, weight percentile, BMI percentile, SBP, and DBP parameters in both the ADHD and control groups (excluding MDA). A weak positive correlation ( $r = 0.424$ ) was found between the MDA values of the control group and DBP ( $p < 0.05$ ).

When the affecting factors were analyzed with BLR by setting ADHD = 1 and control group = 0, the increase in MDA value and the decrease in SOD and DBP values increased the probability of ADHD. In comparison with the control group, MDA was higher and the SOD and DBP values were lower in the ADHD group. These factors were seen to be predictors for ADHD and explained 93.9% of the disease presence (Nagelkerke  $R^2 = 0.939$ ). The factors of age, SBP, WP, HP (borderline insignificant), TOS and OSI, which differed significantly between the ADHD and control groups in the univariate tests, were not included in the table because they were not statistically significant when analyzed with the BLR forward model (Table 2).

The MDA and SOD cut-off values were determined with a receiver operating characteristic (ROC) curve and the area under the curve (AUC) values were 0.915 (0.851-0.960, 95% Confidence Interval [CI]) for SOD and 0.868 (0.777- 0.958, 95% CI) for MDA ( $p < 0.001$ ) (Figure 1-2). When the cut-off value for SOD was  $\leq 17.65$ , sensitivity was 90.2% and specificity was 78.0%. When the cut-off value for MDA was  $\geq 0.295$ , sensitivity was 86.3% and specificity was 81.2%. These two parameters can be used as predictors for the diagnosis of ADHD.

When factors that affect oxidative stress parameters (TAS, TOS, OSI, MDA and SOD) were analyzed with linear regression (Table 3), the decrease of SOD ( $\beta = -0.399$ ) and TOS ( $\beta = -0.320$ ) values (in the order of importance) and the increase of BMI-P ( $\beta = 0.217$ ) value affected TAS. These 3 parameters explained 16.9% ( $\text{Adj.R}^2 = 0.169$ ) of the change in TAS. TOS was affected by the presence of ADHD ( $\beta = 0.400$ ), an increase in MDA ( $\beta = 0.334$ ), and a decrease in TAS ( $\beta = -0.207$ ) (in order of importance). These 3 parameters explained 45.2% ( $\text{Adj.R}^2 = 0.452$ ) of the change in TAS. The increase in MDA ( $\beta = 0.528$ ) only affected the OSI (TOS / TAS) value and explained 27.0% of the change in OSI ( $\text{Adj.R}^2 = 0.270$ ). MDA was affected by presence of ADHD ( $\beta = 0.564$ ), and an increase in TOS ( $\beta = 0.365$ ) and DBP ( $\beta = 0.230$ ) values (in order of importance). These 3 parameters explained 49.5% ( $\text{Adj.R}^2 = 0.495$ ) of the change in MDA. SOD was affected by the presence of ADHD ( $\beta = -0.694$ ) and a decrease in TAS ( $\beta = -0.176$ ). These 2 parameters explained 53.0% ( $\text{Adj.R}^2 = 0.530$ ) of the change in SOD.

In the ADHD group, 41.2 % (21/51) of the patients used medication; 19 used methylphenidate and 2, atomoxetine. gender, age, weight, height and BMI percentile, SBP and DBP values were found to be significantly different according to the drug use status in the ADHD group. The oxidative stress parameters (TAS, SOD, TOS and OSI) were significantly higher in patients who did not use medication. The MDA levels, ADHD disease duration, and ADHD type were not different according to drug usage ( $p > 0.05$ ). The average dose of drug was 24.57 mg / g, and the average duration of use was 18 (median 5) months (Table 4). When the factors found to be significant at  $p < 0.2$  in univariate tests were analyzed with BLR, only the increase in TOS value was found to be significant, while the changes in TAS, MDA and SOD were not significant.

