

## ОГЛЯДИ ТА РЕЦЕНЗІЇ

УДК 616.71/.72+616.71-007.234]:615.326Mag](045)=161.2=111

DOI: <http://dx.doi.org/10.15674/0030-598720234121-127>**Effect of magnesium deficiency on bone health****N. V. Dedukh, N. V. Grygorieva, A. S. Musienko**

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*Objective.* To assess the impact of magnesium deficiency on bone metabolism based on an analytical analysis of current literature, as well as to systematize data on the impact of magnesium deficiency on the development of osteoporosis, bone regeneration, and to consider it as a risk factor for fracture. *Methods.* The review is based on the analysis of literature sources from PubMed, Scopus, Web of Science, Cochrane Library, Google, Google Scholar, and RLNS. The search was conducted by keywords: magnesium, deficiency, magnesium and bone tissue, magnesium and osteoporosis, magnesium and fractures, magnesium and bone regeneration. *Results.* Magnesium is a key element in the metabolic and regulatory processes of the body. Its effects on bone tissue are direct and indirect. The direct magnesium effect on genes involved in osteogenesis is accompanied by proliferation of mesenchymal stem cells and osteoblasts, but magnesium deficiency leads to their reduction and apoptosis. In case of magnesium deficiency, the number and activity of osteoclasts increases. Magnesium regulates bone mineralization in a concentration-dependent manner. Magnesium deficiency increases bone resorption and affects osteopenia and osteoporosis, which can occur indirectly through decreased vitamin D levels, increased biosynthesis of parathyroid hormone, increased oxidative stress and biosynthesis of proinflammatory cytokines. However, data on bone mineral density at different skeletal sites in magnesium deficiency are ambiguous. Magnesium deficiency is considered a risk factor for fracture. It is of great importance for bone regeneration, affecting in various ways: it stimulates the proliferation and differentiation of mesenchymal stem cells and osteoblasts, periosteum cells, increases the movement of osteoblasts to the area of traumatic bone injury, and activates signaling pathways. At the early stage of regeneration magnesium has a positive effect on macrophages, its specificity of action is inhibition of transformation of M2 macrophages into M1 at the tissue-specific stage of regeneration. One of the mechanisms stimulating regeneration may be the effect of magnesium on axons, release and increase of calcitonin-related polypeptide  $\alpha$ . *Conclusions.* Since hypomagnesemia is a potentially modifiable factor, this opens up prospects for maintaining bone health and requires further research in this area.

*Мета.* На підставі аналізу сучасних джерел літератури систематизувати інформацію щодо впливу дефіциту магнію на метаболізм кісткової тканини, розвиток остеопорозу, регенерацію кістки та розглянути його як чинник ризику перелому. *Методи.* Систематичний огляд ґрунтується на аналізі джерел літератури з PubMed, Scopus, Web of Science, Cochrane Library, Google, Google Scholar та RLNS. Пошук проведено за ключовими словами: магній, дефіцит, магній і вплив на кісткову тканину, магній і остеопороз, магній і переломи, магній і регенерація кістки. *Результати.* Магній є одним із ключових елементів у метаболічних і регуляторних процесах організму. Його вплив на кісткову тканину має прямий і опосередкований характер. Пряма дія магнію на гени, які беруть участь у остеогенезі, супроводжується проліферацією мезенхімальних стовбурових клітин та остеобластів, а його дефіцит призводить до зниження їхньої кількості й апоптозу. В умовах дефіциту магнію підвищується чисельність і активність остеокластів, посилюється резорбція кістки, розвивається остеопенія та остеопороз, що може відбуватися непрямым шляхом: через зниження рівня вітаміну D, підвищення біосинтезу паратиреоїдного гормону, посилення оксидативного стресу та біосинтезу прозапальних цитокінів. Дефіцит магнію розглядають як чинник ризику виникнення перелому. Він має велике значення для регенерації кістки, впливаючи різними шляхами: стимулює проліферацію та диференціацію мезенхімальних стовбурових клітин та остеобластів, клітин окістя, підвищує рух остеобластів до зони травматичного ушкодження кістки, активує сигнальні шляхи. На ранній стадії регенерації магній позитивно впливає на макрофаги, його особливістю є інгібування трансформації макрофагів M2 у M1 на тканинно-специфічній стадії регенерації. Одним із механізмів, який стимулюють регенерацію, може бути вплив магнію на аксони, вивільнення та підвищення поліпептиду- $\alpha$ , пов'язаного з геном кальцитоніну (CGRP). *Висновки.* Оскільки гіпомagneзія є потенційно модифікованим чинником, це відкриває перспективи підтримки здоров'я кісток і потребує подальших досліджень у цьому напрямку. *Ключові слова.* Магнійзалежні порушення кісткової тканини, остеопороз, переломи, регенерація кістки.

