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Oxidative metabolism and urotensin-II levels among bipolar disorder patients in a manic episode

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Abstract

According to the previous studies, it has been noted many times that oxidative balance is disrupted in bipolar disorder. However, we did not found any research investigating the relationship between Urotensin-II (U-II) levels and oxidative metabolism among bipolar disorder patients in the literature. In this study, we aimed to investigate the relationship between U-II levels and oxidative metabolism among bipolar disorder patients in the manic episode.

Forty-two patients diagnosed as bipolar disorder manic episode according to DSM-5 and 55 healthy controls enrolled in the study. Serum total antioxidant status (TAS), total oxidant status (TOS), nitric oxide (NO), U-II and oxidative stress index (OSI) measurements were done in the biochemistry laboratory of Gaziantep University. When TAS, TOS, OSI, NO, and U-II levels were compared between bipolar disorder manic episode patients and control group; TAS, TOS, OSI, NO and U-II levels were significantly higher in the patient group than the control group ($p=0.003$, $p=0.001$, $p=0.001$, $p=0.001$ and $p=0.009$ respectively). According to the correlation analysis, U-II levels were found to have a weak linear correlation in the positive direction with TOS and OSI ($r=0.326$, $p=0.035$ for TOS; and $r=0.369$, $p=0.016$ for OSI). In the earlier studies, data have been obtained about the effects of U-II on behavior, sleep, inflammatory system and oxidative metabolism and relevant hypotheses have been established. In the light of these studies in the literature, our study proposes that increased U-II levels could be a factor affecting the elevated oxidative stress and inflammation in patients with bipolar disorder manic episode. Our study is the first one to examine relationship between U-II levels and oxidative parameters in manic episode of bipolar disorder; therefore, it may significantly contribute to the literature.

Keywords: Bipolar disorder, urotensins, nitric oxide, oxidative stress

Introduction

Bipolar Disorder (BD) is a prevalent psychiatric disorder that has a 6% prevalence when considered together with its all subtypes [1]. Although some deteriorations are visible in cognitive functions and physiology in BD, these disorders continue in recovery episodes, especially in cognitive terms. The neurochemical etiology of BD has not yet been clearly clarified. Recently, the data of studies show that oxidative stress might be useful in the pathophysiology of the disease [2-5].

Oxidative stress has the potential of causing neuronal damage and is the deterioration of the balance in favor of prooxidant capacity in prooxidant-antioxidant metabolism. Since the brain is one of the organs that is affected at the highest level by the increase of oxidants and oxygen is used more and is an organ in which the antioxidant mechanisms are limited, it is one of the organs that is affected by the increase of oxidants. Neuronal oxidative stress has detrimental effects on signal conveyance, cellular flexibility, and structural plasticity. Oxidants can react with proteins that are associated with membrane, and cause damage to enzymes or prevent neurotransmitter intake [6]. Oxidative stress usually causes cell death with lipid peroxidation in membranes, proteins, and genes, and by triggering cell death, or by aggregating oxidized proteins [6]. Also, oxidative stress can cause psychiatric symptoms as a result of the effects occurring in essential brain circuits.

Urotensin-II (U-II) is a cyclic peptide which was first isolated from teleost urophysis, and contains 11 amino acids in human [7]. In the experiments done in rats, it was shown that there are U-II receptors in brain regions including olfactory bulbus, hippocampus, thalamus, hypothalamus, pineal gland, tectum, tegmentum, pituitary gland, pons, medulla oblangata, and spinal cord [8]. Also, in studies conducted on rats, it was shown that intracerebroventricular microinjection of U-II causes changes in

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oxidative metabolism, motor activity, behavior, and sleep [9-11]. In human studies conducted so far, schizophrenia, schizoaffective disorder, and BD were investigated for U-II levels, and different results were reported [9,12,13]. In these studies, attention was drawn to the relations between U-II and oxidative metabolism arguing that U-II might have roles in the etiology of psychiatric disorders.

In the present study, the purpose was to investigate oxidative metabolism levels, U-II levels, and the relations between these parameters in patients in BD manic episode. We believe that the findings of this study will contribute to the literature on understanding the neurochemical etiology of BD and the relations between U-II and psychiatric disorders.

Material and Methods

The approval for the study was received from Gaziantep University, Medical Faculty, Medical Ethics Committee, with the decision number 22.10.2013/346. The consecutive 42 manic episode patients and 55 healthy volunteers (the Control Group), who applied to the Department of Mental Health and Diseases of Gaziantep University, Faculty of Medicine between November 2013 and November 2014, and who were diagnosed with BD manic episode were included in the study.

