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# The serum concentration of magnesium as a potential state marker in patients with diagnosis of bipolar disorder

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**Summary**

**Aim**. Few scientific reports indicate changes in the concentration of magnesium in the blood of patients with bipolar disorder (BD). So far very little studies concerning these issues have been conducted. Therefore, the aim of this study was to evaluate the serum magnesium level in patients with bipolar disorder (in different phases of the disease) in comparison to healthy volunteers.

**Methodology**. The study included 129 patients (58 subjects in depressive episode, 23 in manic episode and 48 patients in remission) with the diagnosis of bipolar disorder type I or II. The control group consisted of 50 healthy people. Magnesium concentration was measured using flame atomic absorption spectrometry (FAAS).

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**Results.** Patients with a current depressive or manic/hypomanic episode had statistically significantly elevated serum magnesium levels compared to healthy volunteers. Moreover, a positive correlation between the duration of the manic/hypomanic episode and the relapse frequency in the last year was observed. The concentration of magnesium in patients in remission was unchanged in relation to the control group.

**Conclusions.** Presented findings suggest a role of serum magnesium level as a potential state marker, reflecting the pathophysiological changes associated with acute episodes of bipolar disorder.

**Key words:** magnesium, affective disorder, bipolar disorder, depression, biomarkers

## Introduction

Clinical trials investigating the pathophysiological processes lying at the base of bipolar disorder has been carried out for many years. The authors of these studies attempt to select factors or biochemical parameters (defined as biomarkers) specific to this process. Biomarkers should be easily labeled substances, specific for the disease, regardless of its phase (trait markers), or should reflect the specific stages/exacerbations of the disease and/or their severity (state markers) [1].The discovery of reliable biomarkers primarily would allow for a better understanding of the pathophysiological mechanisms responsible for the development of bipolar disorder. Biomarkers also would give the clinicians more effective tool to identify bipolar disorder, as well as to assess the effects of treatment, the risk of relapse or drug resistance [1]. An important area of the research for markers of affective disorder is to investigate the role of bioelements (including the magnesium ions).

Magnesium as a co-factor of tyrosine and tryptophan hydroxylase, is necessary for the normal function of the serotonergic and adrenergic receptors. Additionally, the direct enhancing effect of magnesium on 5-$HT_{1A}$ serotonin receptor transmission was reported [2–5]. Magnesium also affects the central nervous system via antagonism of the N-methyl-D-aspartate (NMDA) receptor. The probable importance of NMDA receptors (especially their excessive activation, leading to damage or impairment of neuronal activity) in the pathophysiology and treatment of affective disorders has long been emphasized by many researchers [2–9]. Besides the direct effect on NMDA receptors, it is also known that magnesium can inhibit neuronal activity by its effect on the GABAergic system, in which it acts as an $GABA_A$ receptor agonist [2, 3].

Animal studies suggest a possible antidepressant and anxiolytic-like activity of magnesium [2–8] and its ability to potentiate of imipramine action [10]. Furthermore, in one clinical study the magnesium supplementation (by intravenous infusion) in patients with severe mania reduced the doses of drugs used in the treatment (lithium, antipsychotics and benzodiazepines) [11].

The existing concepts on the role of magnesium in affective disorders indicate the relationship between hypomagnesaemia and the risk of depression [12], although the data on the magnesium concentration in the blood of patients suffering from affective disorders are contradictory. During depressive episodes, both decreased or increased

level of magnesium as well as no differences compared to healthy subjects have been shown [8].

## Aim

The aim of the presented study was to assess the concentration of magnesium in the blood serum of patients in different phases of bipolar disorder in comparison to the healthy volunteers, as well as an attempt to answer the question whether these measurements (concentrations) may be used as a marker of bipolar disorder.

This study is a part of the research project entitled DEMETER, whose aim was to determine the relationship between bipolar (or unipolar) disorder and changes in blood serum activity/concentrations of biometals, inflammatory and oxidative stress markers involved in the pathophysiology of affective disorders.

## Material and methods

### Place and subjects of the clinical trail

The subjects were in-patients and out-patients recruited in the Department of Psychiatry of University Hospital in Krakow during the period from 21 September 2009 to 30 July 2013.

The recruited patients have fulfilled diagnostic criteria of bipolar disorder – for any of phases – according to DSM-IV-TR. The healthy subjects without psychiatric disorders were recruited and studied as a control group. The informed consent for participation in the study was obtained from all subjects after explaining to them the significance of tests, the aims of the study and the anticipated results by the recruiting doctor. The bioethical committee of Jagiellonian University approved the protocol of this study. During the study the subjects were receiving monotherapy or combined therapy, with proven efficacy, adequate to current phase of disease and its clinical picture (see Table 1).

