Available online at www.sciencedirect.com

ScienceDirect

Journal of Magnesium and Alloys 9 (2021) 779–804

www.elsevier.com/locate/jma

Review

# Magnesium-based biomaterials as emerging agents for bone repair and regeneration: from mechanism to application

Hang Zhou[a,d,1], Bing Liang[b,d,1], Haitao Jiang[a], Zhongliang Deng[a,*], Kexiao Yu[c,d,**]

[a] *Department of Orthopedics, The Second Affiliated Hospital of Chongqing Medical University, 76 Linjiang Road, Yuzhong Distinct, Chongqing 400010, PR China*

[b] *Department of Pathology, College of Basic Medicine, Chongqing Medical University, 1 Yixueyuan Road, Yuzhong Distinct, Chongqing 400016, PR China*

[c] *Department of Orthopedics, Chongqing Traditional Chinese Medicine Hospital, No.6 Panxi seventh Branch road, Jiangbei District, Chongqing 400021, PR China*

[d] *Institute of Ultrasound Imaging of Chongqing Medical University, The Second Affiliated Hospital of Chongqing Medical University, 76 Linjiang Road, Yuzhong Distinct, Chongqing 400010, PR China*

Received 27 August 2020; received in revised form 1 February 2021; accepted 4 March 2021
Available online 6 April 2021

**Abstract**

Magnesium (Mg) is the fourth most abundant element in the human body and is important in terms of specific osteogenesis functions. Here, we provide a comprehensive review of the use of magnesium-based biomaterials (MBs) in bone reconstruction. We review the history of MBs and their excellent biocompatibility, biodegradability and osteopromotive properties, highlighting them as candidates for a new generation of biodegradable orthopedic implants. In particular, the results reported in the field-specific literature (280 articles) in recent decades are dissected with respect to the extensive variety of MBs for orthopedic applications, including Mg/Mg alloys, bioglasses, bioceramics, and polymer materials. We also summarize the osteogenic mechanism of MBs, including a detailed section on the physiological process, namely, the enhanced osteogenesis, promotion of osteoblast adhesion and motility, immunomodulation, and enhanced angiogenesis. Moreover, the merits and limitations of current bone grafts and substitutes are compared. The objective of this review is to reveal the strong potential of MBs for their use as agents in bone repair and regeneration and to highlight issues that impede their clinical translation. Finally, the development and challenges of MBs for transplanted orthopedic materials are discussed.



*Keywords:* Magnesium-based biomaterials; Bone reconstruction; Orthopedic applications; Future perspectives; Clinical transformation.

## 1. Introduction

Due to the increased incidence of sports-, trauma-, inflammatory- and age-related musculoskeletal injuries and defects, the demand for orthopedic implant materials has greatly increased [1]. Currently, permanent rigid metals (such as stainless steel and titanium) are widely used as orthopedic implants to facilitate healing of musculoskeletal injuries. However, their limitations include 'stress shielding' elicited by their high Young's modulus [2] and the necessary invasive removal surgeries that increase patient burden and risk [3]. As emerging novel biomaterials, biodegradable polymers have received much attention due to their suitable mechanical properties, which are close to those of cancellous bone; excellent biodegradability; and compatibility with diagnostic imaging for healing assessments [4]. Nevertheless, biodegradable polymers suffer from insufficient mechanical strength and long-term inflammatory responses induced by byprod-

* Corresponding authors.
** Corresponding author at: Department of Orthopedics, Chongqing Traditional Chinese Medicine Hospital, No.6 Panxi seventh Branch road, Jiangbei District, Chongqing 400021, PR China.
*E-mail addresses:* zhongliang.deng@qq.com (Z. Deng), csyxk@126.com (K. Yu).

[1] Hang Zhou and Bing Liang are co-first authors who contributed equally to this study.

https://doi.org/10.1016/j.jma.2021.03.004

ucts in peri-implant tissue [5]. Therefore, the development of more reliable orthopedic implants with favorable biological and physical properties for use as bone substitutes, fixatives and stabilization devices is crucial.

Magnesium (Mg)-based biomaterials (MBs) have been used as orthopedic implants for more than one hundred years due to their desirable mechanical and osteopromotive properties. In addition, their advantages over standard counterparts have been extensively explored, with Mg and Mg alloys, bioceramics, bioglasses, and polymer composite materials [6-8] displaying unique superiority in the acceleration of bone formation and fracture healing. Due to the similarity of their Young's modulus values to that of human cortical bone, these new Mg and Mg alloy implant materials are an excellent choice to resolve the refracture limitation [9,10]. Mg-based bioceramics and bioglasses can be gradually degraded and replaced by new bone, demonstrating their potential as alternative biodegradable bone graft substitutes [7]. For Mg-based polymer materials, the incorporation of magnesium not only neutralizes their acidic degradation products but also improves their osteopromotive efficacy [6,11].

However, the development of MBs has long been blocked by an undesirable degeneration rate and a rapid decrease in mechanical strength, especially for Mg and Mg alloys, and major breakthroughs have not been achieved in the clinical translation of MBs. In recent decades, advancements in production processes and methods have greatly improved the biological performance of MBs, especially in terms of the corrosion of Mg and Mg alloys, leading to renewed interest in MBs as bone implant materials [12]. In addition, the rapid development of bioengineering provides the possibility of using MBs for bone repair and regeneration through fabrication of versatile modalities with an abundance of compositions, mechanical properties, and functionalities, which are fortunately desirable for further translation to clinical applications. For instance, in recent decades, various Mg-incorporated biomaterial scaffolds have been developed for bone defect repair and have been engineered to be bioactive and/or bioresorbable to enhance bone growth by harboring different growth factors, drugs, genes, and/or stem cells [13].

In this review, we summarize the recent developments in MBs and highlight the underlying enhanced bone regeneration mechanisms and the advancement and special properties of Mg-based orthopedic implants, thereby clarifying some of the obstacles that block mainstream use of MBs as bone graft substitutes. The diverse selection of implantable MBs, including Mg and Mg alloys, bioceramics, bioglasses, and biopolymer-based composites, can enhance osteogenesis, inhibit metabolic activity and osteoclast differentiation and promote osteoblast adhesion and motility to facilitate bone recovery (Fig. 1). Furthermore, these novel MBs have shown high degradation performance and desirable mechanical properties and biocompatibility when applied in bone and soft tissue repair. These properties have been especially encouraged by several corresponding technological innovations that provide an abundance of opportunities to continue advancing the field of Mg-based orthopedic implants. The application forms of these MBs are also presented, and the challenges and prospects for further clinical translation are discussed.

## 2. Mechanism of the enhanced bone regeneration activity of MBs

Bone is a dynamic tissue that is continuously remodeled via the precisely coordinated resorption and synthesis processes of skeletal tissues [14,15]. Consequently, the content of inorganic compositions stored in bone tissue continuously changes. Approximately 67% of Mg in the human body is stored in bone tissues, and 30% is exchangeable on the crystal surface of bone, providing a dynamic supply for maintaining intra- and extracellular Mg concentrations [16,17]. Previous studies have suggested that magnesium ions ($Mg^{2+}$) have an effect on the overall rate of seeded calcium phosphate crystallization and the subsequent growth of hydroxyapatite (HA) [18]. Moreover, as a participatant, $Mg^{2+}$ induces osteogenic differentiation and osteoblast differentiation, which occur with the use of degradable magnesium metals and alloys, thereby promoting bone regeneration [19,20]. In contrast, $Mg^{2+}$ deficiency (approximately 0.04–10%) lead to suppressed bone formation for a decrease in osteoblasts and bone mass and an increase in osteoclastic bone resorption resulting from enhanced secretion of proinflammatory cytokines [21-23]. The degradation products of Mg and Mg alloy implants were observed to promote new bone tissue growth and bone remodeling in animal models (i.e., rats, guinea pigs, and rabbits) [24-29]. However, the underlying mechanism remains unclear because only a few studies have examined the direct influence of $Mg^{2+}$ on osteogenesis. Based on the results of previous in vitro and in vivo experiments, we summarize the current understanding of the possible cellular and molecular mechanisms underlying the osteopromotive properties of Mg.

### 2.1. Osteogenesis enhancement

As a typical metal ion, $Mg^{2+}$ determines intracellular protein and DNA synthesis, and has been postulated to be a key regulator in cell proliferation and differentiation [30,31]. The MAPK/ERK pathway is one of the signaling pathways governing the osteogenic differentiation of stem cells [32]. $Mg^{2+}$ has been reported to selectively activate the MAPK/ERK pathway and further induce the stem cell differentiation. During this process, magnesium transporter 1 (MagT1), one of the major $Mg^{2+}$ transporters, can influence the osteoinductive effect of magnesium by mediating the influx of $Mg^{2+}$[33] (Fig. 2A). Zhao et al. investigated the effect of $Mg^{2+}$ on fracture healing with an intramedullary nail containing magnesium (Mg-IMN). Their results indicated that the internalization of $Mg^{2+}$ into neurons in the dorsal root ganglia (DRG) was mediated by MagT1 and transient receptor potential 7 (TRPM7). The increased influx of magnesium ions significantly improved the release of neuronal calcitonin gene-related polypeptide-a (CGRP) from the DRG. Additionally, CGRP was bound to its receptor expressed on the surface of periosteum-derived stem cells (PSCs) and induced activation

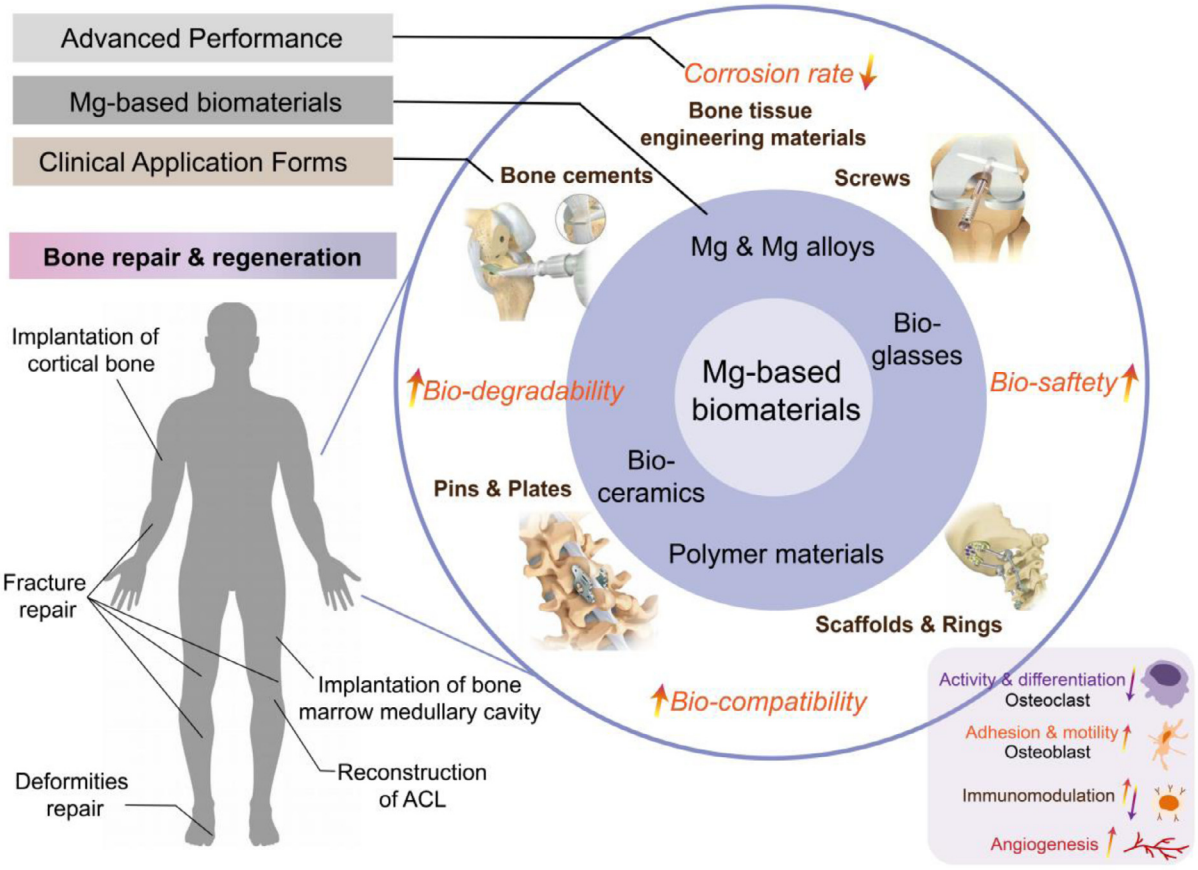


Fig. 1. Graphical representation of the application forms of the various Mg-based biomaterials and their corresponding physiological processes.

of cAMP-responsive element-binding protein 1 (CREB1) and SP7 (also known as osterix). The upregulated expression of these proteins enhanced the osteogenic differentiation ability of PDSCs. This result suggests that $Mg^{2+}$ participates in the cross-talk between DRGs and PSCs and prompts increased formation of new bone by improving osteogenic differentiation [34] (Fig. 2B). To identify specific intracellular signaling pathways through which $Mg^{2+}$ enhances bone regeneration, Sayuri et al. [35] treated human bone marrow stromal cells (hBMSCs) with various concentrations of $MgSO_4$, with and without osteogenic factors. They observed that the addition of $10 \times 10^{-3}$ mol/L (M) $Mg^{2+}$ to cell cultures enhanced the mineralization of the extracellular matrix (ECM) by upregulating the expression of COL10A1 (an ECM component in healing bone) and vascular endothelial growth factor (VEGF). Furthermore, western blotting results showed that undifferentiated cells cultured without osteogenic factors were stimulated by HIF-2$\alpha$, whereas osteogenic cells cultured with osteogenic factors were stimulated by PGC-1$\alpha$. This result provides further evidence that the induction pathway of osteogenic proteins might be different depending on the hBMSCs differentiation status (Fig. 2C). Recently, Huang et al. [36] reported that additional $Mg^{2+}$ can activate the canonical Wnt signaling pathway and significantly upregulate the expression of $\beta$-catenin and its downstream genes (LEF1, DKK1), which in turn causes hBMSCs to differentiate toward their osteoblast lineage and induces an osteogenic effect (Fig. 2D).

### 2.2. Prompt adhesion and motility of osteoblasts

It is critical to establish and maintain mature bone at the bone/device interface after MBs implantation. During this process, cell adhesion to orthopedic implants, which is primarily mediated by integrins (membrane-associated adhesion receptors belonging to the integrin superfamily), is a crucial step for successful implantation [37]. Integrins consist of noncovalently associated $\alpha$ and $\beta$ subunits, which act as signal transduction and adhesion proteins. In addition, the motifs of the extracellular domain of the $\alpha$-subunit can bind divalent ions, such as $Ca^{2+}$, $Mg^{2+}$, and $Mn^{2+}$. Changes in extracellular ions affect integrin affinities to their respective ligands [38,39]. Zreiqat et al. [40] found that human bone-derived cell (HBDC) adhesion decreased significantly when the fibronectin receptor $\alpha5\beta1$ and $\beta1$-integrins were blocked. In contrast, as a result of enhanced levels of $\alpha5\beta1$, $\beta1$, and $\alpha3\beta1$-integrin receptors, cell adhesion was dramatically improved when HBDCs grew on a $Mg^{2+}$-modified bioceramic surface. This research revealed that $Mg^{2+}$ might promote adhesion of HBDCs in an $\alpha5\beta1$- and $\beta1$-integrin-mediated manner, thereby contributing to good osteointegration and more

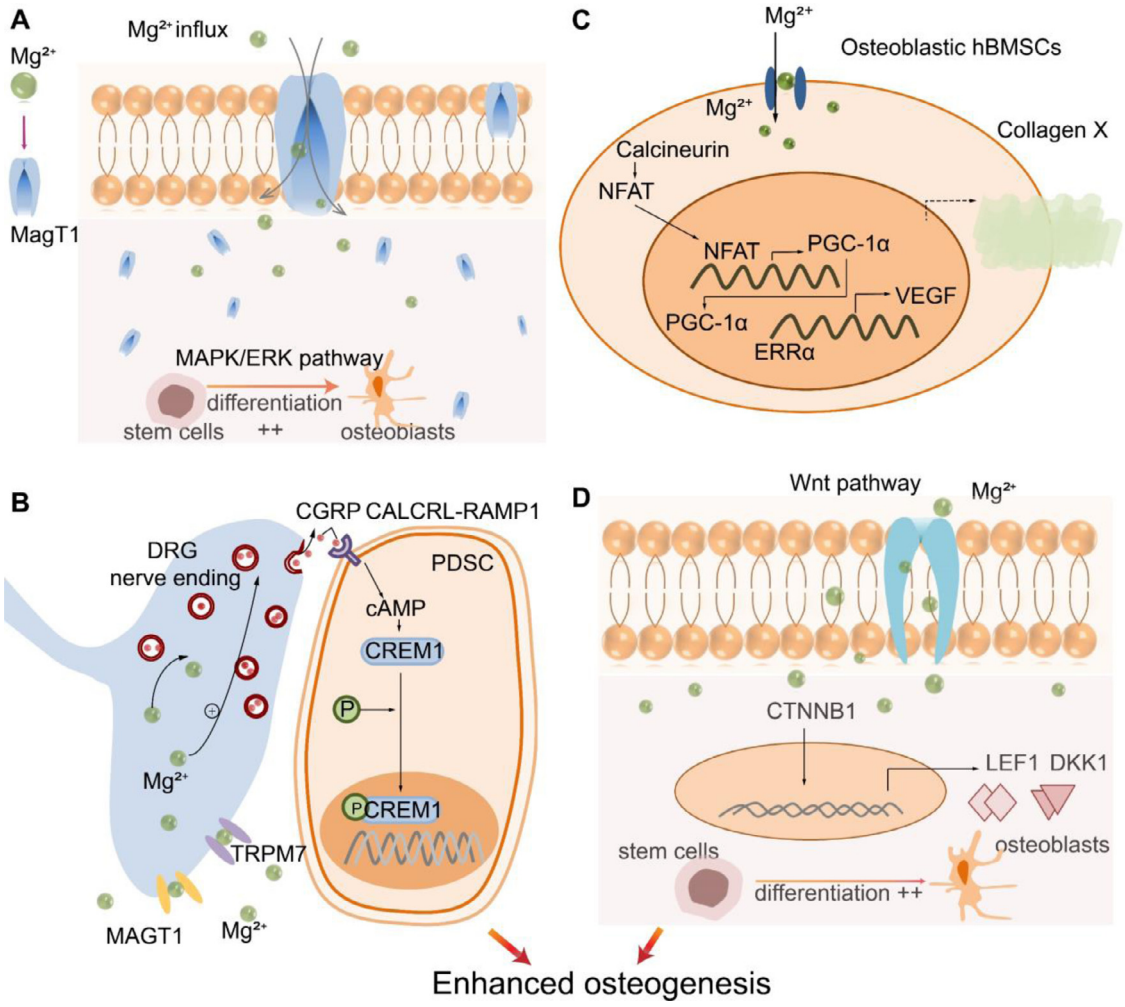


Fig. 2. Illustration of how $Mg^{2+}$ enhances osteogenesis by promoting proliferation and differentiation. A. $Mg^{2+}$ promotes stem cell differentiation to osteoblasts through the MAPK/ERK pathway. B. $Mg^{2+}$ promotes new bone formation by improving osteogenic differentiation. C. $Mg^{2+}$ enhances bone regeneration by upregulating COL10A1 and VEGF expression in hBMSCs. D. $Mg^{2+}$ activates the canonical Wnt signaling pathway to upregulate the expression of $\beta$-catenin and its downstream genes (LEF1, DKK1).

bone formation surrounding Mg-incorporated implants. Jin-Woo et al. [41] found that Mg incorporation significantly increased attachment of MC3T3-E1 preosteoblast cells on the smooth surface of Ti materials.

