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SERUM ANTIOXIDANT DERANGEMENTS AS DIAGNOSTIC AND PROGNOSTIC MARKER IN BIPOLAR DISORDER: A COHORT STUDY.

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Abstract

Background

Bipolar disorder causes recurrent mania/hypomania and depression. According to the inflammatory idea, oxidative stress and antioxidants may be imbalanced throughout this illness. This study was undertaken to study the role of non-enzymatic antioxidants - serum uric acid, serum albumin, and serum bilirubin in different phases of bipolar disorder and compare them with healthy controls.

Method

Three groups were studied in this cohort research. One group had bipolar affective disorder patients with manic episodes, the second with depressed episodes, and the third with healthy controls. Serum uric acid, albumin, and bilirubin were measured before and after 4 weeks of treatment. The YRMS scale was used for manic episodes and the HAM-D scale was used for depressive episodes to assess disease severity.

Results

The study included 107 participants: 53 bipolar maniacs, 24 bipolar depressives, and 30 healthy controls. Bipolar mania was associated with considerably higher uric acid levels (5.40 mg/dl) compared to bipolar depression (4.09 mg/dl) and healthy controls (3.16 mg/dl) ($p<0.001$). Serum albumin levels were lower in bipolar depression (3.08 mg/dl) compared to mania (4.37 mg/dl) and healthy controls (4.60 mg/dl) ($p<0.001$). Results found no difference in serum bilirubin ($p=0.367$). Serum uric acid was reduced in bipolar mania (4.08 mg/dl) and depression (3.24 mg/dl) after 4 weeks ($p<0.001$), but albumin rose in depression (4.03 mg/dl) ($p<0.001$). Bipolar depression also increased serum bilirubin (0.72 mg/dl, $p=0.01$).

Conclusion

These findings suggest a potential role for serum uric acid and albumin as biomarkers in bipolar disorder, reflecting oxidative stress in these patients. This might also have a role in monitoring the progress and treatment of the patients.

Recommendation

Antioxidants can play a significant role in bipolar disorder but more research work is required. Further research with larger cohorts, consideration of confounding factors, and including measurement of more antioxidant molecules is essential to validate these findings.

Keywords: *Bipolar Disorder, Serum Antioxidants, Uric Acid, Albumin, Biomarkers.*
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Introduction

Bipolar disorder is a common psychiatric disorder with an age-standardized global prevalence of 490 per 10,000 population [1]. In India, 7.6 million people, or 0.6% of the population, suffer from bipolar disorder [2]. It is also associated with significant disability [1,2]. Bipolar disorder is associated with high healthcare costs and humanistic burdens [3,4].

Bipolar disorder is characterized by episodic and pathological changes in mood states that last for days to weeks. The diagnostic requirement for bipolar disorder is having an episode of mania/hypomania with or without a major depressive episode [5]. Depression is defined by the presence of low mood and decreased interest in pleasurable activities while mania is associated with an elevated mood and increased goal-directed activities.

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Various theories have been put forward to explain the underlying pathophysiology of bipolar disorder. One of the eminent theories proposes the role of oxidative stress and purinergic dysfunction. The brain, susceptible to damage caused by reactive oxygen species and neuroinflammation, is particularly susceptible to these mechanisms. On the other hand, the purinergic system plays a key role in both energy metabolism and neurotransmission regulation, therefore, affecting cognitive function, mood regulation, motor activity, sleep, and behavior. These theories help in understanding the symptoms of the illness, periodic exacerbations, as well as the clinical progression and neuro-progression seen in patients with bipolar disorder [6–12]. Uric acid is the end product of purinergic metabolism and is also a part of the non-enzymatic antioxidant system of the body. Similarly, serum albumin and serum bilirubin are also important parts of the non-enzymatic oxidant systems of the body [13–15]. Multiple studies have tried to find the association of serum levels of various non-enzymatic antioxidants - uric acid, bilirubin, albumin, and albumin with bipolar disorder and its different phases [8,9,16]. It has been shown that medications used to treat bipolar disorder alter the levels of uric acid and protect against oxidative stress-induced neuronal damage [17].

