Biomaterials Translational

Research progress on the role and mechanism of magnesium-containing materials in bone repair

Yuanchao Zhu[1#], Junyu Su[1#], Tiantian Qi[2,3#], Geng Zhang[2,3], Peng Liu[3], Haotian Qin[2,3], Qi Yang[4], Sen Yao[5], Yien Zheng[6], Jian Weng[2,3*], Hui Zeng[7*], and Fei Yu[2,3*]

ABSTRACT

Bones can fulfill functions in movement, attachment, and protection of internal organs. Bone diseases caused by ageing, trauma, infection, and other reasons may seriously affect the daily life of patients. Magnesium ions are closely associated with the maintenance of bone health. Integrating magnesium ions into delivery systems and hydrogels can improve their application, thus directly acting on the osteoblast cell lineage and influencing the proliferation and differentiation of relevant cells. The slow release of magnesium ions allows for their effects on the target site for a long time, reducing the clearance of magnesium ions in the body, which significantly contributes to bone repair. Magnesium-based bioalloy scaffolds have received widespread attention for their favourable biocompatibility, degradability, and bone-forming properties and play an important role in bone regeneration and repair. This article presents a review on the role and mechanism of magnesium-containing materials in bone repair and regeneration. By discussing the current challenges and future directions for magnesium-containing biomaterials, new insights are provided into the development of these materials in the field of orthopaedics. In conclusion, magnesium-containing biomaterials have great application value in orthopaedics.

Keywords:
Bone repair; Delivery system; Magnesium ions; Magnesium-based bioalloy scaffolds; Magnesium-loaded hydrogels

#Authors contributed equally.

***Corresponding authors:**
Jian Weng,
jweng@pku.edu.cn;
Hui Zeng,
zenghui_36@163.com;
Fei Yu,
yufei89@pku.edu.cn

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1. Introduction

The repair of critical bone defects represents a significant challenge for surgeons. If the length of the bone defect is greater than 2 cm or the defect area is more than half the circumference of the bone, it is impossible to achieve spontaneous healing. These bone defects are categorised into critical bone defects and osteoporotic fractures are a common cause of critical bone defects.[1,2] With increasing age, the body undergoes cellular senescence, slow metabolism, the development of chronic inflammation, diminished hormone levels, and degradation of vascular function (**Figure 1**), which senesces the skeleton and leads to osteoporosis. Osteoporosis is a group of systemic bone diseases, mainly characterised by a decrease in bone density and bone mass, leading to increased bone fragility.[3,4] According to statistics, about 18.3% of the global population suffers from osteoporosis.[5] osteoporosis often presents with clinical symptoms such as decreased height, painful aches and pains, and fragility fractures (**Figure 2**). When osteoporosis occurs, bone regeneration and healing are further slowed down. With the advancement in technology, transportation, and the ageing population, the prevalence of fractures caused by trauma and bone tumours is increasing every year, which often leads to bone defects in case of inappropriate treatment.[6,7] Bones have a good regenerative repair ability, and most bone defects can heal spontaneously without surgery. In many cases, critical bone defects necessitate surgical intervention. Although autologous bone grafting is the clinical gold standard for treating bone defects, its use in clinical practice is

limited by insufficient sources, deformed healing of the donor site, secondary trauma, and secondary infection.[8,9] When osteoporosis occur, the quality of life of patients is significantly impaired, which would increase the health care burden on the patient's family and the whole country. Hence, there is an urgent demand for new protocols for the treatment of bone defects.

In recent years, it has been demonstrated that elemental magnesium and magnesium-based biomaterials play an important role in the treatment of bone defects, providing new ideas for the repair of bone defects. As one of the most important elements in the organism, magnesium, with a relative atomic mass of 24.31 and an atomic symbol of Mg^{2+}, ranks 4th in the human body with a content of about 25 g. Further, 60–65% of magnesium ions are distributed in bones and teeth, and they exert significant effects on regulating energy metabolism and maintaining cellular homeostasis and life health.[10,11] The concentration of magnesium ions in the blood is below 1%, which indicates that some patients with normal serum magnesium ion concentrations (0.75–1.25 mM) may exhibit magnesium deficiency. Magnesium ions or magnesium-containing biomaterials such as magnesium ions, magnesium wiresmagnesium alloy wires, magnesium mesh, magnesium cardiovascular scaffolds have also been used in many studies.[12-15] Magnesium ions in the body can promote the proliferation and differentiation of osteoblasts and bone marrow mesenchymal stem cells (BMSCs), as well as the formation of new blood vessels, which contributes to maintaining bone health and preventing osteoporosis.[16,17] Therefore, magnesium and magnesium-based biomaterials are of great significance for bone repair and have received much attention.[18] The terms "magnesium", "magnesium ion", "Mg", "bone", "osteoporosis",

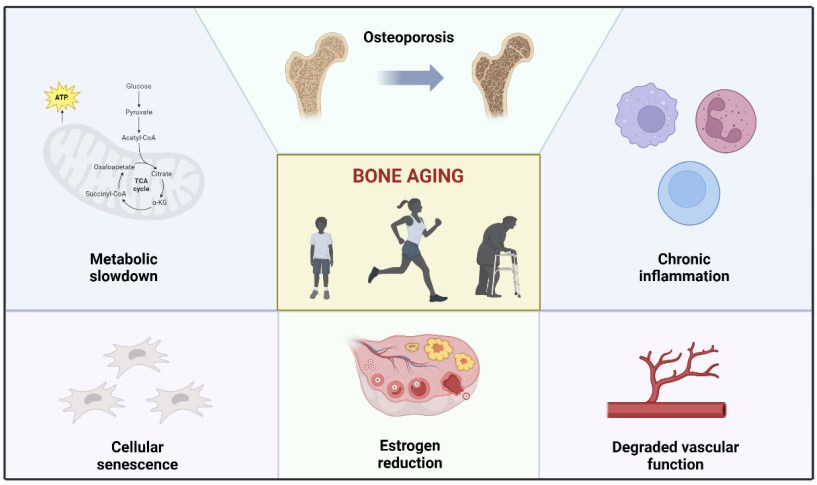

Figure 1. Common causes of bone ageing. Created with BioRender.com.

