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Evaluation of serum natural antioxidant levels in patients with schizophrenia, schizoaffective disorder, and bipolar disorder

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ABSTRACT

Aims: Evidence for the role of oxidative stress in psychiatric disorders is growing. This study aimed to evaluate laboratory parameters related to oxidative stress, such as uric acid, albumin, and total bilirubin, which can be easily measured in serum in patients with schizophrenia, schizoaffective disorder, and bipolar disorder, and to compare them with healthy controls.

Methods: The study included 221 patients diagnosed with schizophrenia, schizoaffective disorder, and bipolar disorder according to DSM-5 criteria and 104 healthy individuals. The patient and control groups were compared in terms of serum uric acid, albumin, and total bilirubin values.

Results: A statistically significant difference was in uric acid levels among the schizophrenia group, schizoaffective disorder, bipolar disorder, and the control group ($p<0.001$ for all). Similarly, significant differences were identified between the patient groups and the control group in terms of albumin levels ($p= 0.002$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). Total bilirubin levels also exhibited significant differences between schizophrenia and schizoaffective disorder, schizoaffective disorder and control group, and bipolar disorder and the control group ($p<0.04$, $p= 0.007$, $p= 0.044$, respectively).

Conclusion: Patients differed from controls in terms of serum natural antioxidants. The findings in our study support a causal relationship between schizophrenia, schizoaffective disorder, and bipolar disorder and uric acid, albumin, and total bilirubin.

Keywords: Psychiatric disorders, oxidative stress, uric acid, albumin, bilirubin

INTRODUCTION

Schizophrenia, schizoaffective disorder, and bipolar disorder are psychiatric illnesses with unclear pathophysiologies and multifactorial etiologies. There is growing evidence of altered immune and oxidative responses in many psychiatric disorders. The number of studies on the role of irregularities in oxidative response in the etiology of these disorders increasing.[1,2]

Oxidative stress is defined as an imbalance between the increased production of reactive oxygen species, or free radicals, part of cellular metabolism, and the body's compromised ability to scavenge these reactive products.[3] It refers to a disruption in the balance between oxidation and the antioxidant defense system, leading to tissue damage, enzyme inactivation, and lipid peroxidation.[4] Antioxidant molecules neutralize the damage, which is caused by oxidant molecules, through both intracellular and extracellular defense. Extracellular defense includes molecules such as uric acid, albumin, bilirubin, transferrin, and ceruloplasmin, whereas intracellular defense involves free radical-scavenging enzymes such as superoxide dismutase, glutathione peroxidase, glutathione reductase, and cytochrome oxidase.[5]

Brain tissue, highly susceptible to free radical damage and oxidative stress due to high oxygen consumption and high lipid content, plays a significant role in the etiology of mental illnesses through these mechanisms. Although there are fewer studies on schizoaffective disorder, research on the etiology of schizophrenia and bipolar disorder focuses on oxidant and antioxidant mechanisms.[6]

There are many parameters to measure oxidative stress, but some of them involve expensive tests. Therefore, there is a need for cheaper and easily available parameters. Uric acid, albumin and bilirubin are simple, relatively inexpensive and easily available laboratory parameters associated with oxidative stress. Therefore, this study aims to evaluate uric acid, albumin, and bilirubin levels as oxidative stress markers in schizophrenia, schizoaffective disorder, and bipolar disorder, where oxidative stress is considered to play a role in etiology and compare them with healthy controls.

METHODS

The study was approved by the Amasya University Non-Invasive Clinical Researches Ethics Committee (Date:16.11.2023, Decision No: 2023/120). All procedures

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were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Antioxidant parameters, particularly uric acid, albumin, and total bilirubin values, for patients and healthy controls were recorded after obtaining them from the hospital record system.

The present study included patients who sought treatment at the Psychiatry outpatient clinic of our hospital between January 1, 2021, and September 1, 2023, and were diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder by a psychiatric specialist using the DSM-5 criteria. For all patient groups, patients were selected among patients in remission. The control group consisted of age- and gender-matched healthy individuals without any psychiatric disease and psychiatric medication use who applied to our hospital for routine delegation procedures on the same dates.

Individuals with conditions that could potentially influence oxidative stress parameters, such as cardiovascular diseases, inflammatory diseases, liver and kidney diseases, hypertension, and diabetes mellitus, and those using steroids, nonsteroidal anti-inflammatory drugs, antiplatelet agents, anticoagulants, alcohol, or substances, and those with comorbid psychiatric disorders, were excluded from the study.

