

OXIDATIVE STRESS AND SERUM S100B LEVELS IN ADOLESCENTS WITH FIRST-EPISODE DRUG-NAIVE UNIPOLAR DEPRESSION

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SUMMARY

Background: Unipolar depression is common among adolescents and has high recurrence rates. Studies conducted with adults show that oxidative stress plays a role in etiology of depression but studies with adolescent patients are limited. In addition, baseline S100B level in adult patients with depression is considered as a marker of response to treatment. The purpose of this study was to measure the levels of serum S100B, Malondialdehyde (MDA), total oxidant status (TOS), and total antioxidant status (TAS), which have not been previously investigated in adolescent patients with first-episode, drug-naïve unipolar depression, and to investigate the relationship of these parameters with disease severity and patient-specific variables.

Subjects and methods: This study was conducted with 37 adolescents diagnosed with unipolar depression and 37 healthy peers. Participants were asked to fill out the Beck Depression Scale, Screen for Child Anxiety Related Disorders, and suicide probability questionnaires. After this procedure, 5 cc blood was collected from the adolescents and serum S100B, MDA, TOS, and OSI levels measured.

Results: Serum S100B, MDA, TOS, and OSI levels were higher and TAS level was lower in patients than their healthy peers. There was no relationship between the patients' severity of depression or suicide probability and these parameters. The serum S100B, MDA, TOS, and OSI levels of female patients were higher than their healthy peers, but the TAS level was not different. Male patients had higher TOS and OSI levels and lower TAS levels than their healthy peers.

Conclusions: The results show that increased serum S100B, MDA, TOS and OSI levels may contribute to etiology of depression regardless of gender. The gender-specific increase in S100B and MDA levels, which were significantly increased in female adolescent patients but not in males, should be supported by further follow-up studies.

Key words: unipolar depression – adolescent - S100B - oxidative stress - gender

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INTRODUCTION

Major depression is an important psychiatric disorder that is common in children and adolescents. It may lead to academic and social difficulties and have devastating consequences, such as substance abuse and suicide attempts. A meta-analysis study has reported that 5.6% of adolescents between the ages of 13 and 18 experience a major depressive episode during their lifetime (Costello et al. 2006). On the other hand, in a natural follow-up study among adolescents, the rate of recurrence within five years in patients with depression was reported as 46.6% (Curry et al. 2011). There is a recurrence observed in almost one of every two adolescents with major depression. Biomarkers, as a determinant of future episodes, are an important area of research in the follow-up of this disorder.

In postmortem studies of patients with affective disorders, it has been repeatedly shown that there is a decrease in the number and density of astrocyte and oligodendrocyte cells, which has led to the interpretation that these disorders are glial diseases (Schroeter et al. 2013).

S100 calcium-binding protein B (S100B) is a protein that can be produced from many different intracerebral (astrocyte, oligodendrocyte) and extracerebral (adipocyte, myocyte) cells and has been shown to play a role in many regulatory and inflammatory processes, including the pathophysiology of depression. This protein is rapidly released from damaged astrocytes into the cerebrospinal fluid, crossing the blood-brain barrier and entering the circulation (Schroeter et al. 2008). Therefore, it is considered an ideal biomarker for brain damage and astrocyte changes. It has been reported that the S100B level increases to restructure the impaired neuroplasticity in patients with depression (Arolt et al. 2003). However, this compensatory mechanism may vary among patients, and accordingly, patients may have high or low S100B concentrations (Schroeter et al. 2008). There are complex data regarding pre-treatment S100B levels in patients. It has been reported that patients with high S100B levels prior to treatment have a better response to treatment, and this may be associated with the severity of the disease at the onset of the disease (Arolt et al. 2003). In addition, there are data

which show that the baseline S100B level is positively correlated with treatment response, regardless of the severity of depression (Ambree et al. 2016, Jang et al. 2008). However, the patient groups included in these studies consist of adults. There is no study that focuses on the pre-treatment S100B levels among adolescents with a diagnosis of depression. On the other hand, in a study conducted with adolescents diagnosed with mood disorders and psychosis, it was found that the S100B levels of the patients were higher compared to their healthy controls regardless of their current diagnosis and that these levels correlated with the severity of suicide risk (Falcone et al. 2010). The authors suggested that S100B was a reliable, easily available, and objective biomarker for determining suicide risk in patients with major depression and may help prevent suicide.