In the ADHD group, 74.5% (38/51) of the patients were combined type ADHD, and the remainder were ADHD-inattentive type (13/51). There were no patients with hyperactive-impulsive type. When the factors affecting the ADHD type were analyzed with the BLR forward

model, only the reduction in age was significant. Younger patients were more likely to be in the ADHD-combined type, and older patients in the ADHD-inattentive type (Table 5). No significant relationship was determined between ADHD types and the parameters of TAS, TOS, OSI, MDA, SOD, height, weight, BMI percentile, SBP, and DBP, included in the BLR analysis forward model.

## DISCUSSION

In this study, the correlation of oxidative stress parameters with BMI, blood pressure, ADHD subtypes, and drug use was investigated in children and adolescents with ADHD. The mean values of oxidative stress parameters (TAS, TOS, OSI and MDA) were higher, while the mean SOD value was lower in the ADHD group compared to the control group (Table 1). The power of determining the presence of ADHD from elevated MDA and low DBP and SOD values was 93.9% (Table 2). High MDA and low SOD were determined as predictive parameters in diagnosing ADHD. In univariate tests, while SOD, TOS and OSI levels were high in drug users, TAS levels were high in patients not using drugs (Table 4). However, only TOS levels were significant in multivariate binary logistic regression ( $p < 0.01$ ) (Table 5).

Although there are inconsistent findings in literature about the relationship between ADHD and oxidative stress, there are studies showing that oxidative stress increases in ADHD, which is consistent with the current study. Güney et al. reported high TAS, TOS, and OSI values in the ADHD group [28]. Even though the TAS (antioxidant parameter) value was not significant in the current study, it was higher than in the control group. Some studies have shown that ADHD patients have higher antioxidant activity than normal [14]. This can be explained by the fact that ADHD patients have normal / high levels of antioxidant production, but as their response to oxidative stress is insufficient, the expected oxidative damage levels are higher [29, 14]. A previous study reported that TOS and OSI were higher and TAS was lower in ADHD patients than in the control group [30]. There are also studies that have reported high TAS, TOS and OSI in adult ADHD patients [14]. However, in those studies, the SOD and MDA parameters were not examined. In the current study, 4 oxidative stress parameters were evaluated together with SBP and DBP using multivariate regression, and the results showed that changes in TOS and TAS were not significant, while the decrease in SOD and DBP and increase in MDA were significant.

An important finding of this study is that according to the ROC analysis, high MDA level and low SOD activity are predictors of ADHD diagnosis in children and adolescents (Figure 1-2).

In parallel with these findings, Joshi et al. reported high lipid peroxidation in children with ADHD and stated that their symptoms improved with antioxidant treatment. In contrast, other studies have reported low MDA levels in children with ADHD [31, 32]. In a study conducted with adult ADHD patients, it was found that the oxidant parameters MDA and nitric oxide (NO) increased, and SOD, which showed antioxidant activity, decreased [15, 33]. While MDA levels have been found to be high in studies conducted with both adult and pediatric ADHD groups at the same time, there are also studies that have reported low MDA. However, it is obvious that MDA, which is the breakdown product of the main chain reactions leading to the oxidation of polyunsaturated fatty acids (PUFAs), is a reliable indicator of oxidative stress [8, 15-18]. Consistent with the current study, there are studies in which SOD activity was low in the ADHD group, as well as studies where there was no significant difference from the control group [33, 34]. Since SOD enzymatic activity is the first and most important defence mechanism against oxidants, the low level in the ADHD group can be considered a strong indicator that oxidative stress may be increased in the ADHD group in the current study [33].

