Magnesium in drug-naïve patients with a short-duration, first episode of major depressive disorder: impact on psychopathological features

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Abstract. Plasma magnesium concentration changes are seen in major depressive disorder (MDD). Dysregulation of magnesium homeostasis is associated with the severity of depression and specific psychopathological features including apathy, anxiety, irritability, fatigue and weakness. Results from studies on magnesium concentrations in MDD patients are inconsistent, and the evidence for magnesium ions being associated with specific features of depression and anxiolytic effects is unclear. This study was designed to examine whether and to what extent plasma magnesium is related to the psychopathological features of depression including severity of symptoms and specific psychopathological aspects. Plasma magnesium levels were studied in this cross-sectional, case-control study and involved 20, non-late-life adults who were treatment-naïve, short-duration, first episode, MDD patients, and 20 age- and sex-matched, healthy controls. Psychometric evaluations were performed using the Hamilton Rating Scale for Depression (HAMD-17) and the Spielberger State-Trait Anxiety Inventory (STAI). A significantly higher magnesium (p = 0.016) concentration was observed in MDD patients compared to controls. No significant correlations were observed between magnesium concentrations and the total HAMD-17 score or with regard to the specific core depression, insomnia, anxiety or somatic HAM-D psychopathological features. In addition, no significant correlations were found between magnesium concentrations and STAIX-1 and STAIX-2 scores. The present study provides evidence of hypermagnesaemia in drug-naïve patients with a short-duration, first episode of MDD. A cross-sectional analysis adds to the evidence linking plasma magnesium concentrations with psychopathology of MDD during early stages of the disease although with no correlations between plasma magnesium concentrations and psychopathology including severity of symptoms and specific psychopathological features.

Key words: magnesium, psychopathology, major depressive disorder, drug-naïve individuals
Magnesium and depression psychopathology

concentrations are generally associated with MDD. However, results from studies on magnesium concentrations in MDD patients are inconsistent and the evidence for magnesium ions being associated with specific features of depression and anxiolytic effects is unclear [4]. Studies may produce confounding results because of the heterogeneity of MDD patients as regards illness stage and severity, with a large proportion of patients suffering from relapsing-remitting and treatment-resistant/chronic depression, with first-episode major depression being underrepresented. Also, the exposure to some psychotropic drugs influences magnesium concentrations and may influence study results [1, 3, 5].

Magnesium deficiency has also been associated with depression severity and specific psychopathological features of MDD, with apathy, anxiety, irritability, fatigue and weakness being attributed to magnesium homeostasis dysregulation [3]. Nonetheless, systematic clinical data on plasma magnesium concentrations in MDD according to the psychopathological profile are limited to a single study involving 53 mild and moderately depressed patients, where no significant correlations between total plasma magnesium concentrations, severity of depression and anxiety were found. Moreover, all patients showed magnesium concentrations within the normal range. However, the study reported a significant positive correlation between plasma magnesium concentrations and psychomotor retardation [6].

A case-control study involving a well-defined cohort of short-duration first-episode, drug-naïve, MDD patients and healthy subjects was designed to examine whether, and to what extent, plasma magnesium is related to the psychopathology including severity of symptoms and specific psychopathological features.

Method

Subjects

Twenty, first-episode, treatment-naïve MDD patients were recruited from the outpatient clinic of a university-affiliated hospital in the city of Gdansk, Poland, immediately prior to the initiation of treatment at their first referral to a psychiatrist. Patients were diagnosed using the Structured Clinical Interview for DSM-IV Axis I Disorders [7]. The severity of depression was evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD-17) [8]. Subjects with an HAMD-17 score of >20 with first-episode major depression being drug-naïve for any psychotropic medication and episode duration ≤24 weeks were eligible for inclusion in the study. Anxiety was assessed using the Spielberger State-Trait Anxiety Inventory (STAI) [9]. All patients underwent routine physical examination. Exclusion criteria were: any other Axis I disorder, any somatic comorbidity, any concomitant medication including dietary supplements, pregnancy or lactation, alcohol or drug abuse in the previous 12 months, tobacco smoking exceeding 25 cigarettes a day, BMI ≤18 and ≥30, age <18 and >55 years.