Oxidative stress is a state of metabolic stress that is caused by increased reactive oxidant species production and decreased antioxidant defense, leading to cell damage (Valko et al. 2007). The brain is highly sensitive to oxidative damage due to the high amount of unsaturated fatty acids present in the brain's neuron structure and the cellular oxygen level consumed by the brain, which is high relative to its own weight (Finkel & Holbrook 2000). Therefore, it is noted that oxidative damage markers are investigated in many psychopathologies (Güney et al. 2014, Kandemir et al. 2013). On the other hand, there are a limited number of studies on oxidative stress in adolescent patients with depression (Tao & Li 2015). Studies conducted on adults show that levels of oxidation metabolites are high and antioxidant levels are low in patients with major depressive disorder, while it is emphasized that this leads to neurodegeneration and apoptosis and decreases neurogenesis and neuroplasticity, and all these factors play an important role in the pathogenesis of depressive disorder and the progression of the disease (Maes et al. 2011). Malondialdehyde (MDA), one of the final products of lipid peroxidation, has been extensively investigated as an oxidative damage index in adult patients with major depressive disorder; however, these studies present conflicting data (Jordan et al. 2018, Liu et al. 2015). MDA level, total oxidant status (TOS), or total antioxidant status (TAS) have not been investigated as markers of oxidative damage in adolescent patients with depression.

Considering the prevalence of major depression among adolescents, its highly repetitive nature, and negative consequences leading to suicide, it can be concluded that there is still a need for biomarkers that can be used to recognize the onset of an episode early or to predict treatment response. The purpose of this study was to measure the levels of S100B, MDA, TOS, and TAS, which have not been previously investigated in adolescent patients with first-episode, drug-naïve unipolar depression, and to investigate the relationship of these parameters with disease severity and patient-specific variables.

SUBJECTS AND METHODS

Participants and procedure

We approached 49 adolescents (12-17 years of age) who presented to a child and adolescent psychiatry clinic between the study dates (November 2019 - April 2020) and were diagnosed with first-episode unipolar depressive disorder according to DSM-5 diagnostic criteria. Among these drug-naïve patients, those who smoke, have autoimmune, allergic, endocrinological, neurological diseases, or have had an infection in the last month, have neurodevelopmental disorders, eating disorders or substance abuse excluded from the study. According to this two of the adolescents were excluded from the study due to vitiligo, one due to rheumatoid arthritis, and one due to autoimmune thyroiditis. In addition, eight children were excluded from the study due to smoking. Two children who were smokers were also evaluated for their first suicide attempts with high doses of medication. These children were excluded, and 37 patients were included in the study. Of these patients, three had comorbid panic disorder, six had generalized anxiety disorder, one had separation anxiety disorder, and eight had social phobia. We selected 37 age- and gender-matched healthy adolescents from the community who did not have any current or previous psychopathology as the control group. Subsequently, participants were asked to fill out the Beck Depression Scale, Screen for Child Anxiety Related Disorders, and suicide probability questionnaires. After this procedure, 5 cc blood was collected from the adolescents into a biochemistry tube in the morning on an empty stomach.

Scales

Beck Depression Scale (BDI)

This 21-item self-assessment scale is used to evaluate the severity of depressive symptoms in individuals. Turkish validity and reliability of the scale was performed by Hisli (1989). Scale items are scored between 0 and 3 points. High scores indicate the severity of the depression experienced by the individual. It was determined that the Cronbach alpha internal consistency coefficient of the scale was 0.86.

Screen for Child Anxiety Related Disorders (SCARED)

It is a self-report scale developed by Birmaher et al. (1997) and adapted to Turkish by Çakmakçı (2004). This scale consists of 41 items that evaluate a child's anxiety level, each item is scored 0, 1, or 2 based on the severity of the symptom. High total scores indicate the severity of the anxiety.

