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Research Progress on Essential Trace Elements Associated with Osteoporosis

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Abstract:

Osteoporosis (OP) is a common skeletal disease affecting millions of people worldwide. The relationship between trace elements and OP has garnered widespread attention in recent years. This study conducts a literature review to comprehensively analyze the mechanisms of iron, copper, and magnesium in OP. The research encompasses multiple fields, including in vitro experiments, in vivo experiments, case-control studies, cross-sectional studies, and materials science, to reveal the impact of trace elements on the occurrence and development of osteoporosis.Iron accumulation promotes the development of OP by causing a reduction in osteoblast activity. Ferroptosis induces a decline in the function of osteoblasts, leading to reduced bone formation functionality; copper intake is positively correlated with bone density to a certain extent, and copper ions aid in the repair and regeneration of bone tissue. Copper-induced cell death may participate in the pathogenesis of OP by affecting the mitochondrial function and the immune response; magnesium ions promote bone formation, and the intake of magnesium is related to bone quality. Magnesium-containing materials show potential in the treatment of osteoporosis. Trace elements such as iron, copper, and magnesium are closely related to the occurrence and development of OP. Future research needs to further explore the specific mechanisms of these elements to develop new treatment strategies for OP.

Keywords: Osteoporosis, trace elements, iron, copper, magnesium.

1. Introduction

Osteoporosis (OP) is a metabolic bone disorder characterized by reduced bone mineral density and compromised bone microarchitecture, which results in bone fragility and a substantially elevated risk of fractures. The escalating trend of global population aging has led to an increasing prevalence of OP, making it a significant public health concern that impacts the quality of life and health of the elderly and imposes substantial medical, economic, and social burdens on society. It is projected that by 2025, the overall burden of OP will escalate by an additional 50%. Trace elements play an important role in bone health and disease. While extensive research and analysis have established the association between calcium, a trace element, and osteoporosis as common knowledge, the specific mechanisms by which iron, copper, and magnesium influence osteoporosis remain not fully understood. Research suggests that both deficiencies and excessive intakes of certain trace elements may be intimately linked to the etiology and progression of OP. This article systematically reviews the impact of essential trace elements—namely iron, magnesium, and copper—on OP, unraveling their specific mechanisms and roles within bone metabolism, and examining the correlation between trace element intake and OP risk. The aim is to offer scientific evidence and guidance for the prevention and management of osteoporosis.

2. Method

2.1 Research Selection

Electronic database searches were conducted in PubMed and CNKI, with a time frame set to the past five years to capture the most recent research findings. The predefined search terms encompassed „osteoporosis“, „osteopenia“, „bone loss“, „bone density“, „nutrition“, „essential trace elements in the human body“, „iron as a trace element“, „magnesium as a trace element“, „copper as a trace element“, and so on.

2.2 Literature Screening and Data Extraction

The retrieved literature was initially screened based on the following criteria:research content related to the impact of trace elements on osteoporosis or bone density, and the availability of complete research data and conclusions.

From the filtered literature, pertinent information was extracted, including research design (e.g., in vitro and in vivo experiments, case-control and cross-sectional studies), sample size, types and intake levels of trace elements, research outcomes, and conclusions.

2.3 Analysis, Discussion and Results

The research conclusions regarding the effects of various trace elements on osteoporosis, the specific mechanisms of each trace element in bone metabolism, and the correlation between trace element intake and osteoporosis risk will be analyzed. The findings will be synthesized into a systematic review report. The discussion section will integrate existing research findings to elucidate the impact mechanisms of different trace elements on osteoporosis and explore their potential application in the prevention and treatment of the disease.

3. Result

In this study, a total of 28 relevant articles that met the criteria were collected, including 15 related to trace element iron, 6 related to trace element copper, and 7 related to trace element magnesium.

