Clinical and pathogenetic values of disorders of mineral metabolism in ankylosing spondylitis

Shakhnoza Pulatova[1], Dildora Nabiyeva[2], Nargiza Abduazizova[3], Sevara Mukhammadiyeva[4], Gulnara Agzamova[5], Bakhitsholpan Isayeva[6]

[1] Assistant of Department of faculty and hospital therapy №1 with course of professional pathology of Tashkent Medical Academy of Uzbekistan

[2] Doctor of medical sciences, associate professor, head of Department of faculty and hospital therapy №1 with course of professional pathology of Tashkent Medical Academy of Uzbekistan

[3] PhD, associate professor of Department of faculty and hospital therapy №1 with course of professional pathology of Tashkent Medical Academy of Uzbekistan

[4] PhD, associate professor of Department of faculty and hospital therapy №1 with course of professional pathology of Tashkent Medical Academy of Uzbekistan

[5] Doctor of medical sciences, associate professor of Department of faculty and hospital therapy №1 with course of professional pathology of Tashkent Medical Academy of Uzbekistan

[6] Doctor of medical sciences, professor of the Department of General Medical Practice № 1 of Kazakh National Medical University named after S. D. Asfendiyarova (Kazakhstan).

Abstract. Controlling and maintaining magnesium homeostasis is important for maintaining bone integrity in ankylosing spondylitis (AS). Most patients with AS have a significant nutritional magnesium deficiency, which leads to the development and aggravation of osteoporosis (OP). The frequency of OP, as well as the mechanism of its development in patients with AS and other forms of spondyloarthritis (SpA) with magnesium deficiency, have been insufficiently studied. In AS, there is a correlation between magnesium titers and a decrease in bone mineral density (BMD) in the lumbar spine (LS) of the spine and the femoral neck (FN). Bone loss during SpA is often detected in patients with an advanced stage of the disease, i.e., with a radiographically confirmed diagnosis of AS, when OP may be due to immobilization. At the same time, it was shown that persistent inflammatory activity is the leading factor of OP in magnesium deficiency in patients with AS. The article discusses the issues of magnesium deficiency associated with osteoporosis, as well as the need to include magnesium citrate in the complex therapy of ankylosing spondyloarthritis.

Keywords: ankylosing spondylitis, bone mineral density, osteoporosis, osteoblasts, osteoclasts, magnesium citrate, magnesium deficiency, magnesium.

Osteoporosis (OP) is a skeletal disease characterized by impaired bone metabolism with a predominance of bone resorption over bone formation processes, impaired microarchitectonics, increased fragility and decreased bone strength and an increased risk of fractures [1]. The frequency of OP, as well as the mechanism of its development in patients with ankylosing spondylitis (AS) and other forms of spondyloarthritis (SpA), have been insufficiently studied. According to various authors [2], the incidence of OP in patients with AS varies from 18.7 to 62%. In AS, there is a correlation between a decrease in BMD in the lumbar spine (LS) of the spine and the femur neck (FN) [3]. Bone loss during SpA is often detected in patients with an advanced stage of the disease, ie, with a radiographically confirmed diagnosis of AS [4], when OP may be due to immobilization. At the same time, it was shown that persistent inflammatory activity is the leading factor of OP in AS [5, 6]. The pathological mechanisms of bone resorption in SpA are based on inflammation, more specifically, an imbalance in the RANKL / OPG system [7]. An important role in the pathogenesis of OP in SpA is played by proinflammatory cytokines with the ability to stimulate bone resorption, such as tumor necrosis factor α (TNFα) [8], interleukin (IL) 6 [8], IL17 [9], IL23 [9] and some others. TNFα inhibitors, having an anti-inflammatory effect, block the activation of osteoclasts [8]. It has been shown that infliximab [10, 11] and etanercept [12] not only suppress clinical and magnetic resonance imaging (MRI) signs of inflammation in AS, but also contribute to an increase in BMD in the spine and femur.

