The serum magnesium concentration as a potential state marker in patients with unipolar affective disorder

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Summary

Aim. The growing body of evidence suggests that magnesium levels can serve as a marker of major depressive disorder (MDD), but findings from clinical trials remain inconclusive. The aim of the presented study was to determine the magnesium concentration in serum of patients with MDD (in the active stage of the disease or in remission) and to analyze the role of magnesium levels as a potential marker of the disease.

Methods. Sixty-nine patients with current depressive episode, 45 patients in remission and 50 healthy volunteers were enrolled into the case-control study. The magnesium concentration was measured by flame atomic absorption spectrometry (FAAS).

Results. The mean serum magnesium concentration of patients in the depressed phase was significantly higher, compared to the control group. Moreover, magnesium levels of patients in the remission were not significantly different from the concentrations recorded in the healthy volunteers. There was also a positive correlation between the magnesium levels

and the severity of depression measured by the Hamilton Rating Scale for Depression (HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS).

Conclusions. The obtained results may suggest a role of magnesium as a state marker reflecting the pathophysiological changes underlying MDD and accompanying severe depressive episodes.

Key words: magnesium, depression, biomarkers, affective disorders

Introduction

The biomarkers are defined as biological parameters that are either the objectively measurable, fixed and specific feature of the disease, which occurs invariably, regardless of whether it is an acute phase of the disease, a remission period (a trait marker), or changing depending on the stage of the disease and reflecting the severity of the symptoms and the mechanisms (a state marker) [1, 2]. Biomarker should characterize with a high level of sensitivity and specificity (preferably above 80%). They should also be inexpensive, and with minimal invasiveness during collecting the material for analysis, to be considered as diagnostically useful in clinical practice [2]. Such biological markers could indicate an increased risk of the depressive episode (or its relapse), be a measure of response to treatment, or indicate the risk of the drug resistance [2, 3].

The involvement of magnesium ions in the modulation processes of multiple neurotransmitter systems and enzymes, the presence of the depressive symptoms in patients with magnesium deficiency [4, 5] and a number of clinical and social problems posed by the high prevalence of major depressive disorder (MDD) (4.5%–5%) [5–11] justify the examination of changes in concentrations of this element in the blood as a potential marker of depression.

Magnesium participates in many fundamental physiological processes, e.g. as a co-factor of several enzymes is involved in the energy metabolism [1, 5, 12–15], and contributes to maintaining the fluidity of the cell membranes, thus indirectly modulates neurotransmission [1, 12, 13, 16, 17]. It is considered that the involvement of magnesium in the pathophysiology of MDD is related mainly to its effects on the N-methyl-D-aspartic (NMDA) acid and γ-aminobutyric acid (GABA) receptors activity [1, 13, 14, 17]. Numerous studies have demonstrated the importance of the NMDA receptor both in the pathogenesis of depression and the treatment of patients with MDD. It has been shown that the NMDA receptor antagonists, both organic and inorganic (including zinc and magnesium), show an antidepressant activity, which was observed both in the preclinical and clinical studies [1, 3, 7, 13–15]. In addition, the magnesium ions can modulate the activity of other neurotransmission systems, including serotonergic, noradrenergic and dopaminergic [1, 13–15].

Despite of the relatively high ambiguity of the published data, the results of some clinical trials show a correlation between hypomagnesaemia and the development of depression, or changes in the magnesium concentration during a depressive episode [7, 16, 18].

Aim

The primary objective of the study has been to evaluate the serum magnesium concentration in patients with recurrent MDD when compared with healthy volunteers. The secondary objective of this study has been to verify the hypothesis that hypomagnesaemia may be a state marker in patients with MDD.

Material and Methods

The presented results are a part of the clinical study named De-Me-Ter ("Depression – Mechanisms – Therapy"), which was aimed to determine the correlation between symptomatology of affective disorders, and the serum changes of bioelements, inflammatory and oxidative stress markers presumably involved in the pathophysiology of the affective disorders [19]. The De-Me-Ter project was conducted by a team of psychiatrists working at the Department of Affective Disorders, Chair of Psychiatry, Jagiellonian University Medical College, and the staff of the Laboratory of Trace Elements Neurobiology, Institute of Pharmacology, Polish Academy of Sciences in Krakow.