Considering that oxidative stress may be affected not only by the presence of ADHD but also by some possible clinical variables, age, BMI and blood pressure were also evaluated in all participants. It is known that oxidative stress increases with age [35]. It is also known that BMI can be affected by oxidative stress, and DNA damage increases and antioxidant capacity decreases in obese patients [36, 37]. Studies have shown that increased blood pressure is also associated with increased oxidative stress. Rodrigo et al. showed that the increase in blood pressure values was in a linear relationship with decreased antioxidant capacity [38]. Low levels of antioxidants such as glutathione, SOD, and vitamin E have been reported in hypertension [39]. In the current study, although the mean age, weight, height, BMI percentile, SBP and DBP values were lower in the ADHD group, their oxidative stress levels were higher. Thus, even low levels of some clinical variables known to increase oxidative stress (BMI, SBP, DBP and high age) did not reduce oxidative stress in the ADHD group. In conclusion, the presence of ADHD alone was found to be a strong predictor of increases in oxidative stress. However, gender may also have affected the high oxidative stress parameters in the ADHD group, since 74.5% of ADHD children and only 37.5% of the control group were male. Studies have shown that estrogen has an antioxidant role and protects against oxidative stress [40].

The results of this study showed high TOS, OSI and SOD activity in ADHD patients using medication (methylphenidate (n=19) and atomoxetine (n=2)), and high TAS levels in those not using medication (Table 4). In an experimental study, chronic methylphenidate use has been shown to increase oxidative stress. It was also found that methylphenidate dose and duration of drug exposure are also important in increasing oxidative stress [41–43]. In the current study, drug dose and duration were not found to be associated with oxidative stress. In another study, oxidative stress levels were compared in children whose treatment did not include medication at first, but methylphenidate was added later and a significant increase in plasma antioxidant levels and a significant decrease in oxidative stress levels were found in these children after methylphenidate was initiated [28]. Another study found that chronic methylphenidate exposure increased SOD activity, which was consistent with the current study results [44]. It is not surprising that the level of TAS was high in the ADHD patients that did not use medication. Some studies have emphasized that the antioxidant capacity is actually sufficient in ADHD, but there may be an insufficient response to oxidative stress [29, 14, 45]. Another view on this issue is that stimulants can increase dopamine levels that tend to affect both antioxidants and oxidants, and have a paradoxical effect [46, 47]. It has been suggested that methylphenidate transforms into a methylphenidyl radical inside the cell and oxidizes its own microenvironment, while outside the cell (plasma) it gives electrons in the serum without being metabolized due to the electron-rich phenyl ring, thus showing antioxidant activity and creating a neuroprotective effect [44, 41]. In the current study, only 2 of the 21 patients that used drugs were taking atomoxetine. A previous study at the cellular level has shown that atomoxetine may play a protective role against oxidative DNA damage [48]. One of the reasons for higher TOS and OSI in ADHD patients using medication may be due to insufficient use of atomoxetine compared to methylphenidate. Therefore, there is a need for further comprehensive studies with titration of different drugs for treatment of ADHD.

When the relationship between ADHD subtypes and oxidative stress was examined, no significant relationship was found between subtypes and oxidative stress. In some studies, TAS values of the ADHD-inattentive type, combined, and hyperactive-impulsive type have been reported to be higher or lower, and the results are not consistent [14, 30]. Factors such as duration of illness and the age of patients may have affected the results, because in the current study, combined type ADHD was predominant, and the mean age was lower than in the ADHD-inattentive type.