In the study the authors used the following exclusion criteria: lack of consent for participation in the study, severe psychiatric diagnosis other than bipolar disorder (for example schizophrenia, schizoaffective psychosis, major depressive disorder), psychoactive substance misuse, (excluding nicotine and caffeine), coexistence of severe somatic diseases (acute and chronic), severe personality disorders, breast feeding or pregnancy. As severe somatic diseases excluding from the study the authors considered the following: chronic autoimmune and inflammatory diseases, acute inflammatory diseases or infections present within a month before a patient was included in the study, primary adrenocortical insufficiency, renal failure, chronic pancreatitis, hypoparathyroidism, hyperthyroidism, primary hipoaldosteronism, carcinomas, megaloblastic anaemia due to iron deficiency, talasemia, hemochromatosis, liver cirrhosis, Wilson disease, nephrotic syndrome, burns. Those diseases were excluded due to the possible influence on concentrations of biomarkers examined in the DEMETER study. Similarly the authors excluded patients that were using the following drugs: hydralazine,

nonsteroidal anti-inflammatory drugs (acetylsalicylic acid, ibuprophen, indometacin), tetracyclines, fluorochinolones, calcium, iron, chelating agents or glucocorticosteroids. Table 1 presents the socio-demographic and clinical characteristics of the examined population.

The group of healthy controls was recruited from people with no present and past history of severe and chronic somatic or psychiatric diseases, with no addiction to any psychoactive substances with the exclusion of caffeine and nicotine addiction and with no psychiatric disorders in the first-degree relatives.

Table 1. **Socio-demographic and clinical characteristics of the study participants**

| | The total study group | Depression | Mania/ Hypomania | Remission |
|---|---|---|---|---|
| | N (%) | | | |
| Female | 80 (62.0%) | 37 (63.8%) | 12 (52.2%) | 31 (64.6%) |
| Male | 49 (38.0%) | 21 (36.2%) | 11 (47.8%) | 17 (35.4%) |
| BD I | 69 (53.5%) | 23 (39.7%) | 18 (78.3%) | 28 (58.3%) |
| BD II | 60 (46.5%) | 35 (60.3%) | 5 (21.7%) | 20 (41.7%) |
| Rapid cycling bipolar disorder | 22 (17.1%) | 11 (19.0%) | 3 (13.0%) | 8 (16.7%) |
| Currently applied treatment | | | | |
| | N (%) | | | |
| SSRI | 24 | 14 (24.1%) | – | 11 (22.9%) |
| SNRI | 35 | 20 (36.5%) | – | 15 (31.3%) |
| Mirtazapine | 5 | 5 (8.6%) | – | – |
| Quetiapine/olanzapine | 81 | 34 (58.6%) | 16 (69.6%) | 31 (64.6%) |
| Valproates | 46 | 22 (37.9%) | 9 (39.1%) | 15 (31.3%) |
| Lithium | 20 | 6 (10.3) | 5 (21.7%) | 9 (18.8%) |
| Lamotrigine | 24 | 10 (17.2%) | 5 (21.7%) | 9 (18.8%) |
| Carbamazepine | 5 | 3 (5.2%) | 1 (4.3%) | 1 (2.1%) |
| Disease course | | | | |
| | Mean (SD) | | | |
| Number of depressive episodes in the last year | 1.53 (1.03) | 1.67 (0.85) | 1.04 (0.88) | 1.4 (0.82) |
| Number of manic/hypomanic episodes in the last year | 0.78 (1.04) | 0.60 (0.79) | 1.13 (0.76) | 0.60 (0.82) |
| Total number of disease episodes throughout life | 11.7 (9.8) | 10.59 (8.34) | 13.81 (11.67) | 12.07 (10.46) |
| Number of hospitalizations in the last year | 0.96 (0.98) | 1.02 (1.10) | 1.00 (0.67) | 1.00 (0.97) |
| Total number of hospitalizations | 5.18 (9.63) | 4.52 (4.62) | 3.91 (3.32) | 5.11 (5.38) |