The inclusion criteria of the study; The patients were aged between 18-65 years, diagnosed as BD manic episode according to DSM-5 diagnostic criteria, and their family voluntarily agreed to participate in the study. For the control group, there was no history of any psychiatric and comorbid medical illnesses and willingly agreed to participate in the study.

The exclusion criteria of the study were the patients who had severe medical disorders like hyperthyroidism, hypothyroidism, diabetes, or other endocrinopathies, the patients who had alcohol, substance dependence, pregnant women, the patients who had moderate-to-severe mental retardation, history of severe head trauma, use of antioxidant agents (vitamin E, vitamin C, N-acetyl cysteine), and xanthine oxidase inhibitors. Twenty-seven patients with morbid obesity, hypertension, diabetes mellitus or hyperlipidemia, one patient with mental retardation, 1 patient with N-acetylcysteine treatment, one patient with folic acid treatment and 5 patients who refused to participate were excluded from the study.

The sociodemographic data like the ages, genders, body mass indices, education levels, marital status, occupational status, smoking status, and history of previous hospitalization, duration of illness, history of suicide attempt, additional treatment, additional medications, and the presence of psychiatric disease were determined by using the semi-structured interview form. The Clinical Global Impression Scale (CGI), Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HAMD), Positive and Negative Syndrome Scale (PANSS) were applied to the patients.

Laboratory Measurements

Blood samples of patient and control groups were taken from antecubital vein after a 12-hour fasting period. Blood samples were taken in approximately 5 ml. Blood was transferred to sampling tubes with a gel separator and centrifuged at 4000 rpm for 10 minutes. Separated serum was immediately transferred to storage at −80°C ultra-low temperature freezer.

The Total Antioxidant Status (TAS) and Total Oxidant Status (TOS) is a fully automatic method that was developed by Erel, and measure the total antioxidant capacity of the body against potent free radicals and radicals [14,15]. The TAS and TOS measurements were made with the Rel Assay Diagnostics fully automatic TAS (Total Antioxidant Status) kit in Tokyo Boeki Prestige I24 autoanalyzer.

Oxidative Stress Index (OSI) was calculated by dividing it as TOS/TAS [OSI (arbitrary unit) = TOS (mmol H2O2 Equiv./l)/TAS (mmol Trolox Equiv./l)] [16].

Nitric Oxide (NO) Measurement: Serum samples and ELISA reagents were allowed to come to room temperature. 80 µL of the standards (35.0, 30.0, 25.0, 20.0, 15.0, 10.0 and 5.0 µM) were added to the wells. 40 µL of the samples were added, and 40 µL of dilution solution was added. Ten µL enzyme cofactor mixture and ten µL nitrate reductase mixture were added to the standard and sample wells. The plate was covered and kept at room temperature for 1 hour. After incubation, 50 µL Griess reagent 1 and 50 µL Griess reagent two were added. It was kept at room temperature for 10 min in dark environment and read at 540 nm with ELISA reader (Biotek Instruments, USA).

Serum Urotensin-II (U-II) Measurement: Urotensin-II (Elabscience, CHINA) was measured using the ELISA method. Serum samples and ELISA reagents were allowed to reach room temperature before starting the study. 50 µL of standards (450, 300, 200, 100, 50 and 25 pg / mL) was added to the wells. Ten µL of the samples were added and 40 µL of the sample dilution was added and incubated at room temperature for 30 minutes. After the incubation was completed, the wells were washed with washing solution, 50 µL of HRP-Conjugate was added and incubated at room temperature for 30 minutes. After half an hour, the wells were washed again, and 50 µL of Chromogen A and 50 µL of Chromogen B were added. Incubate at room temperature for 15 minutes. Incubate in the dark for 15 minutes, 50 µL of Stop solution was added and read at 450 nm with ELISA reader (Biotek Instruments, USA).

Statistical Evaluation

Kolmogorov Smirnov test was employed to check the normal distribution of the continuous variables. The Student's t-test was used to compare two independent groups of the variables that had normal distribution, and the Mann Whitney U-Test was used to compare two separate groups that had normally distributed variables. The Kruskal Wallis test was used to compare the numerical variables in more than two groups. The relations between the categorical variables were tested with the Chi-square Analysis, and the relations between binary variables were tested with the correlation coefficient. The SPSS for Windows version 22.0 was used for statistical analyses, and $P<0.05$ was considered to be statistically significant.

