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Thiol/Disulfide Homeostasis: A Potential New Peripheral Biomarker in Adolescent Depression

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ABSTRACT

Background: Thiol-disulfide homeostasis (TDH), one of the most important antioxidants, is involved in the non-enzymatic removal of reactive oxygen molecules in the body and is one of the many methods to measure the level of oxidative stress (OS). In the present study, TDH is investigated in adolescent depression, and its relationship to clinical variables is examined.

Methods: Thirty-two (50.0%) patients diagnosed with major depressive disorder (MDD) and without psychotropic drug use and 32 (50.0%) healthy controls were included in the present study. The subjects MDD and control groups were between 13 and 18 years old. Participants completed the DSM-5 Level-2 scales for depression and irritability. A colorimetric method proposed by Erel and Neselioglu was used to analyze the TDH parameters of serum samples.

Results: Biochemical analyses of samples from the MDD and control groups showed significant differences between the groups in native thiol (SH) levels ($P = .002$), disulfide (SS) levels ($P = .021$), disulfide/total thiol (SS/ToSH) ($P = .009$), and disulfide/native thiol (SS/SH) ($P = .003$) levels. Analysis of receiver operating characteristic showed that the area under the curve values with "acceptable discrimination potential" for the TDH parameters were significantly able to discriminate individuals with MDD from healthy controls.

Conclusion: Thiol-disulfide homeostasis, one of the OS parameters, was found to be impaired in adolescents with depression. Our results suggest that TDH may contribute to the etiopathogenesis of adolescent MDD and that TDH may be a novel approach to assess OS in adolescent depression.

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INTRODUCTION

During adolescence, when rapid emotional, cognitive, and social development occurs, the incidence of major depressive disorder (MDD) has increased significantly over the past decade.[1] Recurrence of depression, onset of other psychiatric disorders, and long-term deterioration in interpersonal, social, academic, and occupational performance are some of the harmful effects of depression in young people.[1] In young people with depression, there is an increased risk of developing mental and physical illnesses in adulthood, including anxiety disorders, eating disorders, somatic complaints, cardiovascular diseases, and obesity.[1]

Many molecules that cause OS can penetrate the brain through the blood-brain barrier, and oxidative elements in other parts of the body also contribute to OS in the brain.[2] There is evidence that MDD is associated with changes in brain function, neuroplasticity, and volume reduction in certain brain regions (particularly the hippocampus and frontal cortex) and that OS is one of the major causes of deterioration in brain structure and function in depression.[2] Meta-analysis studies have shown that in people with an acute depressive episode, total antioxidant capacity and some antioxidant substances (uric acid, albumin, zinc) decrease significantly, and molecules indicative of oxidative damage, such as malondialdehyde and isoprostane, increase.[3] Researchers have shown that depression patients have increased oxidative damage not only in their peripheral blood but also in their white matter.[4] In this context, the increased production of ROS and the decrease in antioxidant defenses, which are responsible

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for the changes in brain structure, are referred to as the "oxidative stress hypothesis in depressive disorders."[5-7]

Thiol-disulfide homeostasis (TDH), one of the most important antioxidants, is involved in the non-enzymatic removal of reactive oxygen molecules in the body and is one of the many methods to measure the level of OS.[8] The thiols in plasma consist primarily of albumin and thiols found in protein structures, but a small percentage consists of low molecular weight thiols such as glutathione, gamma-glutamylcysteine, and homocysteine.[9] Thiol groups in both small molecules and proteins are highly reactive to oxidation reactions leading to loss of biological activity.[10] As one of the key molecules for altering post-translational protein interaction and protein function, thiols are particularly sensitive to redox changes.[11] Thiols can also act as electron donors, donating electrons to reduce oxidized molecules. This helps to maintain cellular redox balance and protect cells from oxidative damage.[11,12]

