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Serum Uric Acid Level in Unipolar and Bipolar Depression

GulcinElboga[1], Muhammet Berkay Ozyurek[1], Zeynel Abidin Sayiner[2], *Şengül Kocamer Şahin[1], Abdurrahman Altindag[1]

[1]Gaziantep University, Faculty of Medicine, Department of Psychiatry, Gaziantep, Turkey, [2]Gaziantep University Medical Faculty Department of Internal Medicine, Endocrinology and Metabolic Diseases Unit, Gaziantep, Turkey. Üniversite avenue-27310 Şehitkamil,Gaziantep, Turkey. *Email: snglkcmr@hotmail.com
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Abstract: The purinergic system plays a role in the regulation of mood, motor activity, cognitive function, sleep, and behavior. Purinergic mechanisms can also play a role in various neuropsychiatric diseases. The objective of this study is to assess whether uric acid levels in patients with unipolar and bipolar depression are different in comparison to healthy controls and to determine the clinical parameters that can be associated with the uric acid level. This retrospective study consisted of 31 patients with major depressive disorder and 31 patients with bipolar disorder depressive episode and 31 healthy control subjects. The mean serum uric acid levels were found as follows: major depression patient group 4.56 (± 1.53) mg/dL, bipolar depression patient group 5.38 (± 1.43) mg/dL and control group 4.86 (± 1.56) mg/dL. There was no significant difference between patients and the control groups in terms of serum uric acid levels (P=0.075). Serum uric acid levels do not differ significantly in bipolar and unipolar depression. Also, there was no difference between patients and control. Therefore, studying the uric acid metabolism in major depression and bipolar disorder depressive episode according to the symptom severity with larger sample groups is suggested.
Keywords: bipolar disorder; major depressive disorder; uric acid; purinergic dysfunction; inflammation

INTRODUCTION

The purinergic system plays a role in the regulation of mood, motor activity, cognitive function, sleep, and behavior. Purinergic mechanisms can also play a role in various neuropsychiatric diseases (Ortiz R. et al. 2015, Cheffer A. et al. 2018). Uric acid is the end product of purine metabolism associated with the activity of xanthine oxidase enzyme on xanthine and hypoxanthine (Grassi D. 2013). Purines such as adenosine and ATP also play an important role in neurotransmission and neuromodulation. They show these effects via P1 and P2 receptors (Burnstock G. 2011). It demonstrated that especially adenosine agonists have antimanic (sedative, anticonvulsant, aggression relieving, etc.) effects. It sees that uric acid levels could use as indirect markers for showing increased purinergic turnover and decreased adenosine levels in patients with bipolar disorder (Machado Vieira R. 2008, 2012). In the studies conducted, uric acid was also found to be associated with altered behavior such as impulsivity, aggressive behavior, and hyperthymic temperament (Ortiz R. et al. 2015). On the other hand, uric acid is a significant antioxidant (Sautin YY & Johnson RJ. 2008). Studies show that Allopurinol that is xanthine oxidase inhibitor using for hyperuricemia can use as reducing mania symptoms in bipolar disorder as add-on treatments (Bartoli F. 2017).

Plasma uric acid levels were found to be lower in unipolar depressive disorders (Black CN., 2018). Meta-analyses found that plasma uric acid levels found to be higher in bipolar disorder patients than healthy controls (Bartoli F. 2016). So recent studies focused on uric acid levels in bipolar depressive episode, and differences of uric acid levels in bipolar and unipolar depression. A study suggested that higher uric acid levels increase the risk for bipolar disorder (Dos Santos Oliveira PM. 2018). A study found that the uric acid levels are reduced in unipolar depression and elevated in bipolar disorder in remission (Kesebir. 2014). To contribute to clarify of association between uric acid levels and bipolar/unipolar depression, we investigated bipolar and unipolar depression patients in the active period. The objective of this study is to assess whether uric acid levels in patients with unipolar and bipolar depression are different in comparison to healthy controls and to determine the clinical parameters that can be associated with a uric acid level.

MATERIALS AND METHODS

The study included patient groups consisting of 31 inpatients diagnosed with major depressive disorder and 31 inpatients diagnosed with bipolar disorder depressive episode in the department of psychiatry of Gaziantep University Medicine Faculty in Turkey between April 2015 and November 2017, and a control group of 31 healthy individuals without any known history of psychiatric disorders. This study approved with Gaziantep University ethics committee. Patient diagnoses determined according to DSM-V, and Hamilton Depression Rating Scale (HamD) used for assessing the disease severity. HamD is a questionnaire which consist 21 items and was developed to assess depression severity. The reliability and validity study conducted in Turkish (Akdemir. 2001). The patient exclusion criteria were as follows using drugs (lithium, antidepressants, and diuretics) that might affect uric acid metabolism, gout disease, hypothyroidism, alcohol use disorder, chronic kidney disease, diabetes, active malignancies, any active metabolic or infectious disease using corticosteroid.