*table continued on the next page*

| | | | | |
|---|---|---|---|---|
| Number of all relapses in the last year | 2.18 (1.71) | 2.25 (1.24) | 2.10 (1.22) | 1.76 (1.07) |
| Age at onset (years) | 31.49 (11.71) | 32.07 (11.46) | 31.72 (12.14) | 30.42 (11.40) |
| Duration of illness (years) | 12.81 (8.12) | 12.99 (8.27) | 14.09 (7.69) | 13.04 (8.40) |
| The duration of the current episode or remission (weeks) | 14.62 (20.76) | 14.50 (15.23) | 16.50 (21.66) | 13.51 (26.44) |
| The severity of symptoms in the current episode/remission | | | | |
| The sum of MADRS scores | – | 27.72 (10.24) | 7.57 (6.04) | 3.33 (3.24) |
| The sum of HDRS scores | – | 20.21 (6.49) | 5.67 (5.0) | 3.38 (3.13) |
| The sum of YMRS scores | – | 1.67 (2.45) | 18.22 (7.44) | 1.54 (2.81) |

SD – standard deviation); BD I – bipolar disorder type I; BD II – bipolar disorder type II; SSRI – selective serotonin reuptake inhibitors; SNRI – serotonin norepinephrine reuptake inhibitors; MADRS – Mongomery–Asberg Depression Rating Scale; HDRS – Hamilton Depression Rating Scale; YMRS – Young Mania Rating Scale

## Diagnostic tools

The severity of depressive symptoms was measured by Montgomery–Asberg Depression Rating Scale – MADRS [13] and Hamilton Depression Rating Scale – HDRS [14]. The severity of manic symptoms was measured by Young Mania Rating Scale – YMRS [15].

## Collection and processing of blood samples. Quantitative determination of Magnesium in blood serum

From each patient and healthy volunteer no more than 9.8ml of blood was obtained from a brachial vein. The blood samples after 45 minutes from collecting were centrifuged at 3 000 revolutions per minute to obtain the serum. Then the samples were stored at – 80 $^{o}$C until use. The serum magnesium levels were measured by a flame atomic absorption spectrometry – FAAS. The authors used Perkin Elmer spectrometer Model 3110 (USA). Measurements' conditions were: air-acetylene flame, 285.2 nm wave length for Mg, slit of 0.7 nm and single-element HCL lamp. Gases flow and burner position were optimized before measurements to achieve high sensitivity. The samples were diluted appropriately to fit into the linear range of calibration curves. The lowest concentration traceability for magnesium was 0.5 μg/L. Determinations were performed in triplicate. The accuracy was tested by means of recovery analysis, which for Mg was in the range of 96–101%.

### Statistical methods

The $\chi^2$ test was used to analyse the differences between the quality variables. Shapiro-Wilk test was performed in order to evaluate the normal distribution of quantitative data. Statistical differences between the normally distributed quantitative data were analysed by one-way normal distribution, parametric analysis of variance (ANOVA). In case of absence of the normal distribution of data we used the Kruskal-Wallis ANOVA or Mann-Whitney U test. Correlations between quantitative variables – due to the lack of normal distribution – were analysed with the Spearman Rank Correlation.

## Results

129 patients (80 women and 49 men) fulfilling BD I (n = 69) or BD II (n = 60) criteria were included in the DEMETER study (58 patients in the depressive episode, 23 patients in the manic episode and 48 in the remission). In the depressive episode group 17 patients (29.3%) have fulfilled the criteria of atypical depression according to DMS-IV TR, 28 patients (48.3%) have fulfilled the criteria of melancholic syndrome according to DMS-IV TR and 8 patients (13.8%) have presented psychotic symptoms. 22 of all patients (17.1%) have presented features of rapid cycling. The control group consisted of 50 healthy subjects (14 men and 36 women).

The mean age in the group of patients (44.26 ± 12.8) did not differ significantly from the control group (45.82 ± 12.43), ($Z = –1.18$, $p = 0.24$, Mann-Whitney U test). There were also no statistically significant differences between the percentage of men and women in two groups (women vs. men: 62% vs. 72%), ($\chi^2 = 1.57$; $p = 0.21$).

The magnesium concentration in the serum of healthy volunteers and patients in the various phases of bipolar disorder subtypes are presented in Table 2.