Moreover, the effect of $Mg^{2+}$ on osteoblast motility has been widely studied [11,42]. To investigate the influence of $Mg^{2+}$ on osteoblast migration, Kim et al. [42] performed two-dimensional migration wound healing assays and transwell migration assays with a range of $Mg^{2+}$ concentrations. Both assays demonstrated that $Mg^{2+}$ at an optical concentration greatly improved the motility of osteoblast cells. Notably, the researchers further measured the migration ability of osteoblasts on Mg-containing polycaprolactone (PCL) scaffolds, which persistently released $Mg^{2+}$ at a concentration of 5 mM after preincubation. After 4 days of incubation, quantification of both the genomic DNA and protein content indicated that the cell count on the inside was higher than that on the outside of the PCL scaffold, revealing that $Mg^{2+}$ facilitated movement of osteoblasts into the scaffold.

### *2.3. Inhibition of osteoclast metabolic activity and differentiation*

In adults, bone tissue is continuously being remodeled, and the overall bone mass is maintained at a constant level via a balance between osteoclastic bone resorption and osteoblastic bone formation. To investigate the influence of increased extracellular magnesium content on human osteoclasts, Wu et al. exposed cultures to various magnesium concentrations (from either magnesium chloride or magnesium extract), thereby simulating the effect of Mg alloy degradation. When analyzing the experimental results, they found that magnesium chloride first favored and then disfavored osteoclast proliferation and differentiation in a concentration-dependent manner, while the magnesium extract appeared to decrease the metabolic activity of osteoclasts [43]. Moreover, they established an attractive coculture that contained bone-forming osteoblasts, bone-resorbing osteoclasts, and Mg extract at various dilutions. The results showed that Mg extract at certain

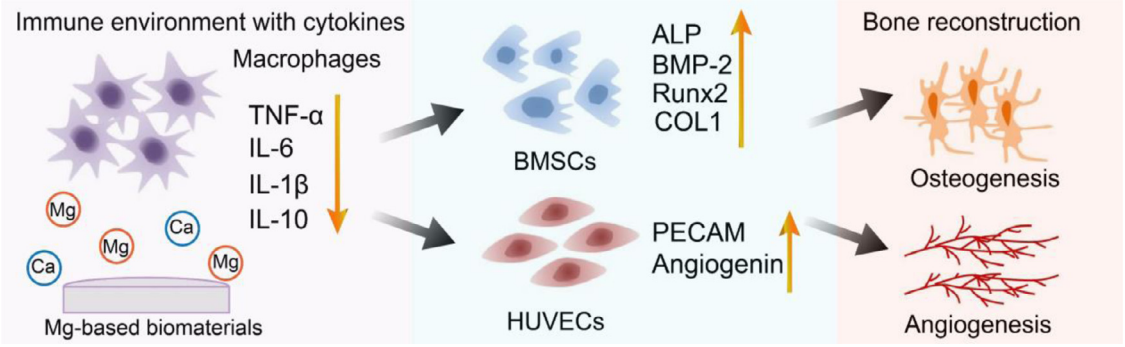


Fig. 3. Schematic illustration of effects of $Mg^{2+}$ on improvement bone regeneration by inducing desired immune microenvironment.

concentrations (14.36 mM and 26.27 mM) had a positive effect on osteoblast formation but an inhibitory effect on osteoclast differentiation [44].

### 2.4. Immunomodulation

Inflammation is a major cause of orthopedic implant failure [45]. Among biomaterial-mediated reactions, the host immune responses are quite normal in the treatment of bone regeneration, and release of inflammatory factors is unfavorable for bone repair. The osteo-immunomodulatory property of bone biomaterials has been found to play a significant role in biomaterial-assisted osteogenesis by triggering the desired immune response. Wang et al. [46] reported that magnesium can affect immune environments by promoting macrophage polarization to the M2 phase. The increased anti-inflammatory M2 macrophages exhibited strong BMP-2 and TGF-$\beta$ expression, thus supporting osteoblast mineralization. Moreover, magnesium suppressed M1 macrophages with a consequent decrease in proinflammatory factors (TNF-$\alpha$, IL-1$\beta$, IL-6), thus acting as an anti-inflammatory agent (Fig. 3). These findings suggest that $Mg^{2+}$ might facilitate bone regeneration by inducing the desired immune microenvironment.

### 2.5. Angiogenesis enhancement

Vessel development is vital for bone formation [47,48]. Several studies have shown that $Mg^{2+}$ can promote angiogenesis by stimulating VEGF, angiogenin and other crucial chemoattractants [8]. Lin et al. [33] provided an embryonic-like environment for stem cells with magnesium-enriched 3D-culture systems. They found that $Mg^{2+}$ stimulated osteogenic differentiation of stem cells with selective activation of the MAPK/ERK pathway; moreover, the expression of VEGF, which is an important factor in angiogenesis [49-51], was significantly upregulated in bone marrow stem cells (BMSCs). In addition to enhanced angiogenesis in vitro, dramatic neovascularization was observed in a rat cranial defect model, with significant vascularized bone regeneration 4 weeks post-operation. Therefore, it could be concluded that magnesium-containing biomaterials not only stimulate osteogenic differentiation of stem cells but also improve angiogenesis.

Overall, the mechanisms by which MBs enhance bone regeneration include various cellular and molecular changes involving the bone, nerve, vessel, and immune systems. These direct and indirect effects are advantages of applying Mg-based materials, thus increasing their promise as candidates for bone repair. The corresponding studies taken into consideration are listed in Table 1.

## 3. History of research on magnesium as a clinical orthopedic implant biomaterial for bone injury repair

In the mid-19th century, soon after commercialization of Mg production, magnesium was first used as a biomaterial [62]. Over the next 50 years, Mg and Mg alloys were widely used for vascular, orthopedic, and general surgery. In 1900, for the very first time, Erwin Payr introduced the idea of using Mg plates and sheets in joint arthroplasties to regain or preserve joint motion [63]. As an important person who greatly promoted the musculoskeletal applications of Mg, Albin Lambotte carried out a series of clinical trials and demonstrated the feasibility of Mg-based orthopedic implants. In 1906, he conducted a trial to repair fractures of the tibia and fibula with Mg plates and steel screws in a 17-year-old boy [64,65]. Unfortunately, the Mg plate degraded at a rapid rate due to electrochemical reactions, which led to insufficient stabilization; thus, a revision surgery had to be performed on the patient. After realizing that the use of two different metals might lead to rapid galvanic corrosion, Lambotte tried to use only a Mg nail to fix supracondylar fractures in several children. Although the high initial corrosion of Mg implants led to gas cavities at the implant site, total restoration of joint function was observed without any complications 1 year after surgery [66]. Interestingly, physicians were initially worried about the formation of gas cavities with quickly corroding Mg implants, yet these cavities had no detrimental influence on the final clinical outcome. In 1934, Verbrugge, Lambotte's assistant, treated a diaphyseal humeral fracture in a child using Mg plates and screws. After 3 weeks, the Mg plate almost completely degraded, and the bone fracture healed well without obvious complications [67]. At some point in approximately 1938, McBride conducted many trials to explore the potential clinical application of Mg implants. Given the corrosion characteristics of Mg, he designed several corresponding operation

Table 1
Mechanisms underlying the osteopromotive properties of MBs.

| | Biomaterials | Mechanism | Index/Signal pathway | Cell line | Animal | Applications | Reference |
|---|---|---|---|---|---|---|---|
| Osteoblast-related | Mg rod | Osteogenesis (+) (Enhanced proliferation and/or osteogenic differentiation of stem cells) | CGRP induced activation of CREB1 and SP7 (+) | rPDSCs | rat | non-fractured/fractured femurs in rats | [34] |
| | Mg extract (0.93–26.67 mM) | | ALP activity (+) osteoblastic specific genes (+) (Mg extract concentration at 14.36 and 26.67 mM) | Osteoblasts (derived from SCP-1) | NA | NA | [44] |
| | Mg plates and screws; $MgSO_4$ solution | | Canonical Wnt signaling pathway (+) | hBMSCs | rabbit | fractured rabbit ulna | [36] |
| | $Mg^{2+}$ containing $Al_2O_3$ bioceramic | Adhesion and motility of osteoblast (+) | $\alpha5\beta1$- and $\beta1$- integrin associated signaling pathway (+) | Human bone-derived cell | NA | NA | [40] |
| | MgO/$MgCO_3$ (PLGA microspheres) | | NA | rBMSCs | rat | critical-sized cranial defects | [11] |
| | $MgSO_4$ solution | Mineralization of ECM (+) | COL10A1 and VEGF (+) (via HIF-2a in undifferentiated hBMSCs and via PGC-1a in osteogenic cells) | hBMSCs | NA | NA | [35] |
| | $MgSO_4$ solution | Osteogenesis (+) Motility of osteoblast (+) | TRPM7/PI3K signaling pathway (+) | Osteoblast (hFOB1.19) | NA | NA | [52] |
| | Mg containing Ti alloy scaffold | Cell proliferation (+), Cell adhesion (+), ECM mineralization (+) | ALP activity (+) osteoblastic specific genes (+) | Osteoblasts (MC3T3-E1 cells) | rabbit | lateral femoral epicondyles defect | [53] |
| | $MgCl_2$ solution; $Mg^{2+}$containing spheroids | Cell proliferation (+), Cell migration (+), Osteogenic differentiation (+) | MagT1 expression (+) MAPK/ERK pathway (+) | rBMSCs | rat | critical-sized cranial defects | [33] |
| Osteoclast-related | $MgCl_2$ solution; Mg extract | Cell proliferation (-) Cell differentiation (-) Cell metabolism (-) | TRAP activity (-) Cathepsin K expression (-) | osteoclasts (derived from human peripheral blood mononuclear cells) | NA | NA | [43] |
| | Mg extract (0.93–26.67 mM) | Osteoclasts differentiation (-) | TRAP activity (-) Osteoclast specific genes (-) (Mg extract concentration at 14.36 and 26.67 mM) | Osteoclast (derived from human peripheral blood mononucleated cells | NA | NA | [44] |
| | Mg2Ag nails (2% Ag) | Osteoclasts differentiation and function (-) | Number and the size of TRAP-positive cells (-) Dentin resorption (-) | Osteoclasts (derived from mice marrow-derived osteoclast precursors) | mouse | femoral fractures | [54] |
| | Mg leach liquor (MLL) | | NF-kB signaling pathway (-) $Ca^{2+}$-dependent calcineurin signaling (-) | Osteoclasts (derived from murine macrophages) | mouse | Titanium particle-induced osteolysis | [55] |
| | $MgSO_4$ solution | | NF-$\kappa$B signaling pathway (-) | murine macrophages (RAW264.7) | NA | NA | [56] |
| | Mg corrosion products | Osteoclastic differentiation (-) Metabolic activity (-) | Osteoclast specific genes (-) | hMSCs | NA | NA | [57] |

(*continued on next page*)

Table 1 (*continued*)

| | Biomaterials | Mechanism | Index/Signal pathway | Cell line | Animal | Applications | Reference |
|---|---|---|---|---|---|---|---|
| Immunomodulation | MCPC | Favorable osteoimmunomodulatory microenvironment (+) | Transform macrophage responses from the M1 phenotype to M2 phenotype (+)<br>TNF-$\alpha$ and IL-6 expression (+)<br>TGF-$\beta$1 expression (-) | murine macrophages (RAW264.7);<br>rBMSCs;<br>HUVECs | NA | NA | [46] |
| | Fibrinogen-Mg scaffolds | | Transform macrophage responses from the M1 phenotype to M2 phenotype (+) | PBMC | NA | NA | [58] |
| | Mg and Mg alloy extracts | | | Human promonocytic cells | NA | NA | [59] |
| | $MgSO_4$ solution | | TNF$\alpha$ expression (-)<br>Oxidative injury (-) | murine macrophages (RAW264.7) | rat | steroid-associated osteonecrosis | [56] |
| Angiogenesis | MCPC | Endothelial cells migration (+)<br>Angiogenin and PECAM (+) | TNF-$\alpha$ and IL-6 expression (+)<br>TGF-$\beta$1 expression (-) | murine macrophages (RAW264.7);<br>rBMSCs;<br>HUVECs | NA | NA | [46] |
| | MCPC | Tubes formation (+) | NA | HUVECs | rat | femur defect model | [60] |
| | PLGA/TCP/ Mg scaffolds | | NA | NA | rabbit | steroid associated osteonecrosis | [57] |
| | $MgSO_4$ solution | Tubes formation (+)<br>Cells migration (+)<br>Blood vessels (+) | NA | The human umbilical vein cell | rat | steroid-associated osteonecrosis | [56] |
| | Mg containing Ti alloy scaffold | Cell proliferation, adhesion, migration (+);<br>Tube formation (+) | HIF-1$\alpha$ and VEGF expression (+) | HUVECs | rabbit | lateral femoral epicondyles defect | [53] |
| | Zn/Mg-Ti alloy | NA | MagT1 transporter (+)<br>HIF-1$\alpha$ (+) | HUVECs | rabbit | implantation of bilateral mid-shaft and condyle of femurs | [61] |
| | $MgCl_2$ solution;<br>$MgCl_2$ and BMSCs containing spheroids | Neovascularization (+) | VEGF expression (+)<br>Cell migration (+) | rBMSCs | rat | critical-sized cranial defects | [33] |

"(+)" represents upregulated or promoted; "(-)" represents downregulated or suppressed.

Note: full name of the abbreviated forms used above.

NA: not applicable, rPDSCs: rat periosteum-derived stem cells, ALP: alkaline phosphatase, SCP-1: osteoblasts derived from hTERT transduced mesenchymal stem cells, Ti: titanium, hBMSCs: human bone marrow stromal cells, TRAP: tartrate-resistant acid phosphatase, rBMSCs: rat bone marrow mesenchymal stem cells, ECM: extracellular matrix, MCPC: magnesium–calcium phosphate cement, HIF-1$\alpha$: hypoxia-inducible factor-1$\alpha$, HUVECs: human umbilical vein endothelial cells, PBMCs: human peripheral blood mononuclear cells, hMSCs: human mesenchymal stem cells, PLGA: poly (lactic-co-glycolic acid), TCP: tricalcium phosphate.

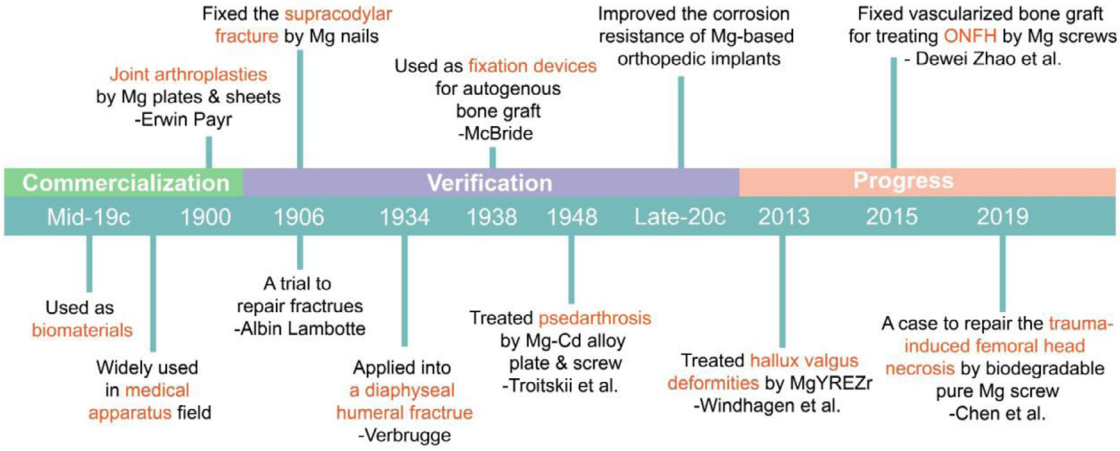


Fig. 4. Timeline of magnesium as a clinical orthopedic implant biomaterial for bone injury repair.

techniques and indicated that Mg implants were more appropriate for use as fixation devices for autogenous bone grafts [68]. In 1948, Troitskii et al. reported successful treatment of 34 cases of pseudarthrosis with a plate and screw combination made of a Mg–Cd alloy. Furthermore, researchers found that the OH- ions from degradation of Mg metal led to an increase in pH in the microenvironment, which positively stimulated the formation of a fracture callus and facilitated faster recovery in patients with osteomyelitis [69] (Fig. 4).

