Psychiatry and Behavioral Sciences 2021;11(4):249-257

Doi: 10.5455/PBS.20210610075010

ORIGINAL RESEARCH

Oxidative Metabolism and Oxidative DNA Damage in Bipolar Disorder: There are No Difference in Acute and Euthymic State

Berna Ermis[1], Eser Sagaltici[2], Ahmet Unal[3], Demet Alici[4], Ayse Binnur Ozyurt[5]

[1] *Psychiatry Specialties Clinic, Bursa, Turkey*

[2] *Bagcilar Training and Research Hospital, Department of Psychiatry, Istanbul, Turkey*

[3] *Inonu University, Faculty of Medicine, Department of Psychiatry, Malatya, Turkey*

[4] *Psychiatry Specialties Clinic, Gaziantep, Turkey*

[5] *Gaziantep University, Faculty of Medicine, Department of Medical Biochemistry, Gaziantep, Turkey*

Abstract

Objective: This study aimed to investigate oxidative metabolism and oxidative DNA damage in the state of euthymic and active disease in patients with Bipolar disorder (BD).

Methods: 40 active (26 mania and14 depression episodes) and 40 euthymic state of disease of the 80 patients with BD and 48 healthy volunteers were included to the study. Measurement of the levels of serum total antioxidant (TAS) and serum total oxidant (TOS), Oxidative Stress Index (OSI), and 8-hydroxy-2-deoxyguanosine (8-OHdG) levels were calculated and evaluated. Hamilton Depression Rating Scale (HAM-D), Young Mania Rating Scale (YMRS) and Clinical Global Impression Scale (CGI) were administered.

Results: In patients with BD, TAS, TOS, OSI, and 8-OHdG levels were significantly higher than controls (all $p<0.001$). TOS level significantly higher in female than men in BD ($p=0.016$). A significantly positive weak correlation was detected between the TAS level and CGI score ($p=0.031$, $r=0.241$), HAM-D score ($p=0.040$, $r=0.231$) in BD. When patients in the active and euthymic state were compared with the control group separately, in both groups TAS, TOS, OSI, and 8-OHdG levels were significantly higher than controls (all $p<0.001$). However, there was no significant difference in TOS, OSI, and 8-OHdG levels between patients in the active or euthymic state of disease.

Conclusion: Oxidants and DNA damage are high in patient with BD. No difference of the oxidants and DNA damage between the active and euthymic state of disease reveals that oxidative stress damages on the body although the symptoms of the disease to quiet down.

Keywords: Bipolar Disorder, Oxidative Stress, Level of Total Antioxidant, Level of Total Oxidant, Oxidative DNA Damage, 8-hydroxydeoxyguanosine

INTRODUCTION

Bipolar disorder (BD) is a psychiatric illness that affects approximately 2.4% of the world population, which often follows a chronic course with recurrent manic, hypomanic, depressive and mixed state, and can lead to serious impairments in functionality (1). It is thought that the etiology of BD is not well understood. With all those, genetic, environmental, neurobiological and neurochemical factors are mentioned for the etiology of BD in last decade and these evidences are increasing gradually (2).

Corresponding Author: Eser Sagaltici

Bagcilar Training and Research Hospital, Department of Psychiatry, Istanbul, Turkey.

E-mail: dresersagaltici@yahoo.com

Citation: Ermis B, Sagaltici E, Unal A, Alici D, Ozyurt AB. Oxidative Metabolism and Oxidative DNA Damage in Bipolar Disorder: There are No Difference in Acute and Euthymic State. Psychiatry and Behavioral Sciences 2021;11(4):249-257.
Doi: 10.5455/PBS.20210610075010

Received: Jun 10, 2021
Accepted: Oct 31, 2021

Although oxygen metabolism is essential for life, it has been shown that reactive oxygen species (ROS) damage many biological molecules such as important proteins, membrane lipids, resulting protein breakdown and loss of the membrane integration and all of these are resulting in cell death. Antioxidant substances, on the other hand, have the ability to capture and stabilize free radicals against the damage of ROS and prevent oxidation (3). Basically, the oxidative stress can be an imbalance between the antioxidant system of the body and free radicals are occurred by lipid peroxidation reactions (4). Oxidative stress leads to multiple forms of DNA damage including base modifications, deletions, strand breakage and chromosomal rearrangements (5). 8-hydroxy-2-deoxyguanosine (8-OHdG) OH radical is the most common DNA lesion formed by free oxygen and single electron oxidants. 8-OHdG represents major oxidative DNA damage repair products such as base excision repair, nucleotide excision repair. It is generally accepted that the oxidative damaged DNA can be repaired, the repair

products are released into the bloodstream and pass from there to urine without being further metabolized (6). In BD patients, high levels of 8-OHdG have been reported in bloodstream and urine (7).

