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Ultra-High Performance Liquid Chromatography Mass Spectrometry-based Metabolic Profiling in Urine for Bipolar Disorder with Manic Episode

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ABSTRACT

Introduction: Bipolar disorder is a complex psychiatric condition marked by recurrent episodes of mania and depression. Despite its prevalence, the underlying pathophysiology remains poorly understood, and there is still a lack of objective biomarkers for diagnosis. Metabolomics is a promising approach for exploring biological alterations associated with specific mood states. This study aimed to investigate differences in the urinary metabolome between patients with bipolar disorder in the manic phase and healthy controls.

Methods: Urine samples were collected from 22 manic bipolar disorder patients and 31 healthy controls. Samples were analyzed using Ultra-High Performance Liquid Chromatography Mass Spectrometry. The data were processed using MZmine and TidyMass, and then subjected to statistical and multivariate analyses in MetaboAnalyst 5.0. Metabolites showing significant fold changes were then evaluated using a receiver operating characteristic analysis.

Results: The levels of two phosphatidylcholine derivatives, 1.2-dioleoyl-sn-glycero-3-phosphatidylcholine and 1-stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine, were significantly higher in the manic group ($p<0.05$). Receiver Operating Characteristic analysis revealed that these metabolites had limited discriminatory performance when evaluated individually.

Conclusion: The findings suggest that the manic phase of bipolar disorder is associated with alterations in urinary lipid-related metabolites. While the identified metabolites exhibited modest diagnostic value individually, they could potentially reflect phase-specific metabolic changes relevant to bipolar disorder. These exploratory results warrant further investigation in larger longitudinal studies that include different mood states.

Keywords: Biomarker, bipolar disorder, mass spectrometry, metabolomics, urine analysis.

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INTRODUCTION

Bipolar disorder (BD), as defined by the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), is a psychiatric illness characterized by extreme fluctuations in energy, mood, and functioning (1). Currently, diagnosis is made based solely on clinical assessment. In cases presenting with subtle or ambiguous symptoms, establishing a definitive diagnosis often requires prolonged observation and follow-up. This cross-sectional diagnostic approach may delay the initiation of appropriate treatment and contribute to a poorer prognosis. Due to the subjective nature of clinical evaluation and the lack of objective diagnostic biomarkers, BD is frequently misdiagnosed and managed as another psychiatric condition (2). The absence of reliable biomarkers with adequate sensitivity and specificity, especially those capable of detecting the illness in its early stages, poses a major challenge in clinical psychiatry (3,4). Therefore, concrete markers are needed to support diagnosis based on the initial presentation, without the need for a cross-sectional process. The aetiology of BD is not clearly understood. For these reasons, concrete, objective data are needed to aid diagnosis.

Highlights

- **Liquid Chromatography Mass Spectrometry analysis can discern in mania.**
- **Urine metabolomic profile may offer potential biomarkers in mania.**
- **Phosphatidylcholine derivatives may be candidate biomarkers for manic episodes.**

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Metabolomics studies examine metabolism and metabolic dynamics from a holistic perspective, examining hundreds of metabolites together rather than a single biomarker (5). It is often difficult to conclude that only one aspect of metabolism is affected by disease pathology. Metabolomics studies are highly suitable for investigating neuropsychiatric conditions such as bipolar disorder, the pathogenesis of which is not yet fully understood. This is because they allow the interaction of various pathways to be considered as a whole (6–8).

Mass spectroscopy is an analytical chemistry technique that separates and quantifies substances based on their mass-to-charge ratio (9). It enables the identification and quantification of thousands of molecules with high sensitivity and specificity (10). Liquid chromatography-mass spectrometry is one of the most popular methods in metabolomics studies thanks to its effectiveness with volatile and thermally unstable substances, the elimination of lengthy sample preparation steps such as derivatisation, a broader range of compounds that can be analysed, and high sensitivity (11).

