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The relationship between magnesium deficiency and anxiety, the therapeutic effects of magnesium supplementation – literature review

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Abstract

Introduction and purpose: The main aim of our study is to summarise existing knowledge and draw conclusions about the impact of magnesium deficiency on the occurrence of anxiety.

Methodology: The literature available in the National Library of Medicine database at https://pubmed.ncbi.nlm.nih.gov and Google Scholar was reviewed. Articles were searched by using keywords: magnesium, deficiency, supplementation, anxiety disorders. Forty-seven research papers and meta-analyses were analysed.

Description of the state of knowledge: Magnesium is an extremely important mineral in the human body involved in many physiological processes. A deficiency of this element affects the whole body and can cause mental disorders - including anxiety disorders. There are many theories showing a link between magnesium and anxiety disorders in both humans and animals. Magnesium has been shown to influence the function of neurotransmitters affecting the experience of anxiety. Supplementation in people with hypomagnesaemia has been proven to improve their health and well-being. However, it should be noted that supplements on the market vary in the bioavailability of the mineral, and the frequency of intake and dosage also affect the bioavailability of magnesium.

Conclusions: It is important to ensure adequate levels of magnesium in the diet, given its impact on the proper functioning of the human body (including the nervous system) and the fact that most people consume insufficient amounts of this macronutrient. Evidence of a link

between magnesium levels and anxiety has led to increased interest in the potential efficacy of magnesium supplementation to alleviate anxiety symptoms.

Key words: magnesium; deficiency; anxiety; supplementation

1. Introduction and purpose

Magnesium is one of the essential minerals found in the human body. Next to potassium, it is the second most important intracellular cation and, as a cofactor of more than 300 enzymes, is involved in many biochemical processes needed to maintain homeostasis, such as protein synthesis, muscle contractility, thermoregulation, nerve conduction and blood pressure regulation [1-4]. It is also essential for DNA and RNA synthesis, participates in adenosine triphosphate (ATP) metabolism and in any activity mediated by intracellular calcium (e.g. insulin release [5]).

It is estimated that there is approximately 22-26g of magnesium in the adult body [6]. Most of it is found intracellularly - 60% is found in the skeletal system, 20% in skeletal muscle, 19% in soft tissues, and only about 1% of this element is found extracellularly [7]. The normal concentration of magnesium in human blood is in the range of 0.65-1.25 mmol/l [8, 9], of which approximately 55-70% occurs in ionised form and the remainder in bound form (mainly with albumin) [2].

The recommended daily requirement for magnesium is approximately 310-320 mg. [10] Foods particularly rich in magnesium are nuts, cocoa, dark chocolate, bananas, cereal products, legumes, fish and some vegetables (especially green vegetables), as well as drinking water, especially hard water [11, 12]. It has been shown in the PONS study that more than

90% of Polish men and almost 70% of women consume insufficient amounts of magnesium (men on average 218.5 mg/day, women 220.8 mg/day) [13].

The main aim of our study is to summarise existing knowledge and draw conclusions about the impact of magnesium deficiency on the occurrence of anxiety. A review of the literature indicates a link between these two phenomena (increasingly prevalent in the modern world), as well as a positive effect of magnesium supplementation in patients with established anxiety disorders.

2. Methodology

The literature available in the National Library of Medicine database at https://pubmed.ncbi.nlm.nih.gov and Google Scholar was reviewed. Articles were searched by using keywords: magnesium, deficiency, supplementation, anxiety disorders. Forty-seven research papers and meta-analyses were analysed. Data from the aforementioned studies were used to formulate conclusions.

3. Description of the state of knowledge

Studies on macronutrient deficiency in animals and humans suggest that magnesium plays an important role in the aetiology of affective disorders. It participates in biochemical pathways involved in e.g. the pathophysiology of depression. Magnesium has been shown to influence hippocampal activity [14,15], adrenal cortex sensitivity to adrenocorticotropic hormone (ACTH) [16,17] and the limbic-hypothalamic-pituitary-adrenal axis [18].

