Magnesium and depression*

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Abstract. Magnesium is one of the most important elements in the human body and is involved in a number of biochemical processes crucial for the proper functioning of the cardiovascular, alimentary, endocrine, and osteoarticular systems. It also plays a vital modulatory role in brain biochemistry, influencing several neurotransmission pathways associated with the development of depression. Personality changes, including apathy, depression, agitation, confusion, anxiety, and delirium are observed when there is a deficiency of this element. Rodents receiving a diet deficient in magnesium displayed depressive behaviour that was reversed by antidepressant drugs. Poor nutrition, gastrointestinal and renal diseases, insulin resistance and/or type 2 diabetes, alcoholism, stress, and certain medications may lead to magnesium deficiency. Since the extracellular concentration of magnesium ions may not reflect their intracellular level, none of the current methods of evaluating magnesium status is regarded as satisfactory. The mood-improving potential of magnesium compounds have been confirmed by the results of numerous pre-clinical and clinical studies. It seems that magnesium supplementation is well-tolerated and enhances the efficacy of conventional antidepressant treatments, and as such could be a valuable addition to the standard treatments for depression, although differences in bioavailability between inorganic and organic compounds should be taken into consideration.

Key words: magnesium, depression, antidepressant therapy

Magnesium is one the most important elements in the human body. It regulates a number of biochemical processes and influences the functioning of the majority of organs. The adult human body contains approximately 24-35 g of magnesium, which is mainly deposited in bones (≈ 60%), muscles (≈ 20%) and other soft tissues. The extracellular fluid contains only 1% of the total body magnesium. Magnesium is a co-factor for hundreds of enzymes, it participates in the cell cycle, metabolism of carbohydrates, proteins, fats, nucleic acids, and is partially responsible for cell membrane permeability, cell signalling and migration, stability of nucleic acids, synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and glutathione, generation and utilisation of adenosine triphosphate (ATP), neuromuscular transmission, bone mineralisation, blood glucose control, and regulation of blood pressure. Magnesium metabolism is closely related to that of calcium and potassium, since it is required for the active transport of their ions through cell membranes. In addition, magnesium plays a vital modulatory role in the central nervous system (CNS) [1].

Magnesium homeostasis depends on magnesium intake and its secretion via urine and faeces. The Recommended Daily Allowance (RDA) of magnesium ranges between 310 and 420 mg, depending on age and sex [2]. Nuts, sunflower seeds, green leafy vegetables, and whole grains are all abundant sources of this element. Magnesium absorption via both facilitated transport and passive diffusion mostly takes place in the small intestines.

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intestine (jejunum); large intestine absorption is not so significant. Acid conditions, parathormone, insulin, a diet rich in animal protein or unsaturated fat, sodium, lactose, vitamin B6, and vitamin D improve absorption of magnesium. On the other hand, supplementation with very high doses of zinc (i.e., 142 mg/day) may inhibit magnesium absorption [3].

In the case of a low magnesium intake, the kidneys are able to partially counteract the decrease in magnesium levels. However, a balanced is crucial [4]. If not, an insufficient magnesium concentration in the human body may occur. Consumption of excessive amount of fat, calcium, phosphates, fibre, coffee, and strong tea either reduces absorption of magnesium ions from the alimentary tract or enhances their elimination. There are also several groups of people at risk of magnesium deficiency, including the elderly, patients with gastrointestinal or renal diseases, patients with insulin resistance and/or type 2 diabetes, alcoholics, individuals treated with loop and thiazide diuretics, antibiotics, hypnotics, sedatives, psychotropic, or cytostatic drugs, and those who have used proton pump inhibitors (esomeprazole, lansoprazole) for a long time. A long-term crash diet, stress, or oral contraceptives may also lead to magnesium deficiency. Magnesium requirements increase in pregnancy, breast-feeding, during periods of intensive growth and strenuous physical exercise [5-8].