In the following decades, due to poor corrosion resistance, the applications of Mg-based orthopedic implants were limited. However, with the current rapid development of science and technology, the number of studies recently investigating the potential of Mg-based implants in orthopedic fields has been growing exponentially. In 2013, Windhagen et al. [20] demonstrated that screws made of the magnesium alloy MgYREZr were biodegradable and safe for treatment of mild hallux valgus deformities; furthermore, these screws were graphically and clinically equivalent to conventional Ti screws. In 2015, Zhao et al. [70] investigated the application potential of Mg screw-fixed vascularized bone grafts for treating osteonecrosis of the femoral head (ONFH). Based on multiple imaging data, Mg screws showed good corrosion resistance and an approximately 25% decrease in diameter within 12 months postoperation. Regarding the functional recovery evaluation index, the Harris hip score (HHS) was significantly improved in the Mg screw group compared with the control group (without Mg screws), indicating better treatment efficacy. In 2019, Chen et al. [71] reported treatment of trauma-induced femoral head necrosis with a biodegradable pure Mg screw-fixed pedicle iliac bone flap. Within 1 year postoperation, an image examination revealed that the volume of the pure Mg screw had decreased by approximately 69.5%, and hip function was significantly improved, with almost completely merged bone flaps. From the first explorations to the present, materials scientists, engineers and surgeons continue to devote themselves to the exploration of the advanced properties of Mg-based biomaterials for their possible benefits in clinical use.

## 4. Application of MBs in orthopedic fields

Typically, as ideal candidates for bone repair, autologous bone and allogeneic bone are the gold standards; however, they are restricted by having a limited source and the potential of immunologic rejection, respectively [72]. Currently, permanent and inert metals with the drawback of being non-degradable have been restricted for clinical use in particular situations. Novel bone implants are capable of uniformly degrading in the human body and are progressively replaced by growing tissue until the bone repair process is completed [73,74]. Additionally, they are typically equipped with desirable mechanical properties, such as appropriate strength, elastic modulus, and hardness. The values of these mechanical parameters should be comparable to or slightly higher than those of natural bone for sufficient load-bearing capacity without looseness or displacement [75]. Moreover, implants should not only be nontoxic or non-inflammatory in the human body [76,77] but also promote bone regeneration via osteoinduction and osteogenesis [78]. Given these considerations, MBs have attracted the attention of researchers due to their outstanding performance. In this section, the characteristics of various kinds of MBs are summarized and discussed. We include their biodegradation behaviors, mechanical properties and biocompatibilities, along with a systematic listing of the strong and weak points of these biomaterials to help researchers learn the current status of Mg-based biomaterials for bone repair and the promising breakthroughs in this field.

### *4.1. Mg and Mg alloys*

As a transition metal, magnesium possesses mechanical properties similar to those of natural bone and has been demonstrated to be a promising bone substitute material, as mentioned above. However, Mg suffers from poor corrosion resistance, especially in the presence of impurities; thus, Mg-based alloys, known as revolutionary metals in biomedical applications, have been prime targets for studies on biodegradable metallic implants in the past decade [72,79].

These alloys, produced by alloying magnesium with other elements, namely, Mg–Al [24,80], Mg–Ca [29,81], and Mg–Zn [82-85], are also recognized to be biodegradable and exhibit potential for use in bone repair applications. Both Mg and Mg-based alloys have been widely studied as orthopedic implants to assist with repair or replacement of diseased or damaged bone tissue.

#### 4.1.1. Mechanical

*Mechanical properties of* Mg and Mg *alloys*: Clinically useful bone implants should possess outstanding mechanical properties. Magnesium is an exceptionally lightweight metal with a density (1.74 g/cm$^3$) similar to that of natural bone (1.8–2.1 g/cm$^3$). The fracture toughness of magnesium is greater than that of ceramic biomaterials, such as HA. With its inherent biodegradability, Mg seems attractive for medical use, particularly for orthopedic implants. However, compared with natural bone (130–180 MPa), pure Mg has relatively low compressive yield strength even after processing (65–100 MPa), and thus, pure Mg is rarely used as a load-bearing implant.

In recent decades, several low toxic alloying elements have been employed to develop Mg alloy systems. As bone implants, they have inherent advantages owing to their similar Young's modulus to human bone, thereby mitigating the stress shielding effect and possessing high specific strength and high specific stiffness [86,87]. Most Mg-based alloys possess hexagonal close-packed structures with only a small number of slip planes [88]. As a result, their ductility is relatively low for bone implant application, with a low elongation rate (E) (less than 6%) and poor ultimate tensile strength (UTS) (approximately 50 MPa). Thus, further improvement is needed before Mg-based alloys can be used in load-bearing biomedical applications.

*Enhancement of mechanical properties:* To date, various methods have been proposed to obtain better mechanical properties. Grain refinement can enhance the mechanical properties of Mg-based alloys mainly by blocking dislocation motion and the dispersion of internal stress. Grain refinement is commonly achieved by adding refiners, including rare earth (RE, Ce, Y, etc.) elements or Ca, Zr, Sr, and Zn, among others. [78]. Wang et al. [89] found that the second phase in an AZ91D Mg alloy transformed from a thick mesh into a fine granular shape with the addition of Ce and Y, improving the UTS of the alloy from 124 to 213 MPa. Moreover, as Brar et al. [90] indicated, the mechanical properties of Mg were significantly improved when the grain size of the matrix decreased with the addition of strontium. In addition, deformation and heat treatment are both important ways to improve mechanical properties by regulating the microstructure and decreasing the internal stress of materials (Table 2).

#### 4.1.2. Degradation

*Mechanism of degradation in the physiological environment:* In 1906, biodegradable Mg was first employed as a fixation device to fix bone fractures [64,65]. However, several attempts failed due to the rapid corrosion of Mg and the formation of gas cavities and subcutaneous bubbles, causing a severe decrease in mechanical strength. Magnesium has high chemical activity and tends to degrade through a galvanic corrosion process [80,91]. The process of Mg and Mg-based alloy degradation primarily involves the following reactions [78]:

$$\text{Anodic reaction } Mg \rightarrow Mg^{2+} + 2e^- \quad (1)$$

$$\text{Cathodic reaction } 2H_2O + 2e^- \rightarrow H_2 + 2OH^- \quad (2)$$

$$\text{Overall reaction } Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2 \uparrow \quad (3)$$

Magnesium hydroxide accumulates on the underlying magnesium matrix, acting as a corrosion protective layer in water. However, this porous $Mg(OH)_2$ layer is likely to fall off, especially in solutions containing chlorine ions based on the following reaction.

$$Mg(OH)_2 + 2Cl^- \rightarrow MgCl_2 + 2OH^- \quad (4)$$

Thus, the $Mg(OH)_2$ layer cannot protect the Mg matrix against further corrosion, and Mg and Mg alloys are easily eroded in the human body due to the presence of chlorine ions.

*Environmental factors influencing biodegradation behavior:* As mentioned before, magnesium hydroxide is converted into highly soluble magnesium chloride in the presence of chloride ions. Therefore, the physiological environment is a corrosive environment for Mg and Mg alloys due to the high concentration of chloride ions. In addition to the chlorine ions in human body fluids accelerating the Mg and Mg alloy degradation process [92,93], many other environmental factors, such as other inorganic ions, organic buffering molecules, dissolved oxygen and stress, have also been found to influence Mg and Mg alloy biodegradation behavior [93]. Xin et al. [94] reported that $HCO_3^-/CO_2$, the most important buffering system in the human body, provided Mg corrosion protection by consuming $OH^-$ and inducing $MgCO_3$ precipitation. In contrast, an amino acid was found to reduce the protective effect of the insoluble salt layer against Mg dissolution. Moreover, altered degradation behavior induced by tension and compression has been observed for Mg biomaterials. Gu et al. [95] reported that the corrosion rates of as-cast AZ91D and as-extruded WE34 alloys were dramatically increased by cyclic tension and compression loads far below the yield tensile stress.

In addition, the area of implantation can influence the degradation of Mg-based implants. The various degradation rates of Mg screws and plates after their implantation was noted by Amy Chaya et al. [96]. They found a greater corrosion rate for the plates than the screws when using them as orthopedic devices in a loaded ulna fracture model. This difference might be attributed to the local environment. Unlike screws largely contained within bone, plates were initially covered by muscle with higher water content and blood flow than bone, both of which might cause acceleration of plate

Table 2
Representative enhancement strategies and the resulting mechanical properties of biodegradable Mg-based metals [78].

| Composition (wt.%) | Reparation methods | Post treatment | YS (MPa) | UTS (MPa) | E (%) |
|---|---|---|---|---|---|
| Mg-3Al | Casting | Solid solution treatment | 150 | 255 | 3 |
| Mg-2Ca | Rapid solidification | NA | NA | 380 | 7.3 |
| Mg-Zn-0.8Sr | Zone solidification | Heat treatment | 117 | 210 | 12 |
| LAE442 | Casting | NA | 148 | 247 | 18 |
| AZ31 | Casting | NA | NA | 260 | 15 |
| Mg-2Sr | Casting | Hot rolling | 147 | 213.3 | NA |
| Mg-6Zn | Casting | Heat treatment& extrusion | 280 | 170 | 19 |
| Mg-Y-RE-Zr | Powder metallurgy | NA | 250 | 275 | 10 |
| Mg-5.0Y-7.0Gd-1.3Nd-0.5Zr | Casting | Extrusion | 162 | 234 | 26 |
| Mg-Y | Casting | NA | 156 | 257 | 14 |
| Mg-5.0Y-7.0Gd-1.3Nd-0.5Zr | Casting | Extrusion & aging | 189 | 243 | 21 |
| Mg-3Sn-0.5Mn | Casting | Extrusion | 150 | 240 | 13 |
| ZW21 | Casting | Squeezing | 200 | 270 | 17 |
| WE43 | Casting | Heat treatment | 170 | 220 | 44 |
| WE43 | Casting | Extrusion & heat treatment | 195 | 280 | 10 |
| Mg-1Zn | Casting | NA | 89 | 187 | 11 |
| Mg-Zn-Mn | Zone solidification | Extrusion | 246 | 280 | 22 |
| Mg-Y-Zn | Casting | Extrusion | NA | 250–270 | 17–20 |
| Mg-Zn-1Sr | Zone solidification | Heat treatment | 130 | 249 | 13 |
| AZ31 | Casting | NA | 110–180 | 255–290 | 15–21 |
| WE43A | Casting | Heat treatment | 162 | 250 | NA |

Note: full name of the abbreviated forms used above.
NA: not applicable or not available, YS: yield strength, UTS: ultimate tensile strength, E: elongation rate.

corrosion [97] and would also explain the similar observation of the various degradation rates for Mg screw heads and shafts [98-101]. According to the implantation site, Remennik et al. [102] revealed that the degradation rate of implants could be ranked in the following order: subcutaneous > muscle > bone.

*Regulation of degradation behavior:* Ideal bone implants ought to have appropriate degradation rates to match the new bone restoration process after implantation and should be progressively replaced by the growing tissue until the bone repair process is completed [74,80]. For Mg and Mg alloys, despite their reported ability to enhance bone regeneration, it is necessary to improve their corrosion resistance for clinical application and thus slow the strength decay in bone repair. Several studies have indicated that Mg and Mg alloys are potential biodegradable orthopedic materials with moderate degradation rates [36].

Bare Mg alloys exhibit a wide range of degradation periods (4–52 weeks) depending on their chemical composition and processing history. Nevertheless, most of them degrade at a high rate, with fast degeneration of mechanical integrity in the body [98]. In this situation, researchers have developed different kinds of physical or chemical methods for the regulation of the degradation rate, which is independent of the implantation site [78,103]. Alloying, mixing Mg with other metals/nonmetallics, can regulate the phase distribution, grain size, and microstructure of Mg-based alloys, fundamentally improving their corrosion resistance. With heat treatment, the second phase is dissolved or uniformly distributed in the matrix. These changes reduce the adverse impact of galvanic corrosion between the second phase and the Mg matrix and play a role in inducing uniform corrosion by mitigating pitting corrosion. Liu et al. observed that the $Mg_{17}A_{l2}$ phase was distributed uniformly in an as-cast AZ63 alloy after solution treatment and aging, and the results showed that relatively uniform corrosion with a half-reduced corrosion rate was achieved compared with the untreated alloy [104,105]. Surface treatment primarily refers to generation of a surface film or passivation layer on the Mg matrix, thereby improving the corrosion resistance of Mg-based alloys at the initial stage of implantation [106-108]. Bordbar-Khiabani et al. conducted a series of studies based on the plasma electrolytic oxidation (PEO) process, a simple, low-cost and environmentally friendly method that can significantly improve the corrosion resistance and biocompatibility of biomaterials through fabrication of protective inorganic layers [109-112]. In addition, purification and deformation treatments are also effective ways to slow the degradation process of Mg-based alloys [113,114]. All these methods significantly improve the corrosion resistance of Mg alloys and ensure their gradual degradation process.

### *4.1.3. Biocompatibility*

As stated above, magnesium is essential for the human body and is naturally found in bone tissue [10]. Although this can be regarded as evidence of good biocompatibility, the magnesium ions released from implants may affect surrounding cells and tissues and may even have systemic toxicity if an excessive amount enters the bloodstream [115]. Moreover, the alloying element in Mg alloys, such as Sr and Al, can

accumulate in the human body and lead to potential health hazards [116,117]. Therefore, investigation of the cytocompatibility, histocompatibility, and hemocompatibility of Mg-based implants is necessary to evaluate their biocompatibility (Table 3).

Cytotoxicity tests can provide an initial indication of the biocompatibility of metal cations. Compared to the in vitro environment of ISO cytotoxicity test standards, the released $Mg^{2+}$ from Mg implants can be promptly diluted by the surrounding body fluid and diffuse into the circulatory system. Thus, dilution of extracts of Mg-based metals are recommended to simulate the level of in vivo degradation products for in vitro testing [118,119]. A $Mg^{2+}$ concentration of 10 mM has been reported to be the critical dose without impairment in cell viability, and 15 mM may be considered nontoxic (above 75% cell viability) [118-120]. Marrow cells treated with Mg presented a common morphology, and cellular lysis and inhibitory effects on cell growth were not detected [121]. For Mg-based alloys, while the incorporation of an alloying element significantly improved their mechanical properties and corrosion resistance as mentioned above, the alloying element of magnesium alloys can be toxic and hinder biocompatibility [117]. Accordingly, we must carefully select the alloying element and its contents. Previous studies have demonstrated that various cell lines are cytocompatible with most Mg alloys, including primary human mesenchymal stem cells, bone-derived cells, mouse fibroblasts, MG-63 human osteosarcoma cells, RAW264.7 macrophages and MC3T3-E1 osteoblasts [35]. The extract of a Mg–Zn alloy showed little impact on the morphology and proliferation of murine fibroblasts, presenting Grade 0–1 cytotoxicity [122]. In addition to no cytotoxicity toward HUVECs and MC3T3-E1 cells, Chen et al. found that extracts of Mg–Cu alloys enhanced cell viability and proliferation [19]. Several studies have reported that the quantity of aluminum released by degrading Mg–Al–Zn alloys (such as AZ31 consisting of 2–3% aluminum and 1% zinc) was within the safe range in vivo and did not exert cytotoxic or harmful effects in the biological environment [99,123-126]. Nevertheless, there has been some controversy and concern about aluminum-containing magnesium alloys due to their potential neurotoxicity (risk of dementia, senile dementia and Alzheimer's disease) [76], and more studies are needed to further verify whether they can be safely used in the human body.

In addition, hundreds of publications are available in which the in vivo biocompatibility of Mg/Mg alloy materials was evaluated to assess the feasibility of their use for biomedical purposes [78,98]. Mg alloys have been implanted in endosseous sites in various models, such as guinea pigs [24], rats [127], and rabbit femora [102], tibiae [100], and ulnae [128], all of which exhibited arguably good biocompatibility and a normal foreign body response. Furthermore, all the conducted research reported good biocompatibility of the Mg alloys, with enhanced new bone formation around the implants and in the vicinity. For the excessive hydrogen accumulation that occurs during the rapid corrosion process, Kraus et al. used micro-CT to study gas formation and Mg pin degradation in rat femora [78] and showed that gas formation closely followed the decrease in the Mg volume. Furthermore, they showed that the produced gas was largely resorbed by the surrounding tissue and did not have adverse effects on bone healing [129]. However, importantly, decreasing the formation of gas pockets is necessary for clinical translation [129]. Notably, in most of the reported cases, gas cavities were observed around Mg and Mg alloy implants due to insufficient diffusion and absorption. These gas cavities, mainly composed of hydrogen, began forming at the early stage (7–30 d) of implantation and gradually disappeared with a moderate inflammatory response [96]. To circumvent this issue, the degradation rates of Mg-based biomaterials must be decreased, thereby slowing hydrogen generation.

As summarized above, magnesium metals and alloys are lightweight, biodegradable, load-bearing, biocompatible, and possibly biologically active implant materials [127]. To date, surgeons have explored Mg and its alloys for numerous clinical applications, including their potential use in cardiovascular, musculoskeletal and general surgery [69].

### 4.2. Mg-based bioceramics and bioglasses

#### 4.2.1. Bioceramics

Bioceramics, consisting of inactive bioceramics and active bioceramics, have been investigated for a long time to repair diseased or damaged hard tissues [145]. Among them, calcium phosphate ceramics (CPCs) are commonly used in the orthopedic field because their chemical composition resembles that of bone minerals [146], including HA, tricalcium phosphate (TCP), and biphasic calcium phosphate (BCP, a mixture of HA and TCP). However, as long-term stable materials, most available CPCs may remain unchanged and are only partially resorbed in the patient's body after a year or perhaps even longer; this poor resorption potentially results in tissue inflammation and poor integration with the patient's bone [147]. Furthermore, the relatively weak mechanical properties of CPCs, in particular their low fracture toughness, greatly limit their clinical application [148]. Therefore, it is necessary to develop more reliable bone ceramics that meet the demands of orthopedic implant surgery. Magnesium-based bioceramics, including a diverse variety of magnesium-containing compounds, such as oxides, phosphates and silicates, have been an eye-catching field in the past 30 years. In this section, we summarize and discuss recent findings on the novel properties of magnesium phosphates and calcium magnesium phosphates.