Artificially induced magnesium deficiency causes depression-like behaviour in rodents [19-22], which is relieved by the administration of antidepressants [20,22]. A magnesium-deficient diet has also been linked to depression in humans [23]. Studies have shown a link between magnesium supplementation and the treatment of depression - in elderly patients with type II diabetes and magnesium deficiency-induced depression, taking 450 mg of magnesium for 12 weeks is as effective in reducing depressive symptoms as 50 mg of imipramine (a drug from the tricyclic antidepressant category) [24]. Effective supplementation effects have also been reported in patients with symptoms of mania [25], bipolar affective disorder with rapid phase change [26] and chronic fatigue syndrome [27].

Depression often co-occurs with anxiety [28]. Anxiety states are among the most common affective disorders found in the population. The lifetime prevalence is more than 15% [29]. The anxiolytic potential of magnesium has been demonstrated in rodent studies. Hypomagnesaemia has been shown to elevate anxiety in mice [18,20,30,31], while supplementing blood magnesium levels reduces anxiety-related behaviour [32,33]. A review of randomised human clinical trials conducted by Boyle et al [34] also found a statistically significant effect of magnesium supplementation on the attenuation of subjective feelings of anxiety (compared with placebo) in four of the eight studies. In three of the other four studies, where such an effect was not proven, the control group were users of the anti-anxiety drugs lorazepam or buspirone [34].

In mentioning magnesium supplementation, it should be noted that the forms of magnesium preparations available on the market differ in their level of absorption from the gastrointestinal tract. Studies show that a significantly higher percentage of absorbed magnesium comes from preparations in the form of water-soluble tablets. This may be due to the fact that magnesium converting to the ionised form Mg2+ in water increases its bioavailability [35]. Magnesium absorption is also favoured by vitamin B6 and D [4,8]. The chemical form of magnesium is also an important issue. In the light of the results of clinical studies, it is not possible to unequivocally identify the form of magnesium with the greatest bioavailability from the gastrointestinal tract, but organic acid salts (citrate, gluconate and lactate) appear to be the most optimal in this aspect [36]. A more important issue affecting the bioavailability of magnesium is its frequency of intake and dose. Taking the mineral in small doses at shorter intervals has been shown to be more effective than taking the same amount in a single dose [36].

There are a number of theories that may explain the relationship between magnesium and anxiety. When a stressful situation occurs, urinary magnesium excretion increases, resulting in a decrease in blood levels of this element [37]. Magnesium affects the activity of the hypothalamic-pituitary-adrenal axis (HPAA), which is involved in the body's response to a stress factor. Activation of the HPAA triggers sympathetic, neuroendocrine and behavioural responses to cope with the stressor - one of these responses is increased anxiety. Magnesium supplementation has been shown to suppress HPAA activity by reducing ACTH [16] and cortisol [38] secretion and, therefore, may have the effect of reducing the incidence of anxiety by moderating the stress response.

Magnesium is also related to glutamate, the main excitatory neurotransmitter in the human brain.

1. Glutamate acts on Ca2+ channel-coupled N-methyl-D-aspartate (NMDA) receptors, which are associated with anxiety disorders [39]. Magnesium binds to this channel, leading to inhibition of NMDA receptor activity. The result is a reduction in the excitation of neurons that trigger the anxiety response[40].

2. Magnesium is also crucial for the activity of G-protein-coupled mGluRs receptors [41,42], which play an important role in glutamatergic activity, glutamate secretion, GABA (γ-aminobutyric acid) neurotransmitter activity and regulation of the neuroendocrine system. The effect of glutamate on mGluR receptors has been linked to stress and anxiety responses [42].

3.Magnesium may further influence the reduction of anxiety sensations by increasing GABAergic availability due to a decrease in presynaptic glutamate release [43]. GABA is the main neurotransmitter in the CNS that balances the excitatory effects of glutamate. The imbalance between GABA and glutamate is related to the neuronal hyperactivity that is characteristic of the pathological experience of anxiety [44].

It is worth noting that the negative effects of anxiety and hypomagnesaemia exacerbate each other in a vicious circle mechanism: magnesium deficiency increases susceptibility to stress, fear and anxiety -> a stronger anxiety response results in a greater need for magnesium -> the greater the magnesium deficit, the more the short- and long-term effects of anxiety (such as fatigue and insomnia, palpitations, dizziness and headaches, eyelid twitching, muscle cramps, tics) are felt [3, 45, 46]. This points to the need to diagnose and treat hypomagnesaemia as soon as possible and the difficulty in treating hypomagnesaemia and the anxiety disorders caused by it when they are already advanced.