Results

Our study consisted of 42 BD manic episode patients and 55 healthy controls. A total of 27 (64.3%) of the patient group were

male, and 15 (35.7%) were female; 31 (56.4%) of the control group were male, and 24 (43.6%) were female. The average age was 31.9±11.3 years in the patient group, and 30.4±6 years in the control group. No significant differences were detected between the groups in terms of age, gender, smoking (p>0.05); however, body mass indices (BMI) were higher at a significant level in BD manic episode patients (p=0.043) (Table-1). The clinical characteristics of the patient group and the data on applied scales were given in Table-2.

Table 1. Comparison of bipolar disorder manic episode patients and controls in terms of age, gender, smoking status, and BMI

		Bipolar disorder manic episode Patients (n:42)	Control (n:55)	p value
Gender (%)	Female	15 (%35.7)	24 (%43.6)	**0.430**
	Male	27 (%64.3)	31 (%56.4)	
Smoking (%)	Yes	17 (%40.5)	15 (%27.3)	0.171
	No	25 (% 59.5)	40 (%72.7)	
Age (average±sd)		31.98±11.31	30.40±6	0.379
Body Mass Index (average±sd)		26.73±3.90	25.24±3.23	0.043

Table 2. Clinical characteristics of the patients

	Bipolar disorder manic episode patients (n:42)
Disease onset age (average±sd)	25.10±8.76
Patience Duration (years) (average±sd)	6.67±6.74
Hospitalization count (average±sd)	2.36±1.63
Past manic episode count (average±sd)	3.24±2.80
Past mixed episode count (average±sd)	0.43±0.96
Past depressive episode count (average±sd)	0.62±1.26
CGI Score (average±sd)	6.71±0.50
YMRS Score (average±sd)	35.5±7.36
HAMD Score (average±sd)	0.24±1.07
PANSS Score (average±sd)	39.38±23.44

CGI: Clinical Global Impression Scale, YMRS: Young Mania Rating Scale, HAMD: Hamilton Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale

When patients with BD manic episode and the control group were compared in terms of TAS, TOS, OSI, NO and U-II values, it was determined that the TAS, TOS, OSI, NO, and U-II values were higher at a significant level in the patient group when compared to the control group (p=0.003, p=0.001, p=0.001, p=0.001, and p=0.009, respectively) (Table-3).

The patients continued their current treatments in our study, the current therapies of 4 patients could not be recorded, and no difference was found in terms of oxidative stress values when the drugs that were used, were classified as typical antipsychotics, atypical antipsychotics, mood stabilizers and their combinations (p>0.005) (Table-4).

Table 3. Comparison of the bipolar disorder manic episode patients and the control group in terms of TAS, TOS, OSI, NO, and U-II values

	Patient Group (n:42)	Control Group (n:55)	p-value
U-II (ng/mL) (average±sd)	13.77 ± 11.73	9.61±6.48	0.009
TAS mmol Trolox Equiv./l (average±sd)	1.95±0.22	1.80±0.16	0.003
TOS (mmol H_2O_2 Eqv/L) (average±sd)	26.29 ± 28.97	10.54±14.49	0.001
OSI (au) (average±sd)	1.32 ±1.51	0.58±0.79	0.001
NO (µM) (average±sd)	18.05±10.87	8.5±5.8	0.001

U-II: Urotensin-II, TAS: Total Antioxidant Status, TOS: Total Oxidant Status, OSI: Oxidative Stress Index, NO: Nitric Oxide

No relations were detected among the genders, marital status, educational status, smoking status, duration of illness, family history of psychiatric illness, number of hospitalizations, history of ECT, used drugs, suicide attempt history, and TAS, TOS, OSI, NO and U-II values in the correlation analysis. A weak and positive correlation was detected between age and OSI (r=0.326, p=0.035). Although no statistically significant relations were detected between the severity of the disease and the BMI and YMRS scores, a weak and linear relation was detected with OSI (with KGI, r=0.359, p=0.020; with YMRS, r=0.311, p=0.045, respectively). Also, about the history of the disease, a negatively moderate linear relation was detected between the number of previous manic episodes and NO (r=0.423, p=0.005); and a positive and weak linear relation was detected between the number of previous mixed episodes and TOS (r=0.311, p=0.045). There was a weak and positive correlation between the U-II levels and TOS and OSI levels of the patients (with TOS, r=0.326, p=0.035; with OSI, r=0.369, p=0.016, respectively). The correlation analysis scales were given in Table-5.