Thiols react with oxidative molecules with the sulfhydryl group they contain to form reversible disulfide bonds (SS), and when oxidative stress ends, the formed SS are reduced back to thiols and protect TDH.[13-15] The ratio between thiols and SS is one of the indicators of the equilibrium between oxidants and antioxidants in the body, and this equilibrium is a dynamic process that is constantly changing through reciprocal reactions.[14] While native thiol (SH) expresses only reduced thiols, total thiol (ToSH) represents the sum of intracellular and extracellular reduced and unreduced thiols.[14]

Many studies address the role of dynamic TDH in a variety of diseases in different age groups. There is growing evidence that TDH plays a role in various medical conditions such as celiac disease, diabetes mellitus, rheumatoid arthritis, and neurofibromatosis[8,16-19] as well as in various mental disorders such as schizophrenia, bipolar disorder (BD)-manic episode, obsessive-compulsive disorder (OCD), and autism spectrum disorder (ASD).[20-23] The aim of this study is to contribute to the etiopathogenesis and treatment of MDD in adolescents by investigating a novel marker for OS, TDH, and determining the relationship between TDH and clinical variables such as depression severity and irritability.

MAIN POINTS

- Thiol/disulfide homeostasis was significantly impaired in adolescents with depression.
- Native thiol levels were found to be significantly decreased in adolescents with depression.
- Adolescents with depression had higher levels of disulfide, disulfide/total thiol, and disulfide/native thiol.
- Impairment of thiol/ disulfide homeostasis correlated with depression scores, suggesting that it may be related to illness severity.

MATERIAL AND METHODS

Participants

This study was conducted between February 2020 and March 2021 at Manisa Celal Bayar University Faculty of Medicine (MCBUFM) and was a cross-sectional study. Adolescents who presented to the child psychiatric outpatient clinic where the study was conducted and were diagnosed with MDD formed the patient group, and adolescents who presented to the pediatric outpatient clinic formed the healthy control group. The patient group consisted of adolescents admitted to the ''MCBUFM'' child psychiatric outpatient clinic between the dates of the study, who had not taken any psychotropic drugs in the 6 weeks prior to admission and who were diagnosed with MDD. The control group consisted of adolescents who were admitted to the MCBUFM pediatric outpatient clinic for various reasons, such as permission to live in a hostel, a medical certificate to play sports, and routine blood tests. Adolescents who were not diagnosed with any acute and/or chronic disease according to the results of blood tests and physical examination were referred to the researcher. The demographic and clinical characteristics of the adolescents referred to the researchers were first determined using the socio-demographic data form developed by the researchers, which asked for demographic and clinical characteristics. Then the Affective Disorders and Schizophrenia in School-aged Children-Current and Lifetime Version Questionnaire for DSM-5 (K-SADS-PL) was applied by the researcher to all adolescents. The diagnosis of MDD and the presence of other concomitant psychiatric disorders were assessed by applying K-SADS-PL. As a result of the K- SADS-PL and the demographic and clinical characteristics obtained, all adolescents who met the inclusion and exclusion criteria of the study were asked to complete the DSM-5 Level-2 Depression (DDS) and DSM-5 Level-2 Irritability (DIS) scales.

Inclusion and Exclusion Criteria

The subjects in the MDD and control groups were between 13 and 18 years old. Adolescents who were diagnosed with active MDD, who did not use psychotropic drugs yet, and who did not have a history of psychotropic drug use in the last 6 weeks were included in the patient group. Adolescents with OCD, ASD, BD, eating disorders, Tourette's syndrome, mental retardation, schizophrenia, and post-traumatic stress disorder were excluded. The healthy control group consisted of adolescents who had no psychiatric disorder according to the K- SADS-PL and who had not been previously diagnosed with any mental disorders. Exclusion criteria for all adolescents were the use of medications that could affect the inflammation and oxidative systems (e.g. immunosuppressants and vitamin E or C) within the last 6 months, a diagnosis of an endocrinological, hematological, or immunological disease, a diagnosis of an infectious

disease within the last 4 weeks, a chronic medical condition (e.g. liver or kidney disease or diabetes mellitus) or a neurological disease (epilepsy, migraine, etc.), a history of alcohol or substance use, and smoking.