An adequate magnesium level in the human body is important for the normal functioning of the CNS. A variety of neuromuscular and psychiatric symptoms have been observed in magnesium deficiency, and there are several pathways by which this ion might contribute to their development [9]. Although higher consumption of magnesium (total intake or with diet) most probably does not protect against the occurrence of depressive disorder, a very low magnesium intake may be a cause of increased depression risk [10]. Reduced magnesium intake with an everyday diet resulted in depression- and anxiety-like behaviour in animals [11]. Mice with low magnesium levels displayed more aggressive behaviour, higher rectal temperature, and increased brain and urine concentrations of noradrenalin as compared to animals with a high magnesium status [12]. There are also reports on the development of depression in a Norwegian community population as a consequence of poor dietary intake of magnesium [13]. Tarleton and Littenberg [14] found that a relationship between very low magnesium intake and depression is particularly evident in the case of younger adults.

### Magnesium levels in depressed people

In spite of the fact that there are several methods for evaluating magnesium status (i.e., measurement in blood, plasma/serum, erythrocytes, cerebrospinal fluid, saliva, urine levels), none of them is regarded as satisfactory. It should be remembered that the extracellular concentration of this element may not reflect its intracellular level. According to literature data, an adequate magnesium concentration in serum is 0.62-1.02 mmol/L [15] and when serum magnesium levels drop below 0.75 mmol/L, hypomagnesaemia is diagnosed [16]. Cerebrospinal fluid (CSF) magnesium levels are higher than those observed in plasma (i.e., 1.2 mmol/L) [17]. As anticipated, studies on magnesium levels in serum/plasma and the CSF of depressed patients have not demonstrated reproducible results. Several authors did not find any differences between healthy and depressed groups in relation to the CSF concentration of magnesium [18, 19]. According to the results from a clinical trial carried out by Levine et al. [20], the calcium:magnesium ratio in the CSF of subjects with depression was increased when compared to controls, although neither the CSF magnesium level nor its calcium:magnesium ratio turned out to be indices of depression severity. On the other hand, Sowa-Kućma et al. [21] reported an association between a reduced content of magnesium in brain and depression. An obvious link between serum/plasma magnesium levels and the presence of symptoms of depression was demonstrated in quite a few studies (e.g., [22-25]), although other scientists have not found similar correlations [26]. Moreover, in some cases a positive relationship was recorded (i.e., depressed patients presented high magnesium levels) (e.g., [23, 25]), while in others – an inverse one (i.e., subjects with depression showed lower magnesium concentrations) (e.g., [27, 28]). A similar discrepancy was observed in studies focused on correlations between magnesium status and severity of symptoms of depression. Sometimes, an association was observed for specific groups of patients (i.e. with chronic depression) [23] or was sex-dependent [24, 25]. It should not be surprising that symptoms, such as depression,
occur no matter whether the serum magnesium level is elevated or within normal ranges, since magnesium ions can be redistributed between pools via compensatory mechanisms (blood, tissues, organs). However, Camardese et al. [26] found that plasma magnesium levels correlated with a patient’s response to antidepressant treatment. The literature data demonstrated higher erythrocyte magnesium levels in the depressed population (e.g., [22, 24, 25]), although this feature was not observed in each trial [29], and may be influenced by other factors [22, 24]. According to the outcomes of some studies [20, 30], a higher serum calcium:magnesium ratio may be associated with both depression and risk of development of this disease. However, this association was not observed by Young et al. [31].