3.1 Iron and Osteoporosis

3.1.1 Iron accumulation and osteoporosis

Iron accumulation is characterized by serum ferritin levels that exceed the norm but are below 1,000 μg/L. In vitro studies have demonstrated that iron accumulation downregulates the expression of glutathione peroxidase 4 (GPX4), heme oxygenase 1 (HO-1), and solute carrier family 7 member 11 (SLC7A11), while upregulating the expression of transferrin heavy chain, resulting in diminished osteoblast activity and function, which in turn promotes the progression of osteoporosis (OP). The application of ferroptosis inhibitors, such as deferoxamine (DFO) and Fer-1, has been shown to reverse these protein expression alterations and ameliorate cell damage and bone loss induced by iron accumulation [1]. One experimental model, established through ovariectomy, revealed that intervention with rapamycin led to significant enhancements in bone density, bone volume fraction, trabecular number, and thickness in mice, along with increased expression of osteogenic markers in both serum and bone tissue. These findings indicate that rapamycin exerts a positive ameliorative effect on iron-accumulation-induced osteoporosis [2]. Furthermore, a negative correlation between iron accumulation and bone density at various skeletal sites has been observed in clinical studies, with elevated serum ferritin levels identified as an independent risk factor for reduced bone density in patients with type 2 diabetes mellitus (T2DM). This suggests that iron accumulation may heighten the risk of osteoporosis in T2DM patients [3]. Additional research indicates that DFO can improve bone metabolism and suppress osteoclast activity by clearing iron deposits from tissues, thereby enhancing bone formation capacity in rats with osteoporosis attributable to iron accumulation [4]. It has also been discovered that hepcidin inhibits osteoclast differentiation and iron accumulation, while high expression levels of SPI1 are associated with osteoporosis and may facilitate osteoclast differentiation by downregulating the expression of divalent metal transporter 1 (DMT1) [5].

3.1.2 Ferroptosis and osteoporosis

Osteoblasts are instrumental in the initial stages of bone formation by secreting bone matrix proteins such as Bone Sialoprotein (BSP) and regulate bone growth and remodeling through the expression of specific growth factors, including Bone Morphogenetic Proteins (BMPs). Preserving the normal function of osteoblasts is, therefore, pivotal for the prevention and treatment of osteoporosis (OP). Emerging research indicates that ferroptosis may cause a decline in osteoblast activity, which could in turn affect bone formation processes, impacting the management of OP.Investigations have revealed that serum levels of Advanced Glycation End-products (AGEs) and fasting blood glucose (FBG) are elevated in OP patients and are inversely related to bone density. AGEs have been shown to significantly inhibit osteoblast proliferation, differentiation, and mineralization while promoting apoptosis and ferroptosis. This suggests that AGEs may impair osteoblast function and contribute to the progression of OP by inducing ferroptosis. The application of the ferroptosis inhibitor Deferoxamine (DFO) has demonstrated the ability to reverse these detrimental effects [6].

Moreover, studies have discovered that a high-glucose environment can activate ATF3, leading to a reduction in Glutathione Peroxidase 4 (GPX4) expression and an increase in the accumulation of Reactive Oxygen Species (ROS) and lipid peroxides, which can ultimately trigger ferroptosis in osteoblasts and diminish bone formation capabilities. Additionally, conditions characterized by elevated glucose and lipid levels raise intracellular iron concentrations, and heightened N6-methyladenosine (m6A) methylation upregulates the expression of the ASK1 gene, thereby activating the p38 Mitogen-Activated Protein Kinase (MAPK) pathway and precipitating osteoblast ferroptosis, which may foster the development of OP [7].Excessive iron accumulation has been linked to the induction of ferroptosis in osteoblasts, impairing their functionality and potentially instigating OP. Both in vitro and in vivo experiments indicate that iron overload augments ROS and lipid peroxidation production, activates

the expression of ferroptosis-associated proteins, induces mitochondrial structural alterations, and attenuates osteoblast activity, thereby impeding osteogenic differentiation and mineralization processes [8]. Research has pointed to iron's disruption of osteogenic differentiation through the downregulation of the Wnt signaling pathway. It has been hypothesized that Wnt agonists, ferroptosis inhibitors, and the antioxidant Melatonin may counteract ROS and Lipid Peroxidation (LPO) induced by iron, thereby restoring Wnt signaling and safeguarding osteoblast function. Iron overload has been shown to initiate ferroptosis in bone marrow stromal cells, disrupting osteoblast differentiation, and the ferroptosis inhibitor Ferrostatin 1 has been observed to ameliorate this process without modifying the iron overload state [9].Furthermore, ferroptosis has been identified to induce the detachment from the iron-responsive element-like (IRE-like) sequence of the NOX4 gene, thereby activating NOX4 expression and fostering the buildup of lipid peroxides. This leads to mitochondrial morphological and functional irregularities in osteoblasts [10]. Significantly, the use of ferroptosis inhibitors, such as Ferrostatin-1 (Ferr-1), in conjunction with iron chelators like Deferoxamine (DFO), has effectively curtailed osteoporotic bone loss in an iron-overload mouse model. This finding suggests a promising therapeutic strategy for osteoporosis that involves intervention in the ferroptosis pathway [11].