10.5281/zenodo.5832045

Modern studies indicate that in patients with axial SpA already in the early stages of the disease, there is a significant loss of bone mass, which correlates with the activity of inflammation [13]. In SpA, the pathological process begins with local inflammation of the entheses. Bone loss occurs in areas adjacent to areas of inflammation: in the spine and proximal femur, but not in the bones of the forearm [14]. An analogy can be drawn with early RA, in which a pronounced decrease in BMD in the bones of the forearm is associated with arthritis of the joints of the hands [15].

Nutrition is an important modifiable factor that determines the development and maintenance of bone mass in AS. A diet balanced in calories, protein (1 g / kg / day), fats and carbohydrates (no more than 60% of the total calorie content of food) contributes to the normal metabolism of calcium (Ca) in bone tissue. Currently, calcium in combination with vitamin D is the basis of nutritional correction for the prevention and treatment of osteoporosis, osteopenia, rickets and AS. [16].

However, the combined intake of calcium and vitamin D does not always successfully prevent osteoporosis, since it does not compensate for all the nutritional requirements of bone tissue in AS.

The importance of nutritional factors such as calcium, phosphorus (P) and vitamin D for bone integrity is undeniable in AS. The vitamin D receptor, like estrogen receptors, is a transcription factor that, in particular, regulates the expression of proteins involved in calcium and phosphorus homeostasis. Experimental data indicate that the physiological effects of vitamin D include inhibition of the secretion of proinflammatory cytokines, adhesion molecules, and proliferation of vascular smooth muscle cells, processes that are important for arterial calcification [17].

At the same time, studies conducted over the past decade have shown that vitamins A, C, E, K and trace elements copper (Cu), manganese (Mn), zinc, strontium, magnesium (Mg) are also required to maintain the structure of bone tissue in AS. Deficiency of these micronutrients slows down the growth of bone mass in childhood and adolescence and contributes to the accelerated loss of bone mass in old age [18]. This paper reviews the results of experimental and clinical studies indicating the importance of compensating for the deficiencies of these microelements in the prevention and treatment of osteoporosis and osteopenia in AS. Particular attention is paid to magnesium - a trace element that has a significant effect on the structure of bone tissue and, nevertheless, is neglected in the vast majority of vitamin and mineral complexes.

Magnesium and Support of Connective and Bone Tissue

One of the fundamentally important nutritional needs of the bone is the supply of bones with magnesium - an element that regulates mineralization, uniform growth, flexibility and strength of bone tissue and increases the reparative potential of bones in AS. Conversely, magnesium deficiency in the body prevents successful therapy and prevention of bone structure disorders (osteoporosis, etc.) in AS. Among the various tissues of the body, it is bone tissue that is the main store of magnesium. In addition to being a magnesium depot, magnesium also has a significant effect on bone mineralization and structure — low magnesium levels are associated with low bone mass and osteoporosis in AS [19].

Magnesium is one of the fundamentally important nutrient factors affecting connective tissue in AS. Insufficient magnesium supply is one of the most important causes of structural disorders (dysplasia) of connective tissue in patients with AS. A systematic analysis of the relationship between the supply of cells with magnesium and the molecular structure of the connective tissue indicated such molecular mechanisms of the effect of magnesium deficiency as weakening of protein synthesis due to destabilization of tRNA, decreased activity of hyaluronan synthetases, increased activity of metalloproteinases, increased activities of hyaluronidases and lysine oxidase in AS [20]. It should be recalled that bone tissue consists of only 70% of calcium compounds, and 22% of collagen, 8% of the water fraction.

The importance of the role of magnesium in maintaining bone structure is also associated with the fact that chronic magnesium deficiency disrupts the most important aspect of bone mineral metabolism - the Mg: Ca ratio in AS. With a decrease in the Mg: Ca ratio towards magnesium deficiency, metabolic processes in the bone are slowed down, toxic metals (primarily cadmium and lead) are deposited faster. Due to the accumulation of toxic elements in the joint due to the violation of the Mg: Ca ratio, the function of the joints gradually deteriorates: the range of motion decreases, deformation of the joints of the limbs and the spine occurs in AS. Epidemiological studies of the incidence of osteoporosis in various countries have shown that a higher Mg: Ca ratio in the diet corresponds to a lower incidence of osteoporosis in AS [21].