A decision dated February 5, 2020, and number 20.478.486 was approved by the Ethics Committee of the Manisa Celal Bayar University Health Sciences Institute, and the study was conducted according to the Declaration of Helsinki. All adolescents and their parents were informed about the study verbally and in writing before they signed the consent form. In the next section, we describe in detail the socio-demographic questions and self-report measures participants were asked to complete.

Data Collection

Socio-Demographic Questionnaire: This is a form designed by the researchers that includes characteristics such as age, gender, psychiatric illness of parents, suicide attempts in the adolescent's past, medical illness of parents, and suicide attempts in the family.

Affective Disorders and Schizophrenia in School-aged Children-Current and Lifetime Version (K-SADS-PL): K-SADS-PL is a semi-structured interview originally developed by Kaufman et al.[24] This test, which takes into account the DSM-5 diagnostic criteria, was developed to diagnose mental illness in children. It consists of 3 components beginning with an unstructured introductory interview, continuing with a screening interview assessing more than 40 psychiatric disorders and nearly 200 symptoms, both past and recent (last 2 months), and ending with diagnostic reinforcements. This form, developed by Kaufman et al, was translated into Turkish by Unal et al.[25]

DSM-5 Level-2 Depression Scale: The adolescents' depressive symptoms were evaluated using the DDS form, and the severity of MDD was determined. This form consists of an 11-item form for parents of children (6-17 years) and adolescents (11-17 years), which is completed with a 14-item self-report form that was used in this study. Each question in this form, which is completed by the children before the session, is designed to determine their level of depression in the past 7 days. According to the form, depression ratings range from 14 to 70, with higher scores reflecting more severe depression.[26]

DSM-5 Level-2 Irritability Scale: The severity of the adolescents' irritability was assessed using the DIS. The irritability symptoms scale was developed to assess adolescents' severity of irritability. This questionnaire contains 7 items to be answered by parents of children aged 6 to 17 years, while adolescents aged 11 to 17 years also complete a 7-item self-report questionnaire.[27]

Biochemical Analysis

After 12 hours of fasting, blood samples (venous) were collected from the adolescents' antecubital veins between 8 AM and 10 AM and placed into tubes without anticoagulants. Blood samples from each subject were centrifuged at 4°C for 15 minutes at 3000 rpm. After centrifugation, the sera were separated and stored at −80°C until analysis. The analysis of each sample was performed in a single experiment.

A colorimetric method proposed by Erel and Neselioglu was used to analyze the TDH parameters of serum samples.[13] In this method (Erel), thiol measurement was performed with modified Elman reagents. Serum ToSH content was analyzed with the addition of sodium borohydride (NaBH4), a reducing reagent. Furthermore, the addition of NaBH4 reduces the reducible dynamic disulfide to functional thiol groups. Subsequently, the unconsumed NaBH4 is separated by formaldehyde. 5,5-Dithiobis 2-Nitrobenzoic acid is used to perform the measurements after all thiol groups containing reduced and SH thiol react with it. In this method, thiol is represented by native thiol (-SH) and oxidized thiol by disulfide (-S-S). While SH refers to reduced thiols, ToSH includes both reduced and unreduced thiols. The values of the coefficient of variation (CV %) calculated at 29.1 mol/L, 16.0 mol/L and 7.15 mol/L were 4%, 5%, and 13%, respectively. The measurement range was 2.8-4000 µmol/L. It includes ToSH, SH and SS. After quantifying SH and ToSH, the amount of SS, the ratio of SS/ToSH (SH+SS) and the ratio of SS/SH were calculated as a percentage. The following formula shows the calculation of SS in the proposed example; (ToSH − SH)/2.