Table 4. Comparison of U-II, TAS, TOS, OSI, and NO levels in the patients in current treatments

	TA	AA	TA+AA	AA+MS	TA+AA+MS	p values
U-II (ng/mL) (average±sd)	8.52±0.90	10.66±4.67	13.92±8.88	17.99±20.64	10.61±2.54	0.855
TAS mmol Trolox Equiv./l (average±sd)	1.77±0.49	2.06±0.24	1.95±0.24	1.90±0.24	1.82±0.12	0.125
TOS (mmol H_2O_2 Eqv/L) (average±sd)	11.98±16.95	17.34±17.86	31.59±37.09	35.21±33.09	16.85±22.25	0.411
OSI (au) (average±sd)	0.66±0.93	0.83±0.87	1.68±1.84	1.62±1.80	0.89±1.14	0.606
NO (μM) (average±sd)	15.56±7.57	15.84±10.95	20.50±12.95	19.37±11.17	13.81±10.46	0.745

TA: Typical Antipsychotics, AA: Atypical Antipsychotics, MS: Mood Stabilizers, U-II: Urotensin-II, TAS: Total Antioxidant Status, TOS: Total Oxidant Status, OSI: Oxidative Stress Index, NO: Nitric Oxide

Table 5. Correlation between variables in the patients.

		TAS	TOS	OSI	NO	U-II
Age	r	-.210	.230	.326*	-.052	.131
	p	.183	.143	.035	.744	.410
Disease onset age	r	-.064	.237	.350*	-.041	.190
	p	.686	.131	.023	.795	.229
Patience duration	r	-.150	.057	.066	-.116	.010
	p	.342	.722	.678	.465	.951
Hospitalization count	r	-.184	.071	-.032	-.119	.143
	p	.242	.656	.840	.454	.365
Past mixed episode count	r	-.146	.311*	.218	-.083	.141
	p	.356	.045	.165	.602	.374
Past manic episode count	r	-.181	.128	.106	-.423**	.075
	p	.251	.418	.502	.005	.635
Past depressive episode count	r	-.442**	-.086	-.149	-.004	.017
	p	.003	.588	.346	.980	.915
CGI score	r	.120	-.290	-.359*	.138	-.032
	p	.449	.063	.020	.385	.838
YMRS score	r	.084	-.294	-.311*	-.030	.004
	p	.596	.059	.045	.851	.978
HAMD score	r	.037	.240	.212	.065	.277
	p	.817	.126	.177	.685	.076
PANSS score	r	.074	.219	.235	.072	.173
	p	.642	.164	.135	.651	.275
BMI	r	.352*	.238	.320*	-.158	.078
	p	.022	.130	.039	.319	.623
TAS	r	1.000	.179	.122	-.111	.063
	p		.257	.441	.483	.692
TOS	r	.179	1.000	.906**	.024	.326*
	p	.257		.000	.881	.035
OSI	r	.122	.906**	1.000	-.034	.369*
	p	.441	.000		.833	.016
NO	r	-.111	.024	-.034	1.000	.006
	p	.483	.881	.833		.970
U-II	r	.063	.326*	.369*	.006	1.000
	p	.692	.035	.016	.970	

CGI: Clinical Global Impression Scale, YMRS: Young Mani Rating Scale, HAMD: Hamilton Depression Rating Scale, PANSS: Positive and Negative Syndrome Scale, U-II: Urotensin-II, TAS: Total Antioxidant Status, TOS: Total Oxidant Status, OSI: Oxidative Stress Index, NO: Nitric Oxide

Discussion

In our study, it was found that TAS, TOS, OSI, NO, and U-II levels were higher at a significant level in BD manic patients when compared to the control group. We also observed a weak and positive correlation between U-II levels, TOS and OSI.