Osteoclasts, derived from the monocyte-macrophage lineage or Bone Marrow Stromal Cells (BMSCs), are large multinucleated cells induced by the Receptor Activator of Nuclear Factor-kappaB Ligand (RANKL) that perform the function of bone resorption. Recent studies have discovered that Saikosaponin A (Ssa) effectively inhibits the generation of osteoclasts in vitro and significantly reduces bone loss in vivo by targeting the Nrf2/SLC7A11/GPX4 signaling pathway. This mechanism primarily induces ferroptosis in osteoclasts through the promotion of lipid peroxidation [12].

Further research indicates that the impairment of mitochondrial transfer leads to a higher propensity for bone marrow cells to differentiate into osteoclasts, accelerating bone resorption through ferroptosis and exacerbating the progression of osteoporosis. Through RNA sequencing and metabolomic analysis, researchers have unveiled the impact of mitochondrial transfer on the glutathione metabolism of osteoclast precursors, offering a novel perspective for mitigating the advancement of osteoporosis [13].

Additionally, the knockout experiments of the MZF1 gene in RAW264.7 cells have revealed the connection between ferroptosis and the differentiation process of osteoclasts. Under the induction of RANKL, cells with the MZF1 gene knocked out exhibit changes in markers associated with ferroptosis, such as malondialdehyde, glutathione, and intracellular iron ion levels, further confirming the significance of ferroptosis in the differentiation and function of osteoclasts [14].

An analysis of serum samples from 100 diabetic patients has shown that the expression of ELAVL1 is upregulated in diabetic osteoporosis (DOP) patients and is negatively correlated with the expression of ferroptosis-related genes GPX4 and Nrf2, and positively correlated with the expression of ACSL4. Experiments have demonstrated that a high-glucose environment induces ferroptosis in osteoclasts, and the knockdown of ELAVL1 can inhibit this process, highlighting the role of ELAVL1 upregulation induced by high glucose in the pathogenesis of DOP [15].

3.2 Copper and Osteoporosis

A study utilizing data from the National Health and Nutrition Examination Survey (NHANES) assessed the association between copper intake and osteoporosis (OP) risk in 8,224 adults. The results indicated that individuals in the highest quartile of copper intake (1.51 mg/day) had greater total femoral and spinal bone mineral density compared to those in the lowest intake group, suggesting a positive correlation between total copper intake and increased bone density, as well as a reduced risk of OP [16]. Experiments have observed that when human dental pulp stem cells (hMSCs) are cultured in the presence of copper-doped bioactive glass nanoparticles (Cu-BGn), extracellular matrix mineralization is enhanced. Additionally, the expression levels of osteogenic-related genes, including COL1A, DMP-1, DSPP, and OCN, were significantly elevated, indicating that copper ions contribute to the repair and regeneration of bone tissue [17].

However, a case-control study involving 31 OP patients and 32 healthy controls revealed that plasma copper (Cu) levels in OP patients were significantly higher than in the healthy control group. Copper was positively correlated with the expression levels of detoxification enzyme genes CAT and MT1E, particularly in the healthy control group. This suggests that copper may play a key role in regulating the expression of these genes, thereby affecting bone density and the development of OP [18].

Furthermore, copper ions have also shown potential in the field of material science. Experiments have precisely loaded Cu2+ onto MgO nanoparticles and found that MgO-Cu nanocomposites, by modulating the loading amount of Cu2+, exhibit dependent regulatory effects on osteoblasts, osteoclasts, and bacterial responses. These materials can promote osteoblast differentiation, inhibit osteoclast formation, and effectively kill bacteria, indicating their potential as multifunctional filler materials for osteoporotic bone tissue engineering scaffolds [19]. In addition, cop-

per-induced cell death, a newly discovered form of cell death, occurs when excessive intracellular copper ions induce protein aggregation in cellular respiration, inhibiting respiration and leading to a reduction in iron-sulfur cluster proteins, ultimately causing cell death [20].

A study analyzing gene expression patterns in the GSE56815 dataset using the WGCNA algorithm and machine learning models found that genes related to copper-induced cell death were dysregulated in OP patients and significantly associated with immune cell infiltration. This suggests that copper-induced cell death may be involved in the pathogenesis of OP by affecting mitochondrial function and immune responses [21].

