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Evaluation of Oxidative Stress in Bipolar Disorder in terms of Total Oxidant Status, Total Antioxidant Status, and Oxidative Stress Index

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ABSTRACT

Introduction: Bipolar disorder is one of the most debilitating psychiatric disorders characterized by disruptive episodes of mania/hypomania and depression. Considering the complex role of biological and environmental factors in the etiology of affective disorders, recent studies have focused on oxidative stress, which may damage nerve cell components and take part in pathophysiology. The aim of the present study was to contribute to the data about oxidative stress in bipolar disorder by detecting the total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) levels of manic episode (ME) and euthymic (EU) patients and by comparing these results with those of healthy controls (HCs).

Methods: The study population consisted of 28 EU outpatients meeting the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for bipolar disorder I and 23 inpatients who were currently hospitalized in a psychiatry ward with the diagnosis of the bipolar disorder ME according to the DSM-5 criteria. Forty-three healthy subjects were included in the study as the control group (HC). Serum TAS, TOS, and OSI levels of all the participants were determined.

Results: Statistical analysis of serum TAS, TOS, and OSI levels did not show any significant differences between the ME patients, EU patients, and HCs. Comparison between the bipolar disorder patients (ME+EU) and HC also did not reveal any statistically significant difference between these two groups in terms of serum TAS, TOS, and OSI levels.

Conclusion: To date, studies on oxidative stress in bipolar disorder have led to controversial results. In the present study, no statistically significant difference was detected between the oxidative parameters of bipolar disorder patients and HCs. In order to comprehensively evaluate oxidative stress in bipolar disorder, further studies are needed.

Keywords: Bipolar disorder, total antioxidant status, total oxidant status, oxidative stress

INTRODUCTION

Bipolar disorder (BD) is one of the most debilitating psychiatric disorders characterized by disruptive episodes of mania/hypomania and depression (1). Owing to unclear pathophysiology, the roles of inflammatory processes and oxidative stress are under investigation along with many other possible etiologic factors (2,3). Oxidative stress presents with an interruption of the balance between antioxidant and pro-oxidant processes, resulting in the production of free radicals and reactive oxygen species (ROS), which may damage cell components [enzymes, receptors, lipids, deoxyribonucleic acid (DNA)] (4). Under normal circumstances, cellular enzymatic and non-enzymatic antioxidant defenses eliminate ROS. As part of the enzymatic mechanisms, superoxide dismutase (SOD) converts the superoxide radical into hydrogen peroxide and catalase and glutathione peroxidase metabolize H_2O_2 into H_2O+O_2 (5). Failure to eliminate ROS can cause oxidative cell injury such as the peroxidation of lipids (membranes and organelles), proteins (receptors and enzymes), and DNA (6). The main sources of ROS in the human body are oxidative phosphorylation in the mitochondria and the activity of some enzymes such as xanthine oxidase (XO), NADPH oxidase, and cytochromes P450 (CYPs). ROS are difficult to measure directly because of their short half-lives; therefore, it is preferable to search for and determine the indirect markers of oxidative stress (7). The total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) are the key factors reflecting the redox balance between oxidation and antioxidation. TAS is an indicator of the activity of all antioxidants; TOS is an indicator of ROS; and OSI is the ratio of TOS to TAS and indicates the level of oxidative stress (8).

Considering the complex role of biological and environmental factors in the etiology of affective disorders, recent research has focused on oxidative stress, which may damage nerve cell components and take part in pathophysiology (9). Evidence about oxidative stress in BD, however, is controversial. Andreazza et al. (10) reported higher SOD levels and Machado-Vieira et al. (11) reported higher SOD and catalase levels in manic episode (ME) patients than in healthy controls (HCs), whereas Gergerlioglu et al. (12) revealed lower SOD levels in ME patients. Yumru et al. (13) detected higher serum TAS in euthymic (EU) BD patients than in HCs, whereas Kunz et al. (14) could not find any statistically significant difference in the serum SOD levels between EU BD patients and HCs. In the same study (14), the serum SOD levels in depressive and manic patients were significantly higher than those in HCs.

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The aim of the present study was to contribute to the data about oxidative stress in BD by detecting TAS, TOS, and OSI of ME and EU patients and by comparing these results with those of HCs.