Different authors have tried to find biomarkers that can help diagnose bipolar disorder, help differentiate it from unipolar depression, predict relapses, and specify the long-term prognosis of bipolar disorder but the data has been inconclusive [9,10]. One of the possible explanations for this is that several racial or gene-specific factors may have a mediating role in the pathophysiology of bipolar disorder. Research on different sample populations with bipolar disorder can uncover these variations and ascertain which populations are better suited for specific biomarkers [7,8,9]. Some recent studies have tried to explore the relationship of the non-enzymatic antioxidant system with the course of bipolar disorder [12-18].

With this background, this study was undertaken to study the role of non-enzymatic antioxidants - serum uric acid, serum albumin, and serum bilirubin in different phases of bipolar disorder and compare them with healthy controls.

Materials and Methods

Study design

This was a prospective observational cohort study conducted using purposive sampling.

Study setting

The study took place at the Department of Psychiatry of a teaching hospital and medical college in north India. The study was a dissertation project and patients attending the psychiatric services of the institution between April 2016 to September 2017 were screened for possible inclusion in the study.

Participants

The patients who were diagnosed with Bipolar Affective disorder (current episode Manic or Depression) as defined by ICD-10, were between 18-60 years of age and provided written informed consent were enrolled in the study. Individuals with any co-morbid physical or mental illness, any substance dependence (except tobacco), and females who were pregnant or breastfeeding were excluded from the study. Thirty healthy individuals from the hospital staff were included in the study as controls.

Hence, three groups were formed - the first group of bipolar affective disorder current episode manic patients (BD-M), the second group of bipolar affective disorder current episode depression patients (BD-D), and the third group of healthy controls (HC). Serum levels of albumin, uric acid, and total bilirubin were done at baseline and at the end of the fourth week. Sample collection was done in the morning at 0800 hours after fasting for at least 10 hours. To quantify the severity of the mood episode and monitor the response to treatment, YMRS was used for patients with manic episodes and HAM-D was used for patients with depressive episodes. Similar to the biochemical parameters, these scales were applied at baseline and the end of the fourth week. The patients were provided treatment as usual in the form of antipsychotics and mood stabilizers, with other adjunct medications as required.

Bias

There was a chance that bias would arise when the study first started, but it was avoided by giving all participants identical information and hiding the group allocation from the nurses who collected the data.

Ethical consideration

The institutional ethics committee approved this study. Informed consent was given by healthy volunteers and by the patients or the legal guardians of the patients.

Statistical analysis

The data was collected, validated, and analyzed using IBM SPSS v26.0. Descriptive statistics were used to present the data, and the Kruskal Wallis test, paired t-test, and Pearson correlation were used for statistical analysis.

Results

A total of 107 participants were included in the study of whom 53 had an episode of mania, 24 had an episode of depression, and 30 participants were healthy controls. The mean age of participants was around 30 years in all three groups. More than half of the subjects were males in either of the groups. Most participants were from the lower socioeconomic strata and belonged to rural communities.

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Tables No. 1 and 2 provide the sociodemographic and clinical details of the study sample.

The average duration of the current mood episode was about 40 days for manic episodes and 70 days for depressive episodes. The mean duration of illness was around 4 years in both groups. Similarly, the mean number of mood episodes was 3 in both groups.

Table 1: Sociodemographic characteristics of the study sample

Variables		Control (n=30)	Bipolar Mania (n=53)	Bipolar Depression (n=24)
Age – Mean ± SD		30.57±11.90	32.13±11.53	32.71±11.42
Gender	Male	16 (53.33%)	31 (58.49%)	14 (58.33%)
	Female	14 (46.67%)	22 (41.51%)	10 (41.67%)
SES	Lower Class	0	4 (7.55%)	7 (29.17%)
	Upper Lower Class	20 (66.67%)	38 (71.70%)	14 (58.33%)
	Lower Middle Class	7 (23.33%)	7 (13.21%)	2 (8.33%)
	Upper Middle Class	3 (10.00%)	4 (7.55%)	1 (4.17%)
Locality	Urban	9 (30.00%)	16 (30.19%)	6 (25.00%)
	Rural	21 (70.00%)	37 (69.81%)	18 (75.00%)