The control group comprised twenty healthy subjects matched by age, sex, and metabolic parameters. They were interviewed by the same psychiatrists using the Structured Clinical Interview for DSM-IV, non-patient edition [7]. All subjects underwent routine physical examination and undertook a STAI inventory [9]. None of them had any history of serious somatic disease or any family history of major psychiatric illness in their first-degree relatives. A score ≤5 for the HRSD-17 was required for inclusion. Exclusion criteria were: positive history of any exposure to psychotropic medication, any concomitant medication along with dietary supplements, pregnancy or lactation, alcohol or drug abuse in the previous 12 months.

The study was carried out in accordance with the Declaration of Helsinki. The study was approved by the Ethics Research Committee of the Institution. For each study participant, written consent was obtained.

Study protocol

The study followed a cross-sectional, case-control design. All subjects fasted from midnight before the test day, and arrived at the laboratory at 07:00 am. Blood samples were taken for the magnesium assay at 09:00 am, being immediately centrifuged. Plasma was stored at -80°C, protected from light.

Assays

The plasma magnesium concentration was determined using flame atomic absorption spectrometry (Avanta Σ GBC with deuterium background
correction). A linear calibration curve was obtained using a certified standard solution (Merck, Darmstadt, Germany). Specimens were diluted by a factor of 50, using 0.01M La in 0.05M HCl. ClinChek Plasma Control for Trace Elements (Recipe), with a recommended value of 0.67 mmol/L (0.60 ± 0.74 mmol/L) of magnesium was used as a control for validating method accuracy and precision. The mean concentration of magnesium measured in quality control samples was 0.61 mmol/L (n = 8, RSD = 2%). The analytical detection limit was 0.004 mmol/L.

The total HAMD-17 score was analysed followed by the exploratory analysis based on the hierarchical Cole and Motivala model [10], including core depression, insomnia, anxiety and somatic psychopathological features. The STAI results were analysed with regard to the differentiation of the anxiety, including anxiety caused by a specific condition (state subscale, STAIX-1), and anxiety as a more permanent characteristic of the personality (trait subscale, STAIX-2) [9].

Statistical analysis

Statistical procedures were performed using StatsDirect v2.7.9 (http://www.statsdirect.com). The Shapiro-Wilk test was used to assess normal distribution of continuous data. Normally distributed variables were compared using Student’s t-test; all other continuous data were compared using the nonparametric Mann-Whitney U-test. Pearson’s correlation coefficient was calculated to quantify the linear association between the variables. All tests were two-tailed with an alpha = 0.05.

Results

Table 1 summarises the demographic and clinical variables. There were no significant differences in terms of gender, age, BMI or WHR between patients with MDD and controls. Post hoc analysis revealed that melancholic MDD subjects were younger (p = 0.015) and had lower BMI scores (p = 0.035) as compared to controls.

Significantly higher magnesium concentrations were observed in depressed patients as compared to controls (p = 0.016). This effect was also seen in exploratory analysis for melancholic MDD (p = 0.029) as compared to controls, whereas in non-melancholic MDD patients, no respective significant difference was observed (p = 0.082). Post hoc analysis revealed that the severity of depressive symptoms in MDD subjects, as measured by the HAMD-17 score, was significantly higher in patients with melancholia as compared to the subpopulation of non-melancholic MDD (p = 0.002). Post hoc analysis with regard to the specific HAMD aspect revealed significantly higher insomnia (p = 0.043), anxiety (p = 0.009), and somatic (p = 0.031) subscores in MDD patients with melancholia as compared to those with non-melancholic major depression (table 2).