METHODS

Participants

The study population consisted of 28 EU outpatients who had applied to the psychiatry department outpatient clinic between June 2014 and December 2014 and who met the DSM-5 criteria for BD I, together with 23 inpatients who were already hospitalized in the psychiatry ward with the diagnosis of a BD ME according to DSM-5 criteria. Forty-three healthy subjects who applied to the Department of Family Medicine for routine follow-up were included as the control group (HCs). The inclusion criteria were: being between 18 and 65 years old and having no dementia or cognitive deterioration. The exclusion criteria were: antioxidant treatment or vitamin supplementation history for 6 months prior to inclusion, history of alcohol or drug dependence or traumatic head injury, any past or present major medical (atherosclerosis, diabetes mellitus, hypertension, …) or neurological illness, and any additional psychiatric disorder or mental retardation. Two trained psychiatrists separately interviewed the patients to confirm the ME patients' (n=23) diagnosis and to corroborate that the outpatients (n=28) did not meet the DSM-5 criteria of any BD episode (depressive, manic, or hypomanic) for at least 6 months and that the control group participants (n=43) had no evidence of a present or previous psychiatric disease. The Hamilton Depression Rating Scale (HAM-D) and Young Mania Rating Scale (YMRS) were also used to strengthen the EU mood (HAM-D<7, YMRS<4) and ME (YMRS>20) diagnoses.

The study was approved by Ankara Numune Training and Research Hospital's local ethics committee. All the participants were competent enough to provide written informed consent, which was obtained after a full explanation of the study procedures.

Instruments

Hamilton Depression Rating Scale (HAM-D): The original version of the scale, which was designed by Hamilton in 1960, contains 17 items, each of which is scored as 0–4; the maximum total score is 53. Williams (15) developed a new version of the HDRS to improve the interrater reliability (Structured Interview for Hamilton Depression Rating Scale-21). The Turkish version of the scale was reported to be valid and reliable (16). In this study patients, were evaluated with the 17-item version.

Young Mania Rating Scale (YMRS): YMRS is an 11-item diagnostic questionnaire used to measure the severity of MEs. Each scale item measures 5 degrees of severity. Five items are answered using a 5-point Likert-type scale items and the other four items use a 9-point Likert-type scale. The Turkish version of the scale was reported to be valid and reliable (17).

Biochemical Analysis

Blood samples were drawn in the morning around 8 a.m. from a forearm vein of the participants at the end of an overnight fasting period of at least 12 hours. Venous blood samples were collected in vacutainer tubes and centrifuged at 1300 g for 10 minutes. Sera were separated and stored at -20°C until analysis.

Total antioxidant capacity of plasma was measured using a novel automated colorimetric measurement method for TAS developed by Erel (18), which measures the total antioxidant capacity of the body against powerful free radicals. Fe2+-o-dianisidine complex gives a Fenton-type reaction with hydrogen peroxide to form the OH radical. The powerful ROS react with the colorless o-dianisidine molecule at the reducing low pH, leading to the formation of yellow-brown dianisidyl radicals. Dianisidyl radicals participate in further oxidation reactions resulting in more color formation. However, antioxidants in the samples suppress these oxidation reactions and inhibit color formation. This reaction is spectrophotometrically measured in automatic analyzers (13).

The TAS results are expressed as mmol Trolox Eq/L. Serum TAS levels were measured by a fully automated third generation colorimetric assay (Rel Assay Diagnostics, Turkey) in a chemistry system analyzer (Beckman Coulter AU680, Tokyo, Japan).

TOS of plasma was measured using a novel automated colorimetric measurement method for TOS developed by Erel (8). The oxidants in the sample oxidize the ferrous ion-odianisidine complex to ferric ion. The glycerol in the media accelerates this reaction about three-fold. Ferric ions form a colored compound with xylenol orange in the acidic media. This color is associated with the amount of oxidant in the sample and is measured spectrophotometrically (13).

The TOS results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L). Serum TOS levels were measured by a fully automated third-generation colorimetric assay (Rel Assay Diagnostics, Turkey) in a chemistry system analyzer (Beckman Coulter AU680, Tokyo, Japan).

The ratio of TOS to TAS was accepted as OSI. For the calculations, the resulting unit of TAS was converted to mmol/L, and the OSI value was calculated according to the following formula (19): OSI (arbitrary unit) =TOS (μmol H_2O_2 Eq/L) / TAS (mmol Trolox Eq/L).