People with an increased demand for magnesium, such as children during intensive growth, people exposed to chronic stress, people practicing professional sports and pregnant and lactating women may be particularly exposed to this problem [3,4,47]. Patients taking proton pump inhibitors, psychotropic drugs, contraceptives, immunosuppressants and antibiotics such as tetracyclines or aminoglycosides, as well as patients with hyperthyroidism, adrenal insufficiency and diabetes are also at risk. All these conditions require the clinician to be particularly vigilant and pay attention to the clinical signs of magnesium deficiency and appropriate supplementation [1-4,8-9].

4. Conclusions

Anxiety is one of the most common affective disorders in the population. It is therefore very important to ensure adequate levels of magnesium in the diet, given its impact on the proper functioning of the human body (including, but not limited to, the nervous and muscular systems) and the fact that, according to research, most people consume insufficient amounts of this macronutrient. Evidence of a link between magnesium levels and anxiety has led to increased interest in the potential efficacy of magnesium supplementation to alleviate anxiety symptoms. Anxiolytic drugs in common use (e.g. benzodiazepines) are often characterised by many negative side effects for patients. For this reason, it is important to discover new effective treatments to alleviate anxiety symptoms.

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References:

1. de Baaij JHF, Hoenderop JGJ, Bindels RJM. Magnesium in man: implications for health and disease. Physiol Rev 2015; 95: 1-46.
2. Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients 2015; 7: 8199-8226.
3. Bancerz B, Duś-Żuchowska M, Cichy W, Matusiewicz H. Effect of magnesium on human health. Gastroenterol Rev 2012; 6: 359-366.
4. Szymczyk H. Magnesium - an element essential for the proper functioning of the body. Farm Współczesna 2016; 9: 217-223. Polish
5. Topf, J.M.; Murray, P.T. Hypomagnesemia and hypermagnesemia. Rev. Endocr. Metab. Disord. 2003, 42, 195–206
6. Karmańska A, Stańczak A, Karwowski B. Magnesium - current state of knowledge. Bromat Chem Toksykol. 2015;4:677-89. Polish
7. Zawadzka M, Pilarska E. Magnesium formulas in the treatment of migraine - a review of the literature. Neurologia dziecięca 2012;21:35-9. Polish
8. Jabłecka A, Korzeniowska K, Skołuda A, Cieślewicz A. Magnesium formulas Farm Współczesna 2011; 4: 29-32. Polish
9. Iskra M, Krasińska B, Tykarski A. Magnesium - physiological role, clinical significance of deficiency in hypertension and its complications, and possibilities for supplementation in the human body. Arter Hypertens 2013; 17: 447-459. Polish
10. Food and Nutrition Board, Institute of Medicine. Magnesium. dietary reference intakes: calcium, phosphorus, magnesium, vitamin D and fluoride. Washington D.C: National Academy Press; 1997. 190- 249
11. Kunachowicz H., Nadolna I., Przygoda B., Iwanow K., Tables of composition and nutritional value of foods, Wyd. 2, PZWL Wydawnictwo Lekarskie, Warszawa, 2017. Polish
12. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Scientific opinion on Dietary Reference Values for magnesium, EFSA Journal, 2015, 13, 7, 4186.
13. Ilow R., Regulska-Ilow B., Różańska D. i wsp., Evaluation of mineral and vitamin intake in the diet of a sample of Polish population – baseline assessment from the prospective cohort ‘PONS’ study, Ann. Agric. Environ. Med., 2011, 18, 2, 235–240.