Statistical Analysis

In the study of continuous variables, means and SDs were calculated, and in the study of categorical variables, numbers and percentage were computed. Chi-square tests and Fisher's exact tests were used for the analysis of categorical variables. The normality of the distributions of the TDH parameters was analyzed using the Kolmogorov-Smirnov test. Thiol-disulfide homeostasis values for the MDD and control groups were analyzed with independent *t*-tests for parameters with normal distributions and Mann–Whitney *U*-tests for parameters without normal distributions. A median (interquartile range) was used to represent non-normalized variables in nonparametric tests. The relationship between depression severity (DDS and DIS total scores) and TDH was analyzed using Spearman correlation analysis. All data from the study were analyzed using the Statistical Package for Social Science Statistics software version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) and were considered statistically significant at a *P*-value of < .050. The best cutoff points of the thiol parameters that distinguish the groups from each other were determined using the receiver operating characteristic analysis (ROC), from which the area under the curve (AUC) was calculated. We used the Youden index to determine the ROC cutoff values.

Table 1. Clinical and Demographic Features

Features	MDD n = 32	Healthy Control n = 32	*P*
Age (mean ± SD)	15.34 ± 1.35	14.87 ± 1.47	.204
Gender (female/male)	28/4	24/8	.337
Presence of mental illness in the family (yes/no)	17/15	6/26	.004
Presence of medical illness in the family	11/21	4/28	.039
Maternal age [Median (IQR)]	40.5 (30-57)	40 (32-62)	.122
Paternal age [Median (IQR)]	45 (35-56)	42 (38-61)	.174
Suicide attempt history	8/24	0/32	.005
Family history of suicide attempts	6/26	0/32	.024
Duration of depressive episode (month) [Median (IQR)]	7.5 (1-12)	-	-
DSM-5 Level-2 Depression Scale [Median (IQR)]	56.5 (18-70)	19 (14-42)	< .001
DSM-5 Level-2 irritability scale [Median (IQR)]	10 (0-12)	3 (0-8)	< .001

IQR, interquartile range; MDD, major depressive disorder.

RESULTS

Demographic and Clinical Characteristics of the Participants

Thirty-two (50.0%) patients diagnosed with MDD and 32 (50.0%) healthy controls without psychiatric disease and psychotropic drug use were included. Major depressive disorder (n = 32) and control (n = 32) groups had mean ages of 15.34 ± 1.35 and 14.87 ± 1.47 years, respectively (*P* = .204). Four (12.5%) of the adolescents in the MDD group and 8 (25.0%) of the adolescents in the control group were male (*P* = .337). Eight patients (25.0%) in the MDD group had a history of suicide, while none of the adolescents in the control group had a history of suicide (*P* = .005). As expected, the depression and irritability scale scores were statistically significantly higher in the MDD group (*P* < .001) (Table 1).

Twenty (62.5%) of the patients in the MDD group had at least 1 comorbid mental disorder. However, no additional mental disorder diagnoses were identified in the remaining MDD patients (37.5%). The most common comorbidities were specific phobia and social anxiety disorder. Of the patients with comorbidity, 25.0% were diagnosed with specific phobia, 7 (21.8%) with social phobia, and 4 (12.5%) with generalized anxiety disorder. In the MDD group, there were no significant differences in thiol parameters between adolescents with and without comorbid disorders (*P* > .050).

Results of Thiol Disulfide Homeostasis Parameters

Biochemical analyses of samples from the MDD and control groups revealed significant differences between the groups in SH (*P* = .002), SS (*P* = .021), SS/ToSH ratio (*P* = .009), and SS/SH ratio (*P* = .003). The concentrations of SS, SS/ToSH ratio, and SS/SH ratio were increased in the MDD group, while the concentrations of SH were decreased. Table 2 shows the TDH values for each group.