Significantly higher STAIX-1 (p <0.0001) and STAIX-2 (p <0.0001) scores were observed in MDD patients compared to controls. The exploratory analysis revealed significantly higher STAIX-1 (p = 0.001) scores in non-melancholic major depression as compared to melancholic MDD, and significantly higher STAIX-2 (p = 0.001) scores in melancholic major depression compared to non-melancholic MDD patients.

No significant correlations were observed between magnesium concentrations and the total HAMD-17 score or with regard to the specific HAM-D aspect. No significant correlations were found between magnesium concentrations and STAIX-1 and STAIX-2 scores either.

No significant correlations were observed between magnesium concentrations and age, BMI, WHR or depressive episode duration in MDD patients compared to age, BMI and WHR parameters in controls.

Discussion

Hypermagnesaemia was seen in depressed subjects as compared to controls but no correlation was observed in MDD between magnesium concentration and the severity of depressive symptoms with HAMD-17. No correlations were seen between plasma magnesium levels and core depression, insomnia, anxiety and somatic psychopathological features in MDD. The lower STAIX-1 scores found post hoc in melancholia compared to non-melancholic MDD seem to correspond with melancholic features related to emotional blunting, while the inverse observation with STAIX-2 might be associated with psychological
Table 1. Demographic characteristics with psychometric variables and plasma magnesium concentrations in MDD and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>MDD</th>
<th>MDD</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Melancholic</td>
<td>Non-melancholic</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>20</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Women (%)</td>
<td></td>
<td>60</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>Median (IQR)</td>
<td>33.5 (30.3, 35.8)</td>
<td>30.5 (24.5, 37.5)</td>
<td>30** (25, 31)</td>
</tr>
<tr>
<td>BMI</td>
<td>Mean (95%CI)</td>
<td>23.9 (22.6, 25.3)</td>
<td>22.8 (21.4, 24.1)</td>
<td>21.5* (19.9, 23.2)</td>
</tr>
<tr>
<td>WHR</td>
<td>Mean (95%CI)</td>
<td>0.82 (0.79, 0.86)</td>
<td>0.82 (0.73, 0.85)</td>
<td>0.82 (0.77, 0.87)</td>
</tr>
<tr>
<td>Episode duration (weeks)</td>
<td>Mean (95%CI)</td>
<td>- (12.2, 16.7)</td>
<td>14.5 (11.1, 18.7)</td>
<td>14.9 (10.9, 17.3)</td>
</tr>
<tr>
<td>HAMD-17#</td>
<td>Median (IQR)</td>
<td>1 (0, 2)</td>
<td>22.5 (21, 24)</td>
<td>24*** (23, 25)</td>
</tr>
<tr>
<td>Core* depression</td>
<td>Median (IQR)</td>
<td>- (5, 5)</td>
<td>5 (5, 5)</td>
<td>5 (5, 5)</td>
</tr>
<tr>
<td>Insomnia*</td>
<td>Median (IQR)</td>
<td>- (3, 4)</td>
<td>3 (3, 5)</td>
<td>4**** (3, 4)</td>
</tr>
<tr>
<td>Anxiety*</td>
<td>Median (IQR)</td>
<td>- (6, 7)</td>
<td>7 (7, 7)</td>
<td>7***** (6, 7)</td>
</tr>
<tr>
<td>Somatic</td>
<td>Median (IQR)</td>
<td>- (6, 8)</td>
<td>7 (7, 8)</td>
<td>8***** (6, 7)</td>
</tr>
<tr>
<td>STAIX-1#</td>
<td>Median (IQR)</td>
<td>33 (30, 37)</td>
<td>54&amp; (52, 58)</td>
<td>52&amp;&amp;&amp; (50, 52)</td>
</tr>
<tr>
<td>STAIX-2#</td>
<td>Median (IQR)</td>
<td>36 (34, 39.5)</td>
<td>48.5&amp;&amp; (46.5, 50.5)</td>
<td>51&amp;&amp;&amp;&amp; (50, 52)</td>
</tr>
<tr>
<td>plasma magnesium</td>
<td>Mean (95%CI)</td>
<td>0.7 (0.65, 0.69)</td>
<td>0.71** (0.68, 0.73)</td>
<td>0.71*** (0.68, 0.74)</td>
</tr>
</tbody>
</table>