Genetic, environmental and biochemical factors play a role in the etiopathogenesis of ADHD. The number of studies of ADHD involving neuroimaging and genetics has increased in recent years [49, 50]. Although there are conflicting results in the field of ADHD and oxidative stress, ADHD, which is a neurodevelopmental brain disease, can be considered to exacerbate the risk of oxidative stress. ADHD is a disease related to the developing brain. It has been shown that obstetric complications causing damage to the developing brain could be another source of oxidative stress [51]. The fact that children and adolescents with ADHD benefit from antioxidant treatments also supports the idea that oxidative stress increases in ADHD. In a meta-analysis, moderate improvements in ADHD symptoms were seen after treatment with antioxidant omega-3 fatty acids. Increased lipid peroxidation (high MDA) in ADHD patients may be the cause of fatty acid deficiency in these individuals. In addition to the findings of omega-3 fatty acids, N-Acetyl Cysteine (NAC), a precursor and NO inhibitor of glutathione, a potent antioxidant, has been shown to reduce inattention and hyperactivity in ADHD rat models [52,53]. In addition to animal models, NAC and Pycnogenol, which are both antioxidants, have been shown to be effective in the treatment of ADHD in humans [54,55]. In a meta-analysis by Bloch et al, omega-3 fatty acids (especially formulations including Eicosapentaenoic acid at higher doses) were shown to significantly reduce ADHD symptoms in individuals diagnosed with ADHD [56]. The low levels of zinc, which act as cofactors in many antioxidative reactions, and ferritin, which limits the formation of iron free radicals in ADHD, and increased exposure to lead, which increases oxidative stress by consuming glutathione, increases the risk of ADHD [57- 59]. In a brain imaging study, the iron levels in the thalamus of ADHD patients were found to be low [60]. However, rather than iron deficiency of low serum ferritin, this was thought to be a parameter showing oxidative stress in ADHD [61].

The main limitation of this study was the small sample size. Homogeneity could not be achieved between the patient and control groups in respect of clinical variables. The mean age and mean SBP and DBP values of the control group were significantly higher than those of the ADHD group. Venous blood samples were able to be taken as there was a low number of very young children and the older age group are more co-operative and willing to give blood. Another limitation of the study was that there were only two patients using atomoxetine, which was not sufficient to investigate the effects of atomoxetine on oxidative metabolism.

However, this study also had several strengths, including the evaluation of BMI and blood pressure, which are thought to affect oxidative stress parameters, the comparison of variables with those of the healthy control group, the use of K-SADS-PL to exclude patients with psychiatric comorbidities other than ODD, evaluation with WISC-R to exclude intellectual disability, and the exclusion of patients with autism spectrum disorders. Moreover, despite the increasing knowledge about the etiology of ADHD, it is not yet fully known how the drugs used in treatment affect the neurobiology and neuroadaptation process of the disease. The inclusion of patients both using and not using medication is therefore another strong aspect.

In conclusion, the results of this study demonstrated that oxidative stress increased in patients with ADHD. TAS and TOS, which have been shown to be important oxidative parameters in previous studies, were not found to be significantly different as a result of multivariate analysis. The main factors that increase oxidative stress were determined to be high MDA and low SOD levels. Therefore, MDA and SOD levels may be effective biomarkers in diagnosing ADHD. Nevertheless, further comprehensive studies are needed to better understand this negative role of oxidative stress in ADHD.

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### **Conflicts of Interest**

The authors have no potential conflict of interests to declare.

### **Author Contributions**

Conceptualization: Dilşad Yıldız Miniksar, Mehmet Akif Cansız. Data acquisition: Dilşad Yıldız Miniksar, Mehmet Akif Cansız. Supervision: Dilşad Yıldız Miniksar, Ayşe Yeşim Göçmen, Mahmut Kılıç, Ökkeş Hakan Miniksar. Writing—original draft: Dilşad Yıldız Miniksar. Writing—review & editing: Dilşad Yıldız Miniksar, Ökkeş Hakan Miniksar, Mahmut Kılıç & Ayşe Yeşim Göçmen.

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**Table 1.** Mean and standard deviation values of variables in the ADHD group and control group