Suicide Probability Scale (SPS)

It is a Likert type scale which consists of 36 items and is scored between 1 and 4. Its validity and reliability study for the Turkish population was performed by Eskin (1993). Higher scores on the scale indicate a high probability of suicide. Cronbach alpha reliability coefficient of the scale was determined as 0.95.

Serum measurements

Determination of Human Serum S100 Calcium-Binding Protein B (S100B) Levels

S100B levels in human sera were determined by the Enzyme-Linked Immunosorbent Assay kit (Elabscience, Cat No: E-EL-H1297, Lot No: E2Z2REN9I3, Wuhan, China) as per the instructions of the manufacturer. The absorbance of the samples was measured using VERSA (Designed by molecular Devices in California, USA) microplate reader at 450 nm wavelength. Results were expressed in pg/mL.

Determination of Serum Malondialdehyde (MDA) Level

Serum samples were stored at -80°C until the biochemical analysis. The quantity of malondialdehyde in serum samples was determined using the TBARS (Thiobarbituric Acid Reactive Substance) method developed by Yagi (1984). The red color formed as a result of the reaction between lipid peroxidation product (MDA) and thiobarbituric acid (TBA) was measured spectrophotometrically. Serum lipids were precipitated using phosphotungstic acid/sulfuric acid system together with protein to remove water-soluble substances that react with thiobarbituric acid and yield the same color. The amount of serum MDA was determined as nM.

Determination of Total Oxidant Status (TOS)

TOS in serum samples was determined using commercial kits (RelAssay, Cat No: RL0024, Lot Number: KM191110, Gaziantep, Turkey). In this method based on colorimetric measurement principle, the oxidants in the sample oxidize the Fe^{2+} ion-o-dianisidine complex cumulatively to the Fe^{3+} ion. Fe^{3+} ions form a colorful complex with "Xylenol Orange" in acidic environment. The intensity of the color increases in proportion with the amount of oxidant present in the sample and is measured spectrophotometrically. Results were expressed in $\mu\text{molH}_2\text{O}_2$ Equivalent/L.

Determination of Total Antioxidant Status (TAS)

TAS determination was performed in serum pools using colorimetric commercial kits (RelAssay, Cat No: RL0017, Lot No: EM19100, Gaziantep, Turkey). The principle of this measurement method is that the antioxidants in the sample transform the dark blue green ABTS radical into the colorless ABTS form. For example, the total antioxidant level is inversely proportional to the color intensity measured at 660 nm. The standard solution for this method is prepared with Trolox equivalent (Vitamin E analog) and has a standard concentration of 1.0mmol equivalent/L. Results were expressed in mmol trolox equivalent/L.

Oxidative Stress Index (OSI) Calculation

The OSI value was calculated by determining the TOS/TAS ratio. During calculation, the unit of TAS values was converted from mmol trolox equivalent/L to μmol trolox equivalent/L in and calculated using the formula. $\text{OSI} = [(\text{TOS}, \mu\text{mol H}_2\text{O}_2 \text{ equivalent/L}) / (\text{TAS}, \mu\text{mol trolox equivalent/L}) \times 100]$.

Statistical analysis

In statistical evaluations, data obtained by measurement are shown as arithmetic mean \pm standard deviation, and data obtained by counting are shown as percentage (%). The normal distribution of data obtained by the measurement was examined using Kolmogorov-Smirnov test. Student's t-test was used for comparing measurement data with normal distribution between the two groups, and the Mann-Whitney U test was used for those without normal distribution. The effect size of the comparison results was evaluated with Cohen's d test for Student's t-test and χ^2 for the Mann-Whitney U test. Chi-square test was used to compare qualitative data. Pearson's correlation test was used to determine the relationship between variables with normal distribution, and Spearman correlation analysis was used for those without normal distribution. Partial correlation analysis was used to evaluate the relationship between depression severity and serum S100B, MDA, TAS, TOS, and OSI values by eliminating the anxiety factor. The level of significance was accepted as $p < 0.05$. In correlation analysis, if the r value was greater than 0.70, it was evaluated as an excellent relationship; if it was between 0.60–0.70, it was evaluated as a strong relationship; if it was between 0.40–0.60, it was evaluated as a medium relationship; if it was between 0.30–0.40, it was evaluated as a weak, medium relationship; and if it was under 0.30, it was evaluated as a weak relationship. Decisive properties of serum S100B, MDA, TAS, TOS, and OSI values in predicting the diagnosis of depression were examined by Receiver Operating Characteristics (ROC) curve analysis. In evaluation of the area under the curve, cases with Type-1 error level below 5% were interpreted as the diagnostic value of the test was statistically significant.