It has been reported that oxidative stress may be involved in the pathophysiology of many psychiatric disorders including schizophrenia, depression, anxiety, social phobia, adult attention deficit and hyperactivity disorder, dementia, and substance abuse (8-10). Although inconsistency has been reported in the results of studies on oxidative stress markers in BD, the idea that oxidative stress markers are potential biomarkers for BD still maintains its current value (11). In a metanalysis performed by Andreazza et al. (2008), a statistically significant increase in lipid peroxidation and nitric oxide has been shown in BD (12). Some studies have detected oxidative damage in DNA, RNA, protein and lipids in BD patients, while others have reported changes in important antioxidant enzymes. These results are supported by evidence such as mitochondrial DNA mutations and reduced levels of protein from the mitochondrial electron transport chain (13, 14). BD is a multifactorial disease of uncertain etiology. Knowing the factors that contribute to the pathophysiology of BD allows clinicians to identify patients who are more likely to develop BD or to better treat. Ideally, the identification of certain etiological factors for BD will interfere with the individual or at the level of the population to prevent the development of the disease and improve outcomes with earlier treatment. In this study, we aimed to investigate oxidative metabolism and oxidative DNA damage during active (manic or depressive episode) and euthymic state of BD.

METHODS

Study Participants

The purpose of the study was explained to the participants and informed consent forms were obtained for all participants before participating in the study. This research was approved by the ethics committee of Gaziantep University (IRB Number: 10-2011/176; IRB Date: 25.10.2011) and was conducted in accordance with the Helsinki Declaration. Eighty patients (inpatients or outpatients) with BD type I were recruited from the Department of Psychiatry in the University of Gaziantep. Of these, 40 were active state (24 of manic and 16 of depressive episodes) and 40 were euthymic state patients. A comparison group with 48 healthy volunteers was also recruited. Psychiatric diagnosis was based on clinical interview and confirmed with the Structured Clinical Interview for DSM-IV-Axis I (SCID-I) (15). Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HAM-D), respectively. Acute manic or depressive episodes were defined by DSM-IV-TR criteria. Patients were divided into two different groups according to the following criteria: 1) euthymia group should not fulfill DSM-IV criteria for mood episode and should have scored HAM-D≤7 and YMRS≤6 for at least 6 weeks; 2) active group; a) manic episode should have YMRS≥20 and HAM-D≤7 and, b) depressive episode should have HAM-D≥17 and YMRS≤6. Patients in mixed episodes were not included.

Patients who are not between 18-65 years of age, have any other axis I disorder, patients with severe medical conditions such as hyperthyroidism, hypothyroidism, diabetes or other endocrinopathies, patients with alcohol, substance abuse, pregnant women, mental retardation, history of severe head trauma, use of antioxidant agents (vitamin E, vitamin C, N-acetyl cysteine), use of xanthine oxidase inhibitors (allopurinol, folic acid), those with severe neurological diseases (epilepsy, parkinson disease, etc.), advanced obese and involuntary candidates were excluded from the study.

The healthy comparison group was screened for psychiatric disorders using SCID-I, non-patient version. The control group of healthy volunteers was recruited from people with no history of psychiatric disorders, no substance abuse (current or in the past) and no additional medical illness or history, with none of the above-mentioned conditions and with no psychiatric disorders in first degree relatives.

Clinical Measures

Sociodemographic and clinical characteristics form such as; patients' age, gender, education level, marital status, professional status, socio-demographic data like smoking and drugs used, hospitalization history, disease duration, active state of the disease, number of previous manic and depressive episodes, history of suicide and body mass index were evaluated in the form created by the authors. HAM-D is a 17-questions scale that measures the level of depression and changes in severity (16, 17). YMRS is a scale prepared by the interviewer to measure the severity and change of the manic situation. It consists of 11 items in total (18, 19). Clinical global impression scale (CGI) is a 3-item scale in which the severity of the disease or improvement in the symptoms of the disease is generally evaluated. Based on his general experience with the disease, the interviewer ranks the severity of the disease or the degree of recovery from 0 (not patient) to 7 (the most severe patients) (20).