The study participants were recruited among the in-patients and the out-patients of the Department of Psychiatry of University Hospital in Krakow during the period between 21.09.2009 and 30.08.2013.

Patients who fulfilled the DSM-IV-TR criteria for recurrent Major Depressive Disorder (MDD) (in both depressed and remission phase) were recruited as well as a group of healthy volunteers for the study. All participants signed an informed consent. Additionally all participants were given by the doctor a detailed information (verbally and in writing) about the aims and rules of the clinical study. The Jagiellonian University Bioethical Committee has approved this study (KBET/77/B/2009 from 25.06.2009).

The basic criteria for exclusion from the study were: lack of consent to the examination, diagnosis of serious mental disorder other than MDD (e.g. schizophrenia, schizoaffective psychosis, bipolar disorder) or disorders associated with substance abuse (except nicotine or caffeine dependence), comorbidity of serious physical illnesses (acute or chronic), the incidence of deep personality disorders, breastfeeding or pregnancy. As severe somatic diseases excluding from the study (due to the possibility of statistically significant change in the concentrations of biomarkers examined in the De-Me-Ter study) the authors considered the following: chronic autoimmune and inflammatory diseases, acute inflammatory diseases or infections present within a month prior to the recruitment in the study, primary adrenocortical insufficiency, renal failure, chronic pancreatitis, hypoporathyroidism, hyperthyroidism, primary hypoaldosteronism, cancer, megaloblastic anaemia due to iron deficiency, thalassemia, hemochromatosis, liver cirrhosis, Wilson disease, nephritic syndrome, burns. The additional excluding criteria was the fact of using the following drugs by the participants: hydralazine, nonsteroidal anti-inflammatory drugs (acetylsalicylic acid, ibuprophen, indometacin), tetracyclines, florochinolones, calcium, iron, chelating agents or glu-

cocorticosteroids. All the patients were receiving pharmacotherapy (mono – or poly-therapy), in accordance with the up-to-date treatment guidelines for MDD (table 1).

The sample of healthy volunteers consisted of 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 presents the socio-demographic and clinical characteristics (including pharmacotherapy) of the examined population.

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

	MDD (Total)	Depression	Remission
N (%)			
Female	86 (75.43%)	52 (75.4%)	34 (75.6%)
Male	28 (24.56%)	17 (24.6%)	11 (24.4%)
Pharmacological treatment			
N (%)			
SSRI	63	35 (51%)	28 (62%)
SNRI	34	21 (30%)	13 (29%)
TCA	15	6 (9%)	9 (20%)
mirtazapine	5	4 (6%)	1 (2%)
Atypical Antipsychotic Drugs	15	10 (14%)	5 (11%)
Lithium	3	2 (3%)	1 (2%)
Lamotrygine	2	1 (1%)	1 (2%)
Disease course			
Mean (SD)			
Number of depressive episodes in the last year	1.31(0.69)	1.4 (0.66)	1.20 (0.71)
Total number of disease episodes throughout life	5.94(4.53)	4.76 (4.31)	6.22 (4.89)
Age at onset (years)	36.14 (12.1)	34.99 (12.24)	38.00 (11.76)
Duration of illness (years)	13.30 (9.82)	12.75 (9.74)	14.16 (10.01)
Total number of hospitalizations	2.13(3.08)	1.92(2.52)	2.45(3.77)
The duration of the current episode or remission (weeks)	-	18.89 (24.255)	15.83 (35.251)
The severity of symptoms in the current episode/remission			
The sum MADRS scores	17.64(13.40)	26.17 (9.74)	4.25 (4.20)
The sum HDRS scores	13.02(8.94)	18.83(6.30)	4.11(3.14)

SD – standard deviation; MDD – major depressive disorder; MADRS – Mongomery-Asberg Depression Rating Scale; HDRS – Hamilton Depression Rating Scale; SSRI – selective serotonin reuptake inhibitors; SNRI – serotonin and norepinephrine reuptake inhibitors; TCA – tricyclic antidepressants

Diagnostic tools

The severity of depressive symptoms was measured using the Montgomery-Asberg Depression Rating Scale – MADRS [20], and the Hamilton Depression Rating Scale – HDRS [21].