MDD: major depressive disorder
BMI: body mass index
WHR: waist-hip ratio
HAMD-17: Hamilton Rating Scale for Depression
STAI: Spielberger State-Trait Anxiety Inventory
IQR: interquartile range
95%CI: 95% confidence interval
* Shapiro-Wilk W p<0.05
** versus control: p = 0.015, Mann-Whitney U test, median difference (95%CI) = -5 (-1, -10)
*** versus non-melancholic: p = 0.002, Mann-Whitney U test, median difference (95%CI) = 3 (2, 4)
**** versus non-melancholic: p = 0.043, Mann-Whitney U test, median difference (95%CI) = 1 (0, 2)
***** versus non-melancholic: p = 0.009, Mann-Whitney U test, median difference (95%CI) = 1 (1, 2)
& versus control: p<0.0001, Mann-Whitney U test, median difference (95%CI) = 21 (18, 24)
&& versus control: p<0.0001, Mann-Whitney U test, median difference (95%CI) = 12 (9, 14)
&&& versus non-melancholic: p = 0.001, Mann-Whitney U test, median difference (95%CI) = -6 (-9, -3)
&&&& versus non-melancholic: p = 0.001, Mann-Whitney U test, median difference (95%CI) = -4 (2, 7)
* versus control: p = 0.035, two-tailed, unpaired t-test, mean difference (95%CI) = -2.4 (-0.17, -4.60)
** versus control: p = 0.016, two-tailed, unpaired t-test, mean difference (95%CI) = 0.04 (0.00, 0.07)
*** versus control: p = 0.029, two-tailed, unpaired t-test, mean difference (95%CI) = 0.04 (0.00, 0.07)
**** versus control: p = 0.082, two-tailed, unpaired t-test, mean difference (95%CI) = 0.03 (0.00, 0.07)
traits with negative affect predisposing to melancholic MDD. The lower BMI score seen in melancholic MDD patients compared to controls, along with greater depression severity and corresponding higher psychopathological feature scores in that group compared to non-melancholic MDD subjects seems to be associated with the traits of melancholia.

Primary hypomagnesaemia in major depression is disputed and unaltered or elevated plasma magnesium levels have been observed. Moreover, the association of plasma magnesium concentration and measures of severity of major depression failed to produce replicable data. High plasma magnesium concentrations were seen in MDD patients that were drug-free for at least two weeks [11], and high plasma magnesium was demonstrated to persist in those patients being treated with antidepressants and followed for three months [12]. Little is known about the impact of magnesium concentrations on clinical features of depression. The only systematic study on plasma magnesium levels in MDD, exploring the psychopathological profile, found no significant correlations between total plasma magnesium concentrations, severity of depression and anxiety, with magnesium concentrations being within the normal range in all patients. The study reported a significant positive correlation between plasma magnesium concentrations and psychomotor retardation [6]. The hypothesised link between high magnesium concentrations and anxiolytic effects was not found in our study or in the study by Barra et al. [6]. It seems that anxiolytic effects the associated with high magnesium levels occur with dietary supplementation in individuals already experiencing magnesium homeostasis dysregulation at the latter stage of the disorder and magnesium itself may not possesses anxiolytic characteristics [13]. The magnesium intake and case-level anxiety was studied in an epidemiological setting and failed to reveal significant association. However, weak and borderline significant inverse relationships between anxiety levels and magnesium were seen [14] and, at the moment, animal models demonstrate well the relationship between hypomagnesaemia and anxiety [2]. This study found hypermagnesaemia in MDD, with no correlation between magnesium concentrations and psychopathological features including severity of symptoms and the specific psychopathological aspects in MDD patients. Symptoms associated with magnesium homeostasis dysregulation in MDD may be non-specific and may embrace a wide spectrum of phenomena including apathy, anxiety, irritability, fatigue and weakness [3].