Blood Samples and Measurement

Patient and control group blood samples were taken from the antecubital vein between 08.00 a.m and 10.00 a.m after a 12-hour fasting period. The blood samples were transferred to plain biochemistry tubes (gel separator) and their serum was separated by centrifugation at 4000 rpm for 10 minutes in no more than 45 minutes after sampling. The separated serums were immediately stored at – 80 °C. TAS and TOS measurements were performed on the Tokyo Boeki Prestige I24 autoanalyzer with Rel Assay Diagnostics fully automatic TAS (Total Antioxidant Status) kit. Serum TAS was determined using an automated measurement method developed by Erel (21) and expressed as mmol Trolox equivalent / L. Plasma TOS was determined using a method previously described by Erel (22) and expressed as µmol H2O2 equivalent / L. OSI was calculated from TOS and TAS values: OSI = [(TOS, µmol H2O2 equivalent / L) / (TAS, µmol Trolox equivalent / L)] × 100. Serum 8-OHdG measurements were performed with Elx 800 instrument (Bio Tek Instruments, Winooski, VT , USA) with Northwest kit (Northwest, NWLSS 8-OHdG ELISA High Sensitivity Kit, Vancouver, Canada) and it was expressed as ng/mL.

Statistical Analysis

The collected data were analyzed using the Statistical Package for the Social Sciences version 20.0 (SPSS 20.0, Chicago, IL). Descriptive statistics were presented as frequency, percentage, mean, standard deviation. The Chi-square test was used to test possible differences between groups in terms of categorical variables. Student's t-test was utilized for comparing the continuous variables. The normality of distribution for continuous variables was tested by the Kolmogorov–Smirnov test. Comparisons of non-normally distributed variables were made with the Mann-Whitney U test. One-way ANOVA was adopted for multiple comparisons, and Tukey's HSD test was used to determine the source of the difference. Analysis of covariance (ANCOVA) was used to investigate the effect of age, gender, smoking and body mass index on the TAS, TOS, OSI and 8-OHdG levels. To assess the relationship between variables, Pearson and Spearman's correlation analysis was used. For all statistical data, P<0.05 was considered significant.

RESULTS

80 BD patients and 48 healthy volunteers were included in the analysis. Among the 80 BD patients, 40 were active (26 mania and 14 depression episodes) and 40 were euthymic state. There were no statistically significant differences in terms of age, gender, smoking status, and body mass index between acute state group (ASG), euthymic state group (ESG) and control group (CG) (Table 1).

Tablo 1. Comparisons of age, gender, BMI and smoking status of acute episode, euthymic and control group

	ASG (n=40) n (%)/ mean±SD	ESG (n=40) n (%)/ mean±SD	CG (n=48) n (%)/ mean±SD	p
Gender				0.404
Females	14 (35.0)	19 (47.5)	23 (47.9)	
Males	26 (65.0)	21 (52.5)	25 (52.1)	
Smoking				0.215
No	17(42.5)	24(60.0)	28(58.3)	
Yes	23(57.5)	16(40.0)	20(41.7)	
Age (years)	30.33±9.93	31.65±8.76	30.85±6.70	0.780
BMI (kg/m^2)	25.98±6.88	26.90 ± 3.69	24.75±3.46	0.118

BMI: body mass index; ASG: acute state group; ESG: euthymic state group; CG: control group. Chi-squared (X^2) and ANOVA tests were used.

Sociodemographic and clinical characteristics of the ASG and ESG patients are described in Table 2. There was statistically difference between ASG and ESG in YMRS (ASG: 23.28±17.71, ESG: 0.28±0.64, p<0.001), HAMD (ASG: 8.23±11.72, ESG: 0.65±1.00, p<0.001) and CGI (ASG: 5.58±1.03, ESG: 1.13±0.33, p<0.001) scores.

When the TAS (BDP: 2.36±0,22, control group (CG): 2.02±0.20, p<0.001), TOS (BDP: 14.03±4.77, CG: 5.39±1.37, p<0.001), OSİ (BDP: 5.98±2.111, CG: 2.68±0.76, p<0.001) and 8-OHdG (BDP: 11.81±5.03, CG: 7.55±3.13 p<0.001) levels were compared between BD patients (including ASG and ESG) (BDP) and the CG, significant higher was found in all of the parameter levels among BDP (Table 3).

We compared the differences of TAS, TOS, OSI and 8-OHdG across groups. One-way ANOVA analysis showed significant differences among groups. Post hoc tests to test pairwise comparisons revealed that TAS, TOS, OSI and 8-OHdG levels in ASG and ESG were significantly higher than CG group (p<0.001). There was no significant difference for TAS, TOS, OSI and 8-OHdG levels between ASG and ESG (respective p values= 0.062, 0.233, 0.616 and 0.463) (Table 4).

Age-gender-smoking, and BMI adjusted TAS, TOS, OSI, 8-OHdG levels of ANCOVA results are shown in Table 5.