In the experiment, a diet with a very low magnesium content (7% of the normal intake level) led to significant hypomagnesemia, hypocalcemia, and changes in bone tissue characteristic of osteoporosis in chickens. Magnesium deficiency leads to a thinning of bone tissue, up to the formation of cavities; compensation of magnesium deficiency - to restore the structure of bone tissue in AS [22].

Higher dietary magnesium intake corresponds to increased BMD in men and women with AS. In a cohort study of 2038 people, the assessment of dietary magnesium intake on the questionnaire correlated with BMD after adjusting for age, caloric intake, calcium and vitamin D intake, body mass index, smoking, alcohol, physical activity, use of thiazide diuretics and estrogen-containing drugs ($p = 0.05$, men; $p = 0.005$, women) [23].

Maternal nutrition during pregnancy has a significant effect on bone mineral density in children. Observations of 173 mother-child couples during 8 years after childbirth showed that BMD of the femoral neck in children increased with an increase in the dietary supply of magnesium to the pregnant woman. The BMD of the lumbar spine depended on the supply of magnesium, potassium, phosphorus and potassium to the pregnant woman. Children whose mothers were adequately provided with the indicated minerals during pregnancy were characterized by significantly higher BMD values (femoral neck + 5.5%, lumbar spine + 12%, whole body + 7%) [24].

Normally, bone structure is constantly remodeled by coordinating interactions between osteoclasts (cells that are primarily responsible for bone resorption) and osteoblasts (cells that support bone formation and mineralization). The imbalance of their functioning, in fact, in OP when the processes of bone resorption prevail, its microarchitectonics deteriorates and the density decreases [25]. This increases the risk of fractures, in particular of the hip and spine, which cause pain and suffering to patients, leading to disability and even death in AS [26].

The beneficial effects of calcium and vitamin D on bone mass at any age in AS are known. They support bone mineral density and are essential ingredients in most preventative strategies. However, OP is a multifactorial disease and the participation of other trace elements and biologically active substances is necessary for bone health. The formation of bone tissue is also influenced by fluorine and strontium, but when they are in excess, the effect becomes the opposite - the strength of the bone decreases. Magnesium supports bone strength, integrity and remodeling in AS. Boron is especially effective in cases of vitamin D, magnesium and potassium deficiencies in AS. Vitamin K is essential for the activation of osteocalcin. Vitamin C is an important stimulus for osteoblasts [27]. Adequate intake of phytoestrogens, flavonoids, vitamins A, B, C, E, K, folic acid, minerals such as potassium, copper, zinc, selenium, iron, fluoride, boron, and magnesium can lead to a significant reduction or even prevention of bone loss, especially in elderly people with AS [28].

Effect of magnesium on bone structure and density

The role of magnesium (Mg) in bone homeostasis has been studied for over 70 years [29]. About 60% of the total Mg content in the body is found in the bones - this is the main Mg depot in the body. Therefore, with a deficiency of a trace element, its transition from bone to blood leads to a decrease in the number and thickness of trabeculae, as well as disruption of the formation processes and increased resorption. As a result, the volume of the cancellous bone, the withstanding maximum load and the modulus of elasticity decrease [26].

It was also established that:

• Mg determines the activity of H + / K + -ATPase in the cells of the periosteum, in the endosteum and the pH of the extracellular bone fluid, which decreases with Mg deficiency (acidosis), which leads to demineralization [30];

• formation of 1,25-hydroxyvitamin D occurs under the control of magnesium-dependent hydroxylase. In the presence of Mg deficiency, the serum 1,25-dihydroxyvitamin D concentration is significantly reduced [25];