3.3 Magnesium and Osteoporosis

Magnesium ions rank as the fourth most abundant element in the human body and act as an essential cofactor for hundreds of enzymatic reactions. At appropriate concentrations, such as 10 mmol/L, magnesium ions have been demonstrated to promote bone formation and angiogenesis. The concentration of magnesium correlates with the presence or absence of osteoporosis [22]. A comparative study of 123 postmenopausal women with osteoporosis and 97 healthy postmenopausal women showed that serum magnesium levels were significantly lower in the group with osteoporosis [23].

An observational study employing quantitative ultrasound (QUS) as a diagnostic tool examined 31 premenopausal women with celiac disease on a gluten-free diet and 39 matched healthy controls. The QUS measurements indicated significantly lower bone mass in celiac patients. Dietary analysis revealed a markedly lower magnesium intake in this group compared to the controls, suggesting that magnesium intake may be linked to bone mass and could influence the development of osteoporosis, either directly or indirectly [24].

Research indicates that magnesium can upregulate the expression of HIF-1α, leading to increased production of TGF-β (Transforming Growth Factor-β). This helps to suppress inflammatory responses and foster bone repair, with Mg2+ playing a pivotal role in the bone repair process [25]. Another study found that Mg2+ enhances the secretion of alkaline phosphatase (ALP), a key enzyme in the osteogenesis process, thus promoting osteogenic differentiation. Furthermore, Mg2+ significantly increased the expression of osteogenic-related genes as determined by qRT-PCR and elevated the protein levels of osteocalcin (OCN) as shown by immunofluorescence staining. These findings suggest that Mg2+ concentration affects both osteoblasts and osteoclasts and has implications for the progression and healing of osteoporosis [26].

Beyond its biological roles, magnesium also shows promise in the material sciences. In vitro and in vivo experiments have shown that a novel injectable magnesium-loaded hydrogel (Mg@PEG-PLGA) has excellent cytocompatibility, reactive oxygen species (ROS) scavenging capacity, and immunomodulatory effects. It inhibits osteoclastogenesis while promoting osteoblastogenesis, which is beneficial for the treatment of osteoporotic fractures [27]. Additional research has created osteogenic composite microspheres through an emulsification method, incorporating magnesium oxide (MgO) and zinc oxide (ZnO) as osteoactive agents. These microspheres have a sequential release profile of Mg2+ and Zn2+, sustaining a high concentration of bioactive ions in a physiological environment. This enhances the biomineralization process at the cellular level and upregulates the expression of osteogenic-related genes and proteins, offering a potential treatment for osteoporosis [28].

4. Limitation

This study‘s scope was limited to literature from the CNKI and PubMed databases within the last five years, with a modest sample size. A more comprehensive literature review and analysis are warranted, incorporating a diverse array of online resources and literature. Osteoporosis encompasses various types, including postmenopausal and age-related osteoporosis, each with its own distinct pathophysiological mechanisms. This study did not provide a detailed differentiation among these types.

5. Conclusion

Trace elements play a pivotal role in maintaining skeletal health and preventing osteoporosis (OP). The balance of iron, copper, and magnesium is crucial for the activity and function of osteoblasts. Excessive accumulation of iron can be detrimental to bone tissue, necessitating controlled intake of this element. Ferroptosis, which affects osteoblast activity, contributes to decreased bone density by inducing cell apoptosis and ferroptosis, thereby impairing osteoblast function. It is essential to prevent or reverse the effects of ferroptosis in patients with osteoporosis to avoid its detrimental impact on bone health. Copper intake is positively correlated with increased bone density, with copper ions showing a beneficial role in promoting bone tissue repair and regeneration. Magnesium ions, as key cofactors in bone formation and angiogenesis, significantly enhance bone formation when supplemented at appropriate concentrations. Comprehensive management of trace element balance is vital for the prevention and treatment of OP. In clinical practice, individual trace element status should be considered, and reasonable regulation should be achieved through nutritional supplementation, lifestyle

adjustments, and pharmacological interventions.

Furthermore, future research should delve deeper into the specific roles of trace elements in the pathogenesis of OP and explore how to develop new treatment strategies by modulating trace element balance, offering more comprehensive and personalized treatment plans for patients with OP.

In addition, patients should be encouraged to maintain a balanced diet to ensure adequate intake of trace elements such as iron, copper, and magnesium. Special attention should be given to high-risk groups for OP, such as postmenopausal women and the elderly. It is recommended to regularly monitor serum levels of ferritin, copper, and magnesium to assess the patient‘s trace element status and adjust nutritional supplementation strategies accordingly. Considering the positive effects of copper and magnesium on bone density, appropriate supplementation of these trace elements under medical supervision is advised, especially in patients with low bone density or OP. Patients should also be encouraged to engage in regular exercise, particularly weight-bearing and resistance training that can improve bone density and strength. Unhealthy lifestyle habits should be avoided, including reducing the intake of high-sugar and high-fat foods to lower the risk of ferroptosis and promote overall health. Strengthening patient education regarding risk factors for OP, prevention measures, and treatment options will enhance their awareness and management of the disease.