A significantly positive correlation was detected between the TAS level and CGI (p=0.031, r=0.241), HAMD (p=0.040, r=0.231) in BDP. In addition, TOS level significantly higher in female than men in BDP (p=0.016). No significant correlations were found among TAS, TOS, OSİ, 8-OHdG levels and age, disease duration, age at disease onset, education level, ages of onset for BD, disease duration, previous number of hospitalizations, previous number of manic episodes, previous number of depressive episodes, previous total number of episodes among BDP.

Table 2. Sociodemographic and clinical characteristics of acute episode and euthymic group patients

	ASG (n=40) n (%)/ mean±SD	ESG (n=40) n (%)/ mean±SD	p
Marital Status			0.823
Married	18 (45)	19 (47.5)	
Single	22 (55)	21 (52.5)	
Working status			0.704
Working	17(42.5)	19(47.5)	
Not working	16(40.0)	13(32.5)	
Student	7(17.5)	8(20)	
History of Hospitalization			0.284
No	7(17.5)	11(27.5)	
Yes	33(82.5)	29(72.5)	
Previous suicide attempt			0.820
No	23(57.5)	24(60.0)	
Yes	17(42.5)	16(40.0)	
Family history of psychiatric disorders			1.000
No	28(70.0)	28(70.0)	
Yes	12(30.0)	12(30.0)	
Medication			0.109
MS	3(7.5)	3(7.5)	
AP	21(52.5)	12(30.0)	
MS+AP	16(40.0)	25(62.5)	
Education Level (years)	9.45±3.90	9.63±4.14	0.846
Ages of onset for BD (years)	21.80±6.28	23.4±8.3	0.314
Disease duration (years)	7.38±8.75	7.85±5.29	0.770
Previous number of hospitalizations	1.73±1.60	2.08±2.03	0.395
Previous number of manic episodes	4.50±4.64	4.45±3.96	0.959
Previous number of depressive episodes	4.25±6.55	3.35±4.36	0.472
Previous total number of episodes	8.75±10.22	7.80±7.37	0.635
CGI	5.58±1.03	1.13±0.33	<0.001*
YMRS	23.28±17.71	0.28±0.64	<0.001*
HAMD	8.23±11.72	0.65±1.00	<0.001*

Chi-squared (X^2), Student's t-test and Mann–Whitney U Test were used. ASG: acute state group; ESG: euthymic state group; CG: control group; MS: mood-stabilizers as mono – therapy (lithium or valproate); AP: antipsychotic mono – therapy; MS+AP: mood – stabilizer in combination with a second generation-antipsychotic; BD: bipolar disorder; HAMD: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; CGI: Clinical Global Impressions. *p<0.001.

Table 3. Comparisons of TAS, TOS, OSI and 8-OHdG levels in BD patients and control group

	BD patients (n=80) mean±SD	Control group (n=48) mean±SD	p
TAS (mmol Trolox Eqv/L)	2.36±0,22	2.02±0.20	<0.001*
TOS (μ mol H2O2 Eqv/L)	14.03±4.77	5.39±1.37	<0.001*
OSI (au)	5.98±2.111	2.68±0.76	<0.001*
8-OHdG (ng/mL)	11.81±5.03	7.55±3.13	<0.001*

Student's t-test and Mann–Whitney U Test were used. BD: bipolar disorder; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; 8-OHdG: 8-hydroxy-2'-deoxyguanosine. *p<0.001.

Table 4. TAS, TOS, OSI and 8-OHdG levels and ANOVA results

	ASG (n=40) mean±SD	ESG (n=40) mean±SD	CG (n=48) mean±SD	ANOVA	ASG vs. ESG	ASG vs. CG	ESG vs. CG
TAS (mmol Trolox Eqv/L) (Min-Max)	2.41±0,22 (1.83-2.79)	2.31±0,22 (1.83-2.76)	2.02±0.20 (1.55-2.43)	F=39.35 p<0.001*	p=0.062	p<0.001*	p<0.001*
TOS (µ mol H2O2 Eqv/L) (Min-Max)	14.74±5.88 (7.45-29.65)	13.33±3.26 (7.25-19.83)	5.39±1.37 (2.26-7.78)	F=77.02 p<0.001*	p=0.233	p<0.001*	p<0.001*
OSI (au) (Min-Max)	6.16±2.62 (3.18-13.92)	5.80±1.45 (3.30-9.72)	2.68±0.76 (1.27-4.37)	F=54.34 p<0.001*	p=0.616	p<0.001*	p<0.001*
8-OHdG (ng/mL) (Min-Max)	12.39±6.52 (6.00-39.2)	11.22±2.83 (6.09-18.3)	7.55±3.13 (3.37-13.8)	F=14.66 p<0.001*	p=0.463	p<0.001*	p<0.001*

ASG: acute state group; ESG: euthymic state group; CG: control group; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; 8-OHdG: 8-hydroxy-2'-deoxyguanosine. *p<0.001.