Ethical consideration

In the first interview with the adolescents, verbal and written information was provided about the study, and consent was obtained from them and their parents. Ethical approval for the study was obtained from the Scientific Research Ethics Committee of University Faculty of Medicine with protocol number 2019/92.

RESULTS

The mean age of the patients included in the study (6 boys, 31 girls) was 14.62 ± 1.62 years, the mean age of the control group (6 boys, 31 girls) was 15.08 ± 0.82 years, and there was no significant difference ($p = 0.263$, $Z = -1.118$). Similarly, body mass index (BMI) of the patients was $22.2 \pm 1.32 \text{ kg/m}^2$, BMI of the healthy participants of the control group was $21.73 \pm 0.96 \text{ kg/m}^2$, and there was no significant difference ($p = 0.360$, $Z = -0.916$). The total mean scores of the patients in the BDI, SCARED and the SPS were significantly higher compared with the controls (Table 1).

Serum S100B, MDA, TOS, and OSI levels of the patients were significantly higher compared with the controls, and TAS levels were significantly lower (Table 2). There was no significant difference in serum parameters between female and male patients.

In the comparison by gender among all participants, it was determined that the TOS and OSI levels of male patients were significantly higher than that of healthy male controls ($t=-2.646$, $p=0.024$; $t=-3.031$, $p=0.013$, respectively), while their TAS levels were significantly lower ($Z=-2.562$, $p=0.009$). Among females, it was determined that S100B, MDA, TOS, and OSI levels of the patients were significantly higher than that of healthy controls ($t=-4.503$, $p<0.001$, $Z=-5.667$, $p<0.001$; $t=-8.902$, $p<0.001$, $t=-8.173$, $p<0.001$, respectively), while there was no significant difference in TAS levels between the patient and control groups.

As a result of the ROC analysis, it was found that all serum parameters were significant variables in predicting the diagnosis of depression (Table 3). There was a positive, moderately significant correlation between the severity of depression and the severity of anxiety and suicide probability (Table 4). In terms of serum parameters, it was shown that there was a negative, weak, medium significant correlation between the severity of anxiety and the S100B level ($r=-0.347$, $p=0.036$). There was no relationship between the severity of depression or the probability of suicide and serum parameters. However, when the effects of anxiety severity were controlled, there was a positive, moderately significant correlation between the severity of depression and S100B ($r=0.529$, $p=0.001$).

Table 1. Comparison of scale scores according to patient and control groups

| | Patient (M±SD) | Control (M±SD) | <i>p</i> | <i>Z</i> | χ^2 |
|---------------------|----------------|----------------|----------|----------|----------|
| BDI ¹ | 26.86±8.84 | 7.38±2.60 | <0.001 | -7.387 | 0.747 |
| SCARED ² | 38.75±9.98 | 13.38±3.11 | <0.001 | -7.397 | 0.749 |
| SPS ³ | 87.62±13.09 | 57.40±8.03 | <0.001 | -7.050 | 0.681 |

¹BDI: Beck depression inventory; ²SCARED: Screen for Child Anxiety Related Disorders; ³SPS: Suicide Probability Scale