**Keywords.** Magnesium-dependent bone disorders, osteoporosis, fractures, bone regeneration

## Introduction

The key determinants of bone health are minerals, but researchers have focused their attention mainly on calcium, despite the fact that many other minerals and nutritional components also influence bone metabolism. Among minerals, the attention of researchers in recent years has been directed to magnesium, which in the form of an ion ( $Mg^{2+}$ ) is present in every type of cell, affects their vitality and has a multifactorial effects on the body [1–6].

The total content of magnesium in the body of a healthy adult weighing 70 kg is about 24 g, of which 99 % of magnesium is found in bones, muscles and soft tissues and less than 1 % — in blood serum [7]. Bones contain between 53–67 % of magnesium. Magnesium during bone tissue remodeling can enter other tissues and organs of the body.

The recommended daily dose of magnesium (Standing Committee on the Scientific Evaluation of Dietary Reference Doses, Food and Nutrition Board, Institute of Medicine) is 420 mg/day for men and 320 mg/day for women 31 years to 51 years of age and older [8]. There is evidence that the global average magnesium intake is low for men and women: in Germany at 250 mg/day and 200 mg/day, in Taiwan 250 mg/day and 216 mg/day (68–70 % of the daily requirement), in the USA 323 mg/day and 228 mg/day, respectively, according to other data 50 % of Americans and in the south of France 71.7 % of men and 82.5 % of women consume less than the calculated average requirement [1].

Magnesium deficiency can be caused by nutritional deficiencies, decreased intestinal absorption, tubular absorption in the kidneys, medications, oral contraceptives, diabetes mellitus, alcoholism, sickle cell anemia, and others. Several inherited forms of hypomagnesaemia have been identified, caused by mutations in transient receptor potential melastatin type 6 (TRPM6), claudin 16, paracellular transport and reabsorption of magnesium and calcium from the renal tubule, and cyclin M2 (CNNM2), the protein is considered essential for renal  $Mg^{2+}$  reabsorption [9]. Magnesium deficiency can affect all body systems, including the neuromuscular, cardiovascular, endocrine, renal, respiratory, bone and gastrointestinal systems [10].

From food and water, magnesium is absorbed in the intestine, filtered and excreted through the kidneys, as well as through feces.

*Objective:* on the basis of analytical analysis of modern literature sources to evaluate the influence of magnesium deficiency on bone tissue metabolism, as well as to systematize the data of magnesium de-

ficiency manifestations in osteoporosis, bone regeneration, and to consider it as a risk factor for fracture.

## Material and methods

The review is based on the analysis of literature sources from PubMed, Scopus, Web of Science, Cochrane Library, Google, Google Scholar, and RLNS. The search was conducted by keywords: magnesium, deficiency, magnesium and bone tissue, magnesium and osteoporosis, magnesium and fractures, magnesium and bone regeneration.

## Results and their discussion

*General ideas about the role of magnesium in the regulation of metabolic processes in the body*

Magnesium is involved in metabolic and regulatory processes, is a cofactor of more than 600 enzymes and an activator of about 200 more enzymes [1]. Adenosine triphosphate (ATP), the main source of energy in cells becomes biologically active by binding to  $Mg^{2+}$ . Magnesium plays a role in the stability of all polyphosphate compounds in cells; due to its positive charge  $Mg^{2+}$  stabilizes cell membranes. Magnesium is associated with DNA and RNA synthesis, essential in DNA replication, repair and stability, in RNA transcription and takes part in protein biosynthesis, cell replication and plays a key role in many other important biological processes [11]. Magnesium is actively involved in the process of neuromuscular excitability; it is indispensable in protein, carbohydrate and lipid metabolism [1]. There are at least 500 magnesium-dependent proteins in the human body.  $Mg^{2+}$  is involved in maintaining the normal function of the nervous and cardiovascular systems [12].

A close relationship between magnesium and vitamin D, which increases magnesium absorption in the intestine and maintains its homeostasis, has been proven; in turn, magnesium is closely functionally related to vitamin D [11–14].

The research-based data (1, 11–14) are summarized in fig. 1.