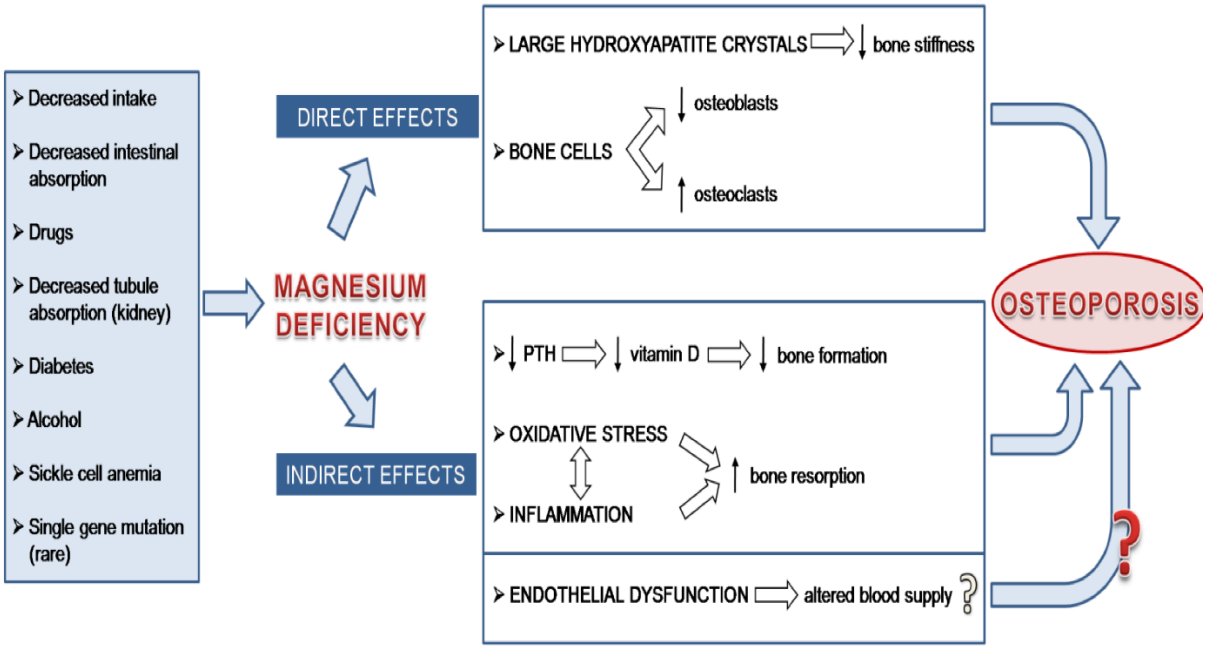
• Mg alters the activity of the enzyme nitric oxide synthetase (iNOS) and participates in the elimination of entrapped nitric oxide (NO), thereby reducing the level of intracellular NO and increasing the activity of osteoblasts, which prevents OP (but only in conditions of normal Mg level) [18].

Deficiency of Mg and OP in AS.

To date, several direct and indirect mechanisms have been established for the negative impact of low levels of Mg on bone density, development and maintenance of OP in AS (see figure 1.):

Figure 1.

Impact of magnesium deficiency on bone tissue, development and maintenance of osteoporosis



1. The crystal structure of the bone changes, the function of osteoblasts decreases, the number and activity of osteoclasts increases, which leads to increased fragility of bones [31]. Low levels of extracellular Mg inhibit osteoblast growth by increasing NO release through upregulation of induced NO [32], while increasing the number of osteoclasts generated by the bone marrow [10];

2. Homeostasis of parathyroid hormone (PTH) and 1,25 (OH) 2-vitamin D is disturbed, which leads to hypocalcemia. On the one hand, with a deficiency of Mg, the secretion of PTH is impaired, which affects target organs through an increase in cAMP and activation of adenylate cyclase. In this case, Mg acts as a cofactor. Resistance of PTH cells is formed [33]. Decreased PTH secretion or impaired peripheral cellular response to the hormone results in low serum concentrations of 1,25 (OH) 2-vitamin D [12]. On the other hand, Mg is necessary for the activity of 1,25-hydroxycholecalciferol-1-hydroxylase and, therefore, the deficiency of the trace element reduces the activity of this enzyme, which leads to a decrease in the level of 1,25 (OH) 2-vitamin D [12-13]. With Mg supplementation, postmenopausal women with vitamin D deficiency, low PTH levels and