	ADHD (n=51)			Control (n=32)			<i>P</i>
	Mean	SD	Range	Mean	SD	Range	
Male n, %	38	74.5%		12	37.5%		0.001 <sup>a</sup>
Female n, %	13	25.5%		20	62.5%		
Age (year)	10.08	2.72	7-18	13.69	3.26	7-18	<0.001 <sup>b</sup>
Weight percentile	47.76	33.64	3-97	66.25	32.26	3-97	0.036 <sup>b</sup>
Height percentile	47.94	32.99	3-97	62.22	34.32	3-97	0.062 <sup>b</sup>
BMI percentile	53.00	31.65	3-97	64.00	30.71	3-97	0.123 <sup>b</sup>
SBP (mmHg)	94.80	8.18	80-110	106.09	13.36	80-150	<0.001 <sup>b</sup>
DBP (mmHg)	54.90	5.70	45-70	65.16	7.13	60-85	<0.001 <sup>b</sup>
TAS (μmol Trolox Eq/L)	0.72	0.08	0.57-0.95	0.70	0.06	0.60-0.80	0.303 <sup>b</sup>
TOS (μmol H <sub>2</sub> O <sub>2</sub> Eq/L)	9.23	1.43	7.21-12.77	7.44	0.74	5.96-9.88	<0.001 <sup>c</sup>

OSI (arbitrary unit)	13.10	3.07	7.84-22.02	10.64	1.11	8.35-12.93	<0.001 <sup>c</sup>
MDA ( $\mu\text{mol/L}$ )	0.33	0.03	0.26-0.40	0.28	0.03	0.25-0.37	<0.001 <sup>b</sup>
SOD (U/ml)	15.81	1.29	13.46-19-23	18.30	1.04	15.06-19.84	<0.001 <sup>b</sup>

<sup>a</sup> Chi-square test, <sup>b</sup> Independent samples t test, <sup>c</sup> Mann-Whitney U test

ADHD: Attention deficit hyperactivity disorder, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, TAS: Total antioxidant status, TOS: Total oxidant status, OSI: Oxidative stress index, MDA: Malondialdehyde, SOD: Superoxide dismutase

**Table 2.** Analysis of factors affecting children with ADHD with the binary logistic regression forward LR model

	B	P	Exp (B)	95% C.I. for EXP(B)	
				Lower	Upper
MDA-Z score	4.943	0.014	140.132	2.707	7254.256
SOD- Z score	-3.331	0.008	0.036	0.003	0.423
DBP- Z score	-7.669	0.020	0.000	<0.001	0.299
Constant	4.620	0.024	101.538		

Independent variables Z score entered model: TOS: Total oxidant status, MDA:

Malondialdehyde, SOD: Superoxide dismutase, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WP: Weight percentile, HP: Height percentile, BMI-P: Body mass index percentile, age

Hosmer and Lemeshow Test  $p=1.000$ , Nagelkerke  $R^2= 0.939$

**Table 3.** Analysis of factors affecting TAS, TOS, MDA and SOD values with the linear regression stepwise model

	Unstandardized	95.0% Confidence		Standardized	t	P
	Coefficients	Interval for B		Coefficients		
	B	Lower	Upper	$\beta$		
		Bound	Bound			
<b>TAS (Adj.R<sup>2</sup> = 0.169)</b>						
(Constant)	1.097	0.893	1.301		10.706	<0.001
SOD	-0.017	-0.026	-0.008	-0.399	-3.658	<0.001
TOS	-0.015	-0.026	-0.005	-0.320	-2.950	0.004
BMI-P	0.000	0.000	0.001	0.217	2.139	0.036
<b>TOS (Adj.R<sup>2</sup> = 0.452)</b>						
(Constant)	6.762	3.090	10.435		3.665	<0.001
MDA	12.972	4.663	21.282	0.334	3.107	0.003
TAS	-4.290	-7.739	-0.840	-0.207	-2.475	0.015
ADHD=PRESENT	1.218	0.564	1.873	0.400	3.704	<0.001

<b>OSI (TOS/TAS)</b>						
(Adj.R <sup>2</sup> = 0.270)						
(Constant)	12.156	11.639	12.673		46.785	0.000
MDA	1.463	0.943	1.983	0.528	5.597	0.000
<b>MDA (Adj.R<sup>2</sup> = 0.495)</b>						
(Constant)	0.142	0.066	0.219		3.701	<0.001
ADHD=PRESENT	0.044	0.027	0.062	0.564	4.988	<0.001
TOS	0.009	0.004	0.014	0.365	3.748	<0.001
DBP	0.001	0.000	0.002	0.230	2.275	0.026
<b>SOD (Adj.R<sup>2</sup> = 0.530)</b>						
(Constant)	21.235	18.678	23.793		16.522	<0.001
ADHD=PRESENT	-2.418	-2.947	-1.890	-0.694	-9.105	<0.001
TAS	-4.182	-7.782	-0.582	-0.176	-2.312	0.023