Table 2. Comparison of serum parameters according to patient and control groups

| | Patient (M±SD) | Control (M±SD) | <i>p</i> | <i>t</i> | Cohen's <i>d</i> |
|--|----------------|----------------|----------|----------|------------------|
| S100B (pg/mL) | 1137.01±399.48 | 728.67±327.49 | <0.001 | -4.808 | 1.118 |
| MDA ¹ (nM) | 2.51±1.57 | 1.04±0.22 | <0.001 | -5.681* | 0.442** |
| TAS ² (mmol troloks eşdeğeri/L) | 1.30±0.11 | 1.39±0.18 | 0.015 | -2.519 | 0.603 |
| TOS ³ (µmol H2O2 eşdeğeri/L) | 11.19±2.15 | 6.96±1.88 | <0.001 | 9.014 | 2.094 |
| OSI ⁴ | 0.86±0.21 | 0.50±0.14 | <0.001 | 8.626 | 2.017 |

¹MDA: Malondialdehyde; ²TAS: Total Antioxidant Status; ³TOS: Total Oxidant Status; ⁴OSI: Oxidative Stress Index. Mann Whitney U test was used to compare the MDA level, which was not normally distributed; *: *Z* value; **: χ^2 value

Table 3. Area under the curve (AUC) of all serum parameters in ROC analysis

| Parameters | AUC | SE | <i>p</i> | 95% confidence interval | |
|--|-------|-------|----------|-------------------------|-------------|
| | | | | Lower bound | Upper bound |
| S100B (pg/mL) | 0.793 | 0.053 | <0.001 | 0.690 | 0.896 |
| MDA ¹ (nM) | 0.884 | 0.040 | <0.001 | 0.805 | 0.963 |
| TAS ² (mmol troloks eşdeğeri/L) | 0.649 | 0.065 | 0.028 | 0.552 | 0.775 |
| TOS ³ (µmol H2O2 eşdeğeri/L) | 0.950 | 0.023 | <0.001 | 0.904 | 0.993 |
| OSI ⁴ | 0.951 | 0.022 | <0.001 | 0.908 | 0.994 |

¹MDA: Malondialdehyde; ²TAS: Total Antioxidant Status; ³TOS: Total Oxidant Status; ⁴OSI: Oxidative Stress Index

Table 4. Correlation between scale scores and serum parameters of patients

| | BDI | SCARED | SPS | S100B | MDA | TAS | TOS | OSI |
|--|---------|---------|--------|--------|--------|----------|---------|-------|
| BDI ¹ | 1.000 | | | | | | | |
| SCARED ² | 0.461** | 1.000 | | | | | | |
| SPS ³ | 0.517** | 0.234 | 1.000 | | | | | |
| S100B (pg/mL) | 0.280 | -0.347* | 0.122 | 1.000 | | | | |
| MDA ⁴ (nM) | -0.030 | -0.246 | -0.152 | -0.036 | 1.000 | | | |
| TAS ⁵ (mmol troloks eşdeğeri/L) | 0.175 | 0.232 | -0.189 | -0.251 | 0.114 | 1.000 | | |
| TOS ⁶ (µmol H2O2 eşdeğeri/L) | -0.049 | 0.003 | 0.267 | 0.347* | -0.176 | -0.288 | 1.000 | |
| OSI ⁷ | -0.014 | -0.106 | 0.288 | 0.393* | -0.159 | -0.626** | 0.918** | 1.000 |

¹BDI: Beck depression inventory; ²SCARED: Screen for Child Anxiety Related Disorders; ³SPS: Suicide Probability Scale;

⁴MDA: Malondialdehyde; ⁵TAS: Total Antioxidant Status; ⁶TOS: Total Oxidant Status; ⁷OSI: Oxidative Stress Indeks