**Biological pathways involved in the antidepressant action of magnesium**

Literature data have indicated both the contribution of magnesium deficiency to the pathophysiology of mood disorders and the antidepressant/anxiolytic potential of magnesium ions. Several pathways are responsible for these effects. Magnesium ions act as natural antagonists of calcium. They block the NMDA receptor channel in a voltage-dependent manner, preventing the flow of calcium ions through it. In addition to that, magnesium ions enhance expression of the GluN2B subunit belonging to the NMDA receptor complex. Low magnesium levels in the hippocampus, plus high levels of both calcium and glutamate, may result in altered functioning of synapses in the human brain that leads to development of mood disorders, including depression [32]. That the magnesium-induced effects in the forced swim test (FST) can be reversed by administration of NMDA receptor agonists (NMDA or D-serine) supports the involvement of the glutamatergic system in the mechanism of action of magnesium [33]. Literature data also indicate the participation of serotonergic neurotransmission in the antidepressant effect of magnesium, since p-chlorophenylalanine-induced serotonergic lesions, as well as 5-HT1A and 5-HT2A/C receptor antagonists, reduced its activity in the forced swim test (FST) [34, 35]. In addition, the research team led by Cardoso et al. [35] confirmed the involvement of both noradrenergic and dopaminergic systems in the mechanism of action of magnesium. Concurrent administration of α1-, α2-, D1-, or D2-receptor inhibitors diminished the anti-immobility effects of magnesium in the Porsolt test. Pochwat et al. [36] suggest a potential relationship between magnesium antidepressant activity and the α-amino-3-hydroxy-5 methyl-4-isoxazolepropionic acid/brain derived neurotrophic factor (AMPA/BDNF) pathway. Magnesium potentiates phosphorylation of the cAMP response element-binding protein (CREB), increases expression of BDNF in the prefrontal cortex (PFC), and enhances activation of calcium/calmodulin-dependent protein kinase II (CaMKII) [32]. Both BDNF and CaMKII expression turned out to be reduced in certain brain areas of patients suffering from different types of depression [37]. By influencing CaMKII function, magnesium ions indirectly increase AMPAergic activity. Additionally, magnesium interacts with other factors that are relevant in the pathophysiology of depression: it suppresses hippocampal kindling, modulates the protein kinase C (PKC) pathway as well as nitric oxide (NO) release in the PFC [32]. Based on the available data, magnesium is a potent inhibitor of the GSK-3 enzyme, and affects mechanisms/systems that play an important role in the stress response (i.e., limbic-hypothalamus-pituitary-adrenal axis, release of adrenocorticotropic hormone, benzodiazepine/GABAA receptors). Most probably, it acts on the access of corticosteroids to the brain via an influence on P-glycoprotein [38]. It is also possible that the anti-inflammatory effects of magnesium contribute to its anti-depressant activity, since systemic inflammation and cell-mediated immune activation are present in major depression. An inverse relationship between magnesium intake and systemic inflammation was observed by King et al. [39]. Pre-clinical studies demonstrated development of sleep disturbances evoked by inadequate magnesium intake [40]. The same research team proved magnesium normalises sleep organisation and related brain bioelectrical activity. Disorders of the sleep/wake cycle are linked with the pathophysiology of depression.

**Antidepressant activity of magnesium in pre-clinical studies (table 1)**

The results of pre-clinical studies have clearly indicated an antidepressant activity of magnesium that was observed after both acute and
Table 1. Pre-clinical studies confirming the anti-depressant potential of magnesium

<table>
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<th>Effect of concurrent administration of magnesium and other agents with antidepressant potential</th>
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<td>- synergistic antidepressant effect with NMDA antagonists [33]</td>
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<td>- antagonistic effect with NMDA agonists [33, 46]</td>
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<td>- synergistic antidepressant effect with conventional treatment [34, 35]</td>
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The antidepressant potential of magnesium in clinical studies (table 2)

Moreover, a significant reduction in immobility time in the FST after concurrent administration of sub-effective doses of both magnesium and several other antagonists of the NMDA receptor complex (i.e., CGP 37849, D-cycloserine, L-701,324, MK-801) was found [33, 46]. However, a similar effect was not detected for ifenprodil, i.e., a selective inhibitor of the GluN2B subunit [47]. No synergistic interaction was observed between magnesium hydroaspartate and adenosine-receptor antagonists with antidepressant potential (i.e., caffeine) in the FST in mice [48]. In addition to that, co-administration of a magnesium compound with a phosphodiesterase type 5 inhibitor (i.e., sildenafil citrate) at a high dose largely reversed the antidepressant properties of the former [49].

Depressive behaviours induced by a magnesium-deficient diet were reversed by treatment with either magnesium salts (with or without vitamin B6) or agents with recognised antidepressant potential (desipramine, hypericum extract) [11]. Nikseresht et al. [50] showed that a single, concomitant administration of zinc, magnesium, and vitamin B6 improved depressive behaviour in female mice.
Table 2. Clinical studies confirming the anti-depressant potential of magnesium