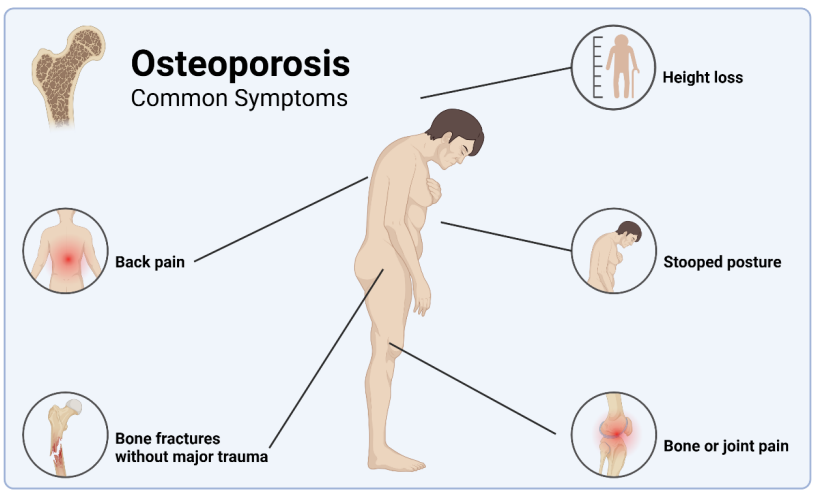

Figure 2. Common clinical manifestations of osteoporosis. Created with BioRender.com.

[1]School of Basic Medical Sciences, Shenzhen University Medical School, Shenzhen, Guangdong Province, China; [2]Department of Bone & Joint Surgery, Peking University Shenzhen Hospital, Shenzhen, Guangdong Province, China; [3]National & Local Joint Engineering Research Center of Orthopaedic Biomaterials, Peking University Shenzhen Hospital, Shenzhen, Guangdong Province, China; [4]Department of Ultrasonography, Peking University Shenzhen hospital, Shenzhen, Guangdong Province, China; [5]Department of Orthopedics, Shenzhen Yantian District People's Hospital, Shenzhen, Guangdong Province, China; [6]Institute for Macromolecular Chemistry, University of Freiburg, Freiburg, Germany; [7]Department of Orthopedics, Shenzhen Second People's Hospital, Shenzhen, Guangdong Province, China

"bone fracture", "bone defect", "drug delivery system", "nanomaterials", "hydrogel", "bioalloy scaffold", "implant", and "screw" were searched in terms of the number of citations, journals, impact factor, and related articles of our group. The related articles of our group were then screened to identify potential journals for consideration. This article reviews the role and mechanism of elemental magnesium and magnesium-based biomaterials in bone repair.

2. Role and mechanisms of magnesium ions in bone health

2.1. Modulation of magnesium ions for bone health

Magnesium ions are essential mineral elements in the human body, with the content being second only to potassium ions at the intracellular level. Magnesium ions are involved in more than 300 known enzymatic reactions and play an important role in living organisms.[19] Magnesium ions are also the second most abundant cation in the cell, usually in concentrations of 10–30 mmol. The U.S. Food and Nutrition Board has established the recommended daily intake of magnesium ions for men and women at 420 mg and 320 mg, respectively. Following ingestion, magnesium ions are absorbed and excreted primarily in the intestines and kidneys.[20,21] An intake of magnesium ions in excess of the body's excretion capacity can result in hypermagnesaemia, which may present clinically as nausea, vomiting, cutaneous vasodilatation, headache, hyperreflexia and lethargy.[22] The relationship between daily magnesium intake and maintenance of bone health has been confirmed in a previous study.[23] These effects of magnesium can be explained that magnesium ions are required for many enzymatic reactions concerning the metabolism and processing of vitamin D in the body. A deficiency in magnesium ions can lead to a decrease in the concentration of $1,25(OH)_2$-vitamin D.[24] Besides, a decrease in the concentration of magnesium in the blood can result in a decrease in the secretion of parathyroid hormone, which leads to a decrease in the concentration of calcium in the blood.[25,26] Bone healing is a dynamic and complex process that requires the interplay of osteoclasts and osteoblasts. Magnesium ions in appropriate concentrations (50–200 ppm) can effectively promote the proliferation and differentiation of osteoblasts, significantly accelerating new bone formation.[27] Studies have shown that Wnt signalling pathway,[28] Notch signalling pathway,[29] and phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) signalling pathway[30] play important roles in magnesium ion promotion of related cell proliferation and osteogenic differentiation (**Figure 3**). At the same time, magnesium ions can increase the expression level of osteoprotegerin in serum, cause osteoprotegerin to bind to receptor activator of nuclear factor-κ B ligand (RANKL), competitively inhibit the binding of RANKL to receptor activator of nuclear factor-kappa B (RANK), regulate the osteoprotegerin-RANK-RANKL signalling pathway, and inhibit osteoclast differentiation.[31] Some researchers also revealed that when 10 mM magnesium ions were applied to MC3T3-E1 cells in combination with type I collagen, the expression of osteogenic markers (osteopontin, osteocalcin, alkaline phosphatase, Runt-related transcription factor 2, and bone morphogenetic protein 2 (BMP-2)) was up-regulated and the osteogenic capacity was enhanced.[32] Chang et al.[33] conducted a meta-analysis on the relationship between the serum concentration of magnesium ions and osteoporosis. They found that the concentration of magnesium ions was lower in female patients with postmenopausal osteoporosis. This may be due to the fact that when the diet is deficient in magnesium, it can lead to a decrease in osteoblasts and an increase in osteoclasts, which may induce a higher possibility of bone fragility and aggravate osteoporosis.[34,35] Although magnesium deficiencies exert adverse effects on osteoblast formation and bone metabolism, this effect can be reversed by magnesium supplementation. Hence, the long-term oral supplementation of magnesium increases bone mineral density in osteoporotic patients.[36] In order to explore the synergistic effect of magnesium ions with other ions, some scholars combined magnesium ions, calcium ions, and namely silicate (Si) in MC3T3-E1 cells. They found that the adhesion effect of MC3T3-E1 cells was significantly enhanced under the tri-ion action.[37] Angiogenesis plays an important role in bone regeneration and repair, and magnesium ions can promote osteoblast differentiation by enhancing the secretion of platelet-derived growth factor-BB by MC3T3-E1 cells, as well as the angiogenic capacity of human umbilical vein endothelial cells.[38] Qin et al.[39] confirmed that 5 mM magnesium ions up-regulated the expression of hypoxia-inducible factor 1α and endothelial nitric oxide synthase (eNOS), which promoted the vascular differentiation of BMSCs. Mg coating was added to the surface of Ti6Al4V, and *in vitro* experiments showed that Mg-coated Ti6Al4V increased the gene expression of hypoxia-inducible factor 1α and vascular endothelial growth factor (VEGF) in human umbilical vein endothelial cells, and angiography demonstrated a significant increase in the number and volume of blood vessels around the Mg-coated Ti6Al4V scaffolds.[40] The function of immune cells is intimately linked to the processes of bone homeostasis and bone regeneration.[41] Macrophages have an important role in the immune response, with a pro-inflammatory M1 phenotype and an anti-inflammatory and regenerative M2 phenotype. It has been demonstrated that magnesium-containing bio-biomaterials can reduce macrophage CD86 expression and inhibit M1 polarisation.[42] Another study showed that in the presence of magnesium ions, the expression of CD^{206} (a marker of M2 polarisation) was increased, promoting macrophage M2 polarisation, while magnesium ions significantly reduced interleukin-1β production in the inflammatory state.[43]

In conclusion, magnesium ions are closely related to human bone health and have been validated to be beneficial to osteoblast growth and bone metabolism in both cellular and clinical studies (**Figure 4**). Therefore, many researchers have integrated magnesium ions into therapeutic strategies for the treatment of bone defects. Besides, they have developed magnesium-based biomaterials using different carriers and applied them to bone repair with favourable outcomes.