Statistical Analysis

The findings of the present study were analyzed with "The Statistical Package for Social Sciences for Windows" (SPSS Inc; Chicago, IL, USA) version 18 software. Nominal values were evaluated with Pearson's chi-squared test. The conformity of continuous variables to normal distribution was tested with the Kolmogorov–Smirnov test. Continuous variables were expressed as the median (min–max) and were compared between the three groups by the Kruskal–Wallis test for all non-parametric variables. The presence of a statistically significant difference between the two groups (BD patients and HCs) in terms of continuous variables was examined with the Mann–Whitney U test for all non-parametric variables. The presence of a correlation between the groups was searched with using the Spearman's rho tests. $p<0.05$ was considered the threshold of statistical significance for all the tests.

RESULTS

There were 23 patients (11 male, 12 female) in the ME group, 28 patients (16 male, 12 female) in the EU group, and 43 participants (32 male, 11 female) in the HC group. The mean ages in the ME, EU, and HC groups 33 (18–60), 37.5 (24–62), and 36 (19–61) years, respectively, and the groups were statistically similar in terms of age (p=0.11). The groups (ME, EU, HC) were also statistically similar in terms of gender (p=0.079) (Table 1). All the patients were undergoing mood-stabilizing treatments.

The oxidative parameters of patients and HCs are given in Tables 1 and 2. Statistical analysis of the serum TAS and TOS levels did not show any significant difference among ME, EU, and HC groups (p=0.06 for TAS and p=0.31 for TOS) (Table 1). In addition, the OSI values of these three groups were not significantly different (p=0.47) (Table 1).

Participants in the ME and EU groups together were then classified as BD patients (BP) (n=51) and compared with HCs. The mean ages in these two groups were similar (p=0.78), while there was a significant difference between the two groups in terms of gender: the male/female ratio was higher in HCs (p=0.032). Furthermore, there was no statistically significant difference among TAS, TOS, and OSI parameters of BP and HC groups (p=0.31 for TAS, p=0.22 for TOS, p=0.22 for OSI) (Table 2).

DISCUSSION

Since researchers started to focus on oxidative stress in psychiatric disorders, many studies have shown that oxidative imbalance might be involved in the pathophysiology of those diseases, especially schizophrenia (5), BD (6), and depressive disorder (20). In a recent paper (21), oxidative stress markers were included as potential biomarkers for BD. SOD, which is an enzyme that plays a role in the conversion of superoxide radical into hydrogen peroxide, was detected at higher levels in BD manic and depressive episode patients than in HCs and EU BD patients by Kunz et al. (14). In the same study, the levels of thiobarbituric acid reactive substances (TBARS), which is a marker of lipid peroxidation, were also found to be higher than in HCs in manic, depressive, and EU patients. SOD was also reported to be elevated in drug-free manic patients by Machado-Vieira et al. (11), while Raffa et al. (22) found no statistically significant difference between BD patients and HCs, and Gergerlioglu et al. (12) reported lower serum SOD levels in ME patients compared with HCs. The same controversial results were also encountered for other oxidative stress markers such as lipid peroxidation and nitric oxide. Banerjee et al. (23) reported significantly increased lipid peroxidation in BD patients, and stated lithium treatment leads to an improvement in this increment. Some other studies about lipid peroxidation reached similar results (14, 24); whereas Magalhaes et al. (25) reported no significantly different lipid peroxidation levels between BD patients and HCs. Nitric oxide (NO) radicals, which are produced by the oxidation of one of the terminal guanidonitrogen atoms of L-arginin, were also found to be at a higher level in BD patients than in HCs in some studies (12,26). Gergerlioglu et al. (12) determined a significant correlation between NO levels of ME patients and the existence of a delusion, and consequently argued that increased NO levels may lead to such an effect via a glutamate pathway. In addition to these results, oxidative imbalance in BD was shown to improve with appropriate treatment (27).

To the best of our knowledge, to date, TAS, TOS, and OSI values in bipolar patients were evaluated only in a few studies. In the present study, statistical analysis revealed no significant difference between EU patients, ME patients, and HCs in terms of serum TAS, TOS, and OSI levels. Kalelioglu et al. (28) previously compared these oxidative parameters of ME patients and HCs, but did not include any EU patient in their study design. They detected decreased TAS values in ME patients than in HCs and reported that OSI values were increased following not electroconvulsive therapy but antipsychotic treatment. They considered that the increased OSI levels might be due to the use of antipsychotics. In the same study (28), similar with our results, no significant difference was reported between ME patients and HCs in terms of serum TOS and OSI levels. Yumru et al. (13) investigated TAS, TOS, and OSI levels of EU BD patients according to subtypes of disorder (BD I, BD II, and previous antidepressant-induced mania). In contrast with our results showing similar TAS, TOS, and OSI levels in EU and HC, they reported that the TAS, TOS, and OSI levels of EU BD I patients were higher than those of the HC group.