Table 2. **Serum concentrations of magnesium [mg/l] (mean ± standard deviation) in healthy volunteers and patients in the various phases and subtypes of bipolar disorder**

| Total BD (type I + II) | | |
|---|---|---|
| Mania/hypomania | Depression | Remission |
| 26.0 ± 9.75 (N = 23) | 24.23 ± 7.8 (N = 58) | 20.60 ± 5.05 (N = 48) |
| BD type I | | |
| 26.46 ± 10.32 (N=18) | 23.3 ± 8.69 (N = 23) | 20.02 ± 5.14 (N = 28) |
| BD type II | | |
| 20.2 ± 2.5 (N = 5) | 24.82 ± 7.5 (N = 35) | 21.65 ± 4.98 (N = 20) |
| Control group | | |
| 18.53 ± 8.90 (N = 50) | | |

The analysis of variance revealed significant influence of presented episode or being in the group of healthy controls on the obtained serum magnesium concentrations (Kruskal-Wallis test, $H = 12.84$; $p = 0.005$). The concentration of magnesium among

the patients with depression (24.23 ± 7.8 mg/l, p = 0.029) and manic/hypomanic episode (26.0 ± 9.75 mg/l; p = 0.032) was statistically higher than in the control group (18.53 ± 8.90 mg/l). The serum Mg concentration in the remission (20.60 ± 5.05 mg/l) have showed no statistical difference from Mg concentration in the group of healthy controls (p = 0.99).

The analysis of variance in the subtypes of bipolar disorder has also confirmed significant influence of the presented episode or being in the group of healthy controls on the obtained concentrations of magnesium in bipolar disorder type II (Kruskal-Wallis test, H = 10.3; p = 0.016), but not in bipolar disorder type I (Kruskal-Wallis test, H = 6.23; p = 0.1). In the depressive episode the Mg concentrations were numerically higher than in the group of healthy volunteers in both BD type I (23.3 ± 8.69 mg/l) and BD type II (24.82 ± 7.5 mg/l). However, the statistical significance was presented only between BD type II patients and control group (p = 0.046). There was no significant differences between the control group and the remission in both BD type I patients (20.02 ± 5.14 mg/l) and BD type II patients (21.65 ± 4.98 mg/l). Due to a small number of patients in the hypomanic episode the analysis of Mg concentrations in types of BD was not preformed.

There were no significant differences between the magnesium concentration in patients diagnosed with bipolar I and bipolar II in the same stages of the disease :mania (Z = –0.60, p = 0.55), depression ( Z = –0.77; p = 0.44) and remission (Z = –0.85, p = 0.40); Mann Whitney U test).

Among the group of patients in current depressive episode there was no significant differences in the serum Mg concentrations between patients with versus without presence of atypical symptoms (ANOVA, f = 0.01; p = 0.93), and also between patients with versus without presence of psychotic symptoms (ANOVA, f = 1.83; p = 0.41). The presence of melancholic syndrome also did not significantly influence serum Mg concentrations (ANOVA, f = 0.68; p = 0.41).

Serum Mg concentrations of patients with the features of rapid cycling did not differ significantly from non-rapid cycling patients in both depression (ANOVA, f = 0.2; p = 0.65) and remission (ANOVA, f = 1.10; p = 0.3) or in the whole BD group (ANOVA, f = 1.36; p = 0.25). There has not been preformed such an analysis in the hypomanic/manic group of patients with or with or without rapid cycling due to a small number of patients.

The Spearman Rank correlation revealed that the serum Mg concentration in the group of patients in manic episode was positively correlated with the duration of the episode (r = 0.64; $p < 0.05$). Additionally the Mg concentration was positively correlated with the number of relapses of all type in the last year in the hypomanic/manic episode (r = 0.59; $p \leq 0.01$), as in the depressive episode (r = 0.32, $p < 0.05$). There were also no significant correlations between the Mg concentration in depression, manic episode or remission and the patient's age or other clinical and demographical features like: age of patients, duration of illness (years), total number of disease episodes throughout life. The Mg concentration did not correlate with the severity of depressive symptoms (measured by MADRS, HDRS) nor with the severity of manic symptoms (measured by YMRS). The only positive correlation was obtained between

the Mg concentration and the total score in YMRS achieved by patients in depressive episode ($r = 0.39$; $p \leq 0.01$; Table 3).

Table 3. **Correlations between serum magnesium concentration and selected quantitative clinical features in depression, mania and remission (Spearman rank correlation)**

| | Mg [mg/l] | | |
|---|---|---|---|
| | Remission | Depression | Mania/hypomania |
| Age | 0.20 | 0.02 | 0.06 |
| Number of episodes in the life | -0.06 | 0.17 | 0.43 |
| The total number of relapses in the last year | 0.17 | 0.32* | 0.59** |
| The duration of illness in years | 0.04 | 0.01 | 0.40 |
| Duration of the episode /remission | -0.17 | -0.02 | 0.64* |
| MADRS score | 0.06 | -0.12 | 0.33 |
| HDRS score | -0.01 | 0.11 | 0.30 |
| YMRS score | -0.11 | 0.39** | 0.10 |

*$p \leq 0.05$; ** $p \leq 0.01$

## Discussion

Analysis of data obtained in the present study indicate significantly higher serum magnesium concentrations in patients with depressive (especially in BD II) and manic/hypomanic episode when compared to that of the healthy individuals. Additionally, levels of magnesium are positively correlated with the duration of the manic/hypomanic episode and the number of exacerbations in the last year. In the remission phase concentration of magnesium was normalized to the level measured in the control group. There were no relationship between concentrations of magnesium and the severity of acute phase of the disease and its specific clinical features.