14. Hallak, M.; Berman, R.F.; Irtenkauf, S.M.; Evans, M.I.; Cotton, D.B. Peripheral Magnesium-Sulfate Enters the Brain and Increases the Threshold for Hippocampal Seizures in Rats. Am. J. Obstet. Gynecol. 1992, 1676, 1605–1610.
15. Cotton, D.B.; Hallak, M.; Janusz, C.; Irtenkauf, S.M.; Berman, R.F. Central Anticonvulsant Effects of Magnesium-Sulfate on N-Methyl-D-Aspartate Induced Seizures. Am. J. Obstet. Gynecol. 1993, 1683, 974–978.
16. Murck, H.; Steiger, A. Mg2+ reduces ACTH secretion and enhances spindle power without changing delta power during sleep in men—Possible therapeutic implications. Psychopharmacology 1998, 1373, 247–252.
17. Glynn, P.; Cooper, D.M.F.; Schulster, D. Modulation of Response of Bovine Adrenocortical Adenylate-Cyclase to Corticotropin. Biochem. J. 1977, 1682, 277–282.
18. Murck, H. Magnesium and affective disorders. Nutr. Neurosci. 2002, 56, 375–389.
19. Muroyama, A.; Inaka, M.; Matsushima, H.; Sugino, H.; Marunaka, Y.; Mitsumoto, Y. Enhanced susceptibility to MPTP neurotoxicity in magnesium-deficient C57BL/6N mice. Neurosci. Res. 2009, 631, 72–75.
20. Singewald, N.; Sinner, C.; Hetzenauer, A.; Sartori, S.B.; Murck, H. Magnesium-deficient diet alters depressionand anxiety-related behavior in mice—Influence of desipramine and Hypericum perforatum extract. Neuropharmacology 2004, 478, 1189–1197.
21. Spasov, A.A.; Iezhitsa, I.N.; Kharitonova, M.V.; Kravchenko, M.S. Depression-like and anxiety-related behaviour of rats fed with magnesium-deficient diet. Zhurnal Vysshei Nervnoi Deyatelnosti Imeni I P Pavlova 2008, 584, 476–485.
22. Whittle, N.; Li, L.; Chen, W.Q.; Yang, J.W.; Sartori, S.B.; Lubec, G.; Singewald, N. Changes in brain protein expression are linked to magnesium restriction-induced depression-like behavior. Amino Acids 2011, 404, 1231–1248.
23. Jacka, F.N.; Overland, S.; Stewart, R.; Tell, G.S.; Bjelland, I.; Mykletun, A. Association between magnesium intake and depression and anxiety in community-dwelling adults: The Hordaland Health Study. Aust. N. Z. J. Psychiatry 2009, 431, 45–52.
24. Barragan-Rodriguez, L.; Rodriguez-Moran, M.; Guerrero-Romero, F. Depressive symptoms and hypomagnesemia in older diabetic subjects. Arch. Med. Res. 2007, 387, 752–756.
25. Pavlinac, D.; Langer, R.; Lenhard, L.; Deftos, L. Magnesium in Affective-Disorders. Biol. Psychiatry 1979, 144, 657–661.

26. Chouinard, G.; Beauclair, L.; Geiser, R.; Etienne, P. A Pilot-Study of Magnesium Aspartate Hydrochloride (Magnesiocard) as a Mood Stabilizer for Rapid Cycling Bipolar Affective-Disorder Patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 1990, 142, 171–180.
27. Cox, I.M.; Campbell, M.J.; Dowson, D. Red-Blood-Cell Magnesium and Chronic Fatigue Syndrome. Lancet 1991, 3378744, 757–760.
28. Arzoz-Fabregas, M.; Ibarz-Servio, L.; Fernández-Castro, J.; Valiente-Malmagro, M.; Roca-Antonio, J.; Edo-Izquierdo, S.; Buisan-Rueda, O. Chronic stress and calcium oxalate stone disease: Influence on blood cortisol and urine composition. Urology 2013, 826, 1246–1252.
29. Kessler, R.C.; Aguilar-Gaxiola, S.; Alonso, J.; Chatterji, S.; Lee, S.; Ormel, J.; Ustün, T.B.; Wang, P.S. The global burden of mental disorders: An update from the WHO World Mental Health (WMH) surveys. Epidemiol. Psichiatr. Soc. 2009, 181, 23–33.
30. Sartori, S.B.; Whittle, N.; Hetzenauer, A.; Singewald, N. Magnesium deficiency induces anxiety and HPA axis dysregulation: Modulation by therapeutic drug treatment. Neuropharmacology 2012, 621, 304–312.
31. Pyndt Jørgensen, B.; Winther, G.; Kihl, P.; Nielsen, D.S.; Wegener, G.; Hansen, A.K.; Sørensen, D.B. Dietary magnesium deficiency affects gut microbiota and anxiety-like behaviour in C57BL/6N mice. Acta Neuropsychiatr. 2015, 2705, 307–311
32. Poleszak, E.; Szewczyk, B.; Kedzierska, E.; Wla ´z, P.; Pilc, A.; Nowak, G. Antidepressant- and anxiolytic-like activity of magnesium in mice. Pharmacol. Biochem. Behav. 2004, 78, 7–12.
33. Iezhitsa, I.N.; Spasov, A.A.; Kharitonova, M.V.; Kravchenko, M.S. Effect of magnesium chloride on psychomotor activity, emotional status, and acute behavioural responses to clonidine, d-amphetamine, arecoline, nicotine, apomorphine, and L-5-hydroxytryptophan. Nutr. Neurosci. 2011, 141, 10–24.
34. Boyle NB, Lawton C, Dye L. The Effects of Magnesium Supplementation on Subjective Anxiety and Stress – A Systematic Review. Nutrients. 2017; 9(5): 429
35. Siener R, Jahnen A, Hesse A. Bioavailability of magnesium from different pharmaceutical formulations.Urol Res. 2011; 39(2): 123–127
36. Schuchardt JP, Hahn A. Intestinal Absorption and Factors Influencing Bioavailability of Magnesium – An Update. Curr Nutr Food Sci. 2017; 13(4): 260–278