Collecting and processing of blood samples. Quantitative analysis of serum magnesium concentration

According to the study protocol, no more than 9.8 ml of blood was obtained from each patient and healthy volunteer from a brachial vein using the Monovette system. After the cloth formation the blood samples were centrifuged for 30 minutes at 1800 RPM. The obtained serum samples were stored at –80oC until use.

The serum magnesium levels were measured by a flame atomic absorption spectrometry – FAAS after they were defrosted. The authors used Perkin Elmer spectrometer Model 3110 (USA), air-acetylene flame and HCL lamp. Wavelength for Mg was 285.2 nm, slit of 0.7 nm.

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. For all serum samples measurements were performed in triplicate. The accuracy of the measurement was tested by means of recovery analysis, which for Mg was in the range of 96–101%.

Statistical methods

The χ^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. Because of absence of the normal distribution of data the Kruskal-Wallis ANOVA or Mann-Whitney U-test were used. Correlations between quantitative variables – due to lack of normal distribution – were analysed with the Spearman's Rank Correlation.

Results

114 patients (86 women and 28 men) who met the DSM-IV-TR criteria for recurrent MDD (69 patient were in a depressive episode and 45 were in a remission) were enrolled into the De-Me-Ter study. Among the recruited group 63 participants were treated with Selective Serotonin Reuptake Inhibitors (SSRI), 34 of them with Serotonin-Norepinephrine Reuptake Inhibitors (SNRI), 15 patients with tricyclic antidepressants (TCA), and 5 patients were treated with mirtazapine. In the examined group 15 patients were treated with atypical antipsychotic drugs (olanzapine or quetiapine) and 5 more were treated with lithium and lamotrygine due to enhance the antidepressive therapy. The control group consisted of 50 healthy volunteers (14 men and 36 women). There were no statistically significant differences in mean age between the group of patients

(49.36 ± 10.67) and the control group (45.82 ± 12.43), (p = 0.064; Mann-Whitney U test). There were also no statistically significant differences in sexes between two groups (χ^2 test; p=0.64). The percentage of women in the examined population of patients was 75.4%, and in the control group it was 72%. In the group of patients there were no differences in the magnesium concentrations between women and men subgroups (21.72 ± 5.94 vs. 19.80 ± 5.7 mg/l).

The mean scores among all patients (both depressive episode and remission) were as follows: 17.64 ± 13.4 points in the MADRS and 13.02 ± 8.94 points in the HDRS scale. In the group of patients in the depressive episode the mean scores were 26.17 ± 9.74 points in the MADRS scale and 18.83 ± 6.3 points in the HDRS scale. The remission group was characterized by the mean score of 4.25 ± 4.2 points in the MADRS scale and 4.11 ± 3.14 points in the HDRS scale.

The analysis of variance has shown significant influence of episode of illness or being in the healthy control group on the obtained concentrations of magnesium (Kruskal-Wallis test, H = 6.87; p = 0.032). The mean concentration of magnesium among the patients with depression (22.36 ± 5.91 mg/l) was statistically higher than Mg concentrations obtained in the control group (18.53 ± 8.90 mg/l; p = 0.046), however Mg concentrations obtained in remission (20.56 ± 6.51) did not differ from Mg concentrations in healthy volunteers.

Among the group of patients currently diagnosed with a depressive episode there were no statistically significant differences in the serum Mg concentrations between patients with versus without presence of: depression with atypical symptoms, melancholic syndrome, psychotic depression, and also with good reaction to therapy versus drug resistance (table 2).