Despite the growing interest in metabolomics as a promising tool for identifying objective biomarkers of psychiatric disorders, the current literature on the metabolomic signatures of bipolar disorder remains limited (12). Existing studies are characterised by small sample sizes, substantial methodological heterogeneity, and a lack of independent validation cohorts. These factors hinder the reproducibility and clinical applicability of findings (4). Furthermore, differences in biological matrices, analytical platforms, and data processing strategies have resulted in inconsistent metabolic profiles across studies (13). The clinical heterogeneity inherent to BD, including variations in mood state and comorbid conditions, further complicates the identification of disorder-specific metabolic markers. Additionally, metabolic pathways that overlap with those of other psychiatric conditions challenge the specificity of proposed biomarkers (12). Consequently, while there is preliminary evidence of metabolic alterations in BD, the current body of research is insufficient to support the use of metabolomics as a reliable diagnostic tool. This underscores the need for further well-designed, standardised studies.

Due to the limited and heterogeneous nature of existing metabolomic research in BD, particularly regarding urinary biomarkers, the present study was designed as an exploratory investigation. The primary objectives were to examine whether patients with bipolar disorder exhibit distinct urinary metabolomic profiles compared to healthy controls and to explore potential associations between identified metabolic alterations. It was hypothesised that individuals with BD would demonstrate differences in urinary metabolite levels compared to controls, reflecting altered metabolic pathways previously implicated in BD, and that these metabolomic variations would show preliminary associations with clinical features of BD. Due to the cross-sectional design and modest sample size, the findings are intended to generate hypotheses for further investigation.

METHODS

Sample Collection and Preparation

Patients aged 18–65 who were hospitalised at the Bagcilar Education and Research Hospital's Psychiatry Clinic and diagnosed with a manic episode of BD were consecutively enrolled in the study. A clinical diagnosis of bipolar disorder Type I was made based on the DSM-5 diagnostic criteria. Patient characteristics such as age, smoking status, and current medications used for bipolar disorder treatment were recorded. Following the diagnostic assessment, the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS) were administered to classify the mood episodes.

The HDRS is known to assess both the severity and changes in depressive symptoms. The cutoff scores were as follows: 0–7 considered normal, 8–13 mild depression, 14–18 moderate depression, 19–22 severe depression, and 23 or above very severe depression (14).

The YMRS measures the severity and changes in manic symptoms but is not diagnostic. As no formal cutoff score is reported for the Turkish version of the YMRS, and given that the literature commonly uses a cutoff of 7, this threshold was also adopted in our study (15,16).

For the healthy control group, participants' age and smoking status were recorded. Additionally, the Turkish version of the Symptom Checklist-90-R (SCL-90-R) was administered, and individuals scoring ≥1 on the Global Severity Index or any of the 10 subscales were excluded from the study (17). This ensured the elimination of potential subclinical psychiatric symptoms among the healthy controls.

Inclusion and Sample Processing Procedures

Participants included in the study (both patients and healthy controls) were required to have completed an 8–10 hour fasting period with the first morning urine to minimize circadian variability and to have no comorbid chronic or infectious diseases, no history of alcohol or substance dependence, and no alcohol or substance use within the past six months. Individuals who had taken any medication for reasons other than bipolar disorder treatment in the last month, had chronic conditions (e.g., neurodegenerative, endocrine, metabolic), were obese, pregnant, in the postpartum period, catatonic, or had intellectual disabilities were excluded. Patients who met the criteria for rapid cycling bipolar disorder (≥4 episodes per year) were also excluded.

Eight patients were excluded due to medical conditions identified during hospitalisation, while five patients were excluded due to contamination of their urine samples, making it impossible to obtain suitable samples. Four participants from the healthy control group were excluded due to contamination and an inability to obtain suitable samples.

Urine samples were collected in sterile urine tubes and centrifuged at 3000 rpm for 5 minutes. The supernatant was transferred into Eppendorf or cryotubes and stored at –80°C until analysis, with a maximum storage duration of five months.

Mass spectrometry analyses were conducted at the Drug Application and Research Center of the Faculty of Pharmacy at Bezmialem Vakıf University. Metabolite alterations in urine were identified using Ultra-High Performance Liquid Chromatography Mass Spectrometry with qualitative and semi-quantitative analysis. Although urinary metabolite concentrations can vary based on hydration status, values were standardized using the creatinine-adjusted metabolite concentration approach (18).

MS Analysis for Urine Samples

Urine is an ideal bioenvironment for disease studies because it is easily accessible and less complex matrix than other bodily fluids (19). The ease with which it can be collected allows for serial sampling to monitor disease and therapeutic response. Consequently, urine has become an increasingly popular sample type in metabolomics studies in recent years (20,21).