So far, there are not many studies evaluating the serum concentration of magnesium in patients with bipolar disorder, therefore the discussion of presented results is a bit difficult. Imada et al. [16] assessed the serum magnesium concentration in a small groups of patients with BD I (17 subjects), BD II (17 subjects) and MDD (37 subjects), but without considering the phases/episodes of the disease, in which the subjects were. Their results indicate elevated levels of serum magnesium in both BD I and BD II in relation to healthy volunteers, and no difference between the various subtypes of BD, which is in line with our findings. In fact, in both studies, participants received pharmacotherapy, but according to the cited authors, the observed alterations in the magnesium concentration are associated with the pathophysiology of affective disorders, and clinical factors characteristic of this disorder have no effect on them [16].

Another study conducted by Frazer et al. on a group of 41 patients with depressive episode and 18 patients experiencing a manic episode, 57 patients with MDD and healthy volunteers indicated a correlation between the age of women in a manic

episode, and concentrations of ionized and plasma magnesium [17]. Moreover, the authors of this study have shown (like in the presented paper) a higher concentration of magnesium in patients with depressive and manic episode compared to healthy volunteers. Simultaneously, there were no differences in the concentrations of ionized magnesium in the various subgroups [17]. Comparing these two studies, it should be noted that Frazer et al. measured the plasma magnesium levels, while in our study, the concentrations in the blood serum of patients have been assessed.

Widmer et al. in a group of 53 patients diagnosed with depression (including 41 unipolar and 12 bipolar disorder patients) showed increased magnesium levels in the plasma and erythrocytes compared to the group of 48 healthy volunteers [18]. In addition, the concentration of magnesium (both in the plasma and erythrocytes) was higher in patients with severe or moderate depression than in patients with mild depression or the control group. In contrast to the above results, in the presented study we have shown no relationship between magnesium levels and the severity of depressive symptoms (as measured by MADRS and HDRS or as reflected by fulfilling the criteria for melancholic syndrome). These discrepancies may arise from methodological differences of the study conducted by Widmer et al., such as: measurement of magnesium concentration in the blood plasma, but not in the serum; recruitment of patients currently not receiving antidepressants or mood stabilizers; inclusion of patients diagnosed both with unipolar and bipolar disorder; application of different criteria for assessment of the severity of depressive episode (AMDP depression scale). Another study carried out by Widmer et al., which again included a heterogeneous group of patients (both with unipolar and bipolar disorder, n = 88), also showed elevated levels of magnesium both in blood plasma and erythrocytes in depressive episode compared to the healthy control group (n = 61) [19].

In turn, in the study conducted by George et al. measurement of the magnesium levels in the cerebrospinal fluid of 76 patients diagnosed with BD I, 54 patients with BD II, 43 people with MDD and 59 healthy subjects indicate no difference between studied groups. This study also confirmed no direct relationship between the concentration of magnesium in the cerebrospinal fluid and severity of depressive or manic symptoms. The authors of the paper showed only a considerably higher concentration of this element in males in relation to females [20].

Concluding, an increase (relative to the group of healthy volunteers) of magnesium concentration in the blood serum in depressive and manic/hypomanic episode presented in our study, correlation of serum Mg with the duration of manic/hypomanic episodes and the numbers of disease episodes in the last year, may suggest the role of the magnesium level as a state marker reflecting the pathophysiological changes associated with acute phase of bipolar disorder.

It should be emphasized, that the authors are aware of the limitations of this study, such as: the lack of a prospective model to test the dynamics of the magnesium concentrations in the same patients, depending on the stage of the disease; substantial heterogeneity (with regard to the applied therapy) of the study groups and the relatively small number of subgroups presenting specified clinical features (e.g. rapid cycling of phases, hypomanic episode, etc.). In view of these restrictions, a small number of

published studies and ambiguity of results, our finding should be confirmed by subsequent studies carried out on a larger populations and allowing for analysis of the impact of applied pharmacotherapy and other clinical factors on the serum magnesium concentration.

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