Table 2: Clinical characteristics of the study sample

Variables	Control (n=30)	Bipolar Mania (n=53)	Bipolar Depression (n=24)
Duration of the current episode (in days)	NA	40.98 ± 28.20	70.00 ± 28.55
Severity of illness (measured using YMRS for bipolar mania and using MADRS for bipolar depression)	NA	32.51 ± 3.47	27.92 ± 7.31
Total duration of illness (in years)	NA	4.52 ± 2.52	3.86 ± 2.33
Number of previous episodes	NA	3.11 ± 1.73	2.88 ± 1.54

The levels of serum markers – serum uric acid, serum bilirubin, and serum albumin were compared between healthy controls, patients with bipolar mania, and bipolar depression at baseline using the Kruskal Wallis test. Table No. 3 provides details of the analysis.

Table 3: Comparison of Serum uric acid, Serum albumin, and Serum bilirubin between the three groups at baseline

Variables	Control (n=30)	Bipolar Mania (n=53)	Bipolar Depression (n=24)	p-value
Serum uric acid (in mg/dl)	3.16±0.51	5.40±0.80	4.09±0.49	< .001
Serum bilirubin (in mg/dl)	0.66±0.25	0.78±0.51	0.61±0.25	0.367
Serum albumin (in mg/dl)	4.60±0.50	4.37±0.46	3.08±0.44	< .001

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A significant difference was obtained between the three groups for serum uric acid and serum albumin levels. Using further pairwise comparisons, a significant difference in the mean serum uric acid was observed between all three pairs. For serum albumin levels, a significant difference was noted between healthy controls and bipolar depression, as well as between bipolar mania and bipolar depression. Mean serum uric acid was highest in patients with bipolar mania, followed by patients with bipolar depression and healthy controls. Similarly, serum albumin levels were lower in patients with bipolar depression.

Pearson correlation was used to find the correlation of serum uric acid, serum bilirubin, and serum albumin at baseline with the different sociodemographic and clinical factors. For patients with manic episodes, a significant and positive correlation was noted between serum uric acid levels and the total number of mood episodes, total duration of illness, and the severity of illness as measured by the YMRS scale. For patients with depressive episodes, a significant and positive correlation was noted between serum uric acid levels and the duration of the current episode (in days) while a significant but negative correlation was noted between MADRS score and serum albumin levels. Table No. 4 and Table No. 5 provide details of these findings.

Table 4: Correlation of serum uric acid, serum albumin, and serum bilirubin with different sociodemographic and clinical in patients with bipolar mania at baseline

Variables		Weeks							
		1	2	3	4	5	6	7	8
1	Age in years	1							
2	Total number of episodes	-0.048	1						
3	Total duration of illness (in years)	-0.029	0.939**	1					
4	Duration of present episode (in days)	-0.253	0.093	0.127	1				
5	Serum uric acid at baseline	-0.011	0.533***	0.501***	0.178	1			
6	Serum albumin at baseline	-0.242	0.125	0.101	0.267	0.087	1		
7	Serum bilirubin at baseline	0.054	-0.121	-0.119	0.013	0.098	0.072	1	
8	YMRS score at baseline	0.094	0.452***	0.449***	-0.035	0.785***	0.016	0.069	1

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Table 5: Correlation of serum uric acid, serum albumin, and serum bilirubin with different sociodemographic and clinical in patients with bipolar depression at baseline

Variables		Weeks							
		1	2	3	4	5	6	7	8
1	Age in years	1							
2	Total number of episodes	-0.089	1						
3	Total duration of illness (in years)	-0.112	0.883***	1					
4	Duration of present episode (in days)	-0.395	-0.104	-0.089	1				
5	Serum uric acid at baseline	-0.215	0.181	0.150	0.441*	1			
6	Serum albumin at baseline	-0.083	-0.071	-0.224	0.187	0.057	1		
7	Serum bilirubin at baseline	0.095	0.262	0.051	0.126	0.308	-0.102	1	
8	MADRS score at baseline	0.098	-0.032	0.005	-0.124	0.055	-0.688***	0.004	1

The mean levels of serum uric acid, serum bilirubin, and serum albumin were compared at baseline and at four weeks from baseline. A significant decrease in serum uric acid levels from baseline to the fourth week was noted in patients with manic episodes. In patients with bipolar depression, a significant decrease in serum uric acid levels along with a significant increase in serum albumin and serum bilirubin levels was noted. Table No. 6 presents the details of these findings.