Mg deficiency return to normal biochemical parameters. Supplementation with Mg in children with diabetes mellitus contributes to the normalization of the level of 1,25 (OH) 2-vitamin D [2];
3.Increases the production of inflammatory cytokines (tumor necrosis factor, interleukin-1 - IL-1 and IL-6 - both in blood serum and in the bone microenvironment), which increases the activity of osteoclasts, inhibits the function of osteoblasts, thereby stimulating bone remodeling and osteopenia [34];
4. Substance P is intensively released, which, in addition to increasing the secretion of cytokines, further stimulates the activity of osteoclasts. This is also important because the decrease in Mg promotes oxidative stress - partly as a result of inflammation, and partly due to the suppression of antioxidant defense mechanisms. An increase in the number of free radicals potentiates the activity of osteoclasts and thereby suppresses osteoblasts [12];
5. Endothelial dysfunction develops, which leads to disruption of adequate blood supply to the bone, thus contributing to a decrease in bone mass [35];
6. Increased metabolic acidosis due to malnutrition (Western "civilized" diet), which is further aggravated by aging. Metabolic acidosis leads to loss of calcium from bone, inhibits osteoblast function and stimulates osteoclast activity, impairs bone mineralization.

Reasons for Mg deficiency in AS.

A person gets magnesium exclusively from food. Therefore, its most common nutritional deficiency. Nutrition monitoring has shown that refined and salty foods, semi-finished products, transgenic fats, phosphoric acid (soda), coffee prevail in the modern “way of eating” of Europeans and the United States, which does not provide the body with the required amount of Mg. The proportion of calcium and sodium intake is increasing, while Mg is decreasing sharply. The lowest levels of OP incidence are recorded in cultures where the ratio of calcium to Mg intake is 1: 1 or 2: 3. In countries with a high level of OP development, the ratio of total calcium and Mg consumed with food and nutritional supplements is at best 2: 1, and usually more than 3: 1. For comparison: the ratio in South Africa is 2 parts of calcium to 3 parts of Mg, with a minimum OP rating of 7, in the USA this ratio is 4: 1 and reflects a high OP rating - 144, in Switzerland - 5.5: 1.0 and the highest OP rating - 188 [36].
High consumption of Mg is associated with higher bone density in older men and women, while various types of dietary Mg restriction contribute to the development of OP [12]. With an Mg-deficient diet, the thickness of the cortical layer of the bone decreases noticeably, and microcracks of trabeculae appear [10].
On average, women in Western countries consume only 68% of the daily value of Mg, which indicates a significant dietary deficiency in most of the population [19].
In Russia, there is also an insufficient average daily intake of microelements (calcium is consumed only 22–31.1% of the norm, Mg - 57.4–117.5%), which leads to their imbalance among themselves, as well as with phosphorus [20]. Mg deficiency is very common in the elderly and alcohol abusers and in people with rheumatological diseases, especially in AS [37].

However, diet is not the only determining factor in AS. Mg deficiency occurs with profuse sweating, prolonged stress, excessive menstruation and vaginal bleeding, with some parasite infestations (pinworms) [23–24]. The micronutrient deficiency is aggravated by diabetes mellitus, sickle cell anemia, and therapy with certain classes of diuretics, antibiotics, anticancer drugs, and GCS [25–26]. Since Mg homeostasis is regulated by a complex network of transporters in the intestine and kidneys, it is not surprising that Mg deficiency is associated with chronic diseases of the gastrointestinal tract and kidneys [27].

Over the past decade, rare cases of hypomagnesemia have been identified with hereditary gene mutations: gene polymorphism associated with a low level of serum Mg (TRPM6, TRPM7) has been established [27-28]. The possibility of detecting hereditary gene mutations in patients with AS is also being studied [20].