Statistical Analysis

The study data were tested for normal distribution by using the Kolmogorov-Smirnov test/Shapiro-Wilk (W) test, whereas one-way analysis of variance (ANOVA, Kruskal-Wallis test) was used for the comparison of quantitative data. Correlations between parameters were analyzed using Pearson correlation analysis. The correlation coefficient (r) was interpreted as follows: 0.00-0.24 a weak relationship, 0.25-0.49 a moderate relationship, 0.50-0.74 a strong relationship, and 0.75-1.00 a very strong relationship. Numerical variables were presented as mean±standard deviation, whereas categorical variables were presented as frequency and percentage. The statistical significance level was set at $p<0.05$.

RESULTS

A total of 325 individuals were included in the present study, consisting of 94 individuals diagnosed with schizophrenia, 54 individuals diagnosed with schizoaffective disorder, 73 individuals diagnosed with bipolar disorder, and 104 healthy individuals (controls). The mean age was found to be 38.34±9.12 for the schizophrenia group, 36.69±9.67 for the schizoaffective disorder group, 38.62±9.34 for the bipolar disorder group, and 37.42±9.33 for the control group. The schizophrenia group consisted of 50 (53.2%) males and 44 (46.8%) females; the schizoaffective disorder group consisted of 24 (44.4%) males and 30 (55.6%) females; and the bipolar disorder group consisted of 35 (47.9%) males and 38 (52.1%) females. There were 52 (50.0%) males and 52 (50.0%) females in the control group. There was no significant difference in age or gender between the patient and control groups (all $p>0.05$). The mean duration of illness for schizophrenia patients was 9.81±5.48 years, that of schizoaffective disorder patients was 8.93±4.73 years, and that of bipolar disorder patients was 7.07±4.88 years. The uric acid levels were found to be 5.69±1.06 mg/L in the schizophrenia group, 5.15±1.29 mg/L in the schizoaffective disorder group, 5.13±1.34 mg/L in the bipolar disorder group, and 4.27±0.91 mg/L in the control group. Comparing uric acid levels between groups, there was no statistically significant difference between the schizoaffective and bipolar disorder groups, whereas significant differences were observed between the schizophrenia group and the schizoaffective, bipolar disorder, and control groups ($p=0.029$, $p=0.012$, $p<0.001$, respectively) (Figure 1-A). Significant differences were also found in uric acid levels between the schizoaffective disorder and control groups, as well as between the bipolar disorder and control groups ($p<0.001$, $p<0.001$, respectively). The serum albumin levels were determined to be 43.16±4.44 g/L in the schizophrenia group, 42.75±4.62 g/L in the schizoaffective disorder group, 42.86±4.12 g/L in the bipolar disorder group, and 45.13±2.64 g/L in the control group. Even though there were no significant differences in albumin values between patient groups, there were significant differences between the schizophrenia group, schizoaffective disorder, and bipolar disorder groups and the control group ($p=0.002$, $p<0.001$, $p<0.001$, respectively) (Figure 1-B). The total bilirubin levels were found to be 0.54±0.25 mg/dL in the schizophrenia group, 0.47±0.35 mg/dL in the schizoaffective disorder group, 0.48±0.27 mg/dL in the bipolar disorder group, and 0.55±0.23 mg/dL in the control group. Significant differences were found between the schizophrenia and schizoaffective disorder groups, schizoaffective disorder and control groups, as well as bipolar disorder and control groups ($p<0.04$, $p=0.007$, $p=0.044$, respectively) (Figure 1-C). Descriptive characteristics of the participants and uric acid, albumin, and total bilirubin levels are given in Table 1.

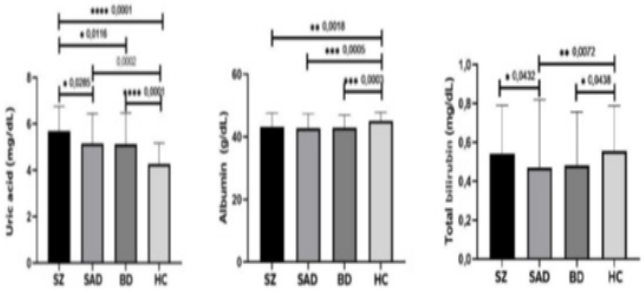

Figure 1. Comparison of uric acid (A), albumin (B) and total bilirubin (C) values in patient and control groups. Lines on the bars indicate statistical significance between groups and show the p-value. Abbreviations; SZ: Schizophrenia, SAD: Schizoaffective disorder, BD: Bipolar disorder; HC: Healthy controls

When examining the correlation between serum albumin, uric acid, total bilirubin levels, and the duration of illness, no significant relationship was observed between the patients' diagnosis duration and the uric acid, albumin, and total bilirubin ($p>0.05$). Correlations between serum parameters and the duration of illness are provided in Table 2.