A modified method was applied, based on the work of Dunn et al. (22). In our study, we used the Ultra High Performance Liquid Chromatography/high-resolution mass spectrometry (UHPLC) method to determine metabolites qualitatively and semi-quantitatively. Analyses were performed at Drug Application and Research Center on a Thermo Q

Exactive Orbitrap high-resolution mass spectrometer coupled to UHPLC with an electrospray ionization (ESI) source. Separation was achieved on a reversed-phase C18 column using a water (0.1% formic acid) / acetonitrile (0.1% formic acid) gradient at a constant flow. Data were acquired in both ESI+ and ESI− modes over m/z 50–750 using full-scan UHPLC-MS with data-dependent MS/MS for feature annotation. Typical source parameters were: sheath gas 45, auxiliary gas 10, spray voltage ~3.8 kV, capillary temperature 320°C, and S-lens RF 50. Blanks and quality control (QC) injections were interleaved throughout the batch.

A QC pool was created by combining 5 µL from each urine sample. Quality control samples were injected into the system after every 10 test samples to monitor instrument stability and data quality. Raw data obtained from the urine samples were preprocessed in conjunction with QC samples before statistical analysis.

Statistical Analysis

Univariate statistical analysis was carried out using IBM Statistical Package for Social Sciences (SPSS) program version 27.0 (IBM Corp., Armonk, NY). The distribution of the quantified resonance signals was assessed using the Shapiro-Wilk test. Descriptive statistics included mean, and standard deviation. Group comparisons were conducted using the Mann-Whitney U test, with statistical significance set at $p < 0.05$.

Peak detection, deconvolution, alignment, and gap-filling were performed using the TidyMass R package. Features were annotated against public spectral and accurate-mass libraries (HMDB, MassBank, MoNA) using exact-mass tolerance, isotopic pattern, retention time, and MS/MS similarity. Data matrices processed in TidyMass were subjected to log transformation and normalization. The fold change analysis included molecules with an Mz Match Score greater than 0.99 and a Total Score greater than 0.80. Significant features were summarized with fold-change, and p-values. Metabolites demonstrating significant differences in the fold-change analysis were evaluated further using a Receiver Operating Characteristic (ROC) curve. The area under the curve (AUC) was then calculated to assess their ability to discriminate between the study groups.

RESULTS

In our study, urine analyses were performed on 31 healthy controls and 22 patients with manic episode. The participants' age, smoking status, and SCL-90-R scores, as well as other sociodemographic and clinical data, are presented in Tables 1 and 2.

In the manic group (n=22), quetiapine was the most commonly prescribed medication, used by 68.2% of patients. This was followed by biperidene (50%), haloperidol (36.4%), valproate (36.4%), and risperidone (18.2%). Lithium, paliperidone, and olanzapine were used by 13.6% of patients. Some patients (13.6%) were not taking medication at the time of assessment, or had not previously received drug treatment. Less frequently used medications included propranolol, zuclopenthixol, sertraline, aripiprazole, and chlorpromazine (each 9.1%). Trifluoperazine, amisulpride, and clozapine were prescribed to a smaller group of patients (4.5% each).

The urine samples from the control group and the group of patients experiencing mania were compared, and the detected differences in biomarkers are presented in Table 3. The fold change analysis revealed that the levels of 1.2-dioleoyl-sn-glycero-3-phosphatidylcholine (p=0.048) and 1-stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine (p=0.048) were significantly higher in the manic group.

Fig. 1 shows the results of the ROC analysis and area under the curve for the 1.2-dioleoyl-sn-glycero-3-phosphatidylcholine and 1-Stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine in the manic group in the fold change analysis. The sensitivity value of 1.2-dioleoyl-sn-glycero-3-phosphatidylcholine and 1-Stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine was found to be 0.5, the specificity value was 0.8, and the AUC value was 0.622. These values indicate a low level of discriminatory power for separating groups.

Table 1. Sociodemographic and clinical data of participants

	Study participants (n=53)			
	Mania group (n=22)	Control group (n=31)		
	Mean ± SD	Mean ± SD	U Score	p value
Age	34.31±10.97	29.83±8.25	247.5	0.091
Cigarettes (pack-years)	8.97±15.07	3.54±6.71	302.5	0.431
YMRS	26.14±9.32			
HDRS	1.27±1.20			

Evaluated using the Mann-Whitney U test; U score shown; HDRS: Hamilton depression rating scale; SD: standard deviation; YMRS: Young mania rating scale.