Factors associated with study selection criteria may contribute considerably to the results observed. We tested antidepressant-naïve MDD patients and there is no effect of past psychotropic pharmacotherapy. Results for plasma magnesium concentrations in patients with depression are conflicting. However, most of the studies used a drug-free interval of one-three weeks, and none reported on antidepressants-naïve MDD patients. Interestingly, studies in drug-free depressed patients systematically found higher or unaltered magnesium concentrations in MDD patients as compared to controls [4]. Moreover, treatment with antidepressants of different classes seems to be associated with lower blood magnesium concentrations as compared to controls at the initial phase of treatment, with a subsequent increase in magnesium concentrations observed during the course of the improvement and remission [1, 5]. This study investigated plasma magnesium concentrations; intracellular concentrations remained unexplored. Low, intracellular magnesium concentrations were also associated with MDD, and generally, negative correlations were demonstrated between intracellular magnesium concentrations and the severity of depression. However, it seems that erythrocyte

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Table 2. Pearson’s correlation coefficient between plasma magnesium concentration and psychometric variables in MDD.

<table>
<thead>
<tr>
<th></th>
<th>HAMD-17 total</th>
<th>HAMD-17 Core depression</th>
<th>HAMD-17 Insomnia</th>
<th>HAMD-17 Anxiety</th>
<th>HAMD-17 Somatic</th>
<th>STAIX-1</th>
<th>STAIX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Mg</td>
<td>-0.16</td>
<td>-0.18</td>
<td>0.04</td>
<td>-0.12</td>
<td>-0.16</td>
<td>-0.15</td>
<td>0.08</td>
</tr>
</tbody>
</table>

HAMD-17: Hamilton Rating Scale for Depression
STAIX: Spielberger State-Trait Anxiety Inventory
magnesium concentrations correlate with psychomotor retardation in depression. In addition, in mild to medium MDD, erythrocyte magnesium was demonstrated to be significantly decreased while no significant changes in plasma concentrations were seen and concordant significantly lower plasma and erythrocyte magnesium concentrations were observed in patients with severe depression [1, 5]. Thus, the intracellular magnesium concentrations in our study population might have been different and may have influence the results. The exclusion of individuals with a history of attempted suicide or with current suicidality may account for the plasma magnesium concentrations observed. Ruljancic et al. [15] found lower serum magnesium concentrations in MDD patients who had attempted suicide as compared to MDD patients who had not, and controls. Thus, hypomagnesaemia in MDD impacting some specific psychopathological features might be a secondary phenomenon corresponding to exposure to antidepressants, drug-resistance, medical comorbidity, suicidality, impulsivity, pronounced anxiety, or the chronic course of the disorder linked to a persistent proinflammatory response [1-5, 15].

As the number of subjects included was relatively low, this study might be underpowered. The cross-sectional study design creates uncertainty as to whether the associations observed represent actual causal relationships between the parameters investigated. The depression might have been accompanied by decreased appetite, influencing overall dietary intake. Nutritional assessment might be important for data interpretation. Finally, the results refer to drug-naïve patients with short-duration, first-episode MDD who were free of comorbid Axis I and II conditions and any history of suicidal tendencies, and closely matched the controls. The outcome may reflect the selection of study subjects, and as a consequence of these limitations, further studies are warranted.

The present study provides evidence of hypermagnesaemia in drug-naïve patients with short-duration first-episode MDD. A cross-sectional analysis adds to the evidence linking plasma magnesium concentrations with the psychopathology of MDD at the early stage of the disease but with no correlations between plasma magnesium concentrations and psychopathology, including severity of symptoms and specific psychopathological aspects.

Disclosure

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