Table 2. **Comparison of mean serum magnesium concentrations (mg/l) in patients with a various clinical picture of depressive episodes**

Depression	Mean magnesium concentration ± SD	Mann-Whitney U test p-value
With atypical features	23.05 ± 6.37	0.64
Without atypical features	22.73 ± 6.97	
With melancholic features	24.27 ± 6.81	0.14
Without melancholic features	21.67 ± 6.68	
Psychotic	19.92 ± 6.91	0.27
Without psychotic symptoms	23.04 ± 6.83	
Drug-resistant	23.77 ± 7.89	0.58
Without drug-resistant features (Non-drug-resistant)	22.03 ± 5.67	

SD – standard deviation

The statistical analysis has not revealed significant correlations between Mg concentration in depressive episode or remission and age of the patients and other clinical parameters such as: duration of the disorder and age of onset, average number of de-

pressive episodes, or length of the current depressive episode, or remission. However, the Mg concentration correlated positively with severity of depression measured with the HDRS (r = 0.26; p < 0.05), and the MADRS scale (r = 0.21; p < 0.05) (table 3).

Table 3. **Correlations between serum magnesium concentration (mg/l) and selected quantitative clinical features in depression and remission (Spearman's rank correlation coefficient)**

	Mg (mg/l)		
	MDD (Total)	Depression	Remission
Age	0.046	0.17	0.092
Number of episodes during lifetime	0.01	-0.12	0.11
The average annual number of relapses in the last year	0.08	0.035	0.098
The disease duration in years	0.07	0.13	0.045
Duration of the episode /remission	-	0.14	0.014
Total MADRS score	0.21*	0.015	0.09
Total HDRS score	0.26*	0.20	0.06

* p < 0.05

Discussion

In the presented study, we have demonstrated that the average serum magnesium levels in patients with the depressive episode were higher than in healthy volunteers. Moreover, the measured levels of this element in remission phase did not show significant differences in relation to the control group. The obtained serum magnesium concentrations in both depressive episode and remission phase were in the normal range (16–29 mg/l) [22]. A positive correlation between the severity of depressive symptoms measured by the HDRS and MADRS scale and the concentration of magnesium in the blood of patients was also observed.   So far, the results obtained from clinical studies on the relationship between the concentration of magnesium in the blood and MDD are ambiguous [12, 17, 23]. Our findings are consistent only with a part of the previously published clinical data.

The substantial part of the clinical trials suggest, contrary to presented theoretical hypotheses and the results of the part of animal studies, that the symptoms of depression are accompanied by elevated levels of magnesium [11, 17, 18, 24, 25]. In the study by Widmer et al., magnesium concentrations were measured in the blood plasma and erythrocytes of 53 untreated depressive patients (including 33 women and 20 men; 41 patients with MDD and 12 patients with BD) and 48 volunteers (including 21 women and 27 men). The obtained results indicate a statistically significant increase in the concentration of magnesium in erythrocytes of patients enrolled in the study. Simultaneously, there were no significant differences between the group of males and females. In turn, the measurement of magnesium in the blood plasma showed its increased

concentrations (versus the control group) in the male subjects with depression [12]. These results were confirmed in our study on a group of bipolar disorder (BD) patients [19]. Widmer et al. have also shown an increased magnesium ion concentration in the fraction of erythrocyte, which correlated positively with the severity of depressive symptoms in subjects. Those findings are consistent with the results presented in this paper. The patients with mild depressive symptoms did not show significant differences in comparison to the control group. It was also observed that in all performed sub-analysis, the magnesium concentration was higher in men than in women. Widmer et al. consider that there is a relationship between the catecholaminergic system and the metabolism of magnesium. They point out to the fact, that if magnesium deficiency increases the metabolism of catecholamines, causing an increase in psychomotor activity, then hypermagnesemia can cause the opposite effect, leading to a reduction in psychomotor activity which is a common symptom in patients with depression [12].

Similar results were obtained by the same authors in another study, which involved a group of 61 women and 27 men with major depression (in the BD and MDD course) who did not receive any antidepressants for at least 2 weeks. This study showed an increased mean concentration of magnesium (both in erythrocytes and in plasma) in patients compared to controls. These findings are consistent with those obtained in the presented study and in the author's previous study on serum magnesium concentrations in a group of BD patients [19]. Almost half of men and women (40% and 38%) during depressive episodes, studied by Widmer et al., demonstrated a very high magnesium concentration measured in erythrocytes (by 25% higher than in the control group). These differences for the plasma concentration were smaller. In the examined group of people there was also a correlation between the reduced psychomotor activity and the increased level of magnesium in both erythrocytes and the plasma. The authors consider, that changes of the magnesium concentration affect the functioning of the receptors (NMDA, GABA, and muscarinic) in the central nervous system. Their proper activity is dependent on magnesium ions. Furthermore, Widmer et al. point out that the cause of the increase in the magnesium concentration in depressed patients can be reduced physical activity, which is often accompanied by episodes of major depression [17].