References

[1] Zhao Y, Du Y, Gao Y, Xu Z, Zhao D, Yang M. ATF3 Regulates Osteogenic Function by Mediating Osteoblast Ferroptosis in Type 2 Diabetic Osteoporosis. Dis Markers. 2022 Oct 26;2022:9872243.

[2] Wu Jiadong, Xu Youjia, Ji Hongjian, et al. Effect of rapamycin on osteogenesis in mice with highly turnover osteoporosis with iron accumulation [J]. Chinese Journal of Osteoporosis and Bone Mineral Salt Diseases, 2023,16 (05): 468-475.

[3] Li Chong Li, Fang Lingna, Hao Yanming, et al. Correlation study of the effect of iron accumulation on bone mineral density in type 2 diabetes patients [J]. Chinese Journal of Osteoporosis, 2023,29 (03): 371-377.

[4] Tian Ai, Li Li, Xiao Tianjiao, et al. Desferriamine mesylate promotes the repair of jaw defects in castrated osteoporotic rats [J]. China Tissue Engineering Research, 2024,28 (20): 3143-3149.

[5] Liu LL, Liu ZR, Xiao YS, Xiao JH, Huang WM, Liu WY, Zhao K, Ye YJ. SPI1 exacerbates iron accumulation and promotes osteoclast formation through inhibiting the expression of Hepcidin. Mol Cell Endocrinol. 2024 Jan 15;580:112103.

[6] Ge W, Jie J, Yao J, Li W, Cheng Y, Lu W. Advanced glycation end products promote osteoporosis by inducing ferroptosis in osteoblasts. Mol Med Rep. 2022 Apr;25(4):140.

[7] Zhao Y, Du Y, Gao Y, Xu Z, Zhao D, Yang M. ATF3 Regulates Osteogenic Function by Mediating Osteoblast Ferroptosis in Type 2 Diabetic Osteoporosis. Dis Markers. 2022 Oct 26;2022:9872243.

[8] Lin Y, Shen X, Ke Y, Lan C, Chen X, Liang B, Zhang Y, Yan S. Activation of osteoblast ferroptosis via the METTL3/ASK1-p38 signaling pathway in high glucose and high fat (HGHF)-induced diabetic bone loss. FASEB J. 2022 Mar;36(3):e22147.

[9] Jiang Z, Wang H, Qi G, Jiang C, Chen K, Yan Z. Iron overload-induced ferroptosis of osteoblasts inhibits osteogenesis and promotes osteoporosis: An in vitro and in vivo study. IUBMB Life. 2022 Nov;74(11):1052-1069.

[10] Luo C, Xu W, Tang X, Liu X, Cheng Y, Wu Y, Xie Z, Wu X, He X, Wang Q, et al.Canonical Wnt signaling works downstream of iron overload to prevent ferroptosis from damaging osteoblast differentiation. Free Radical Biology and Medicine 2022 188 337–350.

[11] Zhang H, Wang A, Li G, Zhai Q, Huang Z, Wang X, Cao Z, Liu L, Liu G, Chen B, Zhu K, Xu Y, Xu Y. Osteoporotic bone loss from excess iron accumulation is driven by NOX4-triggered ferroptosis in osteoblasts. Free Radic Biol Med. 2023 Mar;198:123-136.

[12] Li TQ, Liu Y, Feng C, Bai J, Wang ZR, Zhang XY, Wang XX. Saikosaponin A attenuates osteoclastogenesis and bone loss by inducing ferroptosis. Front Mol Biosci. 2024 Jul 24;11:1390257.

[13] Chen Y, Zhao W, Hu A, Lin S, Chen P, Yang B, Fan Z, Qi J, Zhang W, Gao H, Yu X, Chen H, Chen L, Wang H. Type 2 diabetic mellitus related osteoporosis: focusing on ferroptosis. J Transl Med. 2024 Apr 30;22(1):409.