*Magnesium phosphate ($MgO$-$P_2O_5$, Mg-P) systems.* Magnesium phosphate may exist in the human body within physiological and pathological mineralized tissues, such as dental calculi and kidney stones [149,150]. As bone substitutes, magnesium phosphates have been studied much less than their Ca-P counterparts. This is perhaps due to the overwhelming attention given to Ca–P. Magnesium phosphate-based cement (MPC), often called chemically bonded phosphate ceramics or cold-setting ceramics, is the primary application form for

Table 3
Strategies used to improve the corrosion resistance and biocompatibility of Mg-based alloys.

| Implants (wt.%) | Strategies | Techniques | Modified parameters | Implantation site | period | Degradation properties | | Biocompatibility | | | | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Corrosion resistance | Degradation rate or residual implant% | Inflammatory reactions | Gas formation | New bone | Bone contact | |
| AZ91 rods Naked | Surface treatment | Plasma treated | $Al_2O_3$ coating | Lateral epicondyle in rats | 2 months | + | 98% | NA | NA | ++ | ++ | [130] |
| AZ91 rod | | MAO and EPD | FHA/MAO coating | Greater trochanter of rabbits | 2 months | + | 4 mg/cm$^2$ | + | – | ++ | NA | [131] |
| AZ31 disk | | Chemical deposition method | HAp and OCP coating | Back of mice | 16 weeks | + | NA | + | - | NA | NA | [132] |
| Mg–Ca alloy (1.4 wt% Ca content) | | Alkaline heat treatment | magnesium oxide layers | NA | NA | + | 2.08–2.29 mm/year | NA | NA | NA | NA | [101] |
| Mg-Mn-Zn alloy rod | | Chemical deposition method | Ca–P coating ($CaHPO_4$•$2H_2O$ layer) | Femoral shaft of rabbits | 4 weeks | + | NA | – | NA | ++ | ++ | [133] |
| AZ31B screws | | Low temperature chemical heat treatment | Fluoride coating | Femur of rabbits | 3 months | + | NA | – | NA | + | ++ | [134] |
| Mg-Ca-Zn alloy | alloying | Alloying Zn | Improved open-circuit potential | Femoral condyle of rabbits | 24 weeks | + | NA | – | - | + | NA | [135] |
| Mg-Ag alloy | | Alloying Ag | NA | Non-fractured and fracture right femur of mice | 30 weeks | + | 0.473 ± 0.038 mm/year | NA | NA | + | NA | [55] |
| Ti containing AZ61 alloy | | Alloying Ti | decreased the volume fraction and size of the $\beta$ phase. | NA | NA | + | NA | NA | NA | NA | NA | [136] |
| Mg-Zn-Sr alloy screw | | Alloying Zn and Sr | Moderated the amounts of the deposited second phases | The tibial and femoral bone tunnel | 16 weeks | + | 0.068 ± 0.007 mm/year | – | + | + | | [137] |
| MgYREZr alloy screw | | Alloying Y, RE and Zr (RE: Nd, Yb, Er, Dy and Gd) | NA | The tibial bone tunnel | | | 0.17 mm/year | | + | + | + | [138] |

(*continued on next page*)

Table 3 (*continued*)

| Implants (wt.%) | Strategies | Techniques | Modified parameters | Implantation site | period | Degradation properties | | Biocompatibility | | | | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Corrosion resistance | Degradation rate or residual implant% | Inflammatory reactions | Gas formation | New bone | Bone contact | |
| Mg-Mn alloys | | Alloying Mn | The refinement of grains and the increase in corrosion potential | NA | NA | + | NA | NA | NA | NA | NA | [139] |
| HA containing Mg-Zn alloys | Mg-based MMC | Selective laser melting | decrease of grain size and the formation of protective layer | NA | NA | + | NA | NA | NA | NA | NA | [140] |
| ZK30/bioactive glass composites | | Selective laser melting | the grain refinement effect Protective layer of precipitates | NA | NA | + | NA | NA | NA | NA | NA | [141] |
| CNTs containing AZ31 | | NA | reduced corrosion current densities and increased corrosion potential | NA | NA | + | 0.214 mm/year | NA | NA | NA | NA | [142] |
| High-purity magnesium screws (99.99 wt% Mg) | purification | NA | in lack of second phases and micro-galvanic corrosion | Femoral condyle of rabbits | 24 weeks | + | $1.38 \pm 0.03$ mm/year for 4 weeks. $0.57 \pm 0.03$ mm/year after 24 weeks | NA | NA | + | + | [143] |
| High-purity magnesium screws (99.99 wt% Mg) | | NA | NA | Tibiae of rabbits | 52 weeks | + | NA | + | + | + | + | [144] |

Note: full name of the abbreviated forms used above.

NA: not applicable or not available, MAO: microarc oxidation, EPD: electrophoretic deposition, FHA: fluoridated hydroxyapatite ($Ca_{10}(PO_4)_6OH_2-xFx$), OCP: octacalcium phosphate, HAp: hydroxyapatite, MMC: metal matrix composites, CNTs: carbon nanotubes.

Mg–P systems in the field of bone repair and regeneration. MPC is typically formed by reacting solid magnesium oxide (or magnesium phosphate) with an acidic phosphate solution, and the specific process includes an acid-base reaction, the formation of an amorphous gel, and crystallization [147].

In the 1990s, Driessens et al. reported biomedical application of MPC for the first time. They found that bone apatite formation could be induced by MPC after 8 weeks of implantation in rats [151]. Compared with CPC, MPC possessed a shorter self-setting time and higher initial compressive strength [152], which provided crucial mechanical support at the initial stage. Furthermore, the Mg–P system has a degradation potential superior to that of Ca–P [153,154]. As with the Ca–P compounds, the physical properties of the Mg–P system can be modified by different parameters [155] or accept other ions [156-160]. Regarding biological safety, in vitro and in vivo experiments revealed that MPC possesses good biocompatibility and degradability [160]. Yonglin Yu et al. evaluated the systemic biocompatibility and genetic toxicity of MPC through in vitro tests and animal implantation, suggesting that bioresorbable MPCs were safe for use in medical applications [161].

Over the past almost 30 years, many experiments have been carried out to develop clinically adoptable MPCs, which were endowed with a more ideal combination of strength, setting time and resorption rate than calcium phosphate cements [147]. Conventional biomedical MPCs are usually prepared by reacting magnesium oxide (MgO) with ammonium or potassium phosphate salts [162]. The product, ammonium MPC, was demonstrated to be more suitable as a bone filling material with their merits of fast setting, high initial strength, and high cohesiveness properties [163]. However, ammonia or ammonia ions released from the setting reaction may lead to an unpleasant environmental odor and possibly compromise biocompatibility [164]. Some attempts were made to overcome these disadvantages by switching from ammonium phosphate to $NaH_2PO_4$ or potassium dihydrogen phosphate ($KH_2PO_4$). Fan et al. [165] showed that a potassium MPC circumvented the $NH_4^+$ issue while preserving the solidification strength; additionally, this potassium MPC had a low temperature increase, which was reduced from 90 to 50 °C, during setting. Although the maximum temperature of the setting reaction was lower for MPC than CPC (over 80 °C), their exothermicity generates a temperature that may cause tissue damage, which has long slowed their use in biomedical applications. To solve this problem, Huan Zhou et al. prepared an MPC via a novel microwave (MW)-assisted technique. They found that the developed self-setting MPC-MW could be directly injected into bone defects without any exothermicity, successfully mitigating the heat problem. Furthermore, the results showed that exposure to microwaves simultaneously improved the mechanical performance of hardened cement and reduced the setting time of both the MPC-MW and CPC-MW groups [166]. Thus, in addition to incorporating other cations, this microwave exposure also provided a novel technique for improving injectable phosphate bone cement composition [162].

To ensure good manageability characteristics, the setting times of MPC should be taken into serious consideration. In general, the first and second setting times of 8 and 15 min are suitable for most clinical applications. For an MPC, setting times can be precisely controlled by modulating and optimizing the material conditions [162]. For instance, Wang et al. [167] found that addition of different amounts of liquid into premixed acid phosphate and oxide powders increased the setting time as the liquid-to-solid ratio (L:S) increased (ranging from less than 10 to 20 min at a calcination temperature of 1500 °C). Moreover, the results indicated that the setting time increased significantly as the calcination temperature increased. Similarly, researchers improved the setting time of MPC by controlling the powder size, surface area, and reactivity [162]. However, the various material conditions may change the microstructure of MPCs and even decrease their compressive strength [167]. Reaction retardants, especially borax, are a simple and effective approach for delaying the setting reaction when the setting time of the MPC is too fast (approximately 3 min), while the bioactivity of current retardants is limited. In this context, another more versatile approach, namely, the development of a composite system, was proposed; suitable bioactivity and physicochemical properties were sought using this composite system [168,169]. Recently, Li et al. [170] developed magnesium phosphate-borosilicate glass bone cement (MPC-BG) by incorporating borosilicate bioglass (BG) into the MPC. The results showed that the setting time was extended with the increase in BG content for all MPC-BGs, and the corresponding setting time was $9.9 \pm 0.7$ min when the MPC/BG ratio was 3:1. On the other hand, the manageability characteristics of MPC are also affected by its injectability, which is clinically important for application in minimally invasive surgeries or for filling of complicated defect sites. Cohesion is intricately related to injectability. The common methods for enhancing injectability by improving cohesion include the addition of additives and increasing the viscosity or altering the wettability of particle surfaces [171-174].

All the above results indicate that MPC exhibits comparable biocompatibility, a higher dissolution rate and better mechanical performance than CPCs, thereby providing a strong alternative to calcium phosphates for clinical applications [161,162,166]. To date, most magnesium phosphate-related studies have focused on orthopedic cements. Among the available MPCs, Thomas Lally's work led to development of the Launches OsteoCrete (U.S.) product form Bone Solution, Inc. (BSI), which is the only magnesium-based cement formulation that has been approved by the FDA and is now used in long-bone and pelvic applications [175].

*Calcium magnesium phosphates (*$CaO–MgO–P_2O_5$*):* The $CaO–MgO–P_2O_5$ system is mostly referred to as magnesium-doped (substituted) calcium phosphates. Most of these materials are synthesized with aqueous media, and the end products of precipitation primarily depend on the solution composition, especially the Mg/Ca and $PO_4^{3-}$ values [176,177].

The products of $Mg^{2+}$ substitution into calcium phosphates can cause a series of changes to the physical and biological

properties of the host. Similar to the negative effects of $Mg^{2+}$ on HA nucleation and growth in the biological mineralization process, the substitution of various calcium phosphates with $Mg^{2+}$ can be disruptive to the crystalline lattice, resulting in an amorphous phase or less stability and greater solubility in many cases [178-184]. In HA, up to 10 at.% of calcium can be substituted with magnesium [185,186], and the degree of crystallinity of Mg-substituted HA decreases with increasing $Mg^{2+}$ content [187,188]. When the total concentration of magnesium reaches 30 at.% in HA, the excessive $Mg^{2+}$ ions can be stored in the amorphous phase and/or on the crystal surface. These $Mg^{2+}$ ions can reduce the crystallinity and/or increase surface hydration [189]. Consequently, magnesium-doped HA displays increased solubility.

In contrast, addition of Mg ions was reported to harm $\beta$-TCP dissolution. After immersing different $\beta$-TCP samples in acidic solution (pH 4.4) for 1 h, Marta Gallo et al. observed that the percentage of the etched surface of samples significantly decreased when the Mg content increased, with 54%, 40% and 20% for the nondoped $\beta$-TCP, low Mg-doped and high Mg-doped samples, respectively. Characteristic spike-like subcrystals resulted from etching in nondoped and low Mg-doped samples but not in high Mg-doped samples. Moreover, they found that doping with magnesium impacted the lattice parameters of $\beta$-TCP, changing the crystal orientations that preferentially resorbed. It was concluded that doping with magnesium impacted the lattice parameters of $\beta$-TCP and further stabilized the $\beta$-TCP phase against dissolution [190]. Similarly, Lee et al. synthesized magnesium-doped brushite with different Mg/(Ca+Mg) ratios (0%, 14%, and 50%) through a precipitation process. The results indicated that magnesium substitution could stabilize brushite and impede its conversion to HA, while excessive $Mg^{2+}$ might be retained at the interstitial site of the brushite structure, which would dramatically distort the structure and inhibit crystallization [191]. In addition, substitution of TCP with $Mg^{2+}$ can also stabilize $\beta$-TCP at high temperatures (up to 1600 °C) [192,193].

On the other hand, magnesium-doped CaP displays a better biological performance than pure CaP. Doping CaP with magnesium was reported to significantly enhance osteoblast attachment and growth compared to the use of pure CaP. Similarly, a calcium magnesium silicate bioceramic (Akermanite) promoted more osteogenesis, biodegradation, and bone formation than $\beta$-TCP after being implanted in rabbit test subjects [183].

The abovementioned findings reveal that calcium magnesium phosphates display different physicochemical properties depending on the degree of magnesium substitution. Therefore, it is feasible to obtain superb Ca–Mg–P bioceramics by modulating the Mg/(Ca+Mg) ratio.

#### 4.2.2. Bioglasses: magnesium glasses ($SiO_2-MgO$)

In bone regeneration, bioactive glasses are more impressive than bioceramics owing to their significant advantages. In addition to their ability to form a strong bond to both hard and soft tissues, bioglasses can improve gene expression in osteoblasts and angiogenesis through dissolution products [194,195]. In the 1970s, Hench and coworkers made the first bioglass, currently known as 45S5, which displayed excellent bioactivity and osteoconductivity [196]. However, 45S5 and in general other bioglasses tend to crystallize during thermal treatment. The residual glassy phase is degraded preferentially, likely reducing the bioactivity of the final system and leading to implant instability [197]. Thus, development of new bioactive glass compositions with a low crystallization tendency is crucial.

E. Verné et al. reported the high stability and low crystallization tendency in $Mg^{2+}$-containing glass as a result of elevated crystallization temperatures [198]. In bioactive $SiO_2-MgO$ binary systems, MgO plays different roles in the glass network: acting as a modifier or as an intermediate oxide or exhibiting anomalous properties [189]. Watts et al. progressively replaced CaO with MgO in a $49.5SiO_2–1.1P_2O_5$-(23.0(1-x))CaO–xMgO–$26.4Na_2O$ (mol%) system (where $0 \leq x \leq 1$). They found that a portion of the MgO (≈14% in the glasses studied) acted as a network intermediate and entered the silicate network of the bioactive glasses. Consequently, the addition of MgO decreased both the glass transition temperature and dilatometric softening point values while increasing the thermal expansion coefficient values, endowing the MgO-containing glasses with a large processing window and thereby enabling processing without crystal formation [199]. Hand et al. observed that addition of MgO to the bioglasses system caused a decrease in elastic modulus, hardness, and brittleness and led to an improved fracture toughness with increasing MgO content [200]. Previous studies have demonstrated that $Mg^{2+}$ can create a tight glass network attributed to its high Dietzel ionic field strength [201]. The other beneficial effects of doping Mg ions into a glass composition include antibacterial efficacy [202], high thermal stability, surface reactivity [203], and glass dissolution via disruption of the silica glass network [204].

As mentioned above, magnesium-based bioceramics and glasses have been investigated for a long time and show great potential as bone replacement materials, particularly MPCs because of their relatively high strengths [204]. Additionally, the sustained release of $Mg^{2+}$ can steadily stimulate bone regeneration. Nevertheless, there is still much room for further improving these materials. For example, compared with natural bone, the mechanical properties of Mg-based ceramics and glasses, especially their compressive strength and brittleness, are still not completely desirable. Further experimental work in large animal models (preferably at partial load-bearing application sites) is necessary to evaluate their biological performance.

### 4.3. Biopolymer-based composites

Biopolymers, consisting of natural and synthetic polymers, have been widely developed for use in biomedical applications [203,205,206]. Among these, polyesters have been

increasingly studied due to their good biocompatibility and biodegradability. Some of them have already been approved by the FDA [207] and are extensively used in biomaterials ranging from sutures to vascular stents and bone substitutes [208-210]. Nevertheless, further studies have shown that the acidic degradation products of polymeric devices may result in local inflammation and infection, which eventually may lead to implant failure [206,211,212]. Moreover, these biopolymers exhibit poor mechanical properties [206], low hydrophilicity, and poor cellular interaction [213]. Thus, all these limitations restrict their use in bone repair applications. To specifically address these problems, composite and blend strategies have been employed. Strategies based on incorporation of different magnesium compounds can potentially provide biodegradable polymers with enhanced mechanical properties and improve their biofunctionality.

#### *4.3.1. Neutral degradation*

Controlling the acidic byproducts of biodegradable polyesters remains a major clinical challenge. In the orthopedic plant field, acidic degradation not only carries a risk of inflammation but can also inhibit full bone regeneration as a result of the unfavorable microenvironment. Implantation of polyglycolide or lactide-glycolide copolymers as internal fixators has been reported to lead to a clinical manifestation of foreign reactions in some patients. In addition to fluctuant swelling, the liquid remnants of degrading implants and an abundance of giant cells were found at the implantation site [212].

Conversely, $OH^-$ ions from degradation of Mg and Mg alloys lead to an increase in pH in the microenvironment [67]. Thus, it is hypothesized that the acidic degradation of polymers can be buffered by the basic degradation products of Mg and Mg alloys. Xu et al. developed self-neutralizing polymer/metal composite biomaterials by combining PLGA with magnesium metal or an alloy (ZK61). Through a simple process, they produced PLGA samples with different magnesium compositions (1, 3, 5, and 10 wt%) using the solvent-casting method. The results indicated that the addition of magnesium could buffer the acidic pH that results from PLGA degradation, and it was found that the PLGA composite with 5 wt% Mg showed a near-neutral degradation pattern under sink conditions [214]. To circumvent these inherent drawbacks of Mg and Mg alloys, Yuan et al. chose MgO and $MgCO_3$ as alternative $Mg^{2+}$ suppliers and encapsulated $MgO/MgCO_3$ particles in PLGA microspheres at different weight ratios. Based on a degradation behavior test, they found that the medium pH was closely related to the $MgO/MgCO_3$ ratio: without $MgCO_3$ ($MgO/MgCO_3$ ratio of 1:0), the medium pH increased significantly within a short time but then rapidly decreased; however, the pH values of media from other groups ($MgO/MgCO_3$ ratio of 3:1, 1:1, 1:3 or 0:1) were stable at a pH of approximately 7 with soaking time[11]. In addition, magnesium hydroxide and other Mg composites have been reported to inhibit acidification caused by polymer degradation and to ameliorate inflammatory responses [215,216].