Plasma uric acid levels of all groups recorded after reviewing the existing medical records. Venous blood sample had been taken from the antecubital vein. Plasma uric acid levels had been measured in mg/dl in the same day by spectrophotometric method. Statistical power analysis does, and 31 patients were found enough for each group. Normal distribution of numerical data was tested by the Shapiro–Wilk test. Mann-Whitney U Test was used to compare variables that did not have a normal distribution in two groups. ANOVA test used in the comparison of the variables that had normal distribution. SPSS 22.0 package software used for the analyses. $P<0.05$ was accepted as statistically significant.

RESULTS AND DISCUSSION

Totally 62 patients and 31 healthy subjects included in this study. In the patient group, 51% (32) were females, and 49% (30) were males. The mean age of the patients included in our study was 40.67. There were no significant differences between groups in terms of mean patient age, marital status, education years, and smoking. The mean serum uric acid levels found as follows: major depression patient group 4.56 (±1.53) mg/dl, bipolar depression patient group 5.38 (± 1.43) mg/dL and control group 4.86 (±1.56) mg/dl. Descriptive statistics of the study shown in Tables 1 and 2.

Table 1. Descriptive statistics

		Count	%
Patient' subtype	Bipolar depression	31	33,3
	Major depression	31	33,3
Control group		31	33,3
Gender	Female	48	51,6
	Male	45	48,4

Table 2. Descriptive statistics

	N	Min	Max	Mean	St. Dev.
HAM-D	62	13,00	39,00	25,4355	5,62087
Uric Acid	93	0,80	9,40	4,9376	1,43980

HAM-D: Hamilton Depression Rating Scale
St. Dev: Standard deviation

Although serum uric acid levels seem to be higher in the bipolar depression group comparison to significant depression and healthy controls (p= 0.062, 0.055 respectively), it wasn't significant (P=0.075). (Table 3). There were no significant differences between uric acid levels in terms of age, gender, and duration of disease.

Table 3. Statistical analysis of uric acid levels between control, bipolar depression and major depression groups

		N	mean	St. Dev	P
Uric Acid	Bipolar depression	31	5,3839	1,42363	0,075
	Major depression	31	4,5645	1,53743	
	Control group	31	4,8645	1,26953	
	Total	93	4,9376	1,43980	

Studies show that inflammatory activity increases in depression (Varma G. S. 2014). Also, studies conducted between the years 1967-2008 reviewed in meta-analyses and seen that there was a positive correlation between depression and CRP, IL-6, and IL-1 (Howren MB. 2009). In another metaanalysis, studies conducted between the years 1960-2009 were reviewed, patients that were on antidepressants it was found that TNF-α levels were higher in the depression group in comparison to the control group, IL-6 levels were higher in the patient group in comparison to the control group and IL-1β levels did not differ between patient and control groups (Dowlati Y et al. 2010). In addition to these results, in a study conducted on schizoaffective disorder, it was found that hs-CRP levels were higher during the depressive phase, and IL-4 levels were lower during the manic period in comparison to the control group, both of which support immune system activation in affective disorders (Elboga G et al. 2017). It also is shown that uric acid level elevated during the inflammatory process. The studies conducted revealed a significantly positive correlation between uric acid levels and several inflammatory markers (Ruggiero C et al. 2006). In our research, there were no significant differences in major

depression, healthy controls, and bipolar depression group in terms of uric acid levels. It might be associated with a limited sample group.

Besides cross-sectional design, lack of control for important factors that may influence uric acid (alcohol use, caffeine, dietary patterns, BMI) is also a limitation of this study. In particular, it shown that uric acid may include variations in subjects with bipolar disorder may be at least partially due to metabolic abnormalities.

Uric acid is a significant antioxidant (Sautin YY & Johnson RJ. 2008). There is evidence about an alteration of oxidative parameters indicating the oxidant system in both bipolar and unipolar depression (Sahin S et al. 2017, Bulut M et al. 2013). But when we consider no differences in uric aside levels between patients and control, this change in the oxidant system may be attributable to the oxidative parameters of non-uric acid.

In the literature, some studies support the opinion that uric acid levels are altered in depression patients (Bartoli F. et al. 2016) A research has shown that the uric acid level is reduced in unipolar depression and elevated in bipolar disorder due to purine metabolism disorder. However, in this study, uric acid was evaluated in patients in remission (Kesebir S. 2014). The lack of difference in our study may be an indication that the antioxidant system is not working well in the active period of disorders. The major limitation is that in these studies, patients are taking medication. Also, uric acid levels are associated with metabolic syndrome and metabolic syndrome prevalence is high in psychiatric disorders and antipsychotics (Sahin et al. 2018, Chaudhary et al. 2013). So another limitation of this study is that patients' body mass index is unknown. Non-medicated patients and large scale studies are needed.

CONCLUSION

Alterations in uric acid levels may not be a predictive marker for the differentiation of major depression and bipolar depression. Examination of uric acid metabolism in patients with major depressive disorder and bipolar disorder depressive episode according to the symptom severity may contribute to the understanding of the disease in larger sample groups and may broaden the horizons of differential diagnosis and treatment.

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