Table 6: Comparison of serum uric acid, serum albumin, and serum bilirubin at baseline and the end of the study (4 weeks) in patients with bipolar depression and bipolar mania

Variables	Bipolar Mania (n=53)			Bipolar Depression (n=24)		
	Baseline	Week 4	p-value	Baseline	Week 4	p-value
Serum uric acid	5.40±0.80	4.08±0.79	< .001	4.09±0.49	3.24±0.56	< .001
Serum bilirubin	0.78±0.51	0.79±0.25	0.816	0.61±0.25	0.72±0.17	0.01
Serum albumin	4.37±0.46	4.24±0.55	0.164	3.08±0.44	4.03±0.42	< .001

On analysis using Pearson correlation a significant positive correlation was noted for change in the YMRS scale and serum uric acid levels in patients with manic episodes. In patients with depressive episodes, a significant negative correlation was noted between changes in the MADRS scale and serum albumin levels. Table No. 7 and Table No. 8 provide the details of the findings.

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Table 7: Correlation of changes in severity of manic episode with changes in serum uric acid, serum albumin, and serum bilirubin levels from baseline to the end of the study (4 weeks)

Variables		1	2	3	4
1	Change in serum uric acid levels	1			
2	Change in serum albumin levels	0.095	1		
3	Change in serum bilirubin levels	0.014	-0.325*	1	
4	Change in the YMRS scale score	0.394**	0.088	0.038	1

Table 8: Correlation of changes in severity of depressive episode with changes in serum uric acid, serum albumin, and serum bilirubin levels from baseline to the end of the study (4 weeks)

Variables		1	2	3	4
1	Change in serum uric acid levels	1			
2	Change in serum albumin levels	0.363	1		
3	Change in serum bilirubin levels	0.153	0.891**	1	
4	Change in the MADRS scale score	-0.284	-0.475*	-0.206	1

Discussion

This study was an observational prospective study that assessed the levels of some important and readily available biomarkers like serum uric acid, serum bilirubin, and serum albumin levels during different phases of illness in bipolar disorder and how they change during the treatment.

All the sociodemographic and clinical characteristics were similar in patients with manic episodes and depressive episodes, except for the duration of the current episode. A possible reason for the comparatively shorter duration of mood episodes in manic patients is that these patients are more disruptive and unmanageable compared to depressive patients prompting early treatment seeking by caregivers. Also, depressive episodes are typically longer and difficult to treat in patients with bipolar disorder [19,20].

The results show that serum uric acid levels were highest in the BD-M phase (5.40±0.80) mg/dl followed by the BD-D phase of illness (4.09±0.49) mg/dl and the HC group (3.16±0.51) mg/dl The findings are in concordance with a study conducted by *Berardis et al., 2008* [9] who found that serum uric acid levels were higher in BD-M group than BD-D/BD-E subgroups ($p<0.001$), and also that serum uric acid levels of BD-D/BD-E groups were higher than the control group. YMRS scoring shows a statistically significant positive correlation with serum uric acid levels ($p<0.01$) when assessed at baseline and follow-up. The results were parallel to diverse studies [7-11] in which, serum uric acid levels were positively correlated with symptom severity and with the improvement of manic symptoms. Even a comparative meta-analysis has shown that patients with bipolar disorder have higher serum uric acid levels compared to controls or patients with major depressive disorder. It was also noted that increased levels of uric acid are associated with manic or mixed-manic phases rather than depressive or euthymic ones as seen in earlier investigations [21-23].