DISCUSSION

In the present study, simple biochemical parameters associated with oxidative stress were examined by comparing patients with schizophrenia, schizoaffective disorder, and bipolar disorder to healthy controls. Significant differences were found in serum natural antioxidants, specifically uric acid, and albumin, between patient groups and healthy controls. Uric acid levels were significantly higher in schizophrenia, schizoaffective disorder, and bipolar

Table 1. Descriptive characteristics of participants and serum levels of parameters

	Schizophrenia (n=94) n (%) (mean±SD)	Schizoaffective disorder (n=54) n (%) (mean ±SD)	Bipolar disorder (n=73) n (%) (mean ±SD)	Healthy control (n=104) n (%) (mean ±SD)
Variables				
Years (mean ±SD)	38.34±9.12	39.69±9.67	38.62±9.34	37.42±9.33
Gender				
Female/male	44/50 (46.8/53.2%)	30/24 (55.6/44.4%)	38/35 (52.1/47.9%)	52/52 (50.0/50.0%)
Uric acid (mg/L)	5.69±1.06	5.15±1.29	5.13±1.34	4.27±0.91
Albumin (g/L)	43.16±4.44	42.75±4.62	42.86±4.12	45.13±2.64
Total bilirubin (mg/dl)	0.54±0.25	0.47±0.35	0.48±0.27	0.55±0.23
Disease duration (years) (mean±SD)	9.81±5.48	8.93±4.73	7.07±4.88	

SD: standard deviation

Table 2. Relationship between disease duration and other parameters

Variables		Uric acid	Albumin	Total bilirubin
Disease duration	r	0.037	-0.109	-0.109
	p	0.582	0.105	0.106

r: correlation coefficient

disorder when compared to controls, whereas albumin values were significantly lower than healthy controls. However, there was no significant difference in total bilirubin levels between the schizophrenia group and healthy controls, but those in schizoaffective disorder and bipolar disorder groups were found to have significantly lower levels when compared to controls.

Previous studies showed that oxidative stress has harmful effects on human neural tissue and is a significant factor in various neurological and psychiatric disorders.[7] Oxidative stress was investigated in schizophrenia, schizoaffective disorder, and bipolar disorder. In a previous study, higher levels of lipid peroxidation product malondialdehyde (MDA), advanced oxidation protein products (AOPPs), and protein carbonyl (PC) concentrations, along with increased glutathione peroxidase (GSH-Px) activities, were observed in schizophrenia and schizoaffective disorder.[2] Another study reported elevated levels of lipid peroxidation, DNA/RNA damage, and nitric oxide in bipolar disorder compared to healthy controls1. Additionally, serum antioxidants like as uric acid, albumin, and total bilirubin, were investigated in various psychiatric disorders.[8,9]

Serum uric acid is one of the non-enzymatic critical components of the antioxidant defense system of the body. Uric acid, which is an antioxidant naturally occurring in the body, protects cells against the harmful effects of oxidative stress by neutralizing reactive oxygen species.[10] The purinergic system plays a role in cognitive function, mood regulation, motor activity, sleep, and behavior.[11,12] Therefore, it became very popular in studies on psychiatric disorders. Uric acid has been investigated in psychiatric disorders due to its role in the antioxidant defense system. Previous studies examining uric acid levels in schizophrenia reported conflicting results. Even though some studies reported higher uric acid levels in schizophrenia patients when compared to healthy controls, there are also studies reporting lower levels.[13,14] A meta-analysis, however, reported no significant difference in uric acid levels between schizophrenia patients and healthy controls, irrespective of the use of antipsychotic medication.[15] Moreover, Reddy et al.[16] reported that first-episode schizophrenic patients not using medication had lower uric acid levels in comparison to healthy controls. In the present study, significantly higher uric acid levels were determined in schizophrenia patients when compared to controls. This result might be explained by factors such as the changes in the purinergic system in schizophrenia, cellular damage due to oxidative stress, the effects of medications used in schizophrenia treatment, accompanying metabolic disorders, nutritional status, lifestyle factors, smoking, and ethnic background. Some studies even propose that uric acid may not be a causative factor in the onset of schizophrenia but could be influenced by the disorder. It makes uric acid useful in monitoring the course of disease.[17] Elevated uric acid levels during inflammation and oxidative stress can potentially alter the levels of neurotransmitters such as serotonin and dopamine, which are crucial in the pathogenesis of schizophrenia. Furthermore, in the present study, when comparing the uric acid levels among patient groups, schizophrenia patients were found to have significantly higher levels compared to both schizoaffective disorder and bipolar disorder patients. This result might be explained by factors such as medication treatments, lifestyle, and metabolic reasons among patients. In studies evaluating serum uric acid levels in patients diagnosed with bipolar disorder, it was reported that uric acid levels are higher in bipolar disorder patients when compared to healthy controls.[18] The authors associated the increased uric acid levels in bipolar disorder patients with increased purine metabolism and decreased adenosine activity.[18] In the present study, uric acid levels in bipolar patients during the remission period were significantly higher when compared to healthy controls, which is consistent with the literature. Albert et al.[19] similarly reported high uric acid levels in the manic and remission phases of bipolar disorder, whereas Kesebir et al.[20] found significantly higher uric acid levels in remitted bipolar patients in comparison to healthy controls. This finding achieved in this study also indicates the presence of oxidative stress and purinergic dysfunction during the remission period in bipolar disorder.