TAS: total antioxidant status, TOS: total oxidant status, MDA: malondialdehyde, SOD: superoxide dismutase

ADHD: attention deficit hyperactivity disorder, DBP: diastolic blood pressure, BMI-P: body mass index percentile

**Table 4.** Mean and standard deviation values of variables according to medication use in children with ADHD

	No medication used (n=30)		Medication (n=21)		Total (n=51)		t test <sup>b</sup>
	Mean	SD	Mean	SD	Mean	SD	P
Male n, %	21	55,3%	17	44,7%	38	100,0%	0,518 <sup>a</sup>
Female n, %	9	69,2%	4	30,8%	13	100,0%	
Age (years)	10.00	2.84	10.19	2.60	10.08	2.72	0.808
Weight percentile	48.50	34.90	46.71	32.56	47.76	33.64	0.854
Height percentile	44.33	31.85	53.10	34.68	47.94	32.99	0.356
BMI percentile	54.80	29.77	50.43	34.75	53.00	31.65	0.632
SBP (mmHg)	94.83	7.93	94.76	8.73	94.80	8.18	0.976
DBP (mmHg)	55.00	5.57	54.76	6.02	54.90	5.70	0.885
TAS (µmol Trolox Eq/L)	.74	.07	.68	.08	.72	.08	<b>0.010</b>
TOS (µmol H <sub>2</sub> O <sub>2</sub> Eq/L)	8.40	.88	10.41	1.22	9.23	1.43	<b>&lt;0.001</b>

OSI (arbitrary unit)	11.43	1.68	15.50	3.04	13.10	3.07	<0.001 <sup>c</sup>
MDA (μmol/L)	.33	.03	.34	.03	.33	.03	0.177
SOD (U/ml)	15.55	1.53	16.19	.74	15.81	1.29	0.006 <sup>c</sup>
ADHD duration	33.33	19.63	26.00	29.25	30.31	24.06	0.289
ADHD-Inattentive type	8	61.5%	5	38.5%	13	100.0	1.000 <sup>a</sup>
ADHD-Combined type	22	57.9%	16	42.1%	38	100.0	
Treatment dose (mg/g)	.	.	24.57	12.24	Min.10.0	Max.54.0	
Treatment duration (month)	.	.	17.95	27.32	Min.1.0	Max.120.0	

<sup>a</sup> Fisher's Exact test, <sup>b</sup> Independent Samples t test, <sup>c</sup> Mann-Whitney U test

ADHD: attention deficit hyperactivity disorder, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TAS: total antioxidant status, TOS: total oxidant status, OSI: oxidative stress index, MDA: malondialdehyde, SOD: superoxide dismutase

**Table 5.** Analysis of factors affecting drug use of children with ADHD with the binary logistic regression forward LR model

Variables	B	P	Exp (B)	95% C.I. for EXP(B)	
				Lower	Upper
<b>Drug use</b>					
TOS	1.792	<0.001	6.003	2.262	15.934
Constant	-17.103	<0.001	0.000		
<b>ADHD-Combined</b>					
Age	-0.298	0.018	0.742	0.580	0.949
Constant	4.198	0.002	66.525		

Independent variables: TAS: total antioxidant status, TOS: total oxidant status, MDA: malondialdehyde, SOD: superoxide dismutase.

ADHD: attention deficit hyperactivity disorder, Hosmer and Lemeshow Test  $\chi^2=4.70$ ,  $p=0.789$ .