2.2. Modulation of bone regeneration by magnesium-loaded hydrogels

During the process of bone regeneration and repair, the extracellular matrix plays an important role in mediating

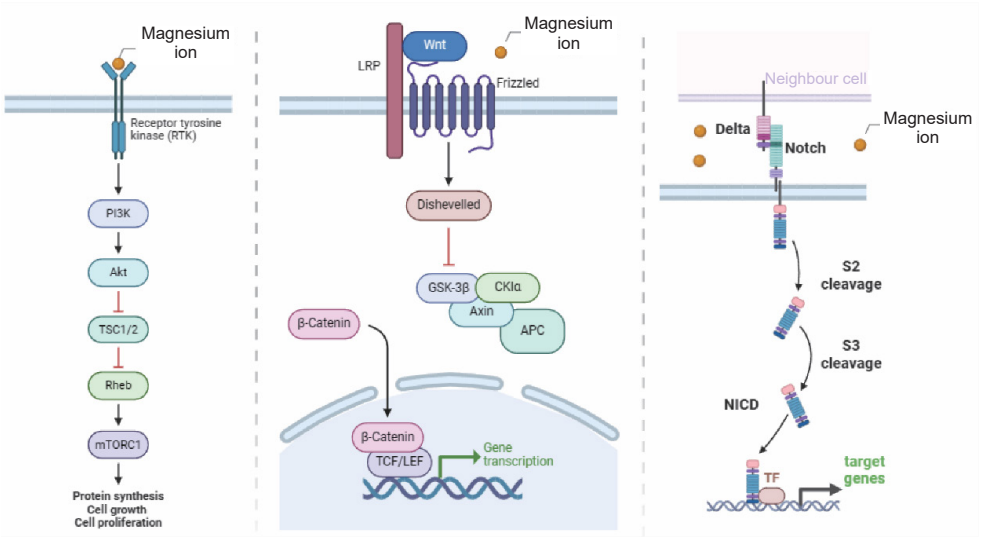

Figure 3. Magnesium ions promote relevant cell proliferation and osteogenic differentiation through activation of PI3K/AKT, Wnt, and Notch signalling pathway. Created with Biorender.com. Abbreviations: Akt: Protein kinase B; APC: Adenomatous polyposis coli; Axin: Axis inhibitor; CKIα: Casein kinase Iα; GSK-3β: Glycogen synthase kinase-3β; LEF: T-cell factor/lymphoid enhancer factor; LRP: Lipoprotein receptor related protein; mTORC1: Mammalian target of rapamycin complex 1; NICD: Notch intracellular domain; PI3K: Phosphatidylinositol 3 kinase; Rheb: Ras homolog enriched in brain; TCF: T-cell factor; TF: Transcription factor; TSC1/2: Tuberous sclerosis complex 1/2.

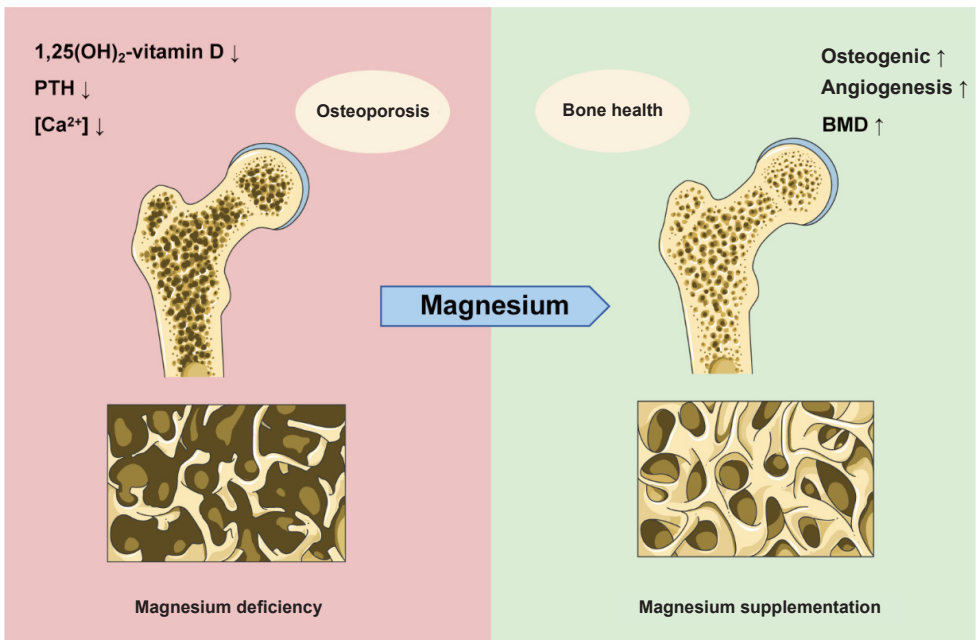

Figure 4. The role of magnesium ions in bone health. Created with BioRender.com. Abbreviation: BMD: bone mineral density.

the signalling, material exchange aspects and cell growth between the new bone tissue and the original bone tissue. Hydrogels are often prepared from natural polymers such as gelatin, chitosan and hyaluronic acid. They are biomaterials that share structural similarities with extracellular matrices. These biomaterials are commonly used in tissue regeneration owing to their biodegradability, biocompatibility, and high porosity.[44,45] Hydrogels are capable of transporting drugs or seed cells that can act on bone defects and expedite their repair.[46] In recent years, magnesium-containing hydrogels prepared by combining the advantages of magnesium ions and hydrogels have made good progress in the field of bone tissue engineering.

