CONCENTRATION OF URIC ACID IN PATIENTS WITH BIPOLAR DISORDER

KONCENTRACIJA MOKRAĆNE KISELINE KOD PACIJENATA SA BIPOLARNIM POREMEĆAJEM

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Abstract

Introduction. Bipolar disorder represents a mood disorder whose aetiology and pathogenesis remain poorly understood. One proposed theory suggests a connection between this condition and uric acid, the final product of purine metabolism. Identifying measurable biomarkers for the prediction and diagnosis of bipolar disorder could open new avenues for a deeper understanding of not only this condition but also psychiatric disorders in general. The aim of this study was to investigate whether a statistically significant association exists between the different phases of bipolar disorder and uric acid concentrations. **Material and Methods.** This retrospective study included all patients hospitalised over the past two years at the Clinic for Psychiatry in Novi Sad with a diagnosis of bipolar disorder. Using data extracted from patient medical records, uric acid concentrations were analysed and compared between patients in manic and depressive phases. **Results.** A total of 103 patients were included in the analyses, of whom 27.18% (n = 28) were male, and 72.82% (n = 75) were female. The mean duration of psychiatric treatment was 10.62 years. Of the total sample, 43.69% (n = 45) of patients were in the manic phase, whilst 56.31% (n = 58) were in the depressive phase of bipolar disorder. The mean uric acid concentration in the manic phase was 342.62 μmol/l ± 105.62, compared to 320.24 μmol/l ± 97.81 in the depressive phase. **Conclusion.** No statistically significant association was found between the uric acid concentration and the phase of bipolar disorder.

Key words: Bipolar Disorder; Depression; Mania; Uric Acid; Purines; Biomarkers

Sažetak

Uvod. Bipolarni poremećaj predstavlja poremećaj raspoloženja čija su etiologija i patogeneza nerazjašnjene. Postoji teorija o povezanosti ove bolesti sa mokraćnom kiselinom kao poslednjom destinacijom u metabolizmu purina. U slučaju pronalaženja merljivih biomarkera za predikciju i dijagnostikovanje, otvorili bismo vrata ka dubljem razumevanju ne samo bipolarnog, već i psihijatrijskih poremećaja uopšte. Cilj je bio ispitati da li postoji statistički značajna povezanost između različitih faza bipolarnog poremećaja i koncentracije mokraćne kiseline. **Materijal i metode.** Ovom retrospektivnom studijom obuhvaćeni su svi pacijenti koji su u poslednje dve godine bili hospitalizovani u Klinici za psihijatriju u Novom Sadu pod dijagnozom bipolarnog poremećaja. Pomoću podataka uzetih iz kliničkog informacionog sistema, analizirane su koncentracije mokraćne kiseline kod pacijenata sa maničnim i kod pacijenata sa depresivnim fazama. **Rezultati.** U ovoj studiji smo pratili 103 pacijenta, od kojih su 27,18% (28/103) muškog, a 72,82% (75/103) ženskog pola. Prosečno trajanje psihijatrijskog tretmana iznosilo je 10,62 godine. U maničnoj fazi bilo je 43,69% (45/103) pacijenata, dok je 56,31% (58/103) bilo u depresivnoj fazi bipolarnog poremećaja. Koncentracija mokraćne kiseline pacijenata u maničnoj fazi iznosila je u proseku 342,62 ± 105,62 μmol/l, a u depresivnoj fazi 320,24 ± 97,81 μmol/l. **Zaključak.** Nije ustanovljena statistički značajna povezanost između koncentracije mokraćne kiseline i faza bipolarnog poremećaja.

Ključne reči: bipolarni poremećaj; depresija; manična faza; mokraćna kiselina; purini; biomarkeri

Introduction

Bipolar disorder, formerly known as manic-depressive psychosis (MDP), is a chronic mental illness classified among mood disorders. It is characterised by recurrent episodes of mania, depression, and mixed states that alternate over varying time periods [1].

Approximately two per cent of the global population is affected by this condition, making it one of the most prevalent mental illnesses worldwide [2]. Onset typically occurs in the third decade of life [1]. Individuals with bipolar disorder have a significantly higher mortality rate and a lifespan of 10-20 years shorter than that of the general population [3]. Whilst increased rates of cardiovascular disease and comorbid substance use disorders contribute to this, suicide remains the leading cause of death [1]. Despite the availability of effective treatment, the interval between disease onset and diagnosis is often prolonged, averaging approximately six years [4].