Table 5. Age-gender-smoking, and BMI adjusted TAS, TOS, OSI, 8-OHdG levels of and ANCOVA results

	ASG (n=40) mean±SD	ESG (n=40) mean±SD	CG (n=48) mean±SD	ANCOVA	ASG vs. ESG	ASG vs. CG	ESG vs. CG
TAS (mmol Trolox Eqv/L)	2.42±1.18	2.31±1.16	2.02± 1.23	F=39.284 P<0.001	P=0.78	p<0.001*	p<0.001*
TOS (µ mol H2O2 Eqv/L)	14.79±4.83	13.05±4.82	5.57±5.06	F=77.044 P<0.001	P=0.116	p<0.001*	p<0.001*
OSI (au)	6.18±3.26	5.67±3.25	2.77±3.4	F=52.730 P<0.001	P=0.553	p<0.001*	p<0.001*
8-OHdG (ng/mL)	12.46±5.35	11.19±5.34	7.53±5.6	F=13.941 P<0.001	P=0.64	P=0.001	p<0.001*

ASG: acute state group; ESG: euthymic state group; CG: control group; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidative stress index; 8-OHdG: 8-hydroxy-2'-deoxyguanosine. *p<0.001.

DISCUSSION

Main results of this study; TAS, TOS, OSI and 8-OHdG levels were significantly higher in BD patients than controls. It was determined that TAS level was associated with severity of disease and depression in BD patients, and TOS levels were higher in female patients than men. While TAS, TOS, OSI and 8-OHdG levels were significantly higher in the active and euthymic state groups than control group, there was no significant difference between active and euthymic patients.

There are many studies in the literature that oxidative stress contributes to the pathophysiology of BD (12-14). It has been reported that in post-mortem studies, there is an increase in oxidative damage and oxidative stress markers in BD patients (23) and this increase in oxidative stress markers are causing more serious cognitive impairment (24) and is associated with more incidence of comorbidity, especially metabolic disorders (25). In our study, it was understood that TAS, TOS and OSI levels were found to be higher in BD patients compared to the control group (26-30). Although there are studies reporting that TAS levels decrease or do not change in BD, there is more evidence that it increases (28, 31). The increase in TAS level could possibly be interpreted as a reaction of metabolism to suppress oxidant increase. This may explain that TAS and TOS levels in our study were higher in BD patients than in controls. According to OSI, we can evaluate both aspects of oxidative metabolism as antioxidant-oxidant and see the ability of antioxidants to suppress oxidants. Based on the controls, increased OSI values indicate that the system deteriorated in the direction of oxidants despite

the increase in stabilizing antioxidants. Corresponding TAS increase cannot ensure balance of metabolism. Clearly there is an oxidative stress in BD and internal regulatory mechanisms are inadequate in regulating oxidative stress. Indeed, in a similar biochemical pattern study in major depression, antioxidants and oxidants were found to be decreased, while OSI was shown to increase in patients (32). In two previous studies, oxidative stress has increased in BD (11, 32). Unlike the parameters we use in our study, many studies have been conducted to define the relationship between BD and oxidative metabolism. Inconsistent results are observed in studies performed in BD with superoxide dismutase (SOD) (12, 14), glutathione peroxidase (GSH-Px) (33, 34) and catalase (CAT) (12, 14, 34) involved in antioxidant metabolism. In many studies, malondialdehyde (MDA), which is a marker of lipid peroxidation, was found to be higher in BD patients compared to controls (14). It has been reported that thiobarbituric acid reactive substances (TBARS) (35) and oxidant nitric oxide (NO) (36), which are lipid peroxidation products, are high in BD patients, and the arginine-NO pathway may be associated with the pathogenesis of bipolar disorder (32). In a recent review about BD biomarkers, lipid peroxidation, DNA / RNA damage, nitric oxide parameters have been put forward (37). In our study, while TAS, TOS and OSI levels were significantly higher in the active and euthymic state groups, there was no significant difference between active and euthymic patients. It has been reported that TAS, TOS and OSI levels are higher in BD patients compared to healthy controls since the first mania episode (29). In another study with manic BD patients, this result was supported (30). In another study investigating the TAS, TOS and OSI levels of euthymic BD patients according to the subtypes of the disorder (BD I, BD II and previous antidepressant-induced mania), it was reported that TAS, TOS and OSI levels were higher than the healthy control group (26). In another study conducted with a low sample number, it was reported that serum TAS, TOS and OSI levels had no differences between euthymic, manic and healthy controls, and were higher than healthy controls in all BD patients [38]. Regardless of psychotropic therapy, increased TBARS in mania and depression has been reported in BD (12, 35). In studies conducted with a small number of samples with euthymic bipolar patients, they identified higher TBARS levels (35), while no difference was found compared to others (39). Parameters such as the course of the disease with different clinical features such as manic, hypomanic, depressive, mixed or euthymic, treatment types differ according to these state, number of samples and methodological differences may be the reason for the variability of the results in BD patients. In the light of the findings of our study, we can say that oxidative metabolism can be disrupted in both active state and euthymic state of BD.