Chen et al.[47] constructed an injectable hydrogel of chitosan functionalised with creatine phosphate containing 5 mg/mL magnesium oxide nanoparticles (CSMP-MgO (5)) was used, Alizarin Red S staining showed larger red-stained areas, and angiogenesis experiments showed denser vascular networks, indicating that the osteogenic-induced differentiation ability and angiogenesis of CSMP-MgO (5) were the strongest, and when it was applied to the rat cranial bone defects, micro-computed tomography (CT) and histological sections also reflected the good osteogenic effect of CSMP-MgO (5) (**Figure 5**). Zhang et al.[48] developed a magnesium-containing double cross-linked hydrogel by combining gelatin, chitosan, and oligomeric silsesquioxane nanoparticles with magnesium

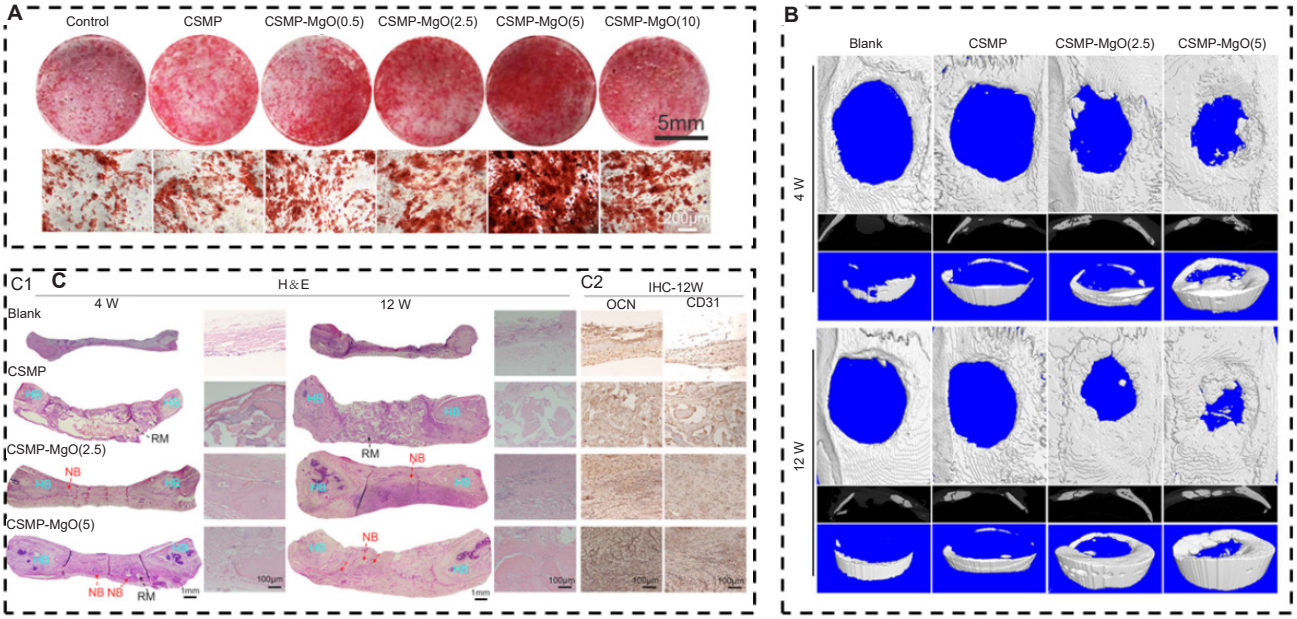

Figure 5. Magnesium oxide nanoparticle-coordinated phosphate-functionalised chitosan injectable hydrogel for osteogenesis and angiogenesis in bone regeneration. (A)Alizarin red staining of MC3T3 cells cultured in magnesium-containing hydrogel. (B) Micro-CT scanning of magnesium-containing hydrogel implanted into cranial defects in rats. (C1) H&E stained images of cranial defects in rats implanted with magnesium-containing hydrogel. (C2) Immunohistochemical stained images of cranial defects in rats implanted with magnesium-containing hydrogel. Reprinted from Chen et al.[47] Copyright 2022, American Chemical Society. Abbreviations: CSMP: Phosphate-functionalized methacryloyl chitosan; CT: Computed tomography; H&E: Haematoxylin-eosin; HB: Host bone; MgO: Magnesium oxide; NB: New regenerated bone; OCN: Osteocalcin; RM: Remained materials (hydrogels).

ions. Immunohistochemical experiments demonstrated that the hydrogel up-regulated the angiogenesis marker CD31, which accelerated the repair of bone defects by promoting angiogenesis. In cases of acute bone defects, reactive oxygen species produced by damaged bone tissues can exacerbate osteoclast damage. Loading magnesium ions combined with C-propylpyrogallol[4]arene into the hydrogel can enhance antioxidant capacity and accelerate bone defect repair.[49] Xu et al.[50] designed a hydrogel containing black phosphorus gelatin methacryloyl modified by magnesium ions. The hydrogel mimicked the special structure of the periosteum. The experimental results showed that this hydrogel contributed to bone defect repair by promoting periosteal neurogenesis and angiogenesis. Xiong et al.[51] developed a dual-network structure hydrogel containing magnesium ions and BMP-2. The hydrogel dissociated and bound magnesium ions locally by ligand bonding, resulting in the slow release of magnesium ions. The hydrogel accelerated the repair of bone defects through the synergistic effect of magnesium ions and BMP-2 (**Figure 6**). Some scholars have loaded magnesium ions and stromal cell-derived factor 1αinto a hydrogel. Specifically, stromal cell-derived factor 1 is released to recruit BMSCs around the bone defect. Then, magnesium ions are released to promote the osteogenic differentiation of BMSCs, thus promoting the repair of bone defects.[52] Although hydrogels have the advantages of good biosafety, biocompatibility and biodegradability, the lack of mechanical strength of hydrogels limits their large-scale use. Incorporation of nanoparticles in hydrogels can increase the mechanical properties of hydrogels. Some scholars added MgO nanoparticles into the hydrogel, and the results of compression experiments showed that the stress increased with the increase of the concentration of MgO nanoparticles, indicating that MgO nanoparticles enhanced the mechanical properties of the hydrogel. Meanwhile, the slowly released magnesium ions from this hydrogel acted on the BMSCs around the defect to promote their proliferation and osteogenic differentiation, and ultimately accelerated bone regeneration.[53] The regenerative capacity of bones decreases in patients with osteoporosis. To address this problem, inspired by the attraction of magnets to metals, Zhao et al.[54] developed an injectable hydrogel that can capture magnesium ions. This bone-targeting hydrogel enhanced the repair of osteoporotic bone defects by activating osteoclasts and vascular endothelial cells through the slow release of magnesium ions.