Frazer et al., in their study undertook the assessment of the magnesium concentrations in the blood of patients with the affective disorders. In the study, which included 36 women and 21 men with a diagnosis of MDD and 79 healthy volunteers, the analysis has shown increased plasma concentrations of magnesium in patients with depression compared to the control group. At the same time there were no such correlations in the measurement of the concentrations of the free fraction of magnesium. In the same study increased levels of erythrocyte magnesium in depressive patients with regard to healthy non-hospitalized people were noted. A analysis of the subgroup of women has shown that the concentration of magnesium in plasma was higher in depressed women and healthy hospitalized volunteers than in healthy non-hospitalized women. However, in the subgroup of men in a group of healthy volunteers has been shown that hospitalized persons were characterized by a lower plasma concentration of magnesium than non-hospitalized volunteers [26].

On the other hand, Imada et al. in the study concerning the analysis of the blood serum magnesium concentration in a group of 16 women and 21 men with MDD versus the control group, have shown a statistically significant increase in the level of the tested element in patients. In addition, no differences between the concentrations of magnesium measured in patients in remission and the depressive phase were observed. There were also no differences between the studied women and men groups. The authors of this study suggest that hypermagnesemia may be a marker characteristic for the MDD – a trait marker [25].

The published data from some of clinical studies have demonstrated that the serum magnesium concentration in patients with depression is reduced [1, 13–15]. However, in the study by Young et al. [27], in the group of 100 women and 45 men with a diagnosis of MDD no differences in the serum magnesium concentration between patients and the control group were demonstrated. The analysis of the results showed that the concentration of magnesium in women was lower than in men. The authors also found no correlation between the magnesium levels and the severity of depressive symptoms. These results differ from those obtained in the presented study.

According to Frizel et al., the magnesium concentrations correlate with the severity of depressive symptoms [28]. In the two studies conducted by Herzberg et al. it was found that the plasma magnesium concentration in depressed women was significantly lower than in the group of men with a diagnosis of MDD. At the same time reduced magnesium levels were not observed in the control group [24, 29].

In the systematic review conducted by Derom et al. [30] regarding the assessment of the relation between magnesium and depression, the author reviewed 21 cross-sectional studies and the obtained results were ambiguous. Only 7 of the included studies concerned the relation between blood magnesium concentration and severity of depressive symptoms. The majority of them did not confirm the correlation. The positive correlation was found only in 2 of the reviewed studies – Widmer et al. [12] and Hasey et al. [31]. However, many of the analysed studies concerned patients with coexisting somatic disease i.e. diabetes, thyroid hormone disturbances or referred to animal model of depression. The authors of this review point out that it is difficult to determine whether hypomagnesaemia leads to depression or depression causes hypomagnesaemia on the basis of the result from cross-sectional studies. The authors suggest that there might be a correlation between hypomagnesaemia and depressive symptoms but there is a need for further investigations on larger groups of patients [30].

Moreover in another systematic review by Cheungpasitporn et al. concerning correlation between hypomagnesaemia and depression, the authors demonstrate a potential correlation between those two conditions. However they also highlight that after performing a sensitive analysis including only cohort and case-control studies this association between hypomagnesaemia and depression becomes statistically insignificant [32].

The studies examining the effect of drugs on blood magnesium level in patients did not provide conclusive results [1, 13, 27, 31, 33].

Despite the fact that the data obtained from studies conducted so far are ambiguous, the authors of this paper show that the serum magnesium level displays some

characteristics of a potential state marker. However, in order to confirm this hypothesis, carrying out clinical trials on a much larger group of patients is necessary.

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