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Short communication

Exploring the association between bipolar disorder and uric acid: A mediation analysis

Francesco Bartoli [a,*], Cristina Crocamo [a], Giulia Maria Gennaro [a], Gloria Castagna [a], Giulia Trotta [a], Massimo Clerici [a], Giuseppe Carrà [a,b]

[a] Department of Medicine and Surgery, University of Milano Bicocca, Milano, Italy
[b] Division of Psychiatry, University College London, London, UK

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ABSTRACT

Objective: Recent evidence shows that bipolar disorder might be associated with a purinergic system dysfunction. This study aimed at (i) testing the association between bipolar disorder and uric acid serum levels, and (ii) clarifying whether this relationship is mediated by metabolic syndrome and other relevant metabolic parameters.
Methods: Patients consecutively admitted to a Mental Health Inpatient Unit, with a diagnosis of bipolar disorder or other severe mental disorders, and an appropriate healthy control sample, were included in this cross-sectional, exploratory study. We performed linear regression analyses, to explore factors associated with uric acid levels, and formal tests of mediation to assess mediating effect of candidate variables.
Results: 176 individuals with mental disorders and 89 healthy controls met inclusion criteria. Bipolar disorder was the only diagnostic subgroup significantly associated with increased uric acid levels. Furthermore, male gender, metabolic syndrome, as well as abdominal circumference and triglycerides levels, had a significant effect on uric acid. Relevant mediation analyses showed that the estimated effect between bipolar disorder and uric acid levels was only partially mediated by metabolic abnormalities.
Conclusion: This study suggests a direct association between bipolar disorder and uric acid levels, only partially mediated by metabolic abnormalities. It seems consistent with results of previous studies highlighting a purinergic dysfunction in bipolar disorder and the role that purinergic modulators, lowering uric acid levels, could have in clinical practice.

1. Introduction

Uric acid is the final product of purine nucleotide catabolism depending from the oxidative activity of the enzyme xanthine oxidase on xanthine and hypoxanthine [1]. Purines play a key role in both energy metabolism and neurotransmission regulation [2,3]. A purinergic dysfunction might be involved in the pathophysiology of mood and other psychiatric disorders [4], influencing the activity of several neurotransmitters, including dopamine, gamma-aminobutyric acid, glutamate, and serotonin [5]. In particular, purinergic system could impact on various behaviors typically altered in people with bipolar disorder, such as sleep, motor activity, aggressive behavior and social interaction [6]. Therefore, it has been hypothesized that subjects suffering from bipolar disorder might have a purinergic dysfunction with higher uric acid levels [7,8], as compared with both healthy individuals [8] and those affected by other mental disorders [7,9]. On the other hand, meta-analytic data have shown that about 37% of people with bipolar disorders have a comorbid metabolic syndrome [10] that, in turn, is often associated with elevated uric acid levels [11,12]. Preliminary findings have shown that elevated uric acid is associated with several metabolic abnormalities, including metabolic syndrome, abdominal obesity and hypertriglyceridemia, also among people with severe mental disorders [13,14]. Moreover, among people with mood disorders, it has been found that uric acid levels are associated with higher triglycerides and lower HDL cholesterol levels, respectively, representing a significant risk factor for insulin resistance and an increased atherogenic potential [15]. Thus, it seems there is sufficient evidence to hypothesize that metabolic abnormalities, known to be frequently associated with bipolar disorder [10,16], could be involved in the relationship between bipolar disorder and increased uric acid levels. However, previous studies did not explore if the association between bipolar disorder and uric acid levels could be at least partially explained by the mediating effect of metabolic syndrome or other relevant parameters. In order to fill this gap in the research literature, we conducted an exploratory study hypothesizing that (i) people with bipolar disorder would have uric acid levels higher than controls, and (ii) the association between bipolar disorder and uric acid levels were mediated by metabolic syndrome and/or individual, candidate, metabolic parameters.

* Corresponding author.
E-mail address: f.bartoli@campus.unimib.it (F. Bartoli).

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2. Methods

2.1. Study design and procedures

This cross-sectional, exploratory study was drawn up following the STROBE Statement — Checklist [17]. Patients consecutively admitted to San Gerardo University Hospital, Mental Health Inpatient Unit, Monza (MB), Italy, with at least one 12-month DSM-IV/SCID diagnosis of mental disorder, were included in this study [18,19]. In the same period, all inpatients never previously treated with antipsychotics, mood stabilizers, and antidepressants, and with no history of mental disorders, admitted for planned, routine (non-emergency), maxillofacial surgery in the same general hospital, were selected as a comparison group. We chose subjects from this clinical population as control group since they were unlikely to suffer from chronic physical conditions potentially influencing metabolic abnormalities. Subjects eligible for this study (i) were aged between 18 and 65 years, (ii) had been tested for serum uric acid levels and relevant metabolic parameters, i.e., glycemia, triglycerides, HDL cholesterol, abdominal circumference or body mass index (BMI), and blood pressure, (iii) had never been diagnosed with gout, and (iv) did not receive a treatment with allopurinol. Blood samples were drawn around 8.00 a.m., after an overnight fast. Metabolic syndrome was defined according to the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [20], with any three of the five following criteria constituting diagnosis:

- Elevated waist circumference (≥102 cm in men or ≥88 cm in women);
- Elevated triglycerides (≥150 mg/dL);
- Reduced HDL-cholesterol (<40 mg/dL in men or <50 mg/dL in women);
- Elevated blood pressure (systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or on antihypertensive drug treatment in a patient with a history of hypertension);
- Elevated fasting glucose (≥100 mg/dL or on drug treatment for elevated glucose).