Hydrogels can be loaded to skow the release of drugs, thereby acting on surrounding tissues, which would improve therapeutic efficacy and drug utilisation.[46] Although hydrogels are not mechanically strong enough,[55] they can be used as local bone fillers and may be employed to carry bioactive substances to accelerate bone repair.

2.3. The role of the magnesium ion delivery system in bone regulation

Owing to its favourable biosafety and simple design, the drug delivery system can provide sustained release of drugs over a period, which conduces to better efficacy and fewer side effects.[56,57] In recent years, drug delivery systems have attracted much attention for their injectability and minimally invasive operability, particularly in the treatment of orthopaedic conditions.[58] **Figure 7** summarises the nanomaterials used in

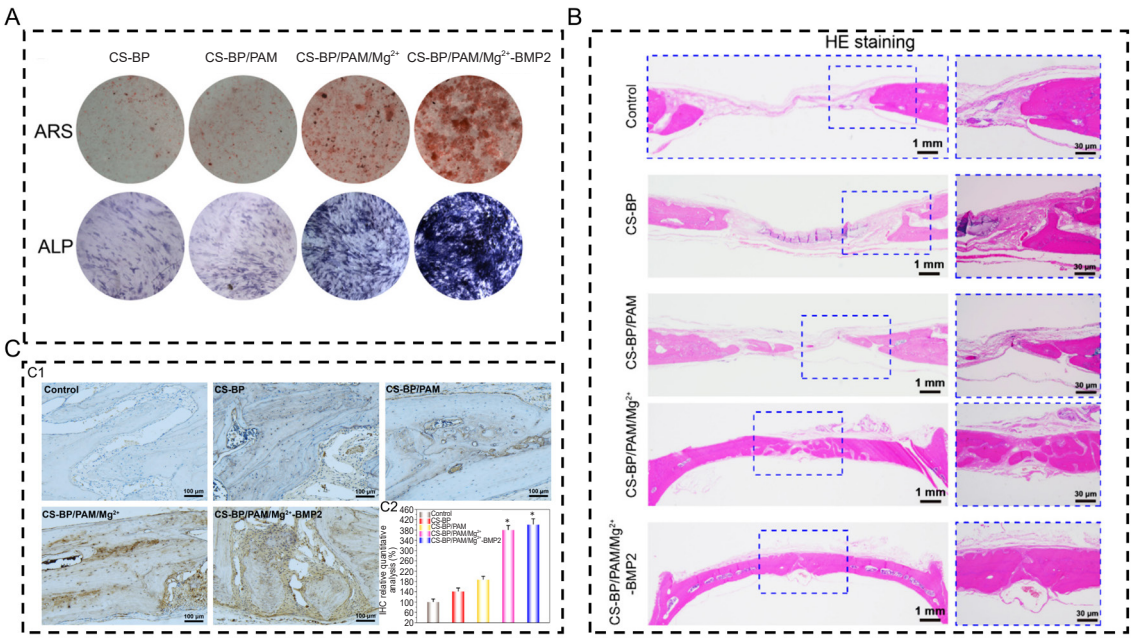

Figure 6. The fabrication of a highly efficient hydrogel based on a functionalised double network loaded with magnesium ion and BMP2 for bone defect synergistic treatment. (A) ALP staining and ARS staining analysis showed that CS-BP/PAM/Mg^{2+}-BMP2 hydrogel promoted BMSC osteogenesis. (B) HE staining of the newly formed bone at 12-week post-operation. (C1) Immunohistochemistry of OCN in the newly formed bone 12 weeks. (C2) The relative quantitative expression statistics for OCN immunohistochemistry. Reprinted from Xiong et al.[51] Copyright 2021, Elsevier B.V. *$P < 0.05$; **$P < 0.01$, *vs.* control. Abbreviations: ALP: Alkaline phosphatase; ARS: Alizarin Red S; BMP2: Bone morphogenetic protein 2; COL-I: Collagen type I; CS-BP: Chitosan-bisphosphonate; HE: Haematoxylin-eosin; Mg2+: Magnesium ion; OCN: Osteocalcin; OPN: Osteopontin; PAM: Poly (acrylamide).

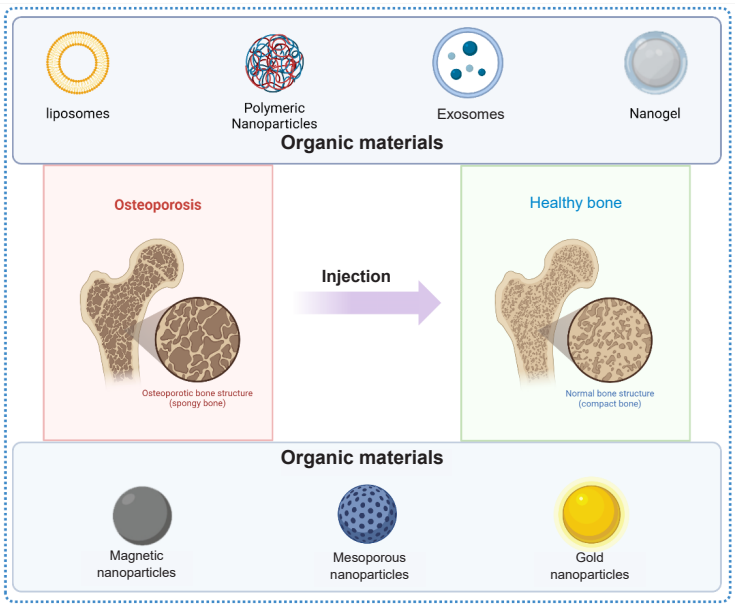

Figure 7. Nanomaterials for bone therapy. Created with BioRender.com.

orthopaedic related diseases, including liposomes, polymeric nanoparticles, exosomes, nanogels, magnetic nanoparticles, mesoporous nanoparticles, and gold nanoparticles. In view of the significant role of magnesium ions in promoting the proliferation and osteogenic differentiation of BMSCs, inhibiting osteoclast differentiation, promoting the generation of neovascularisation, regulating macrophage polarisation and inhibiting the production of inflammatory factors, scholars have attempted to use a delivery system carrying magnesium ions to promote bone regeneration and repair, and have achieved satisfactory efficacy in animal experiments.