Other physiological effects of Mg on the body

The data of more than 80 thousand clinical, biochemical, cellular and molecular studies published over the past 30 years show that intracellular Mg, in addition to its structural role in bones, ensures the normal functioning of the body, and the maintenance of the physiological level of Mg in the tissues of the body is a fundamental parameter of human health [29].

And above all, Mg is a fundamental element in the synthesis of ATP (the main source of energy in cells) and a cofactor of several hundred enzymes involved in the metabolism of lipids, proteins, neurotransmitter molecules and the synthesis of nucleic acids.

Mg ion is a natural antagonist of calcium ion: it stabilizes cell membranes, regulates the permeability of cell membranes and vascular tone, increases the sensitivity of cells to insulin, stabilizes NMDA- receptors, and participates in collagen synthesis [39]. Mg, by changing the activity of the iNOS enzyme, regulates the level of intracellular NO and reduces the synthesis of peroxynitrite, which protects cells from the damaging effects of the latter [8, 30]. Cellular Mg deficiency causes pathological processes leading to functional and structural damage underlying the pathogenesis of various diseases.

According to epidemiological studies, low consumption of Mg leads to a violation of the Ca2 + / Mg2 + ratio, which determines a high risk of developing II type of diabetes mellitus, metabolic syndrome, atherosclerosis, coronary heart disease, cerebrovascular diseases, increased levels of C-reactive protein, arterial hypertension, stress associated, anxiety and depressive disorders, Alzheimer's disease and other cognitive impairments, multiple sclerosis, sudden cardiac death, migraine, premenstrual syndrome, bronchial asthma, colon cancer and OP [24, 31–32]. Mg deficiency is of particular importance from the standpoint of impaired synthesis of RNA and DNA, the end portions of which (telomeres) are necessary both to maintain the integrity of the genome and to curb cellular senescence [33]. The activity of the enzyme telomerase (adding DNA fragments) is Mg-dependent. Under conditions of Mg deficiency, DNA replication, transcription, and translation become erroneous, which leads to telomere shortening, disruption of protein synthesis and mitochondrial function, and, as a consequence, cell aging and death [38].

Thus, the presence of a sufficient amount of Mg in the body is a critical factor for normal cellular homeostasis and determines the relationship between Mg deficiency, age, aging and the risk of developing somatic diseases, incl. and OP.

Conclusion

Effective prevention and treatment of OP in AS is a complex process that requires a multidimensional approach, in which Mg plays an important role. An increase in Mg consumption with food, which is possible only in a healthy diet with a high content of fruits and vegetables [38, 41], and the inclusion of Mg preparations in the complex treatment of OP in AS will increase the effectiveness and adherence of the patient to therapy. Many factors affect Mg homeostasis; it is not enough just to prescribe magnesium-containing drugs with basic anti-inflammatory drugs for AS. It is necessary to increase the intake of Mg with food in patients with AS, since ignoring this fact leads to disappointment from the insufficient effectiveness of drug therapy. Results from a prospective study of 73,684 postmenopausal women with AS, published in 2014, showed that physical activity and baseline bone mineral density were higher in women who consumed more than 422.5 mg of Mg per day compared with those who consumed less than 206 , 5 mg / day. And despite evidence that Mg increases skeletal strength, results from The Women’s Health Initiative Study, published in 2009, showed that postmenopausal women with high Mg intake had the highest incidence of wrist fractures. An attempt was made to explain these results using in vitro studies: given the antagonism with calcium, high levels of Mg in bones disrupt the calcium / magnesium balance, which possibly leads to changes in bone structure and bone cell function, as well as bone dystrophy in chronic renal insufficiency and with prolonged forced adynamia (the concentration of Mg in the serum in these patients is often increased and correlates with bone demineralization). However, more detailed study of the results of this study, as well as subsequent clinical studies, showed that high levels of Mg intake, although associated with an increased risk of wrist fracture, but only because these people lead a more active lifestyle with a high probability of falls on their

hands. Before starting therapy with OP and after 3 months, it is recommended to study the dynamics of markers of bone resorption in patients with AS (for example, degradation products of type I collagen - N-telopeptide - NTX in urine or C-telopeptide - CTX in blood serum). A decrease in their level by 30% indicates the effectiveness of the treatment for AS. In order to monitor the effectiveness of treatment of OP in AS, it is recommended to assess bone mineral density with an interval of 1–2 years. At the same time, an increase in mineral density or even the absence of negative dynamics is interpreted, as well as an effective treatment of AS.