Early diagnosis remains a considerable challenge in clinical practice, as bipolar disorder frequently presents initially as a depressive episode that is clinically indistinguishable from unipolar depression. This is significant because misdiagnosing bipolar disorder as depression may result in the prescription of antidepressants without mood stabilisers, which carries a risk of triggering a switch to hypomania or mania [5].

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Abbreviations
MDP – manic-depressive psychosis
GABA – gamma-aminobutyric acid

As more information has been gathered on the epidemiology of bipolar disorder, it has become increasingly evident that some patients do not experience full manic episodes, yet exhibit noticeable elevations in mood (hypomania). This gave rise to the classification of the disorder into Type I (mania ± depression) and Type II (hypomania ± depression) [5].

On average, a manic episode lasts three to four months, whilst a depressive episode lasts four to six months [1]. The core triad of manic symptoms comprises: (1) emotional disturbance (euphoric or irritable mood), (2) psychomotor symptoms and signs (hyperactivity), and (3) expansive or inflated self-esteem and self-confidence (cognitive symptoms) [6]. By contrast, the hallmark features of depression are loss of interest and pleasure in all activities (anhedonia) [1,6].

Despite numerous studies, the aetiology of bipolar disorder remains poorly understood. Genetic factors are considered the principal cause, with environmental influences thought to act as triggers [7].

Several theories have been proposed to explain the mechanisms underlying the onset of bipolar disorder. One hypothesis suggests that purinergic dysfunction plays a role in the pathophysiology of mood disorders and other psychiatric conditions [8]. Purines are central to neurotransmission and neuromodulation, influencing the activity of several neurotransmitters, including dopamine, gamma-aminobutyric acid (GABA), glutamate, and serotonin [8,9]. A growing body of evidence supports the involvement of the purinergic system in mood regulation, motor activity, cognitive function, sleep, and behaviour [10]. Consequently, research attention has turned to uric acid, the end product of purine metabolism [11].

The relationship between bipolar disorder and uric acid has been a subject of discussion since the early days of psychiatry. In the latter half of the nineteenth century, Danish physician Karl Lange introduced the concept of "uric acid diathesis" in the pathogenesis of depression – the notion that mental disorders may arise from imbalances in uric acid levels [11]. In 1921, German psychiatrist Emil Kraepelin described associations between manic symptoms, uric acid excretion, hyperuricaemia, and gout [12]. Later, in 1949, psychiatrist John Cade proposed that a condition involving uric acid was responsible for the "psychotic excitement" observed in his manic patients [13]. Since the 1960s, certain psychological traits, including disinhibition, hyperthymic temperament, impulsivity, and excitement seeking, have been associated with elevated uric acid levels [11].

Uric acid is thought to contribute to the pathogenesis of bipolar disorder through oxidative stress and other mechanisms [7]. Elevated uric acid levels are associated with accelerated purinergic transformation and reduced adenosine transmission. It has been hypothesised that reduced adenosine activity, principally at the A1 receptor level – accompanied by correspondingly elevated uric acid levels - disrupts neurotransmitter pathways and is associated with manic behaviour [14].

Several studies suggest that impairment of the purinergic system plays a role in the pathophysiology of mood disorders, including both bipolar disorder and unipolar depression [15]. Uric acid levels and impulsivity have both been found to be elevated in bipolar disorder, with increased impulsivity showing a positive correlation with higher uric acid levels [16]. Research also indicates that serum uric acid levels may serve as prognostically accurate biomarkers for identifying depressive patients at risk of conversion to bipolar disorder [4,7].

Further support for a link between bipolar disorder and uric acid comes from the antimanic and antipsychotic effects of allopurinol, a xanthine oxidase inhibitor that reduces uric acid synthesis [17,18]. Given that psychiatry currently lacks clinically validated biomarkers for predicting and diagnosing bipolar disorder, further investigation into the role of uric acid in its pathogenesis is of considerable importance. A deeper understanding of this condition may help address the problem of delayed diagnosis and, in turn, pave the way for more effective treatment.

This study aimed to examine whether a statistically significant correlation exists between different phases of bipolar disorder and uric acid levels.

The hypothesis proposed was that uric acid levels are higher in patients experiencing a manic episode than in those in the depressive phase of bipolar disorder.

Material and Methods

A retrospective study was conducted and approved by the Ethics Committee of the University Clinical Center of Vojvodina, Novi Sad (reference number 00-1141/8; date: 1.12.2023). The study included adult patients hospitalised at the Clinic for Psychiatry in Novi Sad during 2021 and 2022, who carried a confirmed diagnosis of bipolar disorder.