Table 2. SCL-90-R scores of control group

Control group (n=31)			
Scales	Mean ± SD	Scales	Mean ± SD
Global severity index	0.30±0.25	Somatization	0.23±0.29
Obsessive compulsion	0.64±0.48	Interpersonal sensitivity	0.36±0.44
Depression	0.34±0.40	Anxiety	0.21±0.27
Hostility	0.20±0.26	Phobic anxiety	0.09±0.14
Paranoid ideation	0.41±0.41	Psychoticism	0.10±0.18
Additional items	0.42±0.38		

SD: standard deviation.

Table 3. Comparison of urinary metabolites between control versus manic groups

Compound name	Adduct	Mz match score	Total score	Fold change	p value
Palmitamide	(M+H)+	0.996646	0.883824	1.02	0.307
Oleamide	(M+H)+	0.999457	0.842868	1.08	0.698
1.2-dioleoyl-sn-glycero-3-phosphatidylcholine	(M+H)+	0.998371	0.812094	0.70	**0.048**
1-Stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine	(M+H)+	0.998371	0.805729	0.70	**0.048**

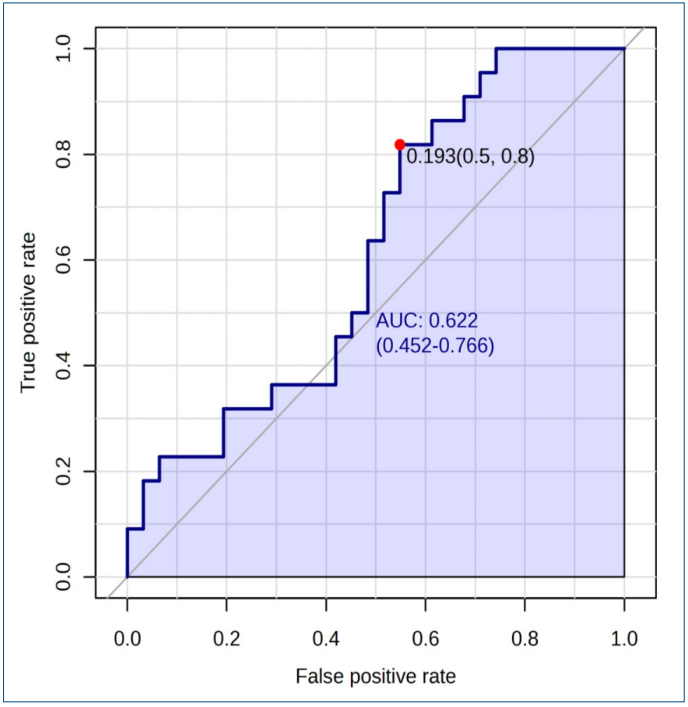

Figure 1. ROC analysis and area under curve (AUC) result of 1.2-dioleoyl-sn-glycero-3-phosphatidylcholine and 1-Stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine

DISCUSSION

In this study, metabolic biomarkers capable of distinguishing individuals experiencing a manic episode of BD from healthy controls were identified. The findings revealed two metabolites with predictive potential for BD. The subsequent discussion focuses on metabolic biomarkers in BD, their predictive utility, and the possible underlying metabolic pathways. Our study provides exploratory evidence of urinary metabolomic alterations associated with the manic phase of BD. As manic episodes are clinically well-defined and show high diagnostic reliability, the present results should be interpreted as reflecting phase-specific biological characteristics rather than as indicators of early diagnosis. In this context, the identified metabolic differences could inform future longitudinal and comparative studies of different phases of BD, aiming to clarify the dynamic metabolic processes underlying the condition. We anticipate that our study will make a valuable contribution to enhancing the precision of BD diagnosis and support the development of objective, biologically based tools for clinical practice.