There was a negative correlation between SH and the severity of depression and irritability (*r* = −0.436, *P* < .001; *r* = −0.336, *P* = .007, respectively), and a positive correlation between SS/SH and SS/ToSH and the severity of depression (*r* = 0.292, *P* = .019; *r* = 0.313, *P* = .012, respectively) and irritability (*r* = 0.292, *P* = .019; *r* = 0.313, *P* = .012, respectively) (Table 3). No significant correlation was found between the duration of depression and the parameters ToSH, SH, SS, SS/ToSH, and SS/SH (*r* = −0.231, *P* = .204; *r* = −0.018, *P* = .921; *r* = −0.228, *P* = .209; *r* = −0.233, *P* = .200, and *r* = −0.233, *P* = .200, respectively).

Receiver Operating Characteristic Results

Native thiol (AUC = 0.730; *P* = .002) showed better discrimination between the MDD group and the healthy

Table 2. Thiol/Disulfide Homeostasis Parameters

	MDD n = 32	Healthy Control n = 32	*P*
Total thiol (μmol/L)	453.87 ± 139.19	444.03 ± 71.41	.724
Native thiol (μmol/L)	228.21 ± 71.50	280.68 ± 56.54	.002
Disulfide (μmol/L)	112.82 ± 72.62	81.67 ± 19.84	.021
Disulfide / total thiol	0.23 ± 0.09	0.18 ± 0.03	.009
Disulfide/native thiol	0.60 ± 0.66	0.30 ± 0.09	.003

Table 3. The Relationship Between Thiol/Disulfide Parameters and Depression and İrritability Severity

	DDS		DIS	
	r	*P**	*r*	*P**
Total thiol	−0.021	.869	0.070	.585
Native thiol	−0.436	<.001	−0.336	.007
Disulfide	0.183	.148	0.266	.033
Disulfide/total thiol.	0.292	.019	0.313	.012
Disulfide/native thiol	0.292	.019	0.313	.012

DDS, DSM-5 Level-2 Depression Scale; DIS, DSM-5 Level-2 irritability scale; *r*, correlation coefficient.
*Spearman's correlation test.

Table 4. Cutoff Values for Thiol Disulfide Homeostasis Parameters in Adolescents with Major Depressive Disorder

Parameters	AUC	Cutoff Values	Sensitivity	Specificity	*P*	95% Confidence Interval	
						Lower Bound	Upper Bound
Total thiol	0.467	433.0	43.8 %	59.4 %	.648	0.321	0.612
Native thiol	0.730	215.5	46.9 %	93.8 %	.002	0.607	0.854
Disulfide	0.667	111.5	43.8 %	96.9 %	.021	0.526	0.809
Disulfide/total thiol	0.715	0.206	68.8 %	84.4 %	.003	0.577	0.854
Disulfide/native thiol	0.715	0.352	68.8 %	84.4 %	.003	0.577	0.854

AUC, area under the curve.

control group as its values decreased. SS (AUC = 0.667; *P* = .021), SS/SH (AUC = 0.715; *P* = .003), and SS/ToSH (AUC = 0.715; *P* = .003) more accurately distinguished the MDD patients from the healthy controls the higher their levels were. According to the analysis of ROC, the cutoff value for SH is 215.5 µmol/L, for SS 111.5 µmol/L, for the ratio SS/ToSH 0.206 and for the ratio SS/SH 0.352, which can be used to predict MDD (Table 4). Figures 1 and 2 show the ROC curves for these parameters.

DISCUSSION

There are various protective mechanisms and systems that protect the organism from excessive production of ROS and reactive nitrogen species (RNS). These mechanisms include the inhibition of enzymes that catalyze the production of ROS and the production of antioxidant molecules that convert ROS into non-toxic metabolites, as well as enzymes such as proteinase and lipase.[28] The fact that the brain consumes more oxygen than other organs, contains a higher proportion of lipids, and has fewer antioxidant defense mechanisms makes the brain more sensitive (vulnerable) to OS. The damage caused by OS is considered the main cause of neuroprogression.[2] ROS are destroyed by enzymatic or non-enzymatic antioxidants such as glutathione, zinc, coenzyme Q10, catalase, and peroxidase, and many of these molecules have been shown to be reduced in depression.[29] It was found that total antioxidant status (TAS) was lower and total oxidant status (TOS) was higher in adolescents experiencing their first depressive episode and not taking psychotropic drugs compared to healthy controls.[30]