Data were obtained from medical records stored in the clinical information system and subsequent-

Table 1. Demographic characteristics of the patients

Characteristic	Manic phase (n=45)	Depressive phase (n=58)	Total (n=103)	P-value
Mean age, years (mean±SD)	44.45±13.91	42.84±15.84	43.39±14.65	0.493
Sex, n (%)				
Male	13 (28.89)	15 (25.86)	28 (27.18)	0.824
Female	32 (71.11)	43 (74.14)	75 (72.82)	
Average age, (mean ± SD)				
Men	41.38±13.23	45.6±18.15	43.64±15.91	0.678
Women	45.22±13.37	41.88±15.07	43.31±14.37	0.324
Level of education, n (%)				
Elementary school	0 (0)	1 (1.72)	1 (0.97)	1.000
Secondary school	6 (13.33)	14 (24.14)	20 (19.42)	0.743
Higher Education Diploma	0 (0)	3 (5.17)	3 (2.91)	0.539
University	7 (15.56)	10 (17.24)	17 (16.50)	0.322

n – number of patients, SD – standard deviation; p – statistical significance

ly categorised and systematised using Microsoft Excel. Uric acid levels measured as part of routine laboratory analyses conducted during hospitalisation were the primary outcome of interest. These were compared between two defined patient groups: those in the depressive phase and those in the manic phase of bipolar disorder. Demographic data including sex, age, marital status, number of children, family history, number of previous hospitalisations, duration of treatment, age at disease onset, and use of alcohol and/or psychoactive substances were also recorded.

The distribution of numerical data was assessed using the Shapiro-Wilk test. Continuous variables with a normal distribution were compared using an unpaired Student's T-test, whilst the Mann-Whitney U test was applied to variables without a normal distribution. Categorical variables were compared using Fisher's exact test, and the Pearson's Goodness-of-fit χ^2 test was used to compare the manic and depressive phase groups. A p-value of less than 0.05 was considered statistically significant.

Statistical analyses were performed using JASP Team (2025). JASP (Version 0.19.3) [computer software].

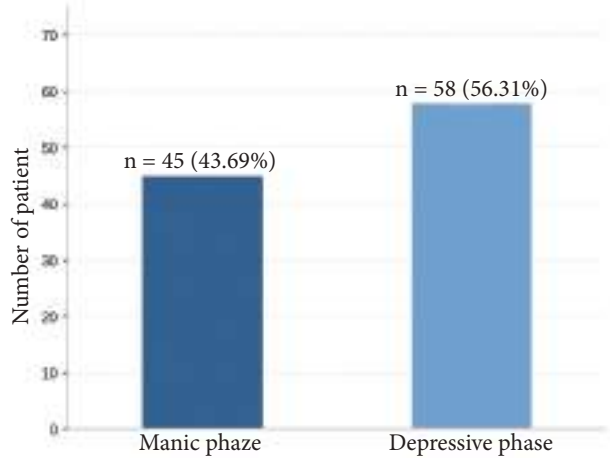
Results

A total of 103 patients were included in this study, of whom 27.18% (n = 28) were male and 72.82% (n = 75) were female. The mean age of the cohort was 43.39±14.65 years; the mean age for male patients was 43.64±15.91 years and for female patients 43.31±14.37 years. With regard to educational attainment, 19.42% (n = 20) had completed secondary school, 16.50% (n = 17) had completed university education, 2.91% (n = 3) had completed higher education, and 0.97% (n = 1) had completed primary school only **(Table 1).**

A positive psychiatric family history was recorded in 32.03% (n = 33) of patients. A total of 26.21% (n = 27) of patients reported use of psychoactive substances and/or alcohol. The mean duration of psychiatric treatment was 10.62±9.82 years. No statistically significant difference was observed in uric acid levels between patients in the manic phase (342.62±105.62 μmol/L) and those in the depressive phase of bipolar disorder (320.24±97.81 μmol/L) (p = 0.2686) **(Table 2).**

No statistically significant associations were identified between the demographic or clinical characteristics of the patients and a specific phase of bipolar disorder.