### *Methods of magnesium determination*

The most widely used method for determining magnesium status in norm and disease is its determination in blood serum. Reference values for magnesium levels in human blood are 0.7–1.0 mmol/l (or 1.7–2.4 mg/dL). However, there are additional methods to assess  $Mg^{2+}$  status:  $Mg^{2+}$  content in erythrocytes, hair, muscle and bone (biopsy),  $Mg^{2+}$  level in daily urine, the ratio of ionized  $Mg^{2+}$  to total, oral magnesium load test [15]. The use of a correlation coefficient between daily magnesium intake and  $Mg^{2+}$  determined in serum is also suggested, and if the concen-

tration is 0.29, this figure corresponds to providing an optimal individual  $Mg^{2+}$  concentration [16].

*Magnesium and bone*

The role of  $Mg^{2+}$  in cell differentiation is complex and strictly depends on the cell type. In the presented review, the role of  $Mg^{2+}$  in bone tissue function will be presented.

A tight control of  $Mg^{2+}$  homeostasis is crucial for bone health. According to experimental and epidemiological studies,  $Mg^{2+}$  deficiency in the body has detrimental effects on bone. There are several ways in which  $Mg^{2+}$  deficiency affects bone tissue, both direct pathways and indirect pathways (fig. 2, 3).

*Direct effect of  $Mg^{2+}$*

To date, the molecular mechanisms of  $Mg^{2+}$  action have been partially established. One of the pathways is MAPK/ERK (mitogen-activated protein kinase / extracellular-signal-regulated kinase) signaling pathway. This is one of the major signaling pathways that is involved in osteogenic differentiation of mesenchymal stem cells (MSCs) [17]. This pathway is associated with the activation of bone morphogenetic proteins (BMP) and through the ligands of the WNT (wingless-related integration site), the specificity of differentiation of progenitor cells in the osteogenic direction is determined. The MAPK/ERK signaling pathway also controls the signaling modulator of mitochondrial biogenesis, mTOR, which regulates cellular energy metabolism. The role of  $Mg^{2+}$  in complex with its transporter-1 (MagT1), one of the major  $Mg^{2+}$  transporters,

in the activation of this signaling pathway has been established. MagT1 significantly affects various cellular behaviours including cell proliferation, differentiation and immunomodulation specific to T cells [9].

Magnesium was also found to stimulate proliferation and osteogenic differentiation of bone marrow MSCs through the Notch1 (Neurogenic locus notch homolog protein 1) signaling pathway by increasing nuclear translocation of the Notch1 intracellular domain (NICD) [18]. At all  $Mg^{2+}$  concentrations (0.8, 1.2, and 1.8 mM), alkaline phosphatase activity, matrix mineralization, and expression of osteogenic genes and proteins (Runx2, Osterix, and Osteocalcin) were increased. In the medium in which MSC were cultured, the level of fibroblast growth factor (FGF23) expressed by osteoblasts and osteocytes, but not by MSC, increased.

When osteoblasts and osteoclasts were co-cultured, the effect of super-high concentrations of magnesium extract (3.5 to 26.67 mM) was evaluated. Based on the results of intracellular alkaline phosphatase activity, protein and gene expression of macrophage colony-stimulating factor (M-CSF), receptor activator of nuclear factor kappa-B ligand (RANKL) and receptor, osteoclast-associated receptor (OSCAR), tartrate-resistant acid phosphatase (TRAP) proved proliferation and differentiation of osteoblasts with inhibition of osteoclastogenesis [19].

Magnesium is involved in the regulation of bone mineralization. However, conflicting data are available.