#### *4.3.2. Mechanical strength*

Currently, biodegradable polymers are used as fixation devices, such as screws [217], pins [218] and darts [219], for soft tissue, cartilage, and pediatric craniotomy fixation. However, their mechanical properties are still inferior to those of other used materials [220]. In contrast to polymers, Mg and Mg alloys have high mechanical strength and stiffness and are beneficial in roles requiring promotion of osteogenesis [98]. Unfortunately, maintaining the mechanical properties of Mg and Mg alloys is difficult as a result of their rapid corrosion rate. To overcome the aforementioned problems, novel materials, consisting of composites of PLA and Mg or Mg alloys, have been proposed. Xu et al. incorporated Mg or Mg alloys into PLGA films and found an increase in the tensile modulus of the PLGA/Mg composites with an increase in Mg loading [214]. Cifuentes et al. constructed a polymer/magnesium composite and observed that the mechanical properties of the polymer matrix (PLLA) were significantly enhanced after reinforcement with Mg particles: the hardness increased from 150 to 340 MPa, the yield strength increased from 58 to 101 MPa, and the Young's modulus increased up to 8 GPa and approached values similar to that of bone. Furthermore, the similar crystallinity of the unloaded and loaded PLLA indicated that the improvement in mechanical properties was purely the effect of particle reinforcement [221]. Additionally, the enhanced corrosion resistance was beneficial for maintaining the mechanical properties of the materials. Thus, the combination of polymers and Mg/Mg alloys counterbalanced the weak mechanical properties of polymers and the relatively poor corrosion resistance of Mg/Mg alloys.

#### *4.3.3. Bacteriostatic and bactericidal effects*

Periprosthetic infection is a clinically challenging complication and the cause of most implant failures. In this situation, the implant surface serves as a substrate for bacterial adhesion, colonization and biofilm formation [222,223], and the emergence of bacterial biofilms further increases the risk of antimicrobial resistance [224,225]. A previous investigation identified antibacterial activity that stemmed from the corrosion products of Mg degradation, for instance, an increase in local alkalinity [226] and a decrease in bacterial adherence, colonization, and biofilm formation [227]. Therefore, magnesium ions were proposed to play an important role in the bactericidal and bacteriostatic potential of MBs [228].

Because of the bactericidal effect associated with $Mg^{2+}$ in vitro and in vivo [229], Mg composites are used as bone substitutes not only for promoting bone regeneration but also for preventing orthopedic implant infection. Compared with the neat polymer, composites of poly-L-D-lactic acid (PLDA) loaded with Mg microparticles possessed better antibacterial activity while preserving good cytocompatibility. With exposure to PLDA/Mg composites, the viability of Staphylococcus epidermidis, one of the most frequently encountered infections in trauma surgery, decreased by up to 65.3% compared with the use of only pure PLDA, owing to the damage to the

bacterial wall induced by the PLDA/Mg composite [230]. In addition to Mg metals, other magnesium composites can act as an alternative to $Mg^{2+}$. For example, Yuan et al. reported that introduction of MgO particles into PLGA microspheres produced excellent bacteriostatic efficacy and reduced the viability of S. aureus to $35.8 \pm 3.8\%$ [11]. In addition to $Mg^{2+}$, some authors have suggested that the antibacterial mechanism of MgO particles includes production of superoxides on the surface and an increase in the pH value in the microenvironment [231,232]. Nevertheless, the antibacterial effect of $Mg^{2+}$ is still limited due to the lack of a uniform concentration at the implantation site. On the other hand, polymers provided MBs with the potential to achieve controllable degradation and tunable $Mg^{2+}$ release, along with their potential use in drug delivery. Thus, magnesium-reinforced polymers display better mechanical and biological properties. Overall, incorporating magnesium composites presents an effective strategy for counteracting the acidic byproducts of biodegradable polyesters.

## 5. MBs and their various clinical application forms

### 5.1. Bone cement

Mg-based bone cement mainly refers to MPCs and is typically made from magnesium oxide (or magnesium phosphate) and an acidic phosphate solution via an acid-base reaction [155,233]. Compared with CPCs, MPCs are the hydraulic cements most commonly used as synthetic bone grafts because they are more comparable to the ideal standard with a desirable setting time, high strength and moderate degradation rate [162,234]. Gemma Mestres and coworkers developed magnesia-phosphate cements containing different amounts of sodium dihydrogen phosphate and measured the setting time with Gilmore needles [234]. The results indicated that the setting times of the MPCs were between 8 and 15 min; additionally, they found that the setting process was very fast and that the plastic paste could turn into a solid body in 1 min. Thus, the MPCs had good handling characteristics and would be acceptable for clinical applications. Importantly, all these MPC formulations showed much higher initial compressive strength than CPCs, with values approximately 30 times higher after 1 h and 6–10 times higher after 2 h. The initial compressive strength allows for early mobility of the patient after cement implantation. As one of its highly attractive properties, the mechanical strength of MPCs is often more than 50 MPa [162], with an observed maximum of 85 MPa [235]. Some authors have found that the mechanical properties of MPCs can be regulated by parameters such as the P/Mg ratio, particle size, and curing conditions [236].

However, the currently available MPCs perform poorly under tension and torsion conditions and are not suitable for load-bearing applications due to their brittle mechanical fracture behavior [147]. Thus, great efforts are needed to improve the mechanical strength of MPCs before their wide application as bone substitutes (Table 4).

### 5.2. Fixation devices

Mg bone-fixation devices mainly include magnesium metals and alloys made of bone screws, pins and plates. In 1906, Lambott et al. conducted the first trial of leg fracture fixation with Mg plates and steel nails. However, within a few days of implantation, the implant was subcutaneously inflated, and insufficient stabilization occurred as a result of corrosion of the materials [64]. Similar results were observed with the rapid corrosion of magnesium and the formation of gas cavities in several studies [65,238,239], resulting in an increase in the authors' concern about the risk of implantation failure. Despite some reports of successful bone fracture treatments with Mg screws and/or plates [67,68], researchers have long been stymied by the poor corrosion resistance of Mg. With the progress in science and technology, renewed enthusiasm among researchers for developing magnesium implants has emerged in the last 20 years [70,71,240]. Recently, Baver Acar reported that biodegradable Mg-compression screw fixation displayed a therapeutic efficacy similar to that of Ti-screw fixation for a modified distal chevron osteotomy in hallux valgus, presenting an alternative bioabsorbable fixation for surgery.

Apart from pure magnesium, the development of various Mg alloys has recently accelerated. As mentioned above (Mg alloy parts), numerous methods have been proposed for enhancing the performance of Mg alloys as bone fixation devices, especially their degradation behavior and mechanical properties. With their inherent advantages, improved Mg alloys have become widely used for bone fixation in clinical trials. In one study, screws of the magnesium alloy MgYREZr were used to treat mild hallux valgus deformities and showed a similar treatment effect as standard titanium screws [241]. In a long-term clinical study, Lee et al. applied a Mg–Ca–Zn screw to fix 53 radius fracture cases. The results showed that the controlled degradation of these alloys prompted the bone formation process by biomimicking the calcification matrix at the degrading interface. Thus, the Mg implants were completely replaced by new bone within 1 year of implantation [242]. Most importantly, some Mg alloys have received approval for clinical use in some countries [12].

Overall, magnesium metals and alloys exhibit good mechanical properties, biocompatibility and osteopromotive efficacy but may suffer from poor corrosion resistance. Fortunately, their biological performance has significantly improved in recent decades with the application of various methods and techniques. Therefore, magnesium metals and alloys are promising orthopedic implant materials (Table 5).

### 5.3. Mg-based bone tissue engineering materials

Recently, bone tissue engineering (BTE) materials have attracted much attention due to their excellent bone regeneration ability in vivo [256]. As a key factor of BTE materials, scaffolds provide a three-dimensional space for cell adhesion, proliferation, osteogenic differentiation and consequent bone formation. The ideal scaffold needs to meet various

Table 4
Comparison of current bone grafts and substitutes.

| | | Osteo-conduction | Osteo-induction | Osteo-genesis | Osteo-integration | Structural support | Disadvantages | References |
|---|---|---|---|---|---|---|---|---|
| Autologous Bone Grafts | Autologous Cancellous | +++ | +++ | +++ | +++ | – | Limited availability and donor site morbidity | [237] |
| | Autologous Cortical | ± | + | + | + | +++ | Same as above | |
| Allogeneic Bone Grafts | Allogeneic Cancellous | + | ± | – | ++ | – | Risk of disease transmission and immune reaction | |
| | Allogeneic Cortical | + | – | – | + | +++ | Sam as above | |
| | DBM | + | ++ | – | ++ | ± | Variable osteoinductivity associated with donors and processing methods | |
| Synthetic Bone Substitutes | Calcium sulfate | + | – | – | ++ | + | Rapid resorption,osteoconductive only | |
| | HA | + | – | – | – | ++ | Slow resorption,osteoconductive only | |
| | Calcium phosphate ceramic | + | – | – | + | ++ | Osteoconductive only | |
| | Calcium phosphate cement | + | – | – | + | + | Osteoconductive only | |
| | Bioactive glass | + | – | – | – | – | Bioactive osteoconductive only | |
| | PMMA | – | – | – | – | +++ | Inert, exothermic,monomer-mediate toxic | |
| | MPCs | + | – | – | ++ | ++ | brittle mechanical fracture behavior | [162,189] |

"+" represents present; "-" represents absent; ±, represents variable.
Note: full name of the abbreviated forms used above.
DBM: demineralized bone matrix, HA: hydroxyapatite, PMMA: poly (methyl methacrylate), MPCs: magnesium phosphate-based cements.

requirements, especially good biocompatibility, an appropriate mechanical strength and a high porosity that is similar to natural bone [257-259]. Magnesium scaffolds have been widely studied for BTE materials owing to their osteopromotive properties and other advantages [260], and many valuable strategies and techniques have been proposed for enhancement or modification of advanced Mg scaffolds. To avoid the rapid loss of mechanical support and unfavorable inflammatory response during Mg corrosion, Chen et al. coated Mg scaffolds with $\beta$-TCP. They found that in addition to an increased corrosion resistance, the modified Mg scaffolds combined the beneficial properties of both materials; thus, these modified Mg scaffolds not only inhibited inflammation but also concurrently shifted the immune microenvironment toward one that favored osteogenesis over osteoclastogenesis. This finding also demonstrated that endowing bone implants with osteoimmunomodulatory properties could be an effective strategy to achieve excellent performance [261].

In addition, the interconnected pore structure and defined porosity of scaffolds are crucial for BTE materials, providing a favorable microenvironment for nutrient and metabolite discharge. Although different methods to obtain porous Mg scaffolds have been introduced [256], there are still many difficulties in accurately controlling the pore morphologies and mechanical properties. Cheng et al. [262] innovatively fabricated open-porous magnesium scaffolds through the titanium wire space (TWSH) method. They produced Ti-Mg composites by immersing three-dimensional entangled Ti wire into high purity Mg melts and then removed the Ti wires with an HF solution. Thus, an open-porous Mg scaffold with controllable microstructures and mechanical properties was produced. Scaffolds with large pore sizes were more favorable for early vascularization and enhanced collagen type 1 and OPN expression, thereby increasing bone mass and mature bone formation. Jia et al. [263] used spherical and irregular polyhedral NaCl particles to make open-porous templates and produced spherical-pore and irregular-pore Mg scaffolds, respectively, through the infiltration casting process. The spherical-pore Mg scaffold with good interconnectivity and structural integrity might be more suitable for use in clinical applications. Of the emerging technologies, laser additive manufacturing has also been applied to produce ideal Mg scaffolds and shows advantages in fabricating complex porous and customized implants [256,264]. Remarkably, further integration of multiple fields of science (nanotechnology, stem cell science and other fields) will continue to prompt the development of Mg scaffolds, especially material/cell hybrids, to achieve better performance. Thus, these scaffolds continue to be a research focus due to their potential use in clinical applications.

Table 5
Representative Mg-based fixation devices compared with other materials in vivo.

| Mg-based devices | Control | Applications | Animal species | Degradation properties | Biological performance | References |
|---|---|---|---|---|---|---|
| Pure Mg Interference screw | Ti | ACL reconstruction | Rabbit | ≈10% volume loss after 16 weeks | Improved tendon graft healing with accelerated mineralization at the tendon-bone interface | [243] |
| Pure Mg Screw | PLA | Femoral intracondylar fractures | Rabbit | ≈30% volume loss after 24 weeks | Enhanced fracture healing | [143] |
| Pure Mg Screw and plate | Ti | Ulna fractures | Rabbit | 0.40 ± 0.04 mm per year | Abundant bone formation around Mg devices;No difference in flexural weight of healed ulnae with Mg devices compared to intact ulnae | [244] |
| Pure Mg Ring | Suture | Repair of the transected ACL | Goat | NA | Improved postsurgical knee function as compared to regular suture repair | [245] |
| Pure Mg Intramedullary pin | stainless steel | Femoral fractures | Rat | NA | Accelerated fracture healing | [34] |
| Pure Mg and Mg alloy (AZ31) Screw | NA | Insertion into cortical bone | Rabbit | the volume fraction of the screw head after 12 weeks: 31.3% for pure Mg and 61.5% for AZ31 | Bone growth around both screw types; Significant bone overgrowth for AZ31 compared to pure Mg | [246] |
| Pure Mg Screw | Ti | Tibial fractures | Rabbit | NA | Increased callus formation at the fracture gap | [247] |
| Mg alloy (Mg-Zn-Sr) Interference screw | PLA | ACL reconstruction | Rabbit | Complete degradation within 16 weeks | Increased bony ingrowth and decreased loss of the peri-tunnel bone tissue | [137] |
| Mg alloy (MgYREZr) Screw | Ti6Al4V | Tendon-bone insertion | Rabbit | ≈25% volume loss after 4 weeks | Stable fixation of the tendon graft and no inflammatory reactions | [248] |
| Mg alloy (Mg–Ag) Intramedullary pin | Stainless steel | Femoral fractures | Mouse | Complete degradation within 133 days | Increased callus formation around the fracture gap | [249] |
| Mg-Zn alloys (ZX50 and WZ21) Pin | NA | Insertion into cortical bone | Rat | ZX50: complete degradation within 12 weeks; WZ21: ≈60% volume loss after 24 weeks | Improved osteoconductive properties for WZ21 pins | [129] |
| Mg alloy (LAE442) intermedullary interlocked nail and screw | Stainless steel | Insertion into bone marrow medullary cavity | Sheep | ≈0.33% and 10% volume loss for nail and screw after 24 weeks | Moderate gas formation and predominant direct bone-to-implant contact without alterations of bone | [250] |
| Mg alloy (Mg-Y) Scaffold | NA | Insertion into femoral condyle | Rabbit | Over 93% volume loss after 12 weeks | No foreign-body reaction and gas formation | [251] |
| Mg alloy (AZ31B) Screw | PLA and Ti | Insertion into the femoral shaft | Rabbit | NA | Improved extraction torque in the coated AZ31B group when compared to other groups | [252] |
| Mg alloy (Mg-Zn-Ca) Pin and screw | Ti | Insertion into the bone shaft of growing animals | Rat and sheep | Rat: 0.08 mm per year; Sheep: 0.045 mm per year | Without inducing serious gas evolution and foreign body response | [253] |
| Mg alloy (Mg-Zn-Ca) Screw | NA | Insertion into the femoral condyle | Rabbit | NA | Excellent biocompatibility and negligible production of hydrogen gas | [254] |
| Mg alloy (AZ31, AZ91, WE43 and LAE442) Pin | PLA | Insertion into femoral cavity | Guinea pig | Lowest in vivo degradation rate for LAE442 compared to other three alloys | Increased new bone formation around Mg rods | [255] |

Note: full name of the abbreviated forms used above.
NA: not applicable, Ti: titanium, ACL: anterior cruciate ligament, PLA: poly (lactic acid), PCL: polycaprolactone.

## 6. Challenges and prospects

Although many encouraging achievements have been made in the field of Mg-based orthopedic biomaterials, with some of these materials having been approved for clinical trials, there are still some issues that need to be resolved before their broad clinical application. Descriptions of some of the challenges as well as future research directions are provided in the following sections.

### *6.1. Improvement of mechanical properties*

The main function of bone implants is to provide structural support for the injured tissue during service. However, the mechanical strength of current MBs remains inferior to that of native bone. For this reason, the clinical applications of Mg-based materials at this time are expected to remain predominately relegated to semiload- or nonload-bearing sites. In this respect, incorporation of other inorganic or organic materials, such as alloying other metal ions with Mg and incorporation of retardants into MPC ceramics, has resulted in certain successes. For most Mg-based materials, optimization of experimental parameters and conditions will significantly improve mechanical properties, and the effect of grain size on Mg-based ceramics is a good example. Additionally, composite systems consisting of multiple materials broaden the potential applications of Mg-based implants, especially for ceramics and glasses, which are inherently brittle.

### *6.2. Degradation rate*

The time to achieve hard bone union varies greatly according to the fracture configuration and location, status of the adjacent soft tissues and patient characteristics [98], and the bone fracture healing process is highly sensitive to the degradation rate of the fixation materials. With deeper knowledge of the effect of dynamic degradation on the morphological and mechanical properties of bone implants, researchers have realized the significance of a moderate degeneration rate for obtaining an ideal biological performance [256]. Importantly, an ideal bone implant should perfectly match the injured tissue reconstruction process in terms of providing temporary mechanical support and then completely dissolving at an appropriate degradation rate. However, most Mg-based biomaterials degrade at a high rate, with a rapid decrease in the mechanical strength of the body, resulting in poor durability. Hence, there is still much room for improving the degradation performance of MBs while preserving the mechanical properties and biocompatibility.