In the current study, the TOS levels were determined to be higher in BD manic patients when compared to the healthy controls, which was similar to previous studies. In a study that examined oxidative metabolism in BD patients, the patients were divided into BD I, II, and antidepressant-induced mania subtypes; and higher TOS values were determined in the 3 groups when compared to the controls [16]. Kuloglu et al. [17] examined the lipid peroxidation products and antioxidant enzyme activities in BD patients and reported that malondialdehyde (MDA) levels, which were among lipid peroxidation products, were higher at a significant level in the patient group when compared to the control group. In post-mortem brain studies, too, it was shown that there were increases in the levels of 4-hydroxynonenal, which is one of the lipid peroxidation products, in the anterior cingulate cortex samples of BD and schizophrenia patients [18]. In previous studies, it was reported that oxidant levels increased as the severity and duration of the disease increased [16,19]. In our study, no relations were detected between duration of the disease and oxidative parameters like TOS and OSI. The reasons for these different results might be the races of the patients, their metabolic and physical differences, the differences in treatment agents that were used, and the fact that the BD is a spectrum disorder. For this reason, follow-up studies that consist of similar patient groups are needed to confirm these studies.

In our study, it was found that the TAS levels were higher in BD patients when compared to the healthy controls. In a study that examined the oxidative metabolism in BD patients, higher TAS values were reported in the patient group when compared to the control group [16]. In the same study, a negative relation was reported between the total number of the episodes and the antioxidant capacity in BD type I patients. In a study that included BD depressive, manic and euthymic patients, the serum superoxide dismutase (SOD), which is an antioxidant, and thiobarbituric acid reactive substance (TBARS), which is a peroxidation product, were measured, and the serum SOD activity was determined as higher in patients with manic and depressive episode compared to the euthymic and healthy controls [20]. In another study that examined antioxidant enzyme activities, a significant increase was detected in SOD enzyme activity in BD patient group when compared to the controls [17]. In a study that examined the antioxidant enzyme levels in both early and late-stage disease, it was reported that glutathione reductase (GR) and Glutathione-S-Transferases (GST) levels were increased in the late-stage of the disease [21]. In our study, too, higher TAS levels were detected in the patient group when compared to the control group, which might be considered as a compensatory mechanism against increasing oxidant damage. There are also other studies in the literature reporting that antioxidant levels in BD patients are decreased or remain unchanged [22,23]. It was reported that these different data might be because there are differences in ethnic origin, lifestyle, dietary characteristics, and treatment modalities that affect oxidative stress and oxidative cell damage [24].

Another finding of our study was that the OSI levels were higher in manic patients compared to the healthy controls. In the literature, OSI levels were examined in a small number of studies in oxidative metabolism studies in BD patients, and in general, OSI levels were reported as being higher at a significant level in BD patients when compared to the controls in these studies [16].

In a meta-analysis that investigated the oxidative stress markers, it was shown that TBARS levels and NO levels, which are important free radicals of the body, were higher at a significant level [19]. In our study, too, it was found that NO levels were higher in manic patients when compared to the healthy controls. In the literature, in general, although there are studies that support the increase of the oxidants in BD patients, NO levels in mania patients were reported to be lower at a significant level in the patient group when compared to the control group [25].

To be able to define the oxidative system dysfunction as a characteristic of the disease, the disease episodes must be followed-up regularly, and recording of changes must be made in oxidative parameters in the process, comparison of oxidative parameters must be made for the treated and untreated patients, oxidative parameters of the patients must be examined in different episodes (active, remission, etc.), and differences between the BD subtypes must be determined [6].

The other important finding of our study was that the U-II levels of the BD manic patients were higher compared to the healthy controls. U-II was examined in schizophrenia, schizoaffective disorder, and BD among the other psychiatric diseases. The U-II values were detected to be higher in schizophrenia patients when compared to healthy controls, and it was argued that U-II might be useful in the etiology of schizophrenia by reducing the prefrontal and temporal blood-flow and by inducing the vasoconstrictor effects, by also inducing the increase of reactive oxygen species (ROS) (9). The fact that BD has a chronic progression like schizophrenia, and that similar genetic and environmental factors are blamed for both diseases support the high U-II levels that were determined in the patient group in our study. The U-II levels were lower in patients that had schizoaffective disorder when compared to the controls [12]. In a study that evaluated the endothelial dysfunction in patients with bipolar disorder, Endocan and U-II were examined, and their levels were determined to be higher compared to the controls [13]. In this study, the number of the patients that had BD manic episode was only 12; and this large sampling size of our study will contribute to the literature.