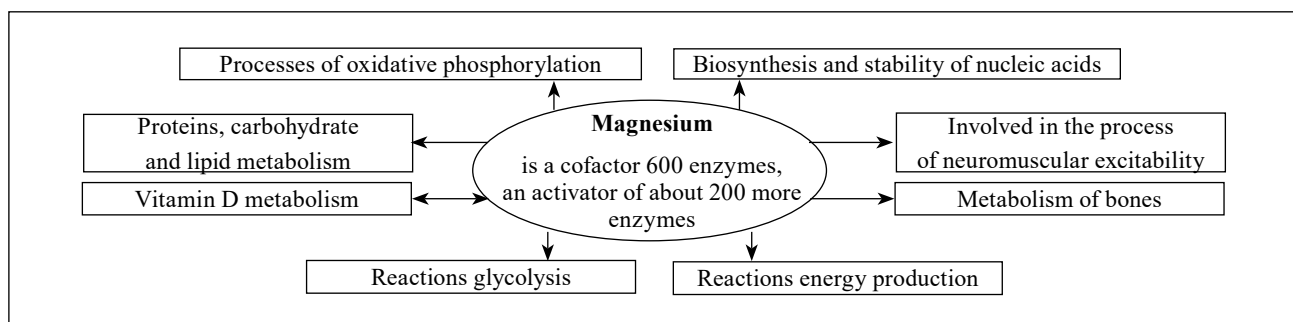


Fig. 1. The role of magnesium in metabolic and regulatory processes

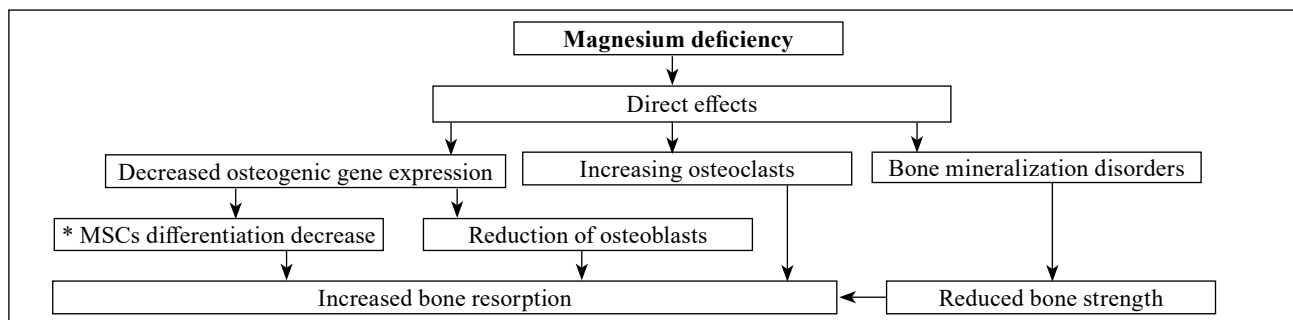


Fig. 2. The direct effect of magnesium deficiency on bone (\*MSCs — mesenchymal stem cells)

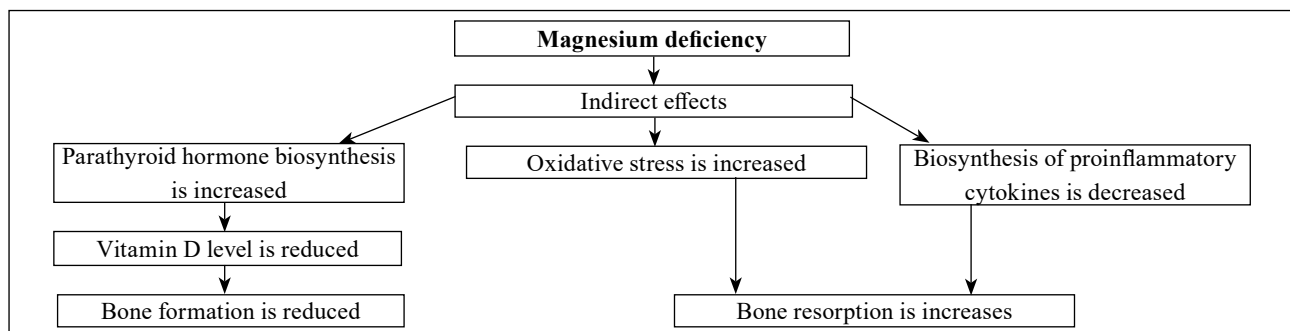


Fig. 3. Mediated effects of magnesium deficiency on bone

One study shows that high  $Mg^{2+}$  inhibits the inclusion of extracellular matrix vesicles, and suppresses mitochondrial  $Ca^{2+}$  accumulation, level and expression of type 1 collagen, along which mineral crystals grow [20]. High  $Mg^{2+}$  concentrations have also been found to impair the degree of bone mineralization by inhibiting collagen and calcium phosphate biosynthesis [21]. At the same time, magnesium deficiency is manifested by impaired crystal formation in bone, resulting in mineralization defects (fig. 2). Studies show that both too low and too high magnesium levels can differentially control mineralization, but the mechanisms of this process need further investigation.