We examined whether dynamic TDH parameters could be used to distinguish adolescent depression from healthy

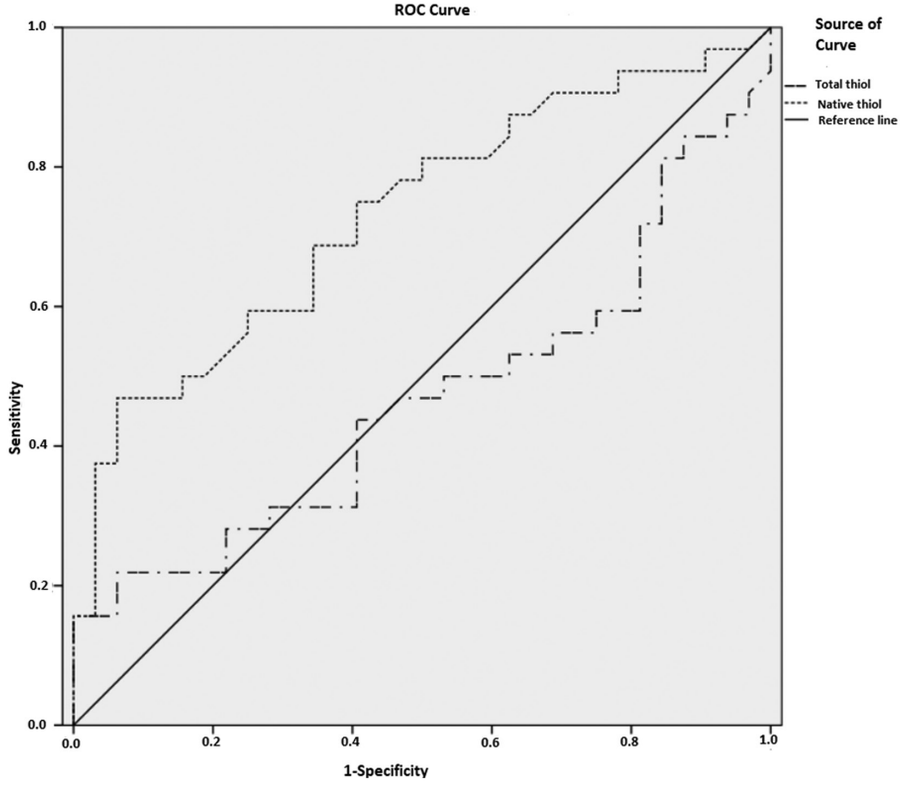

Figure 1. Receiver operating characteristic curves of thiols.

