Update on the research and development of magnesium-based biodegradable implants and their clinical translation in orthopaedics

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Key Words:
ACL reconstruction; clinical translation; fracture model; magnesium; orthopaedic implants

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ABSTRACT

Biodegradable magnesium (Mg) or its alloys are desirable materials for development into new-generation internal fixation devices or implants with high biocompatibility, adequate mechanical modulus, and osteopromotive properties, which may overcome some of the drawbacks of the existing permanent orthopaedic implants with regard to stress-shielding of bone and beam-hardening effects on radiographic images. This review summarises the current research status of Mg-based orthopaedic implants in animals and clinical trials. First, detailed information of animal studies including bone fracture repair and anterior cruciate ligament reconstruction with the use of Mg-based orthopaedic devices is introduced. Second, the repair mechanisms of the Mg-based orthopaedic implants are also reviewed. Afterwards, reports of recent clinical cases treated using Mg-based implants in orthopaedics are summarised. Finally, the challenges and the strategies of the use of Mg-based orthopaedic implants are discussed. Taken together, the collected efforts in basic research, translational work, and clinical applications of Mg-based orthopaedic implants over the last decades greatly contribute to the development of a new generation of biodegradable metals used for the design of innovative implants for better treatment of orthopaedic conditions in patients with challenging skeletal disorders or injuries.

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Introduction

Orthopaedic trauma is one of the leading causes of mortality