Nagelkerke R<sup>2</sup>=0.622

## **FIGURE LEGENDS**

**Figure 1.** ROC curve analysis of the effect of SOD (superoxide dismutase) values in the detection of ADHD (attention deficit hyperactivity disorder)

Note: The SOD AUC value was smaller, which indicates a more positive effect on the detection of ADHD.

**Figure 2.** ROC curve analysis of the effect of MDA (malondialdehyde) values in the detection of ADHD (attention deficit hyperactivity disorder)



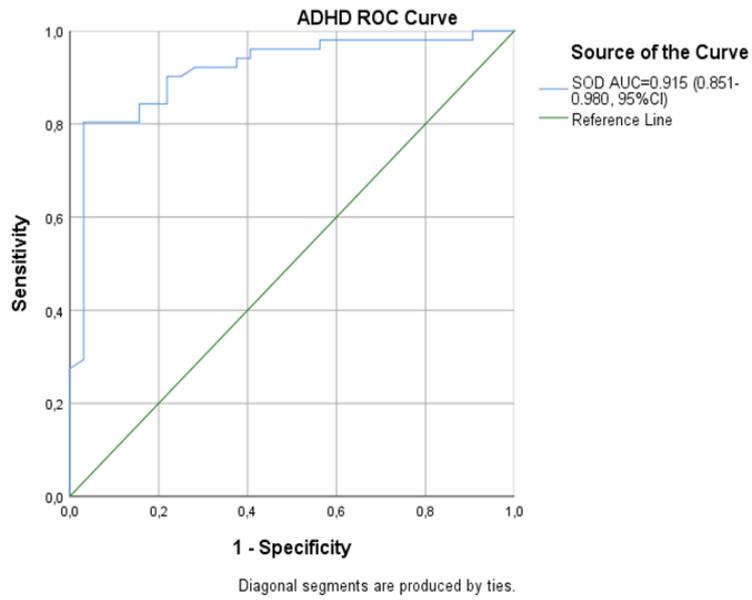


Fig. 1. ROC curve analysis of the effect of SOD (superoxide dismutase) values on detecting ADHD (attention deficit hyperactivity disorder)

Note: The SOD AUC value was smaller, which indicates more positive effect on the detecting ADHD.

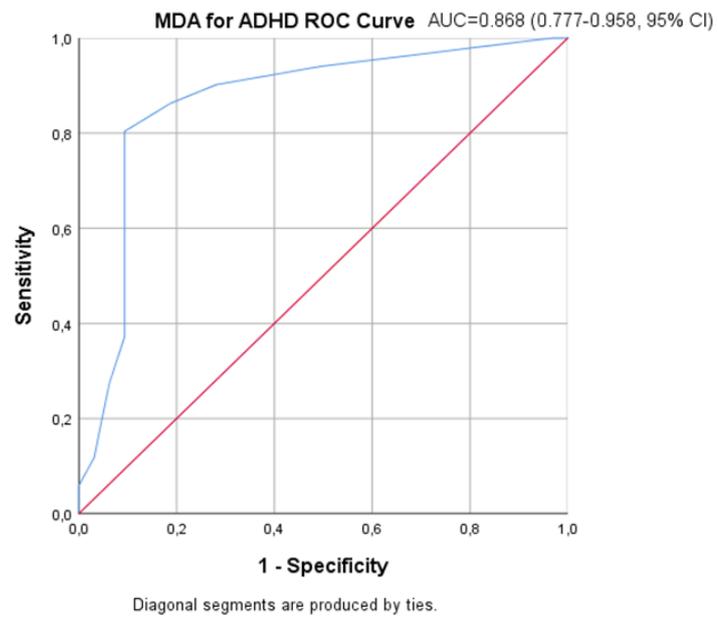


Fig. 2. ROC curve analysis of the effect of MDA (malondialdehyde) values on detecting ADHD (attention deficit hyperactivity disorder)