* $p<0.05$; ** $p<0.01$

DISCUSSION

Variable clinical characteristics of major depression and variables with a wide distribution such as age, lifestyle, triggering psychological stressors, in addition medical and psychiatric disorders accompanying depression in patients limit the studies of biomarker development specific to depression (Lopresti et al. 2014). Studies conducted with adults have focused on malonaldehyde (MDA), 8-OH 2-deoxyguanosine (8-OH-2dG), protein carbonyl content (PCC), 8-iso-prostaglandin F_{2α}, and nitric acid metabolites (NO_x) as oxidative stress indicators; enzyme activities such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase, and peripheral biomarkers such as serum uric acid, ascorbic acid, or plasma total antioxidant potential (TRAP) levels as antioxidant level indicators in the diagnosis of depression (Jordan et al. 2018, Vargas et al. 2013, Tsai & Huang 2016, Wiener et al. 2014, Stefanescu & Ciobica 2012). In these studies, selected patient groups were distributed in a wide age range, study groups included patients with recurrent depression in addition to those diagnosed with first-episode depression as well as patients diagnosed with bipolar depression in addition to patients diagnosed with unipolar depression, and patients with and without psychiatric medication were sometimes evaluated together. There are limited studies which evaluate oxidative stress parameters in adolescents with a diagnosis of depression (Freeda et al. 2017). In our study, all the patients selected are adolescents with a diagnosis of unipolar, first-episode depression who did not use medication or smoke, thus creating a homogeneous patient group. In our study, it is found that MDA, TOS, and OSI levels are significantly higher in adolescents with a diagnosis of depression when compared with their healthy peers, and their TAS levels are lower. In a study which evaluated antioxidant capacity in adolescent patients with depression based on glutathione (GSH) analysis with MRI spectroscopy, it is shown that GSH levels are significantly lower in patients, but not associated with disease severity (Freeda et al. 2017). On the other hand, in a study on adult patients with depression shows that the levels of antioxidant enzymes, such as SOD and GPx, were significantly lower than healthy controls (Yang et al. 2008). In our study the low TAS level in adolescents with depression supports the previous data. In addition, our study showed for the first time that, as an indicator of oxidative stress, MDA levels in adolescent patients with first-episode depression are higher compared to healthy controls. In a study conducted with adults it is shown that MDA level is not different in patients with acute depressive episode compared with their healthy controls (Jordan et al. 2018). There is another study which emphasize that MDA level is higher in patients with first-episode depression when compared with controls, and that it is higher in patients with recurrent depression than the first episode (Stefanescu & Ciobica 2012).

Major depressive disorder is defined as an affective disorder characterized by specific glial changes (Hamidi et al. 2004). S100B is defined as a glial marker that can show glial tissue changes and be measured easily from serum (Schroeter et al. 2013). In a systematic review of studies conducted with adults, it is emphasized that the S100B levels increase in acute depression episodes (Kroksmark & Vinberg 2018). In studies on the S100B level of patients with depression, variable data have been reported in terms of gender. There are studies which report that female patients with depression have higher S100B levels compared to males (Yang et al. 2008) as well as studies which show that there is no difference in gender between the patients (Arolt et al. 2003, Arora et al. 2019). On the other hand, Arora et al. (2019) reported that higher S100B levels were obtained in adult female patients with a diagnosis of depression compared to healthy controls, but the same difference was not detected in male patients. Our study also supports the results of the study by Arora et al. (2019). In addition, in our study, it is found that there is a similar gender difference in terms of MDA level, female patients had higher MDA levels when compared with healthy controls, but this difference was not observed in males. There is no such data regarding MDA levels in the literature. In this respect, it is thought that the results of the study should be supported by further research. Another difference observed specific to gender in our study is that while TAS level did not differ between the female patients and healthy females, it was found to be lower in male patients compared to healthy males. The effect of sex hormones on these results is intriguing. For example, it is reported that estrogen is a neuroprotective agent that limits blood-brain barrier destruction secondary to peripheral inflammation and has antioxidant properties (Maggioli et al. 2016). This effect may explain the different results between genders regarding TAS levels in our study. However, as emphasized in the study by Wiener et al. (2014), it is surprising that despite the antioxidant properties of female sex hormones, TOS and OSI levels are high in women with depression, as in men. It has been suggested that the increased oxidative stress in patients may adversely affect the integrity of the blood-brain barrier, which may result in an increase in serum S100B levels (Rothermundt et al. 2001). Our study has shown that there is a positive correlation between the oxidant levels and S100B, which supports this hypothesis.