In context to serum albumin, its level was found to be significantly lower in BD-D group (3.08±0.44) gm/dl when compared to BD-M group (4.37±0.46) gm/dl and HC group (4.60±0.50) gm/dl. The study found statistically lower serum albumin levels only in the BD-D group although levels in the BD-M group were lower than in the HC group the difference was not statistically significant. This might be because the duration of the present episode in the BD-M patients was shorter in comparison to BD-D, therefore, the total duration of oxidative stress faced was longer for BD-D, leading to more depletion of serum albumin, which is known for its serum antioxidant properties. Secondly, the total oral intake of depressive patients may also be decreased, leading to a decreased total intake of proteins. It was also noticed that MADRS scoring shows a statistically significant inverse correlation with serum albumin levels ($p<0.01$) when assessed at baseline and follow-up, i.e., MADRS scoring decreased gradually with an increase in serum albumin levels with the treatment. The findings are in concordance with the study conducted by Tiao-Lai Huang in 213 Taiwanese patients, which found that serum albumin levels were lower in patients with mood disorders than those in the control group and improved with treatment [10].

In the results, no significant difference in serum bilirubin levels, and the mean bilirubin levels among the three groups were found to be nearly comparable, i.e. (0.78±0.51), (0.61±0.25), and (0.66±0.25) mg/dl in the BM, BD, and HC groups, respectively. In the context of serum bilirubin levels, no correlation is seen in the study groups with the severity of illness or any other variables, which parallels other studies [9,24].

The search for specific biomarkers has largely been unsuccessful in the case of psychiatric disorders, and this is

understandable considering the complex nature of bipolar disorder. This implies that probably the most feasible and appropriate way forward is to identify multiple simple routine low-cost investigations with small effects and analyze them together in tandem. The authors hope that this data can also be useful in the coming generation of artificial intelligence and machine learning which can incorporate several factors together to complement screening, differentiate unipolar from bipolar depressive episodes, identify those at risk of disease progression, and manage bipolar disorder more effectively.

Generalizability

The study suggests serum uric acid and albumin as biomarkers for diagnosing and monitoring bipolar disorder. These findings could aid in early diagnosis and personalized treatment in larger populations. Significant post-treatment changes in these markers highlight their potential for tracking treatment efficacy. Recognizing oxidative stress's role may lead to new antioxidant-based therapies, improving patient outcomes. Further research with larger cohorts is needed to validate and expand these findings, potentially making these biomarkers a routine part of psychiatric evaluations.

Conclusion

The study tried to identify how some routine, easily available biochemical laboratory markers might be deranged in patients with bipolar disorder. It was noted that higher levels of serum uric acid were present in patients with bipolar disorder regardless of the nature of the mood episode, with higher levels in manic episodes compared to depressive episodes. On the other hand, mean serum albumin levels were lower in bipolar affective disorder patients with current depressive episodes. Greater uric acid levels were correlated with more severe manic episodes, whereas lower serum albumin was associated with more severe depressive episodes. During follow-up, it was noted that these biochemical derangements tend to normalize as the severity of mood episodes decreases and the patient recovers. Taken together, these findings support the role of antioxidant system dysfunction in the pathophysiology of bipolar disorder and can be part of the growing data for early diagnosis and assessing the prognosis of the disease.

The strength of this study is its longitudinal design with a month-long follow-up and the consideration of a change in the severity of mood episodes with the change in these biochemical parameters.

Limitation

The unequal number of participants in the three groups, unrelated control population, non-consideration for confounding factors (gender, diet, metabolic profile, psychotropic medication), a single-center study design with small sample size, non-specific biomarkers, and no direct relationship of these biomarkers with the nature of the bipolar disorder.

Recommendation

These biomarkers can be a soft sign to predict the risk of a particular depressive episode being associated with underlying recurrent depressive disorder versus bipolar affective disorder. These biomarkers might also help determine the factors that influence the outcome of the mood episode and the time required to recover from it.

Acknowledgment

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List of abbreviations

ICD-10 - International Classification of Diseases, Tenth Revision
HAM-D - Hamilton Depression Rating Scale
YRMS - Young Mania Rating Scale
BD - Bipolar Disorder
BD-M - Bipolar Affective Disorder Current Episode Manic
BD-D - Bipolar Affective Disorder Current Episode Depression Patients
HC - Healthy Controls

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Conflict of interest

The authors declare no conflict of interest.

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