DNA damage in BD has been shown in postmortem brain tissue (40) and peripheral blood (35). In our study, 8-OHdG levels in BD were significantly higher than the control group. While 8-OHdG levels were significantly higher in BD in both acute and euthymic patients than in the control group, there was no significant difference between patients in acute and euthymic state. An increase in 8-OHdG levels in blood and urine samples was observed in BD patients (7, 41). There are a limited number of studies specifically investigating nucleoside oxidation. Che et al. (23) showed 8-OHdG levels by immuno-histochemical methods in the postmortem hippocampus samples of patients with bipolar disorder, schizophrenia and major depression, and reported that oxidative damage of nucleic acids increased in the hippocampus in all 3 diseases. DNA damage was measured in different studies by single cell gel electrophoresis technique called Commet assay (CA) method, and increased DNA damage was observed in bipolar disorder patient groups (35, 42). In a DNA oxidation study conducted on BD patients, it was reported that 8-OHdG levels in peripheral blood were higher than the control group (41). It has been suggested that these studies cannot provide sufficient and reliable information in a methodological manner (43). In a recent review, it has been reported that euthymic, manic and depressive episodes of BD and disease progression may be related to oxidative stress, DNA / RNA damage, and mitochondrial dysfunction. In the same review, the authors stated that more focused on 8-OHdG to demonstrate DNA damage in BD, yet there is insufficient and consistent evidence, and large-scale studies involving DNA damage and repair mechanisms and how they respond to treatment are needed in BD (44). When our current literature and study findings are evaluated together, we can say that oxidative stress causes DNA damage in BD, however, even if the symptoms of the disease subsides, DNA damage does not return, and DNA damage continues in the euthymic state of the disease and the literature needs more study in this regard.

In BD patients; It was determined that TAS level was associated with disease severity and depression severity, and TOS levels were higher in female patients

than in men. The results of a double-blind randomized placebo-controlled study showed that an antioxidant supplement, N-acetyl cysteine (NAC), can reduce depressive symptoms in BD (45). In our study, the relationship between the severity of depression and TAS level can be evaluated as that more antioxidant supplements may be needed in depressive patients. Although there have been previous studies reporting that antioxidant metabolism is associated with disease severity in BD (46), there is limited information in this field. In previous studies, as far as we know, the relationship between general disease severity and TAS has not been studied, and this finding suggests that it may be emphasizing the support needed by the body against disease severity in BD. These findings of our study emphasize the importance of antioxidant therapy in BD patients. Although the literature does not focus on examining the differences between genders in particular, it has been reported that in most studies, there is no difference between the genders in terms of oxidative stress in BD (28). To the best of our knowledge, there are no studies reporting gender difference in the BD, except for a study (47) that reported that male patients in BD had significantly higher TBARS levels than women, and that this may be due to a mechanism that exhibits estrogen and progesterone or other antioxidant properties in female patients. The fact that the level of TOS was higher in women compared to men and that TAS and OSI did not differ in our study also supports that there are different oxidative mechanisms in women than in men. Of course, this will be an interesting subject to be emphasized and studied in BD patients.

Our study has some limitations. All of our patients continued to use their medications, including antipsychotics and mood-stabilizers, over the duration of the study due to ethical issues known to affect their oxidative status. As in previous studies, it was not possible to fully control environmental factors such as diet intake and exercise, which are known to affect our results. Another important limitation is merging manic and depressive episodes as acute state. Furthermore, longitudinal studies are needed to evaluate these different episodes. Finally, our sample size was not large enough and it was a cross-sectional study.

In conclusions, the results of our study show that TAS, TOS, OSI and 8-OHdG were higher in BD patients in both acute and euthymic state compared to the healthy control group, TAS level increased with disease severity and depression severity, and TOS levels were higher in female patients than in men. In BD patients; It is observed that oxidative metabolism is shifting in favor of oxidant, increased TAS cannot compensate for this, and this process continues in both acute and euthymic state with an increase in DNA damage. It can be said that in BD patients, the need for antioxidants may increase with the severity and severity of depression, and the body tries to do this relatively. In BD, different gender-based antioxidant mechanisms are an issue that needs to be emphasized and need further study.

Acknowledgments: Funding for this study was provided by a grant from the Scientific Research Project Coordination Unit of University of Gaziantep (TF.12.05/2013).