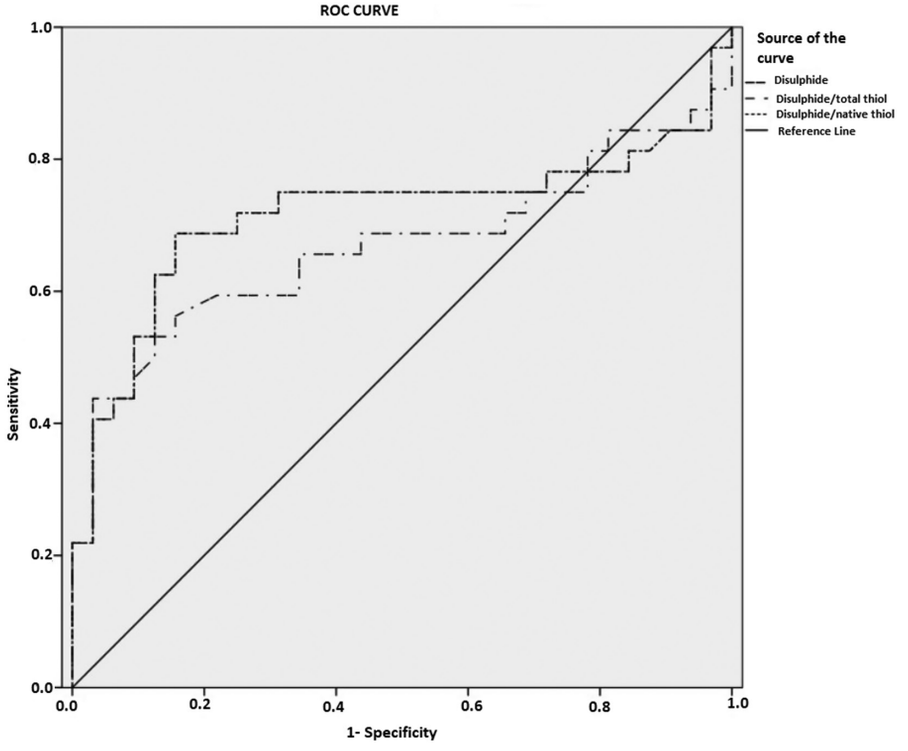

Figure 2. The receiver operating characteristic curves of disulfide, disulfide/native thiol, and disulfide/total thiol.

controls using an oxidative biomarker. By measuring TDH, a novel method for determining oxidative stress, this study investigated the role of OS in the etiopathogenesis of adolescent depression. The levels of SS, the ratio SS/ToSH and SS/SH, which are indicators of oxidation, were found to be higher in the MDD group. In addition, SH level decreased in the MDD group. The severity of depression and irritability was negatively correlated with the level of SH and positively correlated with the level of SS/SH, SS/ToSH. Furthermore, SS and the severity of irritability were positively correlated. The results show that OS is elevated and TDH is thereby impaired in favor of SS. The authors suggest that SH consumption is increased for antioxidant defense against the increased OS in depression, leading to an increase in disulfide bonds formed between thiols and ROS. In addition, ROC analysis showed that the AUCs with "acceptable discrimination potential"[31] for SH, SS, SS/ToSH and SS/SH were significantly able to distinguish individuals with MDD from healthy individuals.

Measuring TDH parameters is a new method for assessing oxidative processes.[13] Since thiols are the first molecules to be consumed during OS in biological systems, determining the thiol content in plasma is important to show how much biological systems are affected by oxidation. Thiol-disulfide homeostasis plays a pivotal role in detoxification, signal transduction, protection from oxidative molecules, apoptosis, cellular signaling mechanisms, and regulation of enzyme activity.[32,33] Several studies have investigated the association between various psychiatric disorders and TDH in adults and children. In untreated schizophrenia patients, Topçuoglu et al[34] found significantly lower SH and ToSH levels as well as higher SS, SS/SH, and SS/ToSH levels as compared to healthy adults. The authors concluded that the lower thiol levels in schizophrenia patients were due to altered disulfide bond formation and impaired TDH. They also suggested that this may be involved in the etiology of many schizophrenia symptoms. Thiol-disulfide homeostasis has been studied in children and adolescents with OCD and autism, and studies have shown that TDH is impaired in these disorders.[22,23] In the study conducted with autism, the balance between oxidants and antioxidants was found to have shifted in favor of OS in the autism group, and the expected compensatory response of antioxidants against OS did not occur.[22]

Although there are studies examining the role of OS in adult depression, there is no study examining the relationship between TDH and adolescent depression. There is conflicting evidence concerning TDH's role in depression etiopathogenesis in adults. Erzin et al[35] reported that adults with unipolar and bipolar depression who were taking psychotropic drugs had significantly higher serum levels SS, SS/ToSH, and SS/SH compared to control participants. Consistent with the present study, SH levels were found to be lower in individuals with bipolar depression and ToSH levels were similar between groups. Hamilton depression scores were positively correlated with TDH parameters. Most patients were taking antipsychotic

medication and a shift towards OS was observed in these patients. In another study, adults were examined after their first depressive episode and it was found that the thiol levels (SH and ToSH) were significantly lower in the patients. Thiol-disulfide homeostasis and the severity of depression showed no significant correlation, in contrast to the previous study.[36] Compared to adults, adolescents have a different course of depression, which may explain the discrepancy between the results from the present study. Furthermore, the age range of the study participants was broad and ranged from 18 to 65 years. It is possible that the oxidative defense decreases with age, which could also be an explanation for the different results. In addition, the earlier study only included patients who were experiencing their first depressive episode, and both the present and the earlier study did not specify the subtypes of depression in the patients.