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<th>Efficacy of magnesium treatment/supplementation</th>
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<td>• mood stabilization in bipolar disorder [52]</td>
<td>mood stabilization in 50% of manic-depressive subjects. Fracchinetti et al. [53] demonstrated that oral administration of magnesium pyrrolidone carboxylate (3 × 360 mg/day for at least one month) relieved premenstrual mood changes. However, Walker et al. [54] observed no alleviation of depressive symptoms during the second month of treatment, in women with premenstrual syndrome (PMS), who had been given 200 mg/day of magnesium as magnesium oxide. A poor efficacy of magnesium oxide was also found by de Souza et al. [61], who supplemented 44 women, for one menstrual cycle with this compound (200 mg of magnesium/day). The authors noted that mild, premenstrual anxiety-related syndromes were slightly reduced by the combination of magnesium oxide with vitamin B6 (50 mg/day), but the effect of monotherapy with magnesium oxide was not significant. After six weeks of intramuscular administration of magnesium sulphate (one injection/week), patients with chronic fatigue syndrome reported improved energy levels, a better emotional state, and less pain [55]. A 28-day treatment of epileptic subjects with magnesium lactate and vitamin B6 (given in addition to anticonvulsant medications) was beneficial in terms of the patients’ mental (anxiety/depressive) state [56]. Eby and Eby [58] reported several cases of patients with major depression who were successfully treated with magnesium compounds: 125-300 mg of magnesium (as glycinate and taurinate) was taken with each meal, and before going to sleep. Basing on the outcomes obtained by Barragan-Rodriguez et al. [59], 12-week treatments with magnesium chloride (450 mg/day) or imipramine (50 mg/day) were comparably effective in newly diagnosed depression in elderly diabetic patients with hypomagnesaemia. Three-month magnesium supplementation (320 mg/day) reduced certain signs and symptoms of depression (e.g., depressed mood, guilt feelings, insomnia, psychomotor retardation, anxiety, somatic gastrointestinal symptoms) in female patients diagnosed with clinical depression and premenstrual dysphoric disorder [60].</td>
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<td>• depressive symptoms in women with premenstrual syndrome [53, 61]</td>
<td>Preparations of magnesium</td>
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<td>• depressive symptoms in chronic fatigue syndrome [55]</td>
<td>There are a plethora of magnesium preparations available in the pharmaceutical and dietary supplement markets. Bioavailability is the most important feature that differentiates them. Since magnesium absorption is poor (only 30-40% of the consumed amount), the compound used as an active ingredient is very important. The highly soluble ones are better absorbed. Magnesium aspartate, citrate, lactate, and chloride are more bioavailable than magnesium oxide or sulphate. When alimentary tracts function properly and the patient does not suffer from hyper- or hypoacidity, the organic magnesium compounds (i.e., citrate, lactate, aspartate) are recommended, as these are the ones whose chemical structure is more similar to magnesium compounds present in diet. Addition of vitamin B6 improves magnesium absorption as well as its transportation and intracellular storage. Moreover, the gastro-resistant or enteric-coated oral dosage forms are preferred, since magnesium is mainly absorbed in the lower parts of the digestive system. The usual daily dose of magnesium supplementation varies between 200 and 1000 mg, and the best effects are observed after long-term administration [62, 63]. Oral magnesium preparations seem to be well tolerated and safe, though some patients (particularly subjects with an impaired renal function) can experience</td>
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<tr>
<td>• depressive/anxiety states that accompany epilepsy [56]</td>
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<td>• depressive states and paresthesia that accompany Gitelman’s syndrome [57]</td>
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<td>• major depression [58]</td>
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<td>• in elderly depressives with hypomagnesaemia and type 2 diabetes [59]</td>
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<td>• depression and premenstrual dysphoric disorder [60]</td>
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adverse effects, including diarrhoea [1, 2]. The tolerable upper intake level for supplemental magnesium was assessed as 350 mg/day [2]. Since magnesium treatment may reduce absorption of several other drugs (i.e., digoxin, nitrofurantoin, anti-malarial medications, bisphosphonates), close monitoring of patients with concomitant diseases is recommended. Moreover, reduced efficacy of chlorpromazine, penicillamine, oral anticoagulants, quinolones, and tetracyclines was reported when co-administered with preparations of magnesium [64].

Disclosure


References

7. U.S. Food and Drug Administration. Proton pump inhibitor drugs (Ppis): drug safety communication – low magnesium levels can be associated with long-term use, 2011.