Conflicts of Interest: No potential conflict of interest was reported by the authors.

REFERENCES

[1] Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 2011;68:241–251.

[2] Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. Ther Adv Psychopharmacol. 2018;8:251-269.

[3] Wang JF, Azzam JE, Young LT. Valproate inhibits oxidative damage to lipid and protein in primary cultured rat cerebrocortical cells. Neuroscience 2003;116:485– 489.

[4] Mercan U. Toksikolojide Serbest Radikallerin Önemi. YYU Vet Fak Derg. 2004;15:91-96.(Turkish)

[5] Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact. 2006;160:1–40.

[6] Hu CW, Chao MR, Sie CH. Urinary analysis of 8-oxo-7,8-dihydroguanine and 8-oxo – 7,8-dihydro-2'-deoxyguanosine by isotope-dilution LC-MS/MS with automated solid – phase extraction: Study of 8-oxo-7,8-dihydroguanine stability. Free Radic Biol Med. 2010;48:89-97.

[7] Ceylan D, Scola G, Tunca Z, Isaacs-Trepanier C, Can G, Andreazza AC. DNA redox modulations and global DNA methylation in bipolar disorder: effects of sex, smoking and illness state. Psychiatr. Res. 2018;261:589-596.

[8] Boll KM, Noto C, Bonifacio KL, Bortolasci CC, Gadelha A, Bressan RA. Oxidative and nitrosative stress biomarkers in chronic schizophrenia. Psychiatry Res. 2017;253:43–48.

[9] Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol. 2008;11:851–876.

[10] Selek S, Bulut M, Ocak AR, Kalenderoglu A, Savas HA. Evaluation of total oxidative status in adult attention deficit hyperactivity disorder and its diagnostic implications. J Psychiatr Res. 2012;46:451-455

[11] Frey BN, Andreazza AC, Houenou J, Jamain S, Goldstein BI,

Frye MA, et al. Biomarkers in bipolar disorder: a positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. Aust N Z J Psychiatry 2013:47:321-332.

[12] Andreazza AC, Kauer-Sant'Anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, et al. Oxidative stress markers in bipolar disorder: a meta – analysis. J Affect Disord 2008:111:135–144.

[13] Steckert AV, Valvassori SS, Moretti M, Dal-Pizzol F, Quevedo J. Role of oxidative stress in the pathophysiology of bipolar disorder. Neurochem Res. 2010;35:1295-1301.

[14] Brown NC, Andreazza AC, Young LT. An updated meta-analysis of oxidative stress markers in bipolar disorder. Psychiatry Res. 2014:218;61-68.

[15] American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 4th ed., text revision (DSM-IV-TR). Arlington, VA: American Psychiatric Association Press; 2000.

[16] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.

[17] Akdemir A, Türkçapar MH, Orsel SD, Demirergi N, Dag I, Ozbay MH. Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. Compr Psychiatry 2001;2:161-165.

[18] Young RC, Biggs JT, Ziegler and Meyer DA. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429-435.

[19] Karadağ F, Oral ET, Aran Yalçın F, Erten E. Young Mani Derecelendirme Ölçeği'nin Türkiye'de geçerlik ve güvenirliği. Türk Psikiyatri Dergisi 2002;13:107 – 114. (Turkish)

[20] Guy W. Clinical global impression. In: ECDEU assessment manual for psychopharmacology, revised National Institute of Mental Health, Rockville, MD 1976;218-221.

[21] Erel OA novel automated method to measure total anti – oxidant response against potent free radical reactions. Clin. Biochem. 2004;37:112–119.

[22] Erel OA new automated colorimetric method for measuring total oxidant status. Clin. Biochem. 2005;38:1103– 1111.

[23] Che Y, Wang JF, Shao L, Young LT. Oxidative damage to RNA but not DNA in the hippocampus of patients with major mental illness. J Psychiatry Neurosci. 2010;35:296.

[24] Vieta E, Popovic D, Rosa AR, Solé B, Grande I, Frey BN. The clinical implications of cognitive impairment and allostatic load in bipolar disorder. Eur Psychiatry 2013;28:21-29.

[25] Mangge H, Almer G, Truschnig-Wilders M, Schmidt A, Gasser R, Fuchs D. Inflammation, adiponectin, obesity and cardiovascular risk. Curr Med Chem. 2010;17:4511-4520.

[26] Yumru M, Savas HA, Kalenderoglu A, Bulut M, Celik H. Oxidative imbalance in bipolar disorder subtypes: a comparative study. Prog Neuropsychopharmacol. Biol Psychiatry 2009;33:1070-1074.

[27] Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N. Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochem Funct. 2002;20:171-175.