Many studies have emphasized that there is no relationship between the S100B levels of patients with depression and the severity of the disease (Arolt et al. 2003, Vargas et al. 2013, Yang et al. 2008). In addition, it is emphasized that the baseline S100B levels of the patients are associated with good treatment response, and that high S100B level is not a status marker for disease severity, but a follow-up marker for treatment response (Arolt et al. 2003, Jang et al. 2008). On the other hand, it is emphasized that increased S100B levels in response to

impaired neuroplasticity act as a compensatory agent in patients with depression and may be an indicator of the regeneration process (Jang et al. 2008, Kroksmark & Vinberg 2018, Rothermundt et al. 2001). In our study, it is shown that there is no relationship between the severity of depression and the S100B levels of the patients. However, there is a weak-moderate, negative correlation between the anxiety severity of the patients and the S100B level. This result is inconsistent with other research data in the literature. Studies demonstrate that there is no relationship between the severity of anxiety, as well as the severity of depression, and the S100B level (Jang et al. 2008, Yang et al. 2008, Arora et al. 2019). Interestingly, in this study, there is a moderate positive correlation between depression severity and S100B when the effect of anxiety severity is controlled. These results raise the question of whether anxiety, which accompanies patients with depression, negatively affects regeneration. New data and molecular level evidence are needed to support this conclusion. Lastly, in a study which evaluated the relationship between suicide probability and S100B level in adolescent patients with affective disorder or schizophrenia, it was suggested that the S100B level could be used as a biomarker for suicide risk (Falcone et al. 2010). In our study, there is no significant relationship between the severity of suicide probability and S100B. It is thought that the difference between studies in terms of patient selection criteria may have caused this result. For example, patients who attempted suicide by taking high doses of medication in the last week were excluded from our study. Only adolescents diagnosed with first-episode unipolar depression were included in our study, and additional diagnoses other than anxiety were excluded. In the study by Falcone et al. (2010), patients who had attempted suicide and had comorbid psychiatric disorders were not an exclusion criterion, and it was reported that patients were diagnosed with affective disorder, but determinants such as bipolar, unipolar, first or recurrent episodes were not defined.

This study presents a number of new results as well as results that support previous studies conducted with adult patients with depression. However, limitations of the study should be noted while interpreting the results of the study. The most important limitation of this study is the small sample size. In addition, comorbid anxiety disorders of the patients were not excluded, instead, the severity of anxiety symptoms were evaluated globally using a self-reporting scale. Furthermore, the evaluation of suicide probability of the patients using a self-reporting scale resulted in coding bias.

CONCLUSIONS

In this study conducted with drug-naïve adolescents diagnosed with first-episode unipolar major depression, it is shown that serum S100B, MDA, TOS, and OSI levels are higher in patients when compared with their healthy controls, TAS levels are lower; however, there was no

relationship between the patients' severity of depression or suicide probability and these parameters. In addition, it is found that there is a weak-moderate negative correlation between the anxiety severity of the patients and serum S100B, and a moderate positive correlation between S100B and the severity of depression when the anxiety severity is controlled. While there is no difference in serum parameters between females and males with depression, it is found that the serum S100B, MDA, TOS, and OSI levels of females with depression are higher than their healthy peers, and the TAS level is not different. It is found that males with depression had higher TOS and OSI levels and lower TAS levels as compared with their healthy peers. Finally, as a result of the ROC analysis, it was found that TOS and OSI levels had a diagnostic value in predicting depression episodes on non-smoker adolescents.

In conclusion, the results of this study have raised the questions of whether a gender-specific biomarker can be determined in patients with depression in the future, whether the levels of increased S100B and oxidative stress parameters in patients after treatment will be similar compared to healthy individuals, and whether these parameters can be used in the follow-up of patients and in determining the recurrence of depression. It is concluded that further research is needed on these issues, and that the gender-specific differences in terms of S100B and MDA shown in this study should be supported by further studies.

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Contribution of individual authors:

Çilem Bilginer: study conception and design, analysis, the first draft.

Hüseyin Yaman: study conception and design, analysis.

Serkan Karadeniz, Sevda Hızarcı Bulut, Serap Özer Yaman & Sevil Aydoğdu: material preparation, data collection.

All authors approved the final manuscript.

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