1.2-Dioleoyl-sn-glycero-3-phosphatidylcholine (DOPC) is a lipid molecule containing choline that integrates into cell membranes (23). Choline and its metabolites play a crucial role in cell membrane signalling and neuronal communication (24). In our study, we found increased DOPC levels in the patient group. In line with the literature, previous studies have reported increased choline levels in the brain in mood disorders, as well as elevated DOPC levels in the urine of patients with insomnia compared to healthy controls (25,26). One possible explanation is that, while DOPC levels may increase in certain biofluids, the amount excreted in urine may also increase in patients with BD. Supplementation with phosphatidylcholine has been reported to alleviate symptoms of bipolar disorder (24). Furthermore, lithium has been shown to bind to phospholipid head groups, which could potentially modulate membrane structure and function, a mechanism that may contribute to lithium's therapeutic effects in bipolar disorder (27). Further studies are needed to clarify the specific role of DOPC in bipolar disorder and to assess its potential as a urinary biomarker.

1-Stearoyl-2-linoleoyl-sn-glycero-3-phosphocholine (SLPC) is a derivative of phosphatidylcholine that contains two distinct fatty acids: stearic acid and linoleic acid. Phosphatidylcholines are essential components of cell membranes and play a critical role in synaptic transmission, neurotransmitter release, and various other neurological functions. In our study, we found that SLPC levels were increased in the patient group. Such changes could influence membrane integrity and synaptic functioning, both of which are often disrupted in BD. Alterations in SLPC levels may therefore reflect disturbances in lipid metabolism associated with the disorder. Previous studies have, also, reported elevated levels of phosphatidylcholines in bipolar disorder (28). Since lipid metabolism may vary across disease phases, phase-specific metabolic alterations may not be directly comparable across studies. Nevertheless, further research is warranted to elucidate the specific role of SLPC in bipolar disorder and to assess its potential as a biomarker for diagnosis or disease monitoring. Area under curve results suggest that this metabolite has a weak ability to discriminate between groups. While this level of performance is statistically distinguishable, it suggests that the metabolite alone has limited clinical utility as a diagnostic biomarkers. However, its performance may be better when it is evaluated as part of a multi-metabolite panel rather than as a double marker.

It should be noted that the majority of patients in the manic group were taking psychotropic medications, including mood stabilisers and antipsychotics. These medications are known to affect lipid metabolism and neurotransmitter-related pathways (29). Previous studies have shown that agents such as lithium, valproate, and atypical antipsychotics can affect phospholipid turnover, fatty acid metabolism, and mitochondrial function (30). Therefore, the observed metabolomic alterations may reflect disease-related mechanisms and pharmacological effects. However, due to the challenges associated with recruiting untreated manic patients, it is difficult to eliminate the effects of medication in clinical metabolomics research. Therefore, these findings should be interpreted as associative rather than causal, given the potential influence of pharmacological treatment on metabolic pathways.

In our study, we aimed to eliminate the confusion caused by different pathologies by examining patients with BD without additional chronic diseases.

There are several limitations to this study that should be acknowledged. Firstly, the relatively small sample size may have limited the statistical power of the analyses. Secondly, the single-centre, cross-sectional design restricts the generalisability of the findings and precludes causal inferences. Thirdly, the absence of a euthymic or depressive group limits the ability to make comparisons with the metabolomic findings. Finally, the use of medication represents an important confounding factor, as mood stabilisers and antipsychotics are known to influence lipid metabolism. Although medication data were documented, it was not possible to fully control for their specific metabolic effects in the analyses. These limitations should be considered when interpreting the findings, and future studies with larger, multicentre, and longitudinal designs are required.

As a result, this study identified differences in urinary metabolites related to lipids between patients with bipolar disorder in the manic phase and healthy controls. Elevated levels of certain phosphatidylcholine derivatives indicate phase-related metabolic changes. However, given the exploratory design of the study, its modest sample size, and the limited discriminatory performance of individual metabolites, these findings should be interpreted with caution. Rather than providing definitive biomarkers, the results highlight potential metabolic pathways for future investigation.

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Sağlık Bilimleri University Hamidiye Scientific Research Ethics Committee on July 05, 2023 with the decision numbered E-46418926-050.99-257390.

Informed Consent: Participants and/or their guardians or first-degree relatives signed the informed consent form.

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Conflict of Interest: The authors declared that there is no conflict of interest.

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Data Availability Statement: The raw data of this study will be openly available on APERTA, TUBITAK's (the funder of the study) open access system, within a maximum of 36 months. APERTA can be accessed via the following link: https://aperta.ulakbim.gov.tr/

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