[28] Kalenderoğlu A, Çelik M. Psikotik Özellikli Mani ile Psikotik Özellik Göstermeyen Maninin Oksidatif Stres Açısından Karşılaştırılması. J. Mood Disord. 2016;6:116-23. (Turkish)

[29] Akarsu S, Bolu A, Aydemir E, Zincir SB, Kurt YG, Zincir S. The Relationship between the Number of Manic Episodes and Oxidative Stress Indicators in Bipolar Disorder. Psychiatry Investig 2018;15:514.

[30] Demir B, Alpak G. Oxidative metabolism and urotensin-II levels among bipolar disorder patients in a manic episode. Medicine 2019;8:703-709.

[31] Raffa M, Barhoumi S, Atig F, Fendri C, Kerkeni A, Mechri A. Reduced antioxidant defense systems in schizophrenia and bipolar I disorder. Prog Neuropsychopharmacol Biol Psychiatry 2012;39:371-375.

[32] Yanik M, Erel O, Kati M. The relationship between potency of oxidative stress and severity of depression. Acta Neuropsychiatry 2004;16:200-203.

[33] Nucifora LG, Tanaka T, Hayes LN, Kim M, Lee BJ, Matsuda T. Reduction of plasma glutathione in psychosis associated with schizophrenia and bipolar disorder in translational psychiatry. Transl Psychiatry 2017;7:e1215-e1215.

[34] de Sousa RT, Zarate Jr CA, Zanetti MV, Costa AC, Talib LL, Gattaz WF. Oxidative stress in early stage bipolar disorder and the association with response to lithium. J Psychiatr Res 2014;50:36-41.

[35] Andreazza AC, Cassini C, Rosa AR, Leite MC, de Almeida LM, Cunha AB. Serum S100B and antioxidant enzymes in bipolar patients. J Psychiatr Res. 2007;41:523-529.

[36] Selek S, Savas HA, Gergerlioglu HS, Bulbul F, Uz E, Yumru M. The course of nitric oxide and superoxide dismutase during treatment of bipolar depressive episode. J Affect Disord 2008;107:89-94.

[37] Teixeira AL, Colpo GD, Fries GR, Bauer IE, Selvaraj S. Biomarkers for bipolar disorder: Current status and challenges ahead. Expert Rev Neurother 2019;19:67-81.

[38] Yirün MC, Kübranur UNAL, Şen NA, Yirün O, Aydemir Ç, Erol GOKA. Evaluation of oxidative stress in bipolar disorder in terms of total oxidant status, total antioxidant status, and oxidative stress index. Archives of Neuropsychiatry 2016;53:194.

[39] Wiener C, Rassier GT, Kaster MP, Jansen K, Pinheiro RT, Klamt F. Gender-based differences in oxidative stress parameters do not underlie the differences in mood disorders susceptibility between sexes. Eur Psychiatry 2014;29:58-63.

[40] Buttner N, Bhattacharyya S, Walsh J, Benes FM. DNA fragmentation is increased in non-GABAergic neurons in bipolar disorder but not in schizophrenia. Schizophr Res. 2007;93:33-41.

[41] Soeiro-de-Souza MG, Andreazza AC, Carvalho AF, Machado-Vieira R, Young LT, Moreno RA. Number of manic episodes is associated with elevated DNA oxidation in bipolar I disorder. Int J Neuropsychopharmacol. 2013;16:1505-1512.

[42] Frey BN, Andreazza AC, Kunz M, Gomes FA, Quevedo J, Salvador M. Increased oxidative stress and DNA damage in bipolar disorder: a twin-case report. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:283-285.

[43] Poulsen HE, Nadal LL, Broedbaek K, Nielsen PE, Weimann A. Detection and interpretation of 8-oxodG and 8-oxoGua in urine, plasma and cerebrospinal fluid. Biochim Biophys Acta 2014;1840:801-808.

[44] Czarny P, Bialek K, Ziolkowska S, Strycharz J, Sliwinski T. DNA damage and repair in neuropsychiatric disorders. What do we

know and what are the future perspectives?. Mutagenesis 2020;35:79-106.

[45] Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I. N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. Biol Psychiatry 2008;64:468-475.

[46] Lv Q, Guo Y, Zhu M, Geng R, Cheng X, Bao C. Predicting individual responses to lithium with oxidative stress markers in drug-free bipolar disorder. World J Biol Psychiatry 2019;20:778-789

[47] Bengesser SA, Lackner N, Birner A, Fellendorf FT, Platzer M, Mitteregger A. Peripheral markers of oxidative stress and antioxidative defense in euthymia of bipolar disorder—gender and obesity effects. J Affect Disord 2015;172:367-374.