References

1. Лесняк О.М. Аудит состояния проблемы остеопороза в Российской Федерации. Профилактическая медицина. 2011;14(2):7–10.
2. Castiglioni S., Cazzaniga A., Albisetti W., Maier J.A. Magnesium and osteoporosis: current state of knowledge and future research directions. Nutrients. 2013;5(8):3022–33.
3. Закроева А.Г. Андриянова О.В., Солодовников А.Г. Сравнительное иссле-дование показателей психического здоровья и их ассоциаций с факторами риска хро-нических неинфекционных заболеваний в сельской и городской популяциях. Уральский медицинский журнал. 2009;2(6):83–93.
4. Schaafsma A., de Vries P.J., Saris W.H. Delay of natural bone loss by higher intakes of specific minerals and vitamins. Crit. Rev. Food. Sci. Nutr. 2001;41(4):225–49.
5. Громова О.А., Торшин И.Ю., Керимкулова Н.В., Гришина Т.Р., Калачева А.Г. Методические рекомендации. Дефицит магния как патогенетический фактор остеопороза, остеопении и рахита. Систематический анализ молекулярных и клинических исследований. М., 2012. 34 с.
6. Takami M., Shinnichi S. Bone and magnesium. Clin. Calcium. 2005;15(11):91–6.
7. Swaminathan R. Magnesium Metabolism and its. Disorders Clin. Biochem. Rev. 2003;24(2):47–66.
8. Leidi M., Dellera F., Mariotti M., Banfi G., Crapanzano C., Albisetti W., Maier J.A. Nitric oxide mediates low magnesium inhibition of osteoblast-like cell proliferation. J. Nutr. Biochem. 2012;23(10):1224–29.
9. Ishii A., Imanishi Y. Magnesium disorder in metabolic bone diseases. Clin. Calcium. 2012;22(8):1251–56.
10. Belluci M.M., Schoenmaker T., Rossa-Junior C., Orrico S.R., de Vries T.J., Everts V. Magnesium deficiency results in an increased formation of osteoclasts. J. Nutr. Biochem. 2013;24(8):1488–98.
11. Pironi L., Malucelli E., Guidetti M., Lanzoni E., Farruggia G., Pinna A.D., Barbiroli B., Iotti S. The complex relationship between magnesium and serum parathyroid hormone: A study in patients with chronic intestinal failure. Magnes. Res. 2009;22:37–43.
12. Rude R.K., Singer F.R., Gruber H.E. Skeletal and hormonal effects of magnesium deficiency. J. Am. Coll. Nutr. 2009;28:131–41.
13. Sahota O., Mundey M.K., San P., Godber I.M., Hosking D.J. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: The role of magnesium deficiency. Osteoporos. Int. 2006;17:1013–21.
14. Mazur A., Maier J.A., Rock E., Gueux E., Nowacki W., Rayssiguier Y. Magnesium and the inflammatory response: Potential physiopathological implications. Arch. Biochem. Biophys. 2007;458:48–56.
15. Baker-LePain J.C., Nakamura M.C., Lane N.E. Effects of inflammation on bone: An update. Curr. Opin. Rheumatol. 2011;23:389–95.
16. Wolf F.I., Trapani V., Simonacci M., Boninsegna A., Mazur A., Maier J.A. Magnesium deficiency affects mammary epithelial cell proliferation: Involvement of oxidative stress. Nutr. Cancer. 2009;61:131–36.