### *6.3. Controllable $Mg^{2+}$ release*

An insufficient $Mg^{2+}$ intake is known to lead to bone osteoporosis or dysplasia due to a decrease in the mechanical strength of bone and a loss of bone mineral density. On the other hand, a high $Mg^{2+}$ concentration can inhibit bone biomineralization at the early stage. Recently, some authors explained the contradictory phenomena of the role of $Mg^{2+}$ in bone biomineralization from a developmental perspective [265]. They found that an appropriate concentration of $Mg^{2+}$ promoted the mineralization of bone marrow mesenchymal stem cells, while excessive $Mg^{2+}$ could impair osteogenesis, thereby changing the crystalline morphology of HA and inhibiting collagen calcification. In particular, the earlier $Mg^{2+}$ was added, the stronger the observed inhibition of mineralization. These results indicate that appropriate regulation of $Mg^{2+}$ concentration over time is vital for normal biological crystallization. Furthermore, other studies have claimed that excessive $Mg^{2+}$ ingestion may result in hypermagnesemia (a serum $Mg^{2+}$ level exceeding 1.1 mM) and certain systemic symptoms, such as muscular paralysis and hypotension [115]. Thus, this knowledge is significant for the future design of orthopedic implants associated with $Mg^{2+}$ content, and we should try to achieve controllable release of magnesium ions from materials.

### *6.4. Development of multifunctional Mg bone implants*

Magnesium-incorporated materials possess some advantages as orthopedic implants due to their osteopromotive properties, while numerous reports indicate that better experimental results may be achieved with enhanced antibacterial performance, such as with incorporation of antibacterial ions. For example, Rtimi and colleagues used Ag and Cu, metals with broad bactericidal spectra, as alloying elements to develop antibacterial Mg alloys, which showed strong bactericidal activity and long-term antimicrobial activity [266]. In addition, over the past few years, since the introduction of various therapeutic agents, especially growth factors, which are of significance for bone regeneration, drug delivery systems containing MBs have increasingly been developed and studied. Yang et al. developed Mg/PLLA composite microspheres as a novel delivery system. Their results demonstrated the feasibility of tailoring the drug release profile and alleviating PLLA-induced inflammation by varying the Mg content or size. Similar controlled delivery of drugs was also confirmed in Mg-based materials with surface coatings, particularly a variety of polymer coatings [267]. Remarkably, mesoporous materials are also an ideal drug carrier, which will be a new research direction for Mg-based sustainable drug release systems.

### *6.5. Innovative technologies and methods: additive manufacturing*

While magnesium-based implants for bone repair have been intensively studied and some have been successfully introduced into the market, patient-specific implants or porous scaffolds are difficult to obtain. Fortunately, the emergence of additive manufacturing provides a solution for the increased demand for customized bone implants and scaffolds. This promising technology may achieve the production of geometrically complex and porous structures, which are expected to have excellent mechanical properties and corrosion behavior. To date, additive manufacturing has already been applied to a

Table 6
Fabrication methods for Mg-based orthopedic implants.

| | Technique process | advantages | examples | reference |
|---|---|---|---|---|
| Casting | Cast with a designed chemical composition (heating the metal components above the melting point in a melting furnace)<br>Pouring the liquid phase into the as-designed mold,<br>Solidify into part with a protective atmosphere (such as $SF^6$ and Ar) | Convenient operation,<br>high productivity,<br>high precision,<br>high surface quality<br>low spending | Mg-Cu alloys<br>Mg-Ag alloys<br>Mg–Sr alloys<br>Mg-Si-Sr alloys | [270]<br>[271]<br>[272]<br>[273] |
| Wrought techniques | Apply mechanical force to deform a bulk metal into parts with desired shape, in an above/below its recrystallization temperature. (hot working or cold working)<br>Commonly used wrought techniques in the fabrication of Mg bone implants: rolling, forging and extrusion. | Fabricate desired shape | Mg–X alloys ($X$ = Gd, Ca, Al, Mn, Sn, Sr, Nd, La, Ce, Zr or Si)<br>Mg-2.0Zn-0.5Zr-3.0Gd alloy | [274]<br>[275] |
| Powder metallurgy method | Pressed the original powder into desired shape under high pressure;<br>A high temperature sintering in a furnace with protective atmosphere.<br>The powder particles achieve a sintering densification by a series of physical and chemical processes. | Fabricate desired shape | Mg–HA Composite<br>MgO/ZK60 nanocomposites<br>Mg-Zn scaffolds<br>Mg-Ca alloys | [276]<br>[277]<br>[83]<br>[278] |
| Laser additive manufacturing | Converting the 3D model into STL file<br>Spreading a layer of metal powder evenly on the forming cylinder;<br>Controls the laser beam to selectively scan the powder layer, and obtain a single layer entity;<br>The height of the molding cylinder is lowered by one layer, and a new layer of powder was paved by the roller. | Net-shape fabrication, rapid fabrication basing on as-designed model, excellent process flexibility; high material utilization rate | porous magnesium<br>magnesium scaffolds<br>WE43 | [265]<br>[279]<br>[280] |

titanium alloy, a Co alloy and stainless steel in the production of conventional implants [268,269].

However, the close melting and boiling points of magnesium pose some obstacles for laser additive manufacturing of magnesium materials. Typical defects are common during laser manufacturing of Mg [269,270]. In view of the above-mentioned issues, further research on the mechanisms affecting processing parameters is necessary. The corresponding fabrication methods are summarized in Table 6.

## 7. Conclusions

Biodegradable materials are very promising in the next generation of orthopedic implants. Based on the excellent biodegradability and biocompatibility of magnesium, various Mg-based biomaterials, including magnesium-based metals, alloys, bioceramics, bioglasses and polymers, have been investigated for their potential as biodegradable bone repair materials. Each of these materials has unique physical and chemical properties while exhibiting similar biological performance and enhanced bone regeneration in bone repair treatments. Numerous basic studies have confirmed the vital role of magnesium in bone regeneration in vitro and in vivo. Although most Mg and Mg-based materials suffer from unsatisfactory corrosion resistance and/or mechanical properties and have therefore been limited to nonload-bearing bone applications, the emergence of innovative technologies and methods has provided new solutions for overcoming these constraints. Notably, the majority of in vivo experiments employing MBs were performed in small animal models, and these results are difficult to transfer to human applications. Therefore, before preclinical and clinical studies, further experimental work in large animal models, especially at load-bearing application sites, is necessary to comprehensively investigate the potential of MBs as orthopedic implants. With the continuous improvement of Mg-based biomaterials, the new generation of bone implant materials will likely have a broad range of potential applications and improve the well-being of patients.

## Author contributions

All authors have approved the final version of the manuscript.

## Declaration of Competing Interest

There are no conflicts to declare.

## Acknowledgments

We acknowledge financial support from the National Natural Science Foundation of China (No. 81672230), the Natural Science Foundation of Chongqing (No. cstc2020jcyj-msxm2234), the Top-notch Young Talent Project of Chongqing Traditional Chinese Medicine Hospital (No. CQSZYY2020008), and the Chongqing Graduate Research Innovation Project (No. CYS20199). Dr. Kexiao Yu does his postdoctoral program in the joint training station by

Chongqing Medicial University and Chongqing traditional Chinese Medicine Hospital, and guided by Prof. Zhongliang Deng and Prof. Weizhong Lu.

## References


[1] R. Agarwal, A. García, Adv. Drug Delivery Rev. 94 (2015) 53–62.
[2] B. Holzapfel, J. Reichert, J.T. Schantz, U. Gbureck, L. Rackwitz, U. Nöth, F. Jakob, M. Rudert, J. Groll, D. Hutmacher, Adv. Drug Delivery Rev. 65 (2012) 581–603.
[3] R.B. Minkowitz, S. Bhadsavle, M. Walsh, K.A. Egol, J. Bone Jt. Surg. 89 (9) (2007) 1906–1912.
[4] A.M.S. Ibrahim, P.G.L. Koolen, K. Kim, G.S. Perrone, D.L. Kaplan, S.J. Lin, Clin. Podiatr. Med. Sur. 32 (1) (2015) 61–72.
[5] A.R. Amini, J.S. Wallace, S.P. Nukavarapu, J. Long Term. Eff. Med. Implants 21 (2) (2011) 93–122.
[6] A. Brown, S. Zaky, H. Ray, C. Sfeir, Acta. Biomater. 11 (2014) 543–553.
[7] M. Nabiyouni, T. Brückner, H. Zhou, U. Gbureck, S.B. Bhaduri, Acta Biomater. 66 (2018) 23–43.
[8] J.L. Wang, J.K. Xu, C. Hopkins, D.H.K. Chow, L. Qin, Adv. Sci. 7 (8) (2020) 1902443.
[9] T. Wik, O. Foss, S. Havik, L. Persen, A. Aamodt, E. Wits, Acta Orthop. 81 (2010) 765–767.
[10] M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias, Biomaterials 27 (9) (2006) 1728–1734.
[11] Z. Yuan, P. Wei, Y. Huang, W. Zhang, F. Chen, X. Zhang, J. Mao, D. Chen, Q. Cai, X. Yang, Acta Biomater. 85 (2018) 294–309.
[12] J.L. Wang, J.K. Xu, C. Hopkins, D.H. Chow, L. Qin, Adv. Sci. 7 (8) (2020) 1902443.
[13] M. Yazdimamaghani, M. Razavi, D. Vashaee, K. Moharamzadeh, A.R. Boccaccini, L. Tayebi, Mater. Sci. Eng. C. Mater. Biol. Appl. 71 (2017) 1253–1266.
[14] L. Raggatt, N. Partridge, J. Biol. Chem. 285 (2010) 25103–25108.
[15] N. Rucci, Clin. Cases. Miner. Bone. Metab. 5 (2008) 49–56.
[16] M. Peacock, Clin. J. Am. Soc. Nephrol. 5 (2010) S23–S30.
[17] S. Wallach, Magnesium 7 (1988) 262–270.
[18] M.H. Salimi, J.C. Heughebaert, G.H. Nancollas, Langmuir 1 (1985) 119–122.
[19] C. Liu, X. Fu, H. Pan, P. Wan, L. Wang, L. Tan, K. Wang, Y. Zhao, K. Yang, P. Chu, Sci. Rep. 6 (2016) 27374.
[20] H. Windhagen, K. Radtke, A. Weizbauer, J. Diekmann, Y. Noll, U. Kreimeyer, R. Schavan, C. Stukenborg-Colsman, H. Waizy, Biomed. Eng. Online 12 (2013) 62.
[21] C. Liu, J.K. Yeh, J.F. Aloia, J. Bone Miner. Res. 3 (1988) S104.
[22] R. Rude, H. Gruber, H. Norton, L. Wei, A. Frausto, B. Mills, J. Nutr. 134 (2004) 79–85.
[23] W. Weglicki, B. Dickens, T. Wagner, J. Chmielinska, T. Phillips, Magn. Res. 9 (1996) 3–11.
[24] F. Witte, V. Kaese, H. Haferkamp, E. Switzer, A. Meyer-Lindenberg, C. Wirth, H. Windhagen, Biomaterials 26 (2005) 3557–3563.
[25] F. Witte, J. Fischer, J. Nellesen, H.A. Crostack, V. Kaese, A. Pisch, F. Beckmann, H. Windhagen, Biomaterials 27 (2006) 1013–1018.
[26] F. Witte, H. Ulrich, C. Palm, E. Willbold, J. Biomed. Mater. Res., Part A 81 (2007) 757–765.
[27] F. Witte, H. Ulrich, M. Rudert, E. Willbold, J. Biomed. Mater. Res., Part A 81 (2007) 748–756.
[28] Y. Chen, S.H. Ye, H. Sato, Y. Zhu, V. Shanov, T. Tiasha, A. D'Amore, S. Luketich, G. Wan, W.R. Wagner, J. Tissue Eng. Regen. Med. 12 (6) (2018) 1374–1388.
[29] Z. Li, X. Gu, S. Lou, Y. Zheng, Biomaterials 29 (2008) 1329–1344.
[30] H. Rubin, Proc. Natl. Acad. Sci. USA 72 (1975) 3551–3555.
[31] H. Rubin, Magn. Res. 18 (2006) 268–274.
[32] A. James, Scientifica (Cairo) 12 (2013) 684736.
[33] S. Lin, G. Yang, F. Jiang, M. Zhou, S. Yin, Y. Tang, T. Tang, Z. Zhang, W. Zhang, X. Jiang, Adv. Sci. 6 (2019) 1900209.
[34] Y. Zhang, J. Xu, Y. Ruan, M. Yu, M. O'Laughlin, H. Wise, D. Chen, L. Tian, D. Shi, J. Wang, S. Chen, J.O. Feng, D.H.K. Chow, X. Xie, L.Z. Zheng, H. Huang, S. Huang, K. Leung, N. Lu, L. Qin, Nat. Med. 22 (2016) 1160–1169.
[35] S. Yoshizawa, A. Brown, A. Barchowsky, C. Sfeir, Acta Biomater. 10 (2014) 2834–2842.
[36] C.C. Hung, A. Chaya, K. Liu, K. Verdelis, C. Sfeir, Acta Biomater. 98 (2019) 246–255.
[37] S. Chen, Y. Guo, R. Liu, S. Wu, J. Fang, B. Huang, Z. Li, Z. Chen, Z. Chen, Colloids Surf. B Biointerfaces 164 (2018) 58–69.
[38] S. Albelda, C.A. Buck, FASEB. J. 4 (1990) 2868–2880.
[39] R. Hynes, Cell 69 (1992) 11–25.
[40] H. Zreiqat, C. Howlett, A. Zannettino, P. Evans, G. Schulze-Tanzil, C. Knabe, M. Shakibaei, J. Biomed. Mater. Res. 62 (2002) 175–184.
[41] J.W. Park, Y.J. Shin, J.H. Jang, H. Song, Clin. Oral Implants Res. 21 (2010) 1278–1287.
[42] K.J. Kim, S. Choi, Y.S. Cho, S.J. Yang, Y.S. Cho, K. Kim, J. Mater. Sci. Mater. Med. 28 (2017) 96.
[43] L. Wu, B. Luthringer, F. Feyerabend, A. Schilling, R. Willumeit, Acta Biomater. 10 (2014) 2843–2854.
[44] L. Wu, F. Feyerabend, A. Schilling, R. Willumeit, B. Luthringer, Acta Biomater. 27 (2015) 294–304.
[45] H.J. Han, S. Kim, Int. J. Oral Max. Impl. 29 (2014) 303–310.
[46] M. Wang, Y. Yu, K. Dai, Z. Ma, Y. Liu, J. Wang, C. Liu, Biomater. Sci. 4 (2016) 1574–1583.
[47] K.K. Sivaraj, R. Adams, Development 143 (2016) 2706–2715.
[48] S. Stegen, N. van Gastel, G. Carmeliet, Bone 70 (2014) 19–27.
[49] H. Wang, Y. Yin, W. Li, X. Zhao, J. Zhu, Z. Qin, Q. Wang, K. Wang, W. Lu, J. Liu, L. Huang, PLoS One 7 (2012) e30503.
[50] N. Ferrara, H.-.P. Gerber, J. Lecouter, Nat. Med. 9 (2003) 669–676.
[51] F. Mirshahi, J. Pourtau, H. Li, M. Muraine, V. Trochon, E. Legrand, J.P. Vannier, S. Jeannette, M. Vasse, C. Soria, Thromb. Res. 99 (2000) 587–594.
[52] X. Zhang, H. Zu, D. Zhao, K. Yang, S. Tian, X. Yu, F. Lu, B. Liu, X. Yu, B. Wang, W. Wang, S. Huang, Y. Wang, Z. Wang, Z. Zhang, Acta Biomater. 63 (2017) 369–382.
[53] B. Fan, X. Yu, W. Liu, J. Wu, L. Shi, D. Yang, L. Tan, P. Wan, Y.L. Hao, S. Li, W. Hou, K. Yang, X. Li, Z. Guo, Bioact. Mater. 5 (2020) 680–693.
[54] K. Jähn-Rickert, H. Saito, H. Taipaleenmäki, A. Gasser, N. Hort, F. Feyerabend, H. Schlüter, J. Rueger, W. Lehmann, R. Willumeit, E. Hesse, Acta Biomater. 36 (2016) 350–360.
[55] Z. Zhai, X. Qu, H. Li, K. Yang, P. Wan, L. Tan, Z. Ouyang, X. Liu, B. Tian, F. Xiao, W. Wang, C. Jiang, T. Tang, Q. Fan, A. Qin, K. Dai, Biomaterials 35 (2014) 6299–6310.
[56] L.Z. Zheng, J.L. Wang, J.K. Xu, X.T. Zhang, B.Y. Liu, H. Huang, R. Zhang, H. Zu, X. He, J. Mi, Q. Pang, X. Wang, Y.C. Ruan, D.W. Zhao, L. Qin, Biomaterials 238 (2020) 119828.
[57] D. Maradze, D. Musson, Y. Zheng, J. Cornish, M. Lewis, Y. Liu, Sci. Rep. 8 (2018) 10003.
[58] M. Gonçalves, A. Silva, J. Brás, H. Helmholz, B. Luthringer, R. Willumeit, M. Barbosa, S. Santos, Acta Biomater. 18 (20) (2020) 471–484.
[59] M.D. Costantino, A. Schuster, H. Helmholz, A. Meyer-Rachner, R. Willumeit, B. Luthringer, Acta Biomater. 101 (2019) 598–608.
[60] X. Lin, J. Ge, D. Wei, C. Liu, L. Tan, H. Yang, K. Yang, H. Zhou, B. Li, Z.P. Luo, L. Yang, J. Orthop. Transl. 17 (2019) 121–132.
[61] Y. Yu, G. Jin, Y. Xue, D. Wang, X. Liu, J. Sun, Acta Biomater. 49 (2016) 590–603.
[62] R. Bettman, L. Zimmerman, Dig. Dis. Sci. 2 (1935) 318–321.
[63] E. Payr, Arch. Klin. Chir. 62 (1900) 67–93.
[64] A. Lambotte, Presse. Med. Belge. 17 (1909) 321–323.
[65] A. Lambotte, Bull. Mem. Soc. Natl. Chir. 28 (1932) 1325–1334.
[66] F. Witte, Acta Biomater. 6 (5) (2010) 1680–1692.
[67] J. Verbrugge, La. Press. Med. 23 (1934) 460–465.
[68] E. McBride, South. Med. J. 31 (1938) 508–514.
[69] D. Zhao, S. Huang, F. Lu, B. Wang, L. Yang, L. Qin, K. Yang, Y. Li,