Tan et al.[59] prepared an injectable bone cement based on magnesium-containing microspheres that provided sufficient space and decelerated the release of magnesium ions while supporting bone defects. Animal experiments showed that Mg-containing microspheres significantly facilitated the repair of cranial defects in rats while inducing the polarisation of M2-type macrophages. Poly(lactide-co-glycolide) (PLGA)

delivery systems can be employed as vehicles for the administration of a variety of macromolecules, including drugs, proteins, and other therapeutic agents, in the context of disease treatment. Yuan et al.[60] used PLGA microspheres coated with MgO and magnesium carbonate ($MgCO_3$) to fabricate PMg microspheres, which up-regulated the expression of alkaline phosphatase, osteocalcin, osteopontin, and collagen type I genes in BMSCs *in vitro*, thus promoting the osteogenic differentiation of these cells. The injection of these PMg microspheres into the rat cranial bone defect model significantly promoted bone regeneration. The PLGA microspheres containing magnesium ions and icariin were also found to significantly promote bone defect repair after 16 weeks of implantation into a critical bone defect (8 mm in diameter) in the rat skull.[61] Lin et al.[62] prepared magnesium-containing PLGA/alginate core-shell microspheres using a microfluidic system, which could control the slow release of 50 ppm magnesium ions within 2 weeks, thus effectively promoting the healing of femoral defects in rats within eight weeks. It has been demonstrated that PLGA/MgO-alendronate microsphere particles can enhance the expression of IL-10, BMP-2, and transforming growth factor-β, promote the maintenance of M2 macrophage phenotype, regulate the bone immune microenvironment, and facilitate the healing of bone defects in rats.[63] Integration of PLGA into different biomaterials and optimisation of delivery modalities, including topical injections, intravascular injections, hydrogels, and three-dimensional-printed scaffolds to facilitate efficient transport of PLGA in the bone, would be one of the ways to enhance therapeutic efficiency (**Figure 8**). Recently, smaller nano-delivery systems have been highlighted due to their ability to facilitate slow drug release, reduce clearance rates, and enhance drug penetration, while also providing superior bone targets. of note, this statement is purely objective and does not contain any subjective evaluation.[64,65] Although drug delivery system have achieved satisfactory results in the repair of bone defects,[66] there is limited research on the use of magnesium-loaded drug delivery system for bone repair. Enhancing the bone-targeting effect of the delivery system allows for precise delivery of the delivery system to bone tissue, which can result in a significant increase in drug concentration in the therapeutic area, as well as a reduction in the impact on non-targeted tissues, and a prolongation of the drug's *in vivo* circulation time, which can further increase the therapeutic efficiency of the drug delivery system (**Figure 9**). Magnesium-loaded drug delivery systems show promise for treating skeletal diseases, particularly osteoporosis. Local injection can facilitate the slow release of magnesium ions in the treatment of bone defects and other conditions.

3. The role and mechanism of magnesium-based bioalloy scaffolds for bone repair

3.1. Characteristics of magnesium-based bioalloy scaffolds

Magnesium is a light, silvery-white metal discovered by Sir Humphry Davy in 1808. Michael Faraday succeeded in producing magnesium metals.[67] In the 1900s, Payr proposed biodegradable bioactive magnesium alloys for orthopaedic applications.[68] Since then, the research into bioactive magnesium material implants has continued for nearly a century. The use of magnesium-based implants has been demonstrated to offer a number of advantages over those based on other common metals, such as titanium alloys and stainless steel alloys. Firstly, magnesium alloy can circumvent the necessity for secondary removal of the internal fixation system subsequent to implantation, due to its favourable biodegradability. This results in a reduction of secondary trauma to the patient and thus facilitates bone healing.[69] Secondly, magnesium alloys have favourable biosafety and bone-enhancing properties (**Figure 10**). The degradation of magnesium alloys mainly produces magnesium ions and hydrogen. Magnesium ions promote osteogenesis,[70] while hydrogen has anti-inflammatory properties[71] and can inhibit bone resorption.[72] Thirdly, This material exhibits robust mechanical properties. The density of magnesium alloys (1.74–2.0 g/cm^3) is similar to that of human bone (1.8–2.1 g/cm^3),

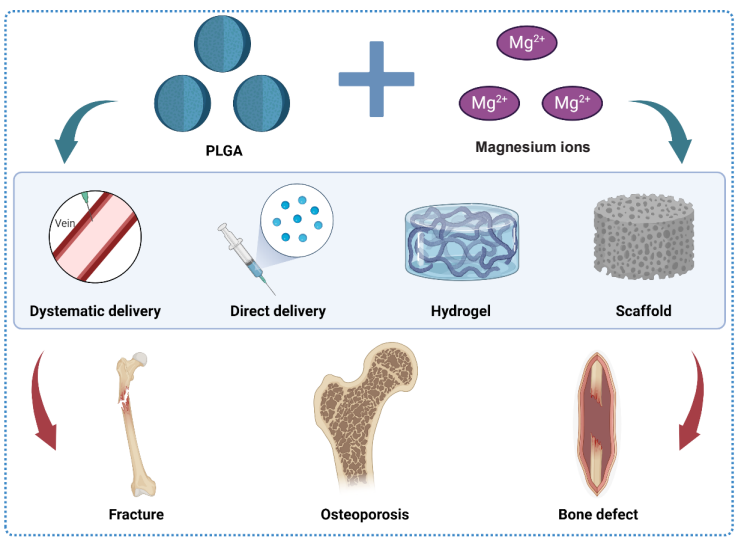

Figure 8. PLGA systemic delivery and local delivery (direct injection, hydrogel, scaffold material) for the treatment of osteoporosis, fractures, and bone defects. Created with BioRender.com. Abbreviations: Mg^2+: Magnesium ion; PLGA: Poly(lactide-co-glycolide).

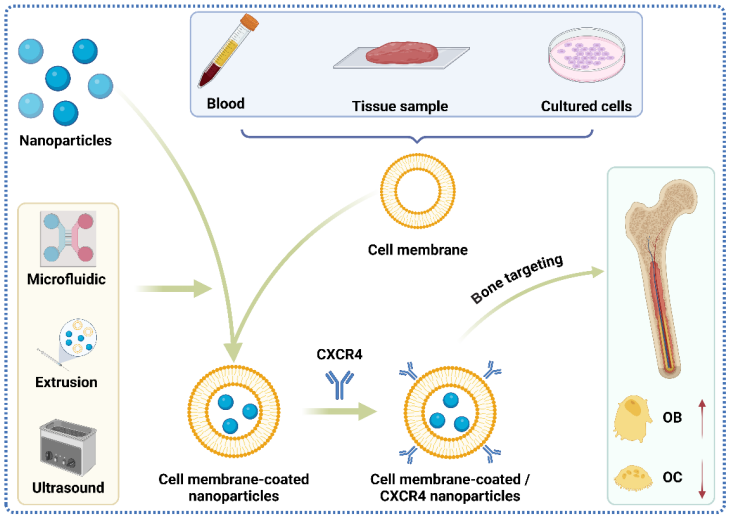

Figure 9. Preparation and application of bone targeted delivery systems. Created with BioRender.com. Abbreviations: CXCR4: C-X-C Chemokine receptor 4; OB: Osteoblast; OC: Osteoclast.