17. Maier J.A. Endothelial cells and magnesium: Implications in atherosclerosis. Clin. Sci. (Lond.) 2012;122:397–407.
18. Warburton D.E., Nicol C.W., Gatto S.N., Bredin S.S. Cardiovascular disease and osteoporosis: Balancing risk management. Vasc. Health Risk Manag. 2007;3:673–89.
19. New S.A., Robins S.P., Campbell M.K., Martin J.C., Garton M.J., Bolton-Smith C., Grubb D.A., Lee S.J., Reid D.M. Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? Am. J. Clin. Nutr. 2000;71(1):142–51.
20. Ковальчук В.К., Иванова И.Л. Особенности обеспеченности кальцием, магнием и фосфором населения в приморском крае. Гигиена и санитария. 2011;1:61–6.
21. Chacko S.A., Song Y., Nathan L., Tinker L., de Boer I.H., Tylavsky F., Wallace R., Liu S. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. Diabetes Care. 2010;33:304–10.
22. Naderi A.S., Reilly R.F. Hereditary etiologies of hypomagnesemia. Nat. Clin. Pract. Nephrol. 2008;4:80–9.
23. Johnson S. The multifaceted and widespread pathology of magnesium deficiency. Med. Hypotheses. 2001;56(2):163–70.
24. Акарачкова Е.С., Котова О.В., Вершинина С.В., Рябоконь И.В. Стресс и расстройства адаптации. Лечащий врач. 2014;6:61.
25. Geiger H., Wanner C. Magnesium in diseases. Clin. Kidney Dis. 2012;5:i25–i38.
26. Rodriguez-Moran M., Simental Mendia L.E., Zambrano-Galvan G., Guerrero-Romero F. The role of magnesium in type 2 diabetes: A brief clinical-based review. Magnes. Res. 2011;24:156–62.
27. Runnels L.W. TRPM6 and TRPM7: A Mul-TRP-PLIK-cation of channel functions. Curr. Pharm. Biotechnol. 2011;12:42–53.
28. Meyer T.E., Verwoert G.C., Hwang S.J., et al. Genetic Factors for Osteoporosis Consortium; Meta Analysis of Glucose and Insulin Related Traits Consortium. Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six loci influencing serum magnesium levels. PLoS Genet. 2010;6(8):e1001045.
29. Громова О.А. Торшин И.Ю., Рудаков К.В. и др. Недостаточность магния – достоверный фактор риска коморбидных состояний: результаты крупномасштабного скрининга магниевого статуса в регионах России. Фарматека. 2013;6:16–28.
30. Dhillon K.S., Singh J., Lyall J.S. A new horizon into the pathobiology, etiology and treatment of migraine. Med. Hypotheses. 2011;77(1):147–51.
31. Rosanoff A., Weaver C.M., Rude R.K. Subopti-mal magnesium status in the United States: are the health consequences underestimated? Nutr. Rev. 2012;70(3):153–64.
32. Barbagallo M., Dominguez L.J. Magnesium and aging. Curr. Pharm. Des. 2010;16(7):832–39.
33. Zhang M.L., Tong X.J., Fu X.H., Zhou B.O., Wang J., Liao X.H., Li Q.J., Shen N., Ding J., Zhou J.Q. Yeast telomerase subunit Est1p has guanine quadruplexpromoting activity that is required for telomere elongation. Nat. Struct. Mol. Biol. 2010;17(2):202–09.
34. Rowe W.J. Correcting magnesium deficiencies may prolong life. Clin. Interv. Aging. 2012;7:51–4.
35. Song C.H., Barrett-Connor E., Chung J.H., Kim S.H., Kim K.S. Associations of calcium and magnesium in serum and hair with bone mineral density in premenopausal women. Biol. Trace Elem. Res. 2007;118:1–9.
36. Громова О.А. Магний и пиридоксин: основы знаний. М., 2006. 223 с.
37. Matsuzaki H. Prevention of osteoporosis by foods and dietary supplements. Magnesium and bone metabolism. Clin. Calcium. 2006;16(10):1655–60.
38. Nieves J.W. Osteoporosis: the role of micronutrients. Am. J. Clin. Nutr. 2005;81(5):1232–39.

39. Jehle S., Hulter H.N., Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: A randomized controlled trial. J. Clin. Endocrinol. Metab. 2013;98:207–17.