The indirect effect of magnesium deficiency on bone is associated with increased secretion and activity of parathyroid hormone (PTH) secretion and vitamin D impairment, which contributes to inflammation, oxidative stress and subsequent loss of bone mass [22]. High levels of  $Mg^{2+}$  similarly to calcium, suppress PTH secretion through activation of calcium-sensitive receptor (CaSR) present on parathyroid gland principal cells [23].  $Mg^{2+}$  deficiency increases oxidative stress and sluggish inflammation (fig. 3).

In turn,  $Mg^{2+}$  is an important cofactor for vitamin D synthesis and activation, vitamin D binding to the transfer protein and vitamin D receptor expression [11, 13].

Since it was found that under conditions of magnesium deficiency the proliferation and differentiation of osteoblasts decreases, the number and activity of osteoclasts increases, this may be due not only to the direct action of  $Mg^{2+}$ , but also indirectly, through increased secretion of PTH, proinflammatory cytokines and decrease vitamin D [3, 24, 25].

#### *Magnesium deficiency, osteopenia, and osteoporosis*

Osteoporosis is a progressive systemic skeletal disease characterized by low bone mass, impaired bone microstructure and decreased bone mineral density (BMD) and bone strength, which increases the risk of osteoporotic fractures. Of particular interest is the role of  $Mg^{2+}$  in the development of osteoporosis, given its role in me-

tabolic and regulatory processes. The combined direct and indirect effects of magnesium deficiency on bone lead to osteopenia and osteoporosis (fig. 2, 3).

A meta-analysis showed that postmenopausal women with osteoporosis, but not osteopenia, have lower serum magnesium concentrations than healthy women [26]. It was found that serum  $Mg^{2+}$  levels in postmenopausal women were positively correlated with estradiol levels, BMD and markers of bone metabolism TRAP-5b and negatively correlated with bone-specific alkaline phosphatase (BSAP) [27]. It was significantly found that baseline BMD of the proximal femur and whole body increased by 3 and 2 %, respectively, in women who consumed > 422.5 mg/day magnesium [28]. There was no correlation between BMD of vertebral bodies and magnesium dose in the lumbar spine [28–30]. In a two-year study of magnesium-deficient women consuming 265 mg/day, a statistically significant increase in the level of a specific marker of bone resorption, type I collagen C-telopeptide (CTX-1), was recorded [31].

In summary, controlling and maintaining  $Mg^{2+}$  homeostasis is an important link for bone health, and magnesium deficiency leads to impaired bone quality in various ways.

#### *Magnesium deficiency and fracture risk*

The incidence of low-energy fractures increases significantly with age and continues to increase due to aging populations worldwide. Given the importance of magnesium to bone tissue, research is being conducted on its role in fracture risk. Based on a systematic review evaluating 119,755 individuals, low serum  $Mg^{2+}$  concentrations were found to increase the risk of fracture (RR = 1.58) [24]. In another study, low serum magnesium levels in men, after adjustment for the age-adjusted hazard ratio, were independently associated with an increased risk of total fractures (HR = 2.10). Statistical significance was maintained for total fractures (HR = 1.80) and hip fractures (HR = 2.13) after adjusting for other parameters such as vigor, socioeconomic status, renal function, and several trace elements [32].

A low incidence of fracture was observed in men with high magnesium intake (491 vs. 161 mg/day, OR = 0.47) and in women (454 vs. 144 mg/day, OR = 0.38) [33]. There is one study of 73,684 postmenopausal women that found that the risk of forearm or wrist fractures increased with magnesium intake > 422.5 mg/day, a level slightly above the recommended dietary allowance. However, the authors attributed this fact not to magnesium but to the increased physical activity of the patients studied and, consequently, to falls [28].

Meta-analyses have shown that high magnesium intake was not associated with an increased risk of proximal femur and other fractures [30], even when magnesium intake ranged from 250 to 1 800 mg/day [34].

Thus, these studies suggest that magnesium deficiency may be considered as a factor that increases the risk of fracture.

#### *Magnesium and bone regeneration*

Currently, biodegradable magnesium alloys have been tested in animal models and used as implants for temporary fixation of various types of fractures in humans [35, 36]. Magnesium can affect bone regeneration in a variety of ways [15]. This ion stimulates proliferation and differentiation of MSCs [37], increases the movement of osteoblasts to the area of traumatic bone injury by disrupting the representative protein of tight contacts 1 (Zona-occludens 1) [3]. The peculiarity of  $Mg^{2+}$  action is a stimulating effect on M2 macrophages, which promotes bone regeneration and inhibits the transformation of M2 macrophages into M1 at the tissue-specific stage of regeneration [38].