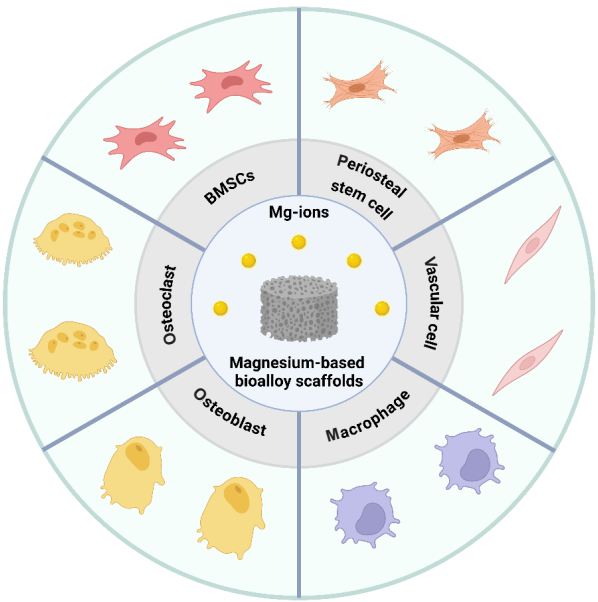

Figure 10. Cell biological behaviour of magnesium ions, a degradation product of magnesium alloys. Created with BioRender.com. Abbreviations: BMSC: Bone marrow mesenchymal stem cell; Mg: Magnesium.

while the Young's modulus of magnesium alloys (10–45 GPa) is also comparable to that of human cortical bone (3–20 GPa), thus effectively avoiding stress masking.[73]

3.2. Application of magnesium-based bioalloy scaffolds

Magnesium-based bioalloy scaffolds have been gradually applied in orthopaedics in clinical practice. Zhao et al.[74] combined magnesium scaffolds with polycaprolactone and prepared a polycaprolactone/Mg composite scaffold using three-dimensional printing, which was implanted into rat cranial defects. The micro-CT results demonstrated that the polycaprolactone/Mg composite scaffold group had better bone volume/tissue volume, trabecular number, trabecular separation, and trabecular thickness than the single scaffold group. Zhang et al.[75] developed a new magnesium alloy scaffold by adding Mn to the AZ31 magnesium alloy scaffold. The *in vitro* experimental results demonstrated that this new alloy significantly enhanced the proliferation, adhesion, and differentiation of cells. Besides, the *in vivo* experimental results also showed that it accelerated the repair of bone defects. In contrast, the AZ31 scaffold also exhibited a good ability to repair bone defects. After the repair of a large segmental femoral defect (1 cm in length) in rabbits for 8 weeks, positive results were observed.[76] In animal models of bone defects at different ages, it was observed that magnesium scaffolds degraded at a faster rate in older rats. However, no significant difference was observed in the effect of bone defect healing between both ages.[77] Scholars fabricated some porous magnesium alloy scaffolds (porosity 75%) using the hot-press sintering process. They then implanted these scaffolds at the femoral defects of osteoporotic rats for 4 weeks. The results of micro-CT

and histological staining tests showed that these scaffolds promoted the repair of osteoporotic bone defects through the Wnt/β-catenin signalling pathway.[78] The results would be more accurate if the new bone could be extracted for mechanistic testing. Considering that inorganic components such as calcium and phosphorus make up the majority of bone tissue, it is not easy to extract proteins, and performing immunohistochemical staining of paraffin sections can also reflect mechanistic changes to a certain extent. RNA sequencing of bone tissue has also been progressively reported.[3] and appropriate use of this technology will help to increase understanding and knowledge of magnesium alloy-regulated bone regeneration. Magnesium alloy scaffolds loaded with zoledronic acid were implanted into bone defects to result in the release of magnesium ions and zoledronic acid. This inhibited osteoclasts while activating osteoblasts, leading to an improved healing rate of osteoporotic bone defects.[7] Magnesium-based bioalloy scaffolds present promising results in treating bone defects in animal models and have been used in clinical practice.

Clinical internal fixation devices are preferably made of titanium, stainless steel, and other inert materials. However, these materials can interfere with bone growth due to tissue irritation and infection.[79] Magnesium screws used in fracture fixation can meet clinical healing standards and degrade within one year, avoiding the requirement for surgical removal.[80] Owing to the avoidance of a secondary removal procedure, magnesium alloy metal implants are gradually accepted by clinicians. Ding et al.[81] designed a degradable magnesium alloy bionic cannulated screw) and compared its biomechanical properties with those of a titanium alloy cannulated screw and a titanium alloy bionic cannulated screwusing finite element analysis. In a meta-analysis of resorbable magnesium alloys versus conventional titanium screws for the treatment of distal metatarsal osteotomies, magnesium alloys were found to have comparable treatment outcomes to titanium alloys.[82] This finding from this meta-analysis of magnesium-based implants was also supported by existing literature reports. In a study involving 20 patients with ankle fractures, a magnesium-based implant (ZX00 screw) was implanted with a medical follow-up for 12 weeks. Imaging results showed favourable fracture healing in all patients, with no fractures occurring during screw degradation. The American Orthopaedic Foot and Ankle Society score for these patients was 92.5.[83] Klauser et al.[84] conducted a study on magnesium alloy screw fixation in 100 patients with bunion osteotomies. Most patients were able to walk with weight 6 weeks after surgery. The magnesium alloy group did not show any significant abnormalities in terms of wound healing and infection rate compared with the group treated with titanium alloy screws. Acar et al.[85] employed medial condylar osteotomy to treat talus chondromalacia. In their study, 11 patients were fixed with resorbable magnesium screws and another 11 patients with peptide screws. The mean follow-up period was 20.7 ± 8.9 months. The magnesium screws gradually degraded, but none of the patients in either group experienced displacement or deformity healing. There was no significant difference in the healing rate and daily function between the two groups.