Moreover, schizoaffective is a condition that exhibits both mood disorder and schizophrenia characteristics. There is limited data on studies evaluating serum uric acid levels in schizoaffective disorder. In one study, serum uric acid levels in schizoaffective disorder patients were found to be higher than in healthy controls.[9] Bülbül et al.[6] reported higher oxidative stress in schizoaffective disorder compared to schizophrenia and bipolar disorder.

Albumin is a significant antioxidant protein with albumin ligand binding and free radical trapping activities. It was reported that

albumin is closely related to oxidative stress and antioxidant capacity.[21] Studies have reported significantly lower levels of albumin in schizophrenia patients in comparison to healthy controls.[8] Another study showed a significant decrease in serum albumin levels after short-term antipsychotic treatment in first-episode untreated schizophrenia patients.[22] In a study examining serum albumin levels in mood disorders, albumin levels were determined to be statistically significantly lower in the control group.[23] In the present study, albumin levels in schizophrenia, schizoaffective disorder, and bipolar disorder patients were significantly lower than in controls. This result supports the hypothesis proposed in previous studies that reduced serum albumin levels might adversely affect the antioxidant defense system, influencing the development of psychiatric disorders.[8]

Bilirubin, the final product of heme metabolism, acts as an endogenous antioxidant with anti-inflammatory properties. It prevents oxidation of low-density lipoprotein and other lipids, eliminating reactive oxygen species through potent antioxidant mechanisms. Studies have demonstrated lower total bilirubin levels in schizophrenia patients compared to healthy controls.[24] On the other hand, Radhakrishnan et al.[25] reported higher total bilirubin levels in schizophrenia patients in comparison to bipolar disorder patients. In the present study, there is no significant difference in total bilirubin levels between schizophrenia patients and healthy controls; however, total bilirubin levels were determined to be significantly lower in schizoaffective and bipolar disorder patients than in healthy controls. These results should be validated in untreated patients, as bilirubin levels might be affected by psychotropic medications.[25]

Examining the correlation between diagnosis duration and serum parameters across all patient groups, no significant relationship was observed between diagnosis duration and any parameter.

Limitations

This study has several limitations. The retrospective design, relatively small sample size, and the lack of consideration for patients' dietary habits, smoking status, and body mass index are among these limitations. Another important limitation of the study is that due to the retrospective nature of the study, tests such as positive and negative symptom rating scales and depression symptom rating scales could not be applied on the patients.

CONCLUSION

The most significant findings in the present study include higher serum uric acid levels and lower albumin levels in schizophrenia, schizoaffective disorder, and bipolar disorder patients when compared to controls. Moreover, total bilirubin levels were statistically significantly lower in schizoaffective and bipolar disorder patients when compared to controls. The results achieved in this study indicate a strong relationship between serum uric acid and albumin levels and schizophrenia, schizoaffective disorder, and bipolar disorder in patients. However, further prospective studies in medication-free patients are necessary to confirm these findings and determine whether these parameters can serve as biomarkers.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki and was approved by the Amasya University Non-invasive Clinical Research Ethics Committee (Date:16.11.2023, Decision No: 2023/120).

Informed Consent

The need for informed consent was waived with the approval of the Amasya University Non-Invasive Clinical Researches Ethics Committee due to the study's retrospective design.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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