37. Grases, G.; Pérez-Castelló, J.A.; Sanchis, P.; Casero, A.; Perelló, J.; Isern, B.; Rigo, E.; Grases, F. Anxiety and stress among science students. Study of calcium and magnesium alterations. Magnes. Res. 2006, 192, 102–106
38. Held, K.; Antonijevic, I.A.; Künzel, H.; Uhr, M.; Wetter, T.C.; Golly, I.C.; Steiger, A.; Murck, H. Oral Mg2+ supplementation reverses age-related neuroendocrine and sleep EEG changes in humans. Pharmacopsychiatry 2002, 354, 135–143
39. Johnson, P.L.; Shekhar, A. Panic-Prone State Induced in Rats with GABA Dysfunction in the Dorsomedial Hypothalamus Is Mediated by NMDA Receptors. J. Neurosci. 2006, 2626, 7093–7104.
40. Coan, E.J.; Collingridge, G.L. Magnesium ions block an N-methyl-D-aspartate receptor-mediated component of synaptic transmission in rat hippocampus. Neurosci. Lett. 1985, 53, 21–26.
41. Masugi, M.; Yokoi, M.; Shigemoto, R.; Muguruma, K.; Watanabe, Y.; Sansig, G.; van der Putten, H.; Nakanishi, S. Metabotropic glutamate receptor subtype 7 ablation causes deficit in fear response and conditioned taste aversion. J. Neurosci. 1999, 193, 955–963.
42. Niswender, C.M.; Conn, P.J. Metabotropic glutamate receptors: Physiology, pharmacology, and disease. Annu. Rev. Pharmacol. Toxicol. 2010, 50, 295–322.
43. Papadopol, V.; Nechifor, M. Magnesium in Neuroses and Neuroticism. In Magnesium and the Central Nervous System; Vink, R., Nechifor, M., Eds.; University of Adelaide Press: Adelaide, Australia, 2011.
44. Lydiard, R.B. The Role of GABA in Anxiety Disorders. J. Clin. Psychiatry 2003, 643, 21–27
45. Zhang X, Xia J, Del Gobbo LC i wsp. Serum magnesium concentrations and all-cause, cardiovascular, and cancer mortality among U.S. adults: Results from the NHANES I Epidemiologic Follow-up Study. Clin Nutr 2018; 37: 1541-1549.
46. Cuciureanu MD, Vink R. Magnesium and stress. W: Magnes. Vink R, Nechifor M (red.). Cent Nerv Syst, University of Adelaide Press 2011; 251-268.
47. Wojtasik A, Woźniak A, Stoś K, Jarosz M. Mineral components. Nutrition standards for the Polish population and their application. Jarosz M, Rychlik E, Stoś K, Charzewska J (red.). National Institute of Public Health - National Institute of Hygiene, Warszawa 2020; 273-282. Polish