The distribution of patients between the manic phase (43.69%, n = 45) and the depressive phase (56.31%, n = 58) did not differ significantly **(Graph 1).**



Graph 1. Distribution of patients by phase of bipolar disorder

Table 2. Uric acid levels and clinical characteristics of patients

Characteristic	Manic phase (n=45)	Depressive phase (n=58)	Total (n=103)	P-value
Uric acid level, μmol/l (mean±SD)	342.62±105.62	320.24±97.81	330.02±100.91	0.269
Psychoactive substance abuse, n (%)	14 (31.11)	13 (22.41)	27 (26.21)	0.370
Psychiatric family history, n (%)	10 (22.22)	23 (39.66)	33 (32.03)	0.088
Average duration of treatment, (mean±SD)	13.86±9.29	10.65±9.13	10.62±9.82	0.143

n-number of patients, SD-standard deviation; p-statistical significance

Discussion

The present study found no statistically significant difference in uric acid concentrations between patients in the manic and depressive phases of bipolar disorder, nor any significant association between demographic or clinical characteristics and disease phase.

Whilst no statistically significant relationship between uric acid and the two phases was observed, further analysis reveals several noteworthy findings about the demographic characteristics of patients with bipolar disorder. With respect to sex distribution, female patients constituted the numerical majority, accounting for 72.82% of our sample. This figure is somewhat higher than the 62.8% reported by Chen et al. [3], though not unexpected, as previous studies have consistently demonstrated a higher prevalence of mood disorders - particularly depression - amongst women, occurring two to ten times more frequently than in men, depending on the specific disorder [19]. The prevailing explanation is that hormonal fluctuations, which are physiologically more pronounced in women due to the menstrual cycle, confer a greater susceptibility to these conditions [19,20]. An alternative explanation is that men are less likely to seek psychiatric help than women [21,22].

Beyond the lower prevalence in men, several authors have associated the manic phase and elevated uric acid concentrations more frequently with male patients, as confirmed by Muti et al. in their study (p=0.000) [11]. Our study did not replicate this finding (p=0.8243). This sex-related association may be related to specific behavioural patterns and lifestyle factors – such as physical activity levels and consumption of caffeine, nicotine, and alcohol as well as dietary habits - that occur more frequently in male patients during the manic phase and are known to elevate uric acid concentrations [22,23].

The mean age of patients diagnosed with bipolar disorder varies across studies, generally falling within the fourth to fifth decade of life [2,3,16]. The mean age reported by Albert et al. was 47.74 ± 15.48 years, which is broadly consistent with the mean of 43.39 ± 14.65 years in our cohort [2]. Insufficient data on age at disease onset precluded direct comparison with other studies; such a comparison, alongside age at the time of clinical presentation, would provide a more complete picture of the natural history of bipolar disorder. Nevertheless, the available data are consistent with the established finding that the first symptoms of bipolar disorder typically emerge in the third decade of life [1]. The mean age of hospitalised patients further reflects the well-documented delay between symptom onset and confirmed diagnosis.

Although no statistically significant association was found in our study between the use of psychoactive substances or alcohol and uric acid (p=0.3701), Sanli et al. investigated the effects of various substances on biochemical parameters and found that uric acid concentrations were lower in individuals using psychoactive substances compared to a control group (p=0.047) [23]. This was attributed in part to nutritional deficiencies amongst substance users, who frequently prioritised drug procurement over adequate nutrition. The co-occurrence of psychiatric disorders in this population is also relevant, as these can suppress appetite and substantially alter nutritional status, directly affecting protein metabolism and, consequently, uric acid levels.

These findings highlight that numerous everyday factors can influence uric acid metabolism – a complexity acknowledged by Chen et al. [7]. Such factors include diet, alcohol and caffeine consumption, psychoactive substance use, medication, and the presence of comorbid conditions that affect uric acid metabolism.

This study has three notable limitations: the relatively small and selected sample of patients hospitalised at the Clinic for Psychiatry in Novi Sad; incomplete data for several included patients; and the absence of a healthy control group. The influence of these factors may account for the failure to confirm the working hypothesis in the present study, notwithstanding the statistically robust findings reported by numerous other authors on this topic.

Further investigation into this subject remains essential. The role of uric acid in the pathogenesis of

bipolar disorder is well-supported, yet highly complex, given the interplay of both exogenous and endogenous factors that collectively influence an individual's mental state. A deeper understanding of this complexity will not only advance knowledge of bipolar disorder but also contribute to a broader understanding of psychiatric phenomena more generally.

Conclusion

Bipolar disorder is amongst the most prevalent chronic mental illnesses. Given the existing evidence linking this condition to uric acid metabolism, we proposed the working hypothesis that uric acid concentrations would be elevated in the manic phase relative to the depressive phase of bipolar disorder. However, no statistically significant difference was identified.

The limitations of the present study are likely to have influenced these results. As such, the putative role of purines in the aetiopathogenesis of bipolar disorder should not be discounted. Further research is warranted to generate new insights and a more complete understanding of this complex and clinically important issue.

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