The experiments on rats showed that intracerebroventricular U-II administration caused increases in ROS levels [9]. In our study, high U-II factor may be accused of the increased high oxidative stress levels. The results of our study showed that there is a linear, weak and positive relation between U-II levels and TOS and OSI. Also, in an animal study, it was shown that stimulating the U-II receptors in vascular endothelial cells caused NO release [26]. In another human study [27], it was shown that U-II activates nitric oxide synthetase (NOS). The high NO levels in BD patients, which was shown in our study and previous studies, may be related to high U-II levels we detected in the patient group. For this reason, the elevated U-II levels might be another etiology that may be responsible for increased ROS in BD manic patients.

In brain blood flow studies in BD, different results were reported according to the episodes of the disease [28]. For example, there are studies which reported that brain blood flow decreases in BD depressive episode, and brain blood flow increases in manic episode [28]. In another study conducted on manic, depressive, and euthymic patients, an increase was detected in the brain blood flow (hyper perfusion) in the prefrontal cortex, and temporal structures of the left hemisphere, and especially the abnormalities in the left hemisphere blood flow were accused in the pathophysiology of BD [29]. In the light of these data in the literature, it may be considered that the increased NO levels might be a factor in hyper perfusion that is detected in the brain blood flow studies. If we consider U-II as a vasoconstrictor, it may be considered that the increased NO levels in manic patients might be a reactive response to the increase in the U-II level in addition to the reasons that have been discussed above. It may also be considered that U-II -although not directly- has an effect in prefrontal and temporal hyper perfusion by increasing NO. Also, the effects of the U-II on the human brain vessels and especially in the prefrontal cortex have not been examined. The relation between brain blood flow and U-II in patients might be the subject of further studies.

It is considered that immune mechanisms might be associated with disease formation or clinical symptoms in BD manic episode. It is known that cytokines interact with the neuroendocrine system, hypothalamo-pituitary-adrenal system, autonomic system, and neurotransmitter systems (dopamine, serotonin, and glutamate) [30,31]. In a study conducted on BD manic episode patients, the levels of proinflammatory cytokine (IL-6, TNF-alpha), inflammatory cytokine (IFN-gamma) and hs-CRP were higher at a significant level, and the levels of anti-inflammatory cytokine (IL-4, IL-10) were similar when compared to the controls [32]. It has been shown previously that U-II played a role in the inflammatory processes. It was found that U-II increases IL-6 levels in different tissues [33]. Interferon-gamma, on the other hand, increases the production of U-II receptors [34]. Also, it is considered that U-II is involved in atherosclerosis, which is a chronic inflammatory process [35]. When considered in this respect, high U-II levels in the patient group might be held responsible for the increase in the inflammation, which is held responsible for the etiopathogenesis of the disease; and in addition to these, it may also be a factor in the formation of the metabolic syndrome and cardiovascular diseases, which are known to be increased in BD patients. In revealing this possible relation, studies are needed particularly in the first-episode patients.

In an animal study that was conducted previously, it was shown that intracerebroventricular U-II microinjection to rats caused increased motor activity and arousal [10]. However, it was determined that this effect was not as high as in the other neuropeptides like CRF and Orexin. In our study, high U-II levels detected in the patient group might be associated with the increased movement in the manic episode, increased efficacy towards purpose, easy irritation, and arousal.

Some studies in which sleep structures were examined in BD manic patients, it was shown that REM latency was shortened whereas REM density was increased [36,37]. In a study conducted on rats, it was shown that intracerebroventricular U-II injection caused an increase in REM sleep [38]. It was also reported that there was a slight increase in the alertness level immediately after the injection. When the high U-II levels detected in our study are evaluated together with these studies in the literature, it may be considered that U-II may be one of the factors that cause decreased sleep needs and increased REM intensity during BD manic episode.

The observation of the findings in the manic episode being observed with increased intracerebroventricular U-II in rats in preclinical studies, U-II receptors being present in olfactory bulbus, hippocampus, thalamus, hypothalamus, pineal gland, tectum, tegmentum, pituitary gland, pons, medulla oblangata and spinal cord and their roles in vascular, hormonal, inflammatory, oxidative systems bring with them the argument that U-II might be effective in the etiopathogenesis of BD manic episode.

Finally, among the limitations of our study, there is a low number of patients, and controls, its cross-sectional design, and the patients using medication. Despite our shortcomings, our study is the first one that investigates the relations between U-II and oxidative parameters in the BD manic episode, might make essential contributions to the literature.

Conflict of interest
The authors declare that there are no conflicts of interest.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The approval for the study was received from Gaziantep University, Medical Faculty, Medical Ethics Committee, with the decision number 22.10.2013/346.

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