This definition accomplishes with recent recommendations in terms of metabolic syndrome definition [21]. Where it was unfeasible to measure waist circumference (i.e. for a small proportion of bedridden patients), we substituted an abdominal obesity criterion equivalent to a body mass index (BMI) value ≥28.8 kg/m^2, without losing reliability [18,22].

2.2. Statistical analysis

Analyses were carried out using Stata for Windows version 13.0. Percentages and means, with relevant standard deviations, were used for descriptive statistics. Demographic and clinical characteristics of the sample were also provided by mental disorder, performing pairwise comparisons accounting for multiple testing. Univariate comparisons were made using Pearson's chi-square or Fisher exact tests for categorical data, and Student's t-test or Wilcoxon Mann–Whitney for continuous variables according to assumptions on data distribution. Bonferroni multiple testing correction was used in order to control the familywise error rate.

In order to test whether the relationship between bipolar disorder and uric acid levels might be explained by metabolic syndrome and relevant parameters, we followed a structured approach.

First, in order to test if subjects with bipolar disorder had increased serum levels of uric acid, after adjusting for other relevant clinical variables, we performed a multiple linear regression analysis including in the model age, gender, diagnosis, metabolic syndrome, as well as other clinical variables associated ($p < 0.05$) with uric acid at univariate level (Model 1). Next, we carried out a multiple regression model, including individual metabolic components, instead of metabolic syndrome as a whole, to test the effects of continuous values of glycemia, triglycerides, HDL cholesterol, systolic and diastolic blood pressure, and abdominal circumference, on uric acid levels (Model 2). We used abdominal circumference, rather than BMI, since it seems a more rigorous index of obesity-related clinical outcomes [23,24]. Then, having confirmed the association between uric acid levels and bipolar disorder, we could test whether the relationship between bipolar disorder (independent variable) and uric acid levels (dependent variable) were direct either there might have been mediators accounting for the relationship between them. We used a sensitivity analysis of mediation effect as framed in the *medeff* command in Stata [25]. We ascertained if the association between bipolar disorder and uric acid levels was direct, partially reduced or totally accounted for by a mediator. Indirect effect was reported as average causal mediation effect. We considered for mediation analyses only those putative mediators that were associated ($p < 0.05$) with uric acid levels according to linear regression analyses (in both Model 1 and 2).

3. Results

Two hundred sixty-five individuals met inclusion criteria, 176 with and 89 without mental disorders, respectively. People with mental disorders were, though not significantly, on average older (45.0 ± 12.2 years vs. 41.3 ± 15.5 years; $p = 0.08$) and more often women (55% vs. 44%; $p = 0.10$). As compared with controls, they also had higher rates of metabolic syndrome (32.4% vs. 13.5%; $p < 0.001$) and of serum uric acid levels (5.0 ± 1.8 vs. 4.4 ± 1.3 mg/dL; $p = 0.002$). Among inpatients with mental disorders, 35 suffered from bipolar disorder (uric acid: 5.3 ± 2.1 mg/dL), 92 from schizophrenia spectrum disorder (uric acid: 5.0 ± 1.8 mg/dL), 25 from major depression (uric acid: 4.6 ± 1.9 mg/dL), and 24 from other mental disorders, i.e., personality and/or alcohol/substance use disorders (uric acid: 4.9 ± 1.6 mg/dL). Among subjects with bipolar disorder, 26 (74%) had a manic or hypomanic episode, 9 (26%) a depressive episode, whereas only four (11%) were treated with lithium. Full details of sample demographic and clinical characteristics are reported in the Supplementary Table 1. Univariate analyses (results available upon request) highlighted that, among variables tested, male gender, current antipsychotic treatment, suffering from bipolar, schizophrenia spectrum disorder either metabolic syndrome, as well as relevant metabolic individual components (abdominal circumference, triglycerides, HDL cholesterol, and blood pressure), all were associated ($p < 0.05$) with uric acid levels, warranting adjustment for multiple comparisons. Multiple linear regression analyses, including metabolic syndrome and values of individual metabolic components, respectively, are shown in Table 1. Bipolar disorder, as compared with controls, represented the only diagnostic group associated with uric acid levels, in both models. We hypothesized a potential mediating role for metabolic syndrome ($p < 0.001$), and, among metabolic parameters tested, for abdominal circumference ($p < 0.001$) and triglycerides ($p = 0.012$).

Relevant mediation analyses, including gender as independent covariate, are reported in Table 2. Metabolic syndrome and abdominal circumference had a partial mediating role, explaining about 22% and 30%, respectively, of the overall effect of bipolar disorder on uric acid levels, whereas no mediating effect was found for triglycerides.

4. Discussion

To our knowledge, this is the first study testing the impact of co-occurring metabolic abnormalities on the relationship between uric acid levels and bipolar disorder. In this exploratory study, we compared a randomly selected sample of inpatients suffering from bipolar disorder and other mental disorders with an appropriate healthy comparison group, investigating factors associated with serum uric acid levels after adjusting for a selected set of demographic and clinical variables.