The stimulatory role of  $Mg^{2+}$  in bone regeneration is associated with activation of the canonical WNT-signaling pathway, which is accompanied by increased expression of  $\beta$ -catenin, which controls the expression of LEF1 (Lymphoid enhancer-binding factor-1) and Dkk1 (Dickkopf1 is inhibitor of WNT signaling pathway 1) genes [37]. Magnesium ions formed as a result of biodegradation of magnesium implants provide osteogenic microenvironment, control pH, regulate gene expression and protein biosynthesis by osteoblasts, such as runt-related transcription factor 2 (RUNX2), osteocalcin and insulin-like growth factor 1 (IGF1) and increase autophagic activity [5]. The use of titanium implants coated with magnesium revealed biocompatibility and adhesiveness of coated osteoblast progenitor cells, their early differentiation, increase of osteoblasts biosynthesis of osteopontin, osteonectin, alkaline phosphatase, RUNX2 and BMP-2, which promotes osteointegration [39].

One of the mechanisms that stimulate bone regeneration may be the penetration of  $Mg^{2+}$  into axons, re-

lease and elevation of calcitonin-related polypeptide  $\alpha$  (CGRP), which induces CALCRL- and RAMP1-dependent activation of cAMP-dependent element-binding protein 1 (CREB1) and osterix 7 (SP7) [40]. CGRP-secreting sensory nerves promote osteogenic differentiation of periosteum stem cells containing a large number of nerves, which in the early stage of fracture healing is the main tissue that regenerates and participates in the fracture healing process. CGRP deficiency, mediated by the loss of  $Mg^{2+}$  in bone, is associated with delayed healing or nonunion of the fracture.

Magnesium also promotes the secretion of vascular endothelial growth factor, which accelerates the process of bone regeneration. Magnesium supplements stimulate the formation of osteoclast precursor cells expressing platelet-derived growth factor-BB, which takes part in osteogenesis through the formation of H-type vessels [41]. Surrounded by osteoprogenitor cells, H-type vessels express factors, including the transcription factor Osterix, that stimulate the proliferation and differentiation of osteoprogenitors in the bone marrow, thereby enhancing bone formation [42]. The participation of  $Mg^{2+}$  in bone regeneration was confirmed using  $Mg^{2+}$  enriched complexes with cells that were implanted into critically sized rat skull defects. After 4 weeks, vascularization and healing of the defect were recorded [43].

Under experimental conditions, it was proved that animals with magnesium deficiency (90 % deficiency compared to controls) after titanium implant insertion into the tibial metaphysis have reduced cortical layer thickness and mechanical strength, which impaired osteointegration [44]. In addition, under conditions of magnesium deficiency, systemic changes in the animals' body were revealed: a decrease in the BMD of vertebral bodies, an increase in the level of parathyroid hormone in blood serum and deoxypyridinoline in urine, a bone tissue-specific marker of resorption.

Calcium is of great importance for bone regeneration. The level of  $Ca^{2+}$  and  $Mg^{2+}$  in 117 people with multiple fractures resulting from traffic accidents was studied and the severity of injury was assessed under the conditions of deficiency of these elements, as well as after supplementation in the diet at the stages of recovery [45]. It was found that  $Ca^{2+}$  and  $Mg^{2+}$  deficiency complicates regeneration, while supplementation of these elements promotes stimulation of fragment consolidation during recovery. In addition, magnesium supplementation significantly reduced serum levels of C-reactive protein and nitrogen oxide, markers of inflammation in human [46] which is important in the setting of fracture.

## Conclusions

Magnesium regulates important biological processes. The presented review has systematised the literature data on the negative effects of magnesium deficiency on bone health, in osteoporosis, osteoporotic fractures and bone regeneration, and shows its role in the osseointegration of magnesium-based implants. Adequate magnesium levels stimulate an increase in BMD and help to reduce the risk of osteoporosis. The data presented support the key role that  $Mg^{2+}$  plays in metabolism and bone health in a variety of conditions. Identification of patients with hypomagnesaemia offers great potential in the prevention of a range of clinical disorders, including osteoporosis. As hypomagnesaemia is a potentially modifiable factor, this opens the door for further research in this direction.

**Conflict of interest.** The authors declare no conflict of interest.

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## ВПЛИВ ДЕФЦИТУ МАГНІЮ НА ЗДОРОВ'Я КІСТОК

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