W. Li, W. Wang, S. Tian, X. Zhang, W. Gao, Z. Wang, Y. Zhang, X. Xie, J. Wang, L. Junlei, Biomaterials 81 (2016) 84–92.
[70] D. Zhao, S. Huang, F. Lu, B. Wang, L. Yang, L. Qin, K. Yang, Y. Li, W. Li, W. Wang, S. Tian, X. Zhang, W. Gao, Z. Wang, Y. Zhang, X. Xie, J. Wang, L. Junlei, Biomaterials 81 (2016) 84–92.
[71] L. Chen, Z. Lin, M. Wang, W. Huang, Y. Zhang, J. Orthop. Transl. 17 (2019) 133–137.
[72] M. Erinc, W.H. Sillekens, R.G.T.M. Mannens, R.J. Werkhoven, Magn. Technol. (2009) 209–214.
[73] L. Tan, X. Yu, P. Wan, K. Yang, J. Mater. Sci. Technol. 29 (6) (2013) 503–513.
[74] G. Katarivas Levy, E. Aghion, Acta Biomater. 9 (2013) 8624–8630.
[75] X. Liang, Y. Qi, Z. Pan, Y. He, X. Liu, S. Cui, Mater. Chem. Front. 2 (2018).
[76] S. Abdelrahman, Pharmacol. Res. 47 (2003) 189–194.
[77] Y. Nakamura, Y. Tsumura, Y. Tonogai, T. Shibata, Fundam. Appl. Toxicol. 45 (1999) P15-15.
[78] E. Ghasali, A. Bordbar-Khiabani, M. alizadeh, M. Mozafari, M. Niazmand, H. Kazemzadeh, T. Ebadzadeh, Mater. Chem. Phys. 225 (2019) 331–339.
[79] D. Tie, R.g. Guan, H. Liu, A. Cipriano, Y. Liu, Q. Wang, Y. Huang, N. Hort, Acta Biomater 29 (2015) 455–467.
[80] L. Tan, X. Yu, P. Wan, K. Yang, J. Mater. Sci. Technol. 29 (2013) 503–513.
[81] A. Santos-Coquillat, M. Esteban-Lucia, E. Martinez-Campos, M. Mohedano, R. Arrabal, C. Blawert, M.L. Zheludkevich, E. Matykina, Mater. Sci. Eng. C. Mater. Biol. Appl. 105 (2019) 110026.
[82] H. Li, Q. Peng, X. Li, K. Li, Z. Han, D. Fang, Mater. Des. 58 (2014) 43–51.
[83] Z. Seyedraoufi, S. Mirdamadi, J. Mech. Behav. Biomed. Mater. 21 (2013) 1–8.
[84] J. Li, P. Cao, X. Zhang, S. Zhang, Y.H. He, In vitro degradation and cell attachment of a PLGA coated biodegradable Mg–6 Zn based alloy, J. Mater. Sci. 45 (2010) 6038–6045.
[85] C. Shuai, Y. Zhou, Y. Yang, P. Feng, L. Liu, C. He, M. Zhao, S. Yang, C. Gao, P. Wu, Materials (Basel) 10 (3) (2017) 307.
[86] M. Staiger, A. Pietak, J. Huadmai, G. Dias, Biomaterials 27 (2006) 1728–1734.
[87] Z. Gui, Z. Kang, Y. Li, J. Alloys Compd. 685 (2016) 222–230.
[88] J. Yang, G. Koons, G. Cheng, L. Zhao, A. Mikos, F.Z. Cui, Biomed. Mater. 13 (2017) 022001.
[89] L. Liu, H. Yu, W. Yang, Z. Wang, Materials (Basel) 12 (5) (2019) 742.
[90] H.S. Brar, J. Wong, M.V. Manuel, J. Mech. Behav. Biomed. 7 (2012) 87–95.
[91] C. Seal, K. Vince, M. Hodgson, IOP Conf. Ser.: Mater. Sci. Eng. 4 (2009) 012011.
[92] F. Feyerabend, J. Fischer, J. Holtz, F. Witte, R. Willumeit, H. Drücker, C. Vogt, N. Hort, Acta Biomater. 6 (2009) 1834–1842.
[93] Y. Zheng, X. Gu, F. Witte, Mat. Sci. Eng. R. 77 (2014) 1–34.
[94] Y. Xin, T. Hu, P.K. Chu, Acta Biomater. 7 (4) (2011) 1452–1459.
[95] X.N. Gu, W.R. Zhou, Y.F. Zheng, Y. Cheng, S.C. Wei, S.P. Zhong, T.F. Xi, L.J. Chen, Acta Biomater. 6 (12) (2010) 4605–4613.
[96] A. Chaya, S. Yoshizawa, K. Verdelis, N. Myers, B. Costello, D.T. Chou, S. Pal, S. Maiti, P. Kumta, C. Sfeir, Acta Biomater. 18 (2015) 262–269.
[97] F. Witte, N. Hort, C. Vogt, S. Cohen, K. Kainer, R. Willumeit, F. Feyerabend, Curr. Opin. Solid State Mater. Sci. 12 (2008) 63–72.
[98] Y.F. Zheng, X.N. Gu, F. Witte, Mater. Sci. Eng., R. 77 (2014) 1–34.
[99] E. Willbold, A. Kaya, R. Kaya, F. Beckmann, F. Witte, Mater. Sci. Eng. B-Adv. 176 (2011) 1835–1840.
[100] N. Erdmann, N. Angrisani, J. Reifenrath, A. Lucas, F. Thorey, D. Bormann, A. Meyer-Lindenberg, Acta Biomater. 7 (2010) 1421–1428.
[101] L. Xu, G. Yu, E. Zhang, F. Pan, K. Yang, J. Biomed. Mater. Res. A 83 (2007) 703–711.
[102] E. Willbold, K. Kalla, I. Bartsch, K. Bobe, M.D. Brauneis, S. Remennik, D. Shechtman, J. Nellesen, W. Tillmann, C. Vogt, F. Witte, Acta Biomater. 9 (2013) 8509–8517.
[103] M. Kaseem, S. Fatimah, N. Nashrah, Y. Ko, Prog. Mater. Sci. (2020) 100735.
[104] C. Liu, Y. Xin, X. Tian, P.K. Chu, J. Mater. Res. 22 (7) (2007) 1806–1814.
[105] H. Kuwahara, N. Mazaki, M. Mabuchi, C. Wein, T. Aizawa, Mater. Sci. Forum. 419-422 (2003) 1007–1012.
[106] A.C. Hänzi, I. Gerber, M. Schinhammer, J.R.F. Löffler, P.J. Uggowitzer, Acta Biomater. 6 (5) (2010) 1824–1833.
[107] K. Chiu, M. Wong, F. Cheng, H. Man, Surf. Coat. Technol. 202 (3) (2007) 590–598.
[108] P. Salunke, V. Shanov, F. Witte, Mater. Sci. Eng. B Solid State Mater. Adv. Technol. 176 (20) (2011) 1711–1717.
[109] A. Bordbar-Khiabani, B. Yarmand, M. Mozafari, Surf. Innov. 6 (2018) 1–21.
[110] A. Bordbar-Khiabani, B. Yarmand, M. Mozafari, Surf. Coat. Tech. 360 (2019) 153–171.
[111] A. Bordbar-Khiabani, S. Ebrahimi, B. Yarmand, Corros. Sci. 173 (2020) 108781.
[112] A. Bordbar-Khiabani, B. Yarmand, S. Sharifi-Asl, M. Mozafari, Mater. Chem. Phys. 239 (2019) 122003.
[113] H. Wang, Y. Estrin, Z. Zuberova, Mater. Lett. 62 (15) (2008) 2476–2479.
[114] Y. Song, S. Zhang, J. Li, C. Zhao, X. Zhang, Acta Biomater. 6 (5) (2010) 1736–1742.
[115] J. de Baaij, J. Hoenderop, R. Bindels, Physiol. Rev. 95 (2015) 1–46.
[116] K. Klotz, W. Weistenhöfer, F. Neff, A. Hartwig, C. van Thriel, H. Drexler, Dtsch. Arztebl. Int. 114 (39) (2017) 653–659.
[117] A. Bordbar-Khiabani, B. Yarmand, M. Mozafari, Emerg. Mater. Res. 3 (8) (2019) 305–319.
[118] J. Fischer, D. Pröfrock, N. Hort, R. Willumeit, F. Feyerabend, Mater. Sci. Eng. B. Solid State Mater. Adv. Technol. 176 (2011) 830–834.
[119] J. Wang, F. Witte, T. Xi, Y. Zheng, K. Yang, Y. Yang, D. Zhao, J. Meng, Y. Li, W. Li, K. Chan, L. Qin, Acta Biomater. 21 (2015) 237–249.
[120] T. Nguyen, D. Liew, H. Liu, PLoS One 8 (2013) e76547.
[121] L. Li, J. Gao, Y. Wang, Surf. Coat. Technol. 185 (2004) 92–98.
[122] S. Zhang, X. Zhang, C. Zhao, J. Li, Y. Song, C. Xie, H. Tao, Y. Zhang, Y. He, Y. Jiang, Y. Bian, Acta Biomater. 6 (2) (2010) 626–640.
[123] B. Kandala, G. Zhang, X. An, S. Pixley, V. Shanov, Med. Res. Arch. 8 (3) (2020) 2067.
[124] B. Kandala, G. Zhang, T. Hopkins, X. An, S. Pixley, V. Shanov, Appl. Sci. 9 (2019) 4503.
[125] J. Wang, L.Y. Cui, Y. Ren, Y. Zou, J. Ma, C. Wang, Z. Zheng, X. Chen, R. Zeng, Y. Zheng, J. Mater. Sci. Technol. 47 (15) (2020) 52–67.
[126] Z.Z. Yin, W. Qi, R. Zeng, C.D. Gu, S.K. Guan, Y. Zheng, J. Magn. Alloy 8 (1) (2020) 42–56.
[127] M.P. Staiger, A.M. Pietak, J. Huadmai, G. Dias, Biomaterials 27 (9) (2006) 1728–1734.
[128] M.R. Smith, P. Atkinson, D. White, T. Piersma, G. Gutierrez, G. Rossini, S. Desai, S. Wellinghoff, H. Yu, X. Cheng, J. Biomed. Mater. Res. 100 (1) (2011) 206–216.
[129] T. Kraus, S.F. Fischerauer, A.C. Hänzi, P.J. Uggowitzer, A.M. Weinberg, Acta Biomater. 8 (3) (2012) 1230–1238.
[130] H.M. Wong, Y. Zhao, V. Tam, S. Wu, P.K. Chu, Y. Zheng, M.K.T. To, F.K.L. Leung, K.D.K. Luk, K.M.C. Cheung, Biomaterials 34 (38) (2013) 9863–9876.
[131] M. Razavi, M. Fathi, O. Savabi, D. Vashaee, L. Tayebi, Mater. Sci. Eng. C Mater. Biol. Appl. 48 (2015) 21–27.
[132] S. Hiromoto, M. Inoue, T. Taguchi, M. Yamane, N. Ohtsu, Acta Biomater. 11 (2015) 520–530.
[133] W. Sun, G. Zhang, L. Tan, K. Yang, H. Ai, Mater. Sci. Eng. C Mater. Biol. Appl. 63 (2016) 506–511.
[134] W. Sun, G. Zhang, L. Tan, K. Yang, H. Ai, Mater. Sci. Eng. C Mater. Biol. Appl. 63 (2016) 506–511.
[135] P.R. Cha, H.S. Han, G.F. Yang, Y.C. Kim, K.H. Hong, S.C. Lee, J.Y. Jung, J.P. Ahn, Y.Y. Kim, S.Y. Cho, Sci. Rep. 3 (2013) 2367.
[136] W.J. Kim, J.Y. Choi, J. Alloys Compd. 614 (2014) 49–55.

[137] J. Wang, Y. Wu, H. Li, Y. Liu, X. Bai, W. Chau, Y. Zheng, L. Qin, Biomaterials 157 (2018) 86.
[138] J. Diekmann, S. Bauer, A. Weizbauer, E. Willbold, H. Windhagen, P. Helmecke, A. Lucas, J. Reifenrath, I. Nolte, M. Ezechieli, Mater. Sci. Eng. C Mater. Biol. Appl. 59 (2016) 1100–1109.
[139] Y.W. Yang, P. Wu, Q.Y. Wang, H. Wu, Y. Liu, Materials (Basel) 9 (4) (2016) 216.
[140] S. Cijun, Z. Yuanzhuo, Y. Youwen, F. Pei, L. Long, H. Chongxian, Z. Mingchun, Y. Sheng, G. Chengde, W. Ping, Materials (Basel) 10 (3) (2017) 307.
[141] Y. Yin, Q. Huang, L. Liang, X. Hu, T. Liu, Y. Weng, T. Long, Y. Liu, Q. Li, S. Zhou, J. Alloys Compd. 785 (2019) 38–45.
[142] K.A. Madhan, H.S. Fida, A.A. Sorour, M. Paramsothy, M. Gupta, Met. Mater. Int. 25 (2018) 105–116.
[143] P. Han, P.F. Cheng, S.X. Zhang, C.L. Zhao, J.H. Ni, Biomaterials 64 (2015) 57–69.
[144] Y.Q. Hua, S. Jiao, Acta Biomater. 75 (2018) 215–224.
[145] L.L. Hench, J. Am. Ceram. Soc. 81 (7) (1998) 1705–1728.
[146] K. Low, T. Huat, S. Zein, J. Roether, V. Mouriño, A. Boccaccini, J. Biomed. Mater. Res. B 94 (2010) 273–286.
[147] N. Ostrowski, A. Roy, P.N. Kumta, ACS Biomater. Sci. Eng. 2 (7) (2016) 1067–1083.
[148] T. Nonami, S. Tsutsumi, J. Mater. Sci.: Mater. Med. 10 (8) (1999) 475–479.
[149] L.S. Burstein, A.L. Boskey, P.J. Tannenbaum, A.S. Posner, I.D. Mandel, J. Oral Pathol. 8 (5) (2010) 284–291.
[150] R. Miano, S. Germani, G. Vespasiani, Urol. Int. 79 (1) (2007) 32–36.
[151] F.C.M. Driessens, M.G. Boltong, M.I. Zapatero, R. Verbeeck, W. Bonfield, O. Bermudez, E. Fernández, M.P. Ginebra, J.A. Planell, J. Mater. Sci.: Mater. Med. 6 (1995) 272–278.
[152] F. Qiao, C.K. Chau, Z. Li, Mater. Struct. 45 (2011) 447–456.
[153] E. McBride, JAMA, J. Am. Med. Assoc. 111 (1938) 2464–2467.
[154] R. Erbel, C. Di Mario, J. Bartunek, J. Bonnier, B. Bruyne, F. Eberli, P. Erne, M. Haude, B. Heublein, M. Horrigan, C. Ilsley, D. Böse, J. Koolen, T. Lüscher, N. Weissman, R. Waksman, Lancet 369 (2007) 1869–1875.
[155] Y. Nan, S. Caijun, Y. Jianming, C. Yuan, J. Mater. Civ. Eng. 26 (10) (2014) 04014071.
[156] S. Mousa, Phosphorus Res. Bull. 24 (2010) 16–21.
[157] M. Mathew, P. Kingsbury, S. Takagi, W. Brown, Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem. 38 (1982) 40–44.
[158] C.K. Chau, F. Qiao, Z. Li, Constr. Build. Mater. 25 (6) (2011) 2911–2917.
[159] S. Vinokurov, Y. Kulyako, O. Slyunchev, S. Rovnyi, A. Wagh, M. Maloney, B. Myasoedov, Radiochemistry 51 (2009) 65–72.
[160] B.E.I. Abdelrazig, J.H. Sharp, Thermochim. Acta 129 (2) (1988) 197–215.
[161] Y. Yu, J. Wang, C. Liu, B. Zhang, H. Chen, H. Guo, G. Zhong, W. Qu, S. Jiang, H. Huang, Colloids Surf. B Biointerfaces 76 (2) (2010) 496–504.
[162] N. Ostrowski, A. Roy, P.N. Kumta, ACS Biomater. Sci. Eng. 2 (7) (2016) 1067–1083.
[163] C. You, J. Qian, J. Qin, H. Wang, Q. Wang, Z. Ye, Cem. Concr. Res. 78 (2015) 179–189.
[164] K. Martinelle, L. Häggström, J. Biotechnol. 30 (3) (1993) 339.
[165] S. Fan, B. Chen, Constr. Build. Mater. 65 (2014) 480–486.
[166] A. Agarwal, S. Bhaduri, Mater. Sci. Eng., C 33 (2013) 4288–4294.
[167] A.J. Wang, J. Zhang, J.M. Li, A.B. Ma, L.T. Liu, Mater. Sci. Eng. C Mater. Biol. Appl. 33 (5) (2013) 2508–2512.
[168] D. Pijocha, G. Łój, W. Nocuń-Wczelik, A. Ślósarczyk, J. Manuf. Sci. Eng. 49 (2) (2011).
[169] W. Liu, D. Zhai, Z. Huan, C. Wu, J. Chang, Acta. Biomater. 21 (2015) 217–227.
[170] C. Li, W. Hao, C. Wu, W. Li, J. Tao, F. Ai, H. Xin, X. Wang, Biomed. Mater. 15 (2019) 045015.
[171] Y.J. No, S.I. Roohani-Esfahani, H. Zreiqat, Nanomedicine 9 (11) (2014) 1745–1764.
[172] G. Wynn-Jones, R. Shelton, M. Hofmann, J. Biomed. Mater. Res. B Appl. Biomater. 102 (2014) 1799–1808.
[173] S. Bose, M. Roy, A. Bandyopadhyay, Trends Biotechnol. 30 (10) (2012) 546–554.
[174] L. Rink, L. Rink, IOSR-JDMS 13 (7) (2011) 18–23.
[175] T.J. Lally, Bio-adhesive composition, method for adhering objects to bone, 2000, US, 6533821.
[176] R. Boistelle, I. Lopez-Valero, F. Abbona, Néphrologie 14 (6) (1993) 265.
[177] P.T. Cheng, J.J. Grabher, R.Z. Legeros, Magnesium 7 (3) (1988) 123.
[178] Z. Amjad, P.G. Koutsoukos, G.H. Nancollas, J. Colloid Interface Sci. 101 (1) (1984) 250–256.
[179] E.D. Eanes, S.L. Rattner, J. Dent. Res. 60 (9) (1981) 1719–1723.
[180] W. Chu, T. Li, G. Jia, Y. Chang, Z. Liu, J. Pei, D. yu, Z. Zhai, Ann. Transl. Med. 8 (2020) 1419 -1419.
[181] A.L. Boskey, A.S. Posner, Mater. Res. Bull. 9 (7) (1974) 907–916.
[182] H. Zhou, S. Bhaduri, J. Biomed. Mater. Res. B Appl. Biomater. 100 (4) (2012) 1142–1150.
[183] H. Zhou, T.J.F. Luchini, S.B. Bhaduri, J. Mater. Sci. Mater. Med. 23 (12) (2012) 2831–2837.
[184] M.S. Tung, B. Tomazic, W.E. Brown, Arch. Oral Biol. 37 (7) (1992) 585–591.
[185] None, Acta Crystallogr. 52 (1) (1996) 87–92.
[186] A. Yasukawa, S. Ouchi, K. Kandori, T. Ishikawa, J. Mater. Chem. 6 (8) (1996) 1401.
[187] A. Krause, N.v.d. Höh, D. Bormann, C. Krause, F.W. Bach, H. Windhagen, A. Meyer-Lindenberg, J. Mater. Sci. 45 (3) (2010) 624–632.
[188] J. Walker, S. Shadanbaz, T.B.F. Woodfield, M.P. Staiger, G.J. Dias, Biomed. Mater. 9 (1) (2014) 015006.
[189] M. Nabiyouni, T. Brückner, U. Gbureck, S. Bhaduri, Acta Biomater. 66 (2017) 23–43.
[190] M. Gallo, B.L.G. Santoni, T. Douillard, F. Zhang, L. Gremillard, S. Dolder, W. Hofstetter, S. Meille, M. Bohner, J. Chevalier, Acta Biomater. 89 (2019) 391–402.
[191] D. Lee, P.N. Kumta, Mater. Sci. Eng. C. Mater. Biol. Appl. 30 (7) (2010) 934–943.
[192] H. Ryu, K. Hong, J. Lee, D. Kirn, J. Mater. Res. 21 (2) (2006) 428–436.
[193] Y. Lai, Y. Li, H. Cao, J. Long, L. Qin, Biomaterials 197 (2019) 207–219.
[194] X. Chen, J. Ou, Y. Wei, Z. Huang, Y. Kang, G. Yin, J. Mater. Sci. Mater. Med. 21 (5) (2010) 1463–1471.
[195] M.R. Badr-Mohammadi, S. Hesaraki, A. Zamanian, J. Mater. Sci. Mater. Med. 25 (2013) 185–197.
[196] L.L. Hench, J. Mater. Sci.: Mater. Med. 17 (11) (2006) 967.
[197] D. Bellucci, V. Cannillo, A. Anesi, R. Salvatori, L. Chiarini, T. Manfredini, D. Zaffe, Materials (Basel) 11 (11) (2018) 2223.
[198] E. Verne, O. Bretcanu, C. Balagna, C.L. Bianchi, M. Cannas, S. Gatti, C. Vitale-Brovarone, J. Mater. Sci. Mater. Med. 20 (1) (2009) 75–87.
[199] S.J. Watts, R. Hill, M.D. O'Donnell, R. Law, J. Non-Cryst. Solids. 356 (2010) 517–524.
[200] R. Hand, D. Tadjiev, J. Non-Cryst. Solids 356 (2010) 2417–2423.
[201] M. Diba, F. Tapia, A. Boccaccini, L. Strobel, Int. J. Appl. Glass Sci. 3 (2012) 221–253.
[202] D. Zamani, F. Moztarzadeh, D. Bizari, Alginate-bioactive glass containing Zn and Mg composite scaffolds for bone tissue engineering, Int. J. Biol. Macromol. 137 (2019) 1256–1267.
[203] E. Vernè, O. Bretcanu, C. Balagna, C. Bianchi, M. Cannas, S. Gatti, C. Vitale-Brovarone, J. Mater. Sci. Mater. Med. 20 (2008) 75–87.
[204] E. Dietrich, H. Oudadesse, A. Lucas-Girot, Y.Le Gal, S. Jeanne, G. Cathelineau, Appl. Surf. Sci. 255 (2008) 391–395.
[205] B. Şengül, R. El-abassy, A. Materny, N. Dilsiz, Polym. Sci. Ser. A. Chem. Phys. 59 (2017) 891–901.
[206] S. Nukavarapu, J. Brown, N. Krogman, A. Weikel, M. Hindenlang, L. Nair, H. Allcock, C. Laurencin, Biomacromolecules 9 (2008) 1818–1825.
[207] G. Mogoşanu, A. Grumezescu, Int. J. Pharm. 463 (2013) 127–136.