However, magnesium-based metal materials are currently limited by insufficient support capacity, and rapid degradation. These limitations have restricted the large-scale application of magnesium-based metal materials in clinical practice.[86] Therefore, the addition of metal elements of different compositions to magnesium alloys has achieved the purpose of increasing the mechanical properties of magnesium alloys and alleviating their excessive degradation. **Table 1** summarises the role of magnesium alloys with different compositional elements in bone repair experiments.[75,87-90] In addition, the addition of coatings can reduce the corrosion rate and control the degradation rate of magnesium alloys without altering the structure and composition of the magnesium alloys themselves, as well as alter the mechanical properties of magnesium-based implants, impart antimicrobial properties, and contribute to bone activity. **Table 2** summarises the advantages and disadvantages of different coatings for magnesium-based alloy scaffolds.[91-95]

4. Limitations

It must be acknowledged that this paper is not without shortcomings. Firstly, this paper provides a summary of the magnesium-containing biomaterials developed in our laboratory, but it does not aim to be a comprehensive review of all magnesium-containing biomaterials in the field. Secondly, with regard to the delivery system, this paper does not attempt a more detailed elaboration and comparison of the various types of magnesium-containing delivery systems, nor does it address the differences between them. The rate of magnesium ion loading and the rate of release; in the section on hydrogels, insufficient attention was paid to the impact of magnesium ions on the performance of hydrogel gel-forming; in the section on magnesium-based bioalloys, there was no comprehensive summary of the preparation technology and methods. In subsequent work, we will devote greater attention to these areas, with a particular focus on the preparation of magnesium-based bioalloys.

5. Summary and outlook

Magnesium ions play a crucial role in maintaining bone health and promoting bone regeneration and repair. They can enhance the proliferation and differentiation of osteoblasts and BMSCs, as well as the formation of new blood vessels. There is a small content of cells in bone tissues, which is dominated by the extracellular matrix, and blood circulation is slightly weaker than that of internal organs. Therefore, magnesium ions may exert more pronounced effects persistently by loading them into drug delivery systems and hydrogels. Besides, they can be directly applied to the bone with a certain bone-targeting ability. Magnesium-based bioalloy scaffolds are highly biocompatible and degradable with excellent bone-enhancing properties. This has made magnesium ions and magnesium-based bioalloy scaffolds a popular area of research in the field of bone regeneration and repair. Magnesium-based biomaterials carrying seed cells or bioactive substances have expanded the potential application range of magnesium-based biomaterials. This will improve the effectiveness of magnesium-based biomaterials in bone regeneration and repair.

Table 1. Different types of magnesium-based bioalloy scaffolds in bone repair experiments

Coating	Methods	Component	Advantage	Disadvantage	Reference
Layered double hydroxide coating	Co-precipitation, hydrothermal, ion exchange, electrodeposition, etc.	Layered double hydroxide consists of a positively charged hydroxide layer and a negatively charged intercalation layer with the molecular formula $[M2 + 1-xM3 + x(OH)_2]$ $[An-]X/N-zH_2O$	Corrosion resistance and biocompatibility. Layered double hydroxide coatings can be intercalated with different anions to achieve specific functions such as photothermal/chemodynamic effects Layered double hydroxide coating facilitates osteogenic differentiation, angiogenesis and induces macrophage M2 polarisation.	Coating preparation costs: The preparation process for layered double hydroxide coatings can be relatively complex, requiring specific equipment and materials and high preparation costs.	75, 87, 88
Bioactive coatings	Chemical conversion coatings, bionic coatings, micro-arc oxidation, etc.	Hydroxyapatite, CaP and fluoride, tricalcium phosphate and glass ceramics	Good biocompatibility, avoids stress masking effect, promotes fracture healing, avoids secondary surgery, resourceful and inexpensive	Too rapid degradation, hydrogen generation, elevated pH and technical difficulties in coating preparation.	89
Biodegradable polymer coatings	Spinning, electrochemical, immersion, dipping, etc.	Chitosan, collagen, and synthetic macromolecules such as polycaprolactone, polylactic acid	Good biocompatibility, controlled drug release, improved corrosion resistance of magnesium alloys, good mechanical properties	Degradation rate needs to be precisely controlled, stability of drug release, adhesion of coating to substrate, *in vivo* reaction, complex preparation process	90

Table 2. Composition and application of magnesium alloy bone implant materials

Mg alloy	Treatment	Composition	Animal model	Reference
ZK60	Sr-D-Ca-P/PLLA-Hap coating	Zn: 5.5% Zr: 0.49% Mg balance	Rat	91
ZK30	Hydrofluoric acid treatment	Mg: residual Zn: 3 wt. % Zr: 0.3 wt. %	Mouse (femur fracture)	92
WE43	High temperature oxidation	Y: 3.87wt. % Nd: 2.24wt. % Gd: 1.16 wt. % Zr: 0.39 wt. % Residual Mg	Rabbit (femoral condylar fracture with bone defect)	93
AZ31B	Si-containing	Al: 3 wt. % Zn: 1.1 wt. % Mn: 0.70 wt. % Si: 0.01 wt. % Fe: 0.002 wt. % Cu: 0.008 wt. % Ni: 0.0008 wt. % Mg balance	Rabbit (bone defect)	94
JDBM	DCPD coating	Mg-Nd-Zn-Zr	Goat femoral condyle fracture	95

Note: Al: aluminium; Ca: calcium; Cu: cuprum; DCPD: JDBM coated with brushite; Fe: ferrum; Gd: gadolinium; Mg: magnesium; Mn: manganese; Nd: neodymium; Ni: nickel; P: platinum; PLLA: poly (L-lactic acid); Si: silicate; Sr-D-Ca-P/PLLA-Hap (Sr dopped Ca-P coating/poly-L-lactic acid-hydroxyapatite); Y: yttrium; Zn: zinc; Zr: zirconium.

However, magnesium-based bioalloy scaffolds have limitations, such as excessive degradation rate, low mechanical strength, and excessive hydrogen (H_2) content of degradation products. To overcome these limitations, other elements can be added to magnesium-based bioalloy scaffolds or coatings can be applied, the objective is to enhance the mechanical properties of magnesium alloys and to mitigate their accelerated deterioration, which may be highlighted in future research. Furthermore, the application of magnesium-based bioalloy scaffolds in clinical scenarios is primarily limited to screws. There are fewer instances of their application in endosseous implants, such as intramedullary nails. However, these areas are expected to be a focus of future research, particularly in addressing the aforementioned limitations of magnesium alloy scaffolds. Moreover, it is necessary to further fabricate various types of magnesium-based bioalloy scaffolds, thus advancing the translational application of such materials in clinical scenarios. Finally, the manufacturing process of magnesium alloy is greatly enhanced by the use of additive manufacturing and three-dimensional printing technologies. These technologies offer significant advantages in terms of material properties and performance, design and manufacturing freedom, production efficiency and cost, as well as technological diversity and innovativeness. This will further enhance the potential of magnesium alloy in the clinical treatment of various diseases.

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