Our results did not show any significant difference in TAS, TOS, and OSI levels between BP (EU+ME) and HC groups. To the best of our knowledge, there is no other previous study investigating TAS, TOS, and OSI levels of BD patients by combining EU and ME patients as a single group and comparing them with HCs. Yumru et al. (13) determined higher TAS, TOS, and OSI levels in EU bipolar patients than in HCs. Unlike our study, they did not include any ME patient as a participant, and also their patient group consisted of not only EU bipolar I patients but also EU bipolar II

Table 1. Demographical features and oxidative parameters of manic episode patients, euthymic patients, and healthy controls

	Manic episode n=23	Euthymia n=28	Healthy controls n=43	p
Gender	11 M/12 F	16M/12F	32 M/11 F	0.079*
Age	33 (18–60)	37.5 (24–62)	36 (19–61)	0.11**
TAS	1.39 (1.1–1.81)	1.48 (1.2–2.07)	1.5 (1.2–2.12)	0.06**
TOS	2.8 (1.01–7.01)	2.95 (1.51–7.18)	3.1 (1.17–9.61)	0.31**
OSI	1.89 (0.6–4.64)	1.96 (0.95–4.43)	2.1 (0.8–6.62)	0.47**

*p value determined by chi-square test, **p value determined by Kruskal–Wallis test. M: male; F: female; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index.

Table 2. Demographical features and oxidative parameters of bipolar disorder patients and healthy controls

	Bipolar disorder patients (mania and euthymia) n=51	Healthy controls n=43	p
Gender	27 M/24 F	32 M/11 F	0.032*
Age	35 (18–62)	36 (19–61)	0.78**
TAS	1.43 (1.1–2.07)	1.5 (1.2–2.12)	0.31**
TOS	2.93 (1.01–7.18)	3.1 (1.17–9.61)	0.22**
OSI	1.95 (0.61–4.64)	2.1 (0.8–6.62)	0.22**

*p value determined by chi-square test, **p value determined by Mann–Whitney U test. M: male; F: female; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index.

patients and EU patients who had antidepressant-induced mania history. They interpreted their results as follows: high TOS levels meant increased oxidants in BD, and that the TAS value was high due to the reactive increment in order to balance the system, but this reactive increment in antioxidants was not sufficient, therefore OSI was also higher in the patient group, indicating the impairment of the system in favor of oxidants. Yumru et al. (13) also determined a negative correlation between the number of total episodes in BD I and TAS, similar with another previous study (12), indicating that there was a negative correlation between SOD and the number of previous MEs.

We would also like to point out that, when our participants were divided into two groups, BP and HC, these groups were not similar in terms of gender and male predominance in the HC group might have affected our results. Despite a number of existing studies, the impact of gender on oxidative processes is not certainly defined yet. Bengesser et al. (29) reported that male bipolar patients in EU phase had significantly higher peripheral markers of oxidative stress than for EU bipolar women. Additionally, in metabolic syndrome patients, Kaya et al. (30) pointed out a higher OSI in men than women. Nevertheless, the study of Vasalle et al. (31) detected a higher oxidative index in women than in men. In a large population based epidemiologic study on oxidative stress markers, Trevisan et al. (32) detected no significant difference between the two sexes for TBARS and glutathione peroxidase. With reference to these data, the dissimilarity of the male/female ratio between bipolar patients and HCs seems to be a limitation of our study.

In spite of some other studies (13,14) reporting significant alterations of TAS, TOS, and OSI values in bipolar patients, our results did not show a statistically significant difference between EU BD I patients, ME patients, and HCs in terms of serum TAS, TOS, and OSI. This incompatibility between our results and previous literature might be due to our small sample size. Also the different male/female ratio between bipolar patients and HCs might have contributed. Since all the patients in the present study were using mood stabilizers, the aforementioned incompatibility also might depend on the potential antioxidative effects (11) of the mood-stabilizing drugs.

The limitations of the present study are thus its small sample size, lack of an age- and sex-matched control group, and difficulties in eradicating other oxidative stress-related factors, such as nutrition and lifestyle.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Numune Training and Research Hospital (2014/920).

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

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