[14] Qu Z, Zhang B, Kong L, Zhang Y, Zhao Y, Gong Y, Gao X, Feng M, Zhang J, Yan L. Myeloid zinc finger 1 knockdown promotes osteoclastogenesis and bone loss in part by regulating RANKL-induced ferroptosis of osteoclasts through Nrf2/GPX4 signaling pathway. J Leukoc Biol. 2024 Apr 29;115(5):946-957.

[15] Huang Bi, Jiang Jie, Shao Huge. Exploring the regulatory effect of ELAVL1 on osteoclast iron death based on the diabetic osteoporosis cell model [J]. Chinese Journal of Modern Medicine, 2024,34 (10): 38-46.

[16] Fan Y, Ni S, Zhang H. Associations of Copper Intake with Bone Mineral Density and Osteoporosis in Adults: Data from the National Health and Nutrition Examination Survey. Biol Trace Elem Res. 2022 May;200(5):2062-2068.

[17] El-Fiqi A, Mandakhbayar N, Jo SB, Knowles JC, Lee JH, Kim HW. Nanotherapeutics for regeneration of degenerated tissue infected by bacteria through the multiple delivery of bioactive ions and growth factor with antibacterial/angiogenic and osteogenic/odontogenic capacity. Bioact Mater. 2020 Aug 11;6(1):123-136.

[18] Visconti VV, Gasperini B, Greggi C, Battistini B,

Messina A, Renzi M, Bakhtafrouz K, Iundusi R, Botta A, Palombi L, Tarantino U. Plasma heavy metal levels correlate with deregulated gene expression of detoxifying enzymes in osteoporotic patients. Sci Rep. 2023 Jun 30;13(1):10641.

[19] Wu H, Yang S, Xiao J, Ouyang Z, Yang M, Zhang M, Zhao D, Huang Q. Facile synthesis of multi-functional nano-composites by precise loading of Cu^{2+} onto MgO nano-particles for enhanced osteoblast differentiation, inhibited osteoclast formation and effective bacterial killing. Mater Sci Eng C Mater Biol Appl. 2021 Nov;130:112442.

[20] Li Y, Ma J, Wang R, Luo Y, Zheng S, Wang X. Zinc transporter 1 functions in copper uptake and cuproptosis. Cell Metab. 2024 Jul 31:S1550-4131(24)00279-1.

[21] Chen T, Gao Z, Wang Y, Huang J, Liu S, Lin Y, Fu S, Wan L, Li Y, Huang H, Zhang Z. Identification and immunological role of cuproptosis in osteoporosis. Heliyon. 2024 Feb 20;10(5):e26759.

[22] Tavasoli A, Afsharkhas L, Parvini B. Evaluating the serum levels of zinc, copper, magnesium, and 25-hydroxy vitamin D in children with idiopathic drug-resistant epilepsy; a cross-sectional study. BMC Pediatr. 2024 Aug 10;24(1):518.

[23] Wei Wei, Li Jian, Huang Linhai, et al. Correlation between serum magnesium concentration and bone turnover index and bone density in postmenopausal osteoporosis [J]. Chinese Journal of Osteoporosis, 2020,26 (1): 54-58.

[24] Schraders K, Coad J, Kruger M. Bone Health in Premenopausal Women with Coeliac Disease: An Observational Study. Nutrients. 2024 Jul 9;16(14):2178.

[25] Dai Y, Wu J, Wang J, Wang H, Guo B, Jiang T, Cai Z, Han J, Zhang H, Xu B, Zhou X, Wang C. Magnesium Ions Promote the Induction of Immunosuppressive Bone Microenvironment and Bone Repair through HIF-1α-TGF-β Axis in Dendritic Cells. Small. 2024 Aug;20(33):e2311344.

[26] Zhang Z, Gong N, Wang Y, Xu L, Zhao S, Liu Y, Tan F. Impact of Strontium, Magnesium, and Zinc Ions on the In Vitro Osteogenesis of Maxillary Sinus Membrane Stem Cells. Biol Trace Elem Res. 2024 Aug 16.

[27] Zhou H, He Z, Cao Y, Chu L, Liang B, Yu K, Deng Z. An injectable magnesium-loaded hydrogel releases hydrogen to promote osteoporotic bone repair via ROS scavenging and immunomodulation. Theranostics. 2024 Jun 17;14(9):3739-3759.

[28] Su BY, Xu Y, Yang Q, Wu JY, Zhao B, Guo ZH, Xu C, Ren H, Xu JZ, Li ZM. Biodegradable magnesium and zinc composite microspheres with synergistic osteogenic effect for enhanced bone regeneration. Biomater Adv. 2024 Jul 30;164:213977.