[208] E. Battistella, E. Varoni, A. Cochis, B. Palazzo, L. Rimondini, J. Appl. Biomater. Biomech. 9 (2011) 223–231.
[209] H. Makadia, S. Siegel, Polymers (Basel) 3 (2011) 1377–1397.
[210] K. Athanasiou, G. Niederauer, C. Agrawal, Biomaterials 17 (1996) 93–102.
[211] J. Anderson, M. Shive, Adv. Drug Deliv. Rev. 64 (2012) 72–82.
[212] O. Böstman, E. Hirvensalo, J. Mäkinen, P. Rokkanen, J. Bone Jt. Surg. 72 (1990) 592–596.
[213] R. Rasal, A. Janorkar, D. Hirt, Prog. Polym. Sci. 35 (2010) 338–356.
[214] T. Xu, H. Kim, T. Stahl, S. Nukavarapu, Biomed. Mater. 13 (2018) 035013.
[215] C. Kum, Y. Cho, S. Seo, y.k. Joung, D. Ahn, D. Han, Small 10 (2014) 3783–3794.
[216] C. Kum, Y. Cho, Y.K. Joung, J. Choi, K. Park, S. Seo, Y. Park, D. Ahn, D. Han, J. Mater. Chem. B 1 (2013) 2764–2772.
[217] F. Barber, W. Dockery, Arthroscopy 22 (2006) 820–826.
[218] Y. Amano, M. Ota, K. Sekiguchi, Y. Shibukawa, S. Yamada, Oral Surg., Oral Med., Oral Pathol., Oral Radiol. Endodontol. 97 (2) (2004) 155–163.
[219] L. Janis, D. Kaplansky, W. DeCarbo, J. Am. Podiat. Med. Assn. 100 (2010) 25–34.
[220] P. Nordström, T. Pohjonen, P. Törmälä, P. Rokkanen, Biomaterials 22 (2001) 2557–2561.
[221] S. Cifuentes, E. Frutos, J.L. González-Carrasco, M. Muñoz, M. Multigner, J. Chao, R. Benavente, M. Lieblich, Mater. Lett. 74 (2012) 239–242.
[222] C. Romanò, G. Manzi, N. Logoluso, D. Romanò, Hip. Int. 22 (2012) 19–24.
[223] R. Darouiche, N. Engl. J. Med. 350 (2004) 1422–1429.
[224] K. Becker, C. Heilmann, G. Peters, Clin. Microbiol. Rev. 27 (4) (2014) 870–926.
[225] M. Koopaie, A. Bordbar-Khiabani, S. Kolahdooz, A.K. Darbandsari, M. Mozafari, Mater. Res. Express 7 (1) (2020) 14.
[226] D. Robinson, R. Griffith, D. Shechtman, R. Evans, M. Conzemius, Acta. Biomater. 6 (2009) 1869–1877.
[227] Y. Li, G. Liu, Z. Zhai, L. Liu, H. Li, K. Yang, L. Tan, P. Wan, X. Liu, Z. Ouyang, Z. Yu, T. Tang, Z.A. Zhu, X. Qu, K. Dai, Antimicrob. Agents Chemother. 58 (2014) 7586–7591.
[228] J. Rodríguez-Sánchez, M. Pacha-Olivenza, M.L. González-Martín, Mater. Chem. Phys. 221 (2018) 342–348.
[229] M. Fernández Calderón, D. Romero-Guzmán, A. Ferrández Montero, C. Pérez-Giraldo, J.L. González-Carrasco, M. Lieblich, R. Benavente, B. Ferrari, M. González-Martín, A. Gallardo-Moreno, Colloids Surf. B Biointerfaces 185 (2019) 110617.
[230] M. Fernández Calderón, S. Cifuentes, M. Pacha-Olivenza, A. Gallardo–Moreno, L. Saldaña, J.L. González-Carrasco, M. Blanco, N. Vilaboa, M. González-Martín, C. Pérez-Giraldo, Biomed. Mater. 12 (2017) 015025.
[231] O. Yamamoto, T. Ohira, K. Alvarez, M. Fukuda, Mater. Sci. Eng. B Solid. State Mater. Adv. Technol. 173 (2010) 208–212.
[232] J. Sawai, H. Kojima, H. Igarashi, A. Hashimoto, S. Shoji, T. Sawaki, A. Hakoda, E. Kawada, T. Kokugan, M. Shimizu, World J. Microbiol. Biotechnol. 16 (2000) 187–194.
[233] S. Thomopoulos, E. Zampiakis, R. Das, M. Kim, M. Silva, N. Havlioglu, R. Gelberman, J. Hand. Surg. 34 (2009) 1066–1073.
[234] G. Mestres, M.-.P. Ginebra, Acta Biomater. 7 (2010) 1853–1861.
[235] E. Babaie, B. Lin, S. Bhaduri, Biomed. Mater. 11 (2016) 055010.
[236] N. Yang, C. Shi, J. Yang, Y. Chang, J. Mater. Civ. Eng. 26 (2014) 04014071.
[237] R. Bhatt, T. Rozental, Hand. Clin. 28 (2012) 457–468.
[238] O. Maier, Deutsche Z. Chir. 253 (8–9) (1940) 552–556.
[239] J. Nagels, M.L. Stokdijk, P.M. Rozing, J. Shoulder Elbow Surg. 12 (1) (2003) 35–39.
[240] B. Acar, O. Kose, A. Turan, M. Unal, Y.A. Kati, F. Guler, BioMed Res. Int. (2018) 1–9.
[241] H. Windhagen, K. Radtke, A. Weizbauer, J. Diekmann, Y. Noll, U. Kreimeyer, R. Schavan, C. Stukenborg-Colsman, H. Waizy, Biomed Eng. Online 12 (2013) 62.
[242] J.W. Lee, H.S. Han, K.J. Han, J. Park, H. Jeon, M.R. Ok, H.K. Seok, J.P. Ahn, K.E. Lee, D.H. Lee, S.J. Yang, S.Y. Cho, P.R. Cha, H. Kwon, T.H. Nam, J.H. Han, H.J. Rho, K.S. Lee, Y.C. Kim, D. Mantovani, Proc. Natl. Acad. Sci. USA 113 (3) (2016) 716–721.
[243] J. Wang, J. Xu, B. Song, D.H. Chow, P. Shu-Hang Yung, L. Qin, Acta Biomater. 63 (2017) 393–410.
[244] A. Chaya, S. Yoshizawa, K. Verdelis, N. Myers, B.J. Costello, D.T. Chou, S. Pal, S. Maiti, P.N. Kumta, C. Sfeir, Acta Biomater. 18 (2015) 262–269.
[245] K.F. Farraro, N. Sasaki, S.L. Woo, K.E. Kim, M.M. Tei, A. Speziali, P.J. McMahon, J. Orthop. Res. 34 (11) (2016) 2001–2008.
[246] S.E. Henderson, K. Verdelis, S. Maiti, S. Pal, W.L. Chung, D.T. Chou, P.N. Kumta, A.J. Almarza, Acta Biomater. 10 (5) (2014) 2323–2332.
[247] L. Tian, Y. Sheng, L. Huang, D.H. Chow, W.H. Chau, N. Tang, T. Ngai, C. Wu, J. Lu, L. Qin, Biomaterials 180 (2018) 173–183.
[248] J. Diekmann, S. Bauer, A. Weizbauer, E. Willbold, H. Windhagen, P. Helmecke, A. Lucas, J. Reifenrath, I. Nolte, M. Ezechieli, Mater. Sci. Eng. C Mater. Biol. Appl. 59 (2016) 1100–1109.
[249] K. Jähn, H. Saito, H. Taipaleenmäki, A. Gasser, N. Hort, F. Feyerabend, H. Schlüter, J.M. Rueger, W. Lehmann, R. Willumeit-Römer, E. Hesse, Acta Biomater. 36 (2016) 350–360.
[250] C. Rössig, N. Angrisani, P. Helmecke, S. Besdo, J.M. Seitz, B. Welke, N. Fedchenko, H. Kock, J. Reifenrath, Acta Biomater. 25 (2015) 369–383.
[251] K. Bobe, E. Willbold, I. Morgenthal, O. Andersen, T. Studnitzky, J. Nellesen, W. Tillmann, C. Vogt, K. Vano, F. Witte, Acta Biomater. 9 (10) (2013) 8611–8623.
[252] L. Tan, Q. Wang, X. Lin, P. Wan, G. Zhang, Q. Zhang, K. Yang, Acta Biomater. 10 (5) (2014) 2333–2340.
[253] N.G. Grün, P. Holweg, S. Tangl, J. Eichler, L. Berger, J. van den Beucken, J.F. Löffler, T. Klestil, A.M. Weinberg, Acta Biomater. 78 (2018) 378–386.
[254] P.R. Cha, H.S. Han, G.F. Yang, Y.C. Kim, K.H. Hong, S.C. Lee, J.Y. Jung, J.P. Ahn, Y.Y. Kim, S.Y. Cho, J.Y. Byun, K.S. Lee, S.J. Yang, H.K. Seok, Sci. Rep. 3 (2013) 2367.
[255] F. Witte, V. Kaese, H. Haferkamp, E. Switzer, A. Meyer-Lindenberg, C.J. Wirth, H. Windhagen, Biomaterials 26 (17) (2005) 3557–3563.
[256] Y.W. Yang, C.X. He, D.Y. E, W.J. Yang, F.W. Qi, D.Q. Xie, L.D. Shen, S.P. Peng, C.J. Shuai, Mater. Des. 185 (2019) 108259.
[257] M.M. Stevens, Mater. Today 11 (5) (2008) 18–25.
[258] P. Gupta, M. Adhikary, J.C. M., M. Kumar, N. Bhardwaj, B.B. Mandal, Acs Appl. Mater. Interfaces (2016) 30797–30810.
[259] Z. Hao, Z. Song, J. Huang, K. Huang, A. Panetta, J. Wu, Biomater. Sci. 5 (2017) 1382–1392.
[260] M. Yazdimamaghani, M. Razavi, D. Vashaee, L. Tayebi, Mater. Lett. 132 (2014) 106–110.
[261] Z. Chen, X. Mao, L. Tan, T. Friis, C. Wu, R. Crawford, Y. Xiao, Biomaterials 35 (30) (2014) 8553–8565.
[262] M.Q. Cheng, T. Wahafu, G.F. Jiang, W. Liu, Y.Q. Qiao, X.C. Peng, T. Cheng, X.L. Zhang, G. He, X.Y. Liu, Sci. Rep. 6 (2016) 24134.
[263] G. Jia, Y. Hou, C. Chen, J. Niu, H. Zhang, H. Huang, M. Xiong, G. Yuan, Mater. Des. 140 (2017) 106–113.
[264] Y. Li, J. Zhou, P. Pavanram, M.A. Leeflang, L.I. Fockaert, B. Pouran, N. Tümer, K.U. Schröder, J.M.C. Mol, H. Weinans, Acta Biomater. 167 (2018) 378–392.
[265] J. Zhang, L. Tang, H. Qi, Q. Zhao, Y. Liu, Y. Zhang, Adv. Healthcare Mater. 8 (21) (2019) e1901030.
[266] R. Sami, D.D. Dionysiou, S.C. Pillai, K. John, Appl. Catal., B 240 (2018) 291–318.
[267] X. Luo, X.T. Cui, Acta Biomater. 7 (1) (2011) 441–446.
[268] C. Liu, M. Zhang, C. Chen, Mater. Sci. Eng. A Struct. Mater. 703 (2017) 359–371.
[269] Y. Yang, P. Wu, X. Lin, Y. Liu, H. Bian, Y. Zhou, C. Gao, C. Shuai, Virtual Phys. Prototyping 11 (3) (2016) 1–9.
[270] C. Liu, X. Fu, H. Pan, P. Wan, L. Wang, L. Tan, K. Wang, Y. Zhao, K. Yang, P.K. Chu, Sci. Rep. 6 (2016) 27374.
[271] D. Tie, F. Feyerabend, M. WD, R. Schade, K. Liefeith, K.U. Kainer, R. Willumeit, Eur. Cells Mater. 25 (25) (2013) 284.

[272] X.N. Gu, X.H. Xie, N. Li, Y.F. Zheng, L. Qin, Acta Biomater. 8 (6) (2012) 2360–2374.
[273] A. Gil-Santos, I. Marco, N. Moelans, N. Hort, O.V.D. Biest, Mater. Sci. Eng. C Mater. Biol. Appl. 71 (2017) 25–34.
[274] F. Cao, Z. Shi, G.L. Song, M. Liu, M.S. Dargusch, A. Atrens, Corros. Sci. 90 (2015) 176–191.
[275] H. Yao, J. Wen, Y. Xiong, Y. Lu, F. Ren, W. Cao, J. Alloys Compd. 739 (2017) 468–480.
[276] A. Dubey, S. Jaiswal, D. Lahiri, J. Mater. Eng. Perform. (2019) 800–809.
[277] Z.Y. Zhang, Y.H. Guo, Y.T. Zhao, G. Chen, J.L. Wu, M.P. Liu, Mater. Charact. 150 (2019) 229–235.
[278] M. Wolff, J.G. Schaper, M.R. Suckert, M. Dahms, T. Ebel, R. Willumeit, T. Klassen, J. Oral Microbiol. 68 (4) (2016) 1191–1197.
[279] A. Kopp, T. Derra, M. Muether, L. Jauer, J.H. Schleifenbaum, M. Voshage, O. Jung, R. Smeets, N. Kroeger, Acta Biomater. 98 (2019) 23–35.
[280] F. Bär, L. Berger, L. Jauer, G. Kurtuldu, R. Schäublin, J.H. Schleifenbaum, J.F. Löffler, Acta Biomater. 98 (2019) 36–49.