In addition, this study contributes to existing research exploring the possibility of using oxidative state-related biological indices for MDD. It was found that SH values below certain cutoff values can be used in the diagnosis of MDD with a sensitivity of 46.9% and a specificity of 93.8%. SS, SS /ToSH and SS/SH values above cutoff values can be used in the diagnosis of depression with a sensitivity of 43.8%, a specificity of 96.9%, a sensitivity of 68.8%, and a specificity of 84.4%, respectively. To date, there has been no study examining the diagnostic value of TDH parameters in depressive disorders. However, there are 2 studies investigating the diagnostic value of TDH parameters in autism in children under 12 years of age. Ayaydın et al[37] showed that all TDH parameters, with the exception of SS, have "excellent discrimination potential" to distinguish children with autism from healthy controls. In the same study, SS was found to have "acceptable discrimination potential" between children with autism and healthy controls. Another study reported that the TDH parameters have acceptable discriminatory power as a marker for the diagnosis of autism.[22]

An easy-to-measure, repeatable, and fully automated method was used to assess a specific marker of OS, TDH, in adolescent patients with MDD. Thiol-disulfide homeostasis measures the redox environment in cells quickly, sensitively, and specifically. The main advantage of this method is that it measures the entire redox environment without focusing on a specific molecule. Choosing patients without psychotropic medication was a strength of this study. This excluded the effects of antidepressants, which have been shown to reduce OS in studies in animals[38] and humans.[39] According to several studies, antidepressants reduce OS by decreasing the production of some proinflammatory cytokines, oxygen radicals, and catalase, which are part of the antioxidant defences.[40] Therefore, patients with infectious diseases, medical conditions, or a history of medication use were excluded, as these characteristics may affect OS.

The study has strengths, but it also has limitations, such as the fact that it is cross-sectional, the small sample size, and the small number of males. In addition, the level of OS may be influenced by several other factors that were not examined in this study, including lifestyle and diet. In addition, dynamic TDH was measured in serum and not in CSF. Thiols and SS levels in the peripheral and central nervous systems may not be similar. Of the many parameters indicative of oxidative damage, only TDH levels were assessed in the current study; TAS and TOS of the study participants were not measured. Finally, MDD patients were not categorized by disease subtype. Comprehensive longitudinal studies with larger samples to examine the different MDD subtypes in the adolescent age group are needed.

Thiol-disulfide homeostasis, one of the parameters of OS, has been found to be impaired in adolescents with depression. The results of this study suggest that TDH parameters may be useful in differentiating adolescents with MDD from healthy controls. Thiol-disulfide homeostasis is a novel, relatively inexpensive, and reproducible method and may therefore be useful to determine OS and disease severity in adolescents with MDD. The effects of pharmacological and non-pharmacological interventions on TDH should also be investigated to determine whether TDH may be a potential therapeutic target in MDD. Thiol-disulfide homeostasis may also be useful for monitoring changes in OS over time and for assessing treatment efficacy in clinical trials. Exploring these possibilities could lead to new, more effective treatments for depression and a better understanding of the link between OS and MDD. This could open the door to better diagnosis and targeted treatments.

Ethics Committee Approval: This study was approved by the Ethics Committee of Manisa Celal Bayar University Faculty of Medicine Health Sciences Institute (Approval No: 20.478.486, Date: February 5,2020).

Informed Consent: Informed consent was obtained from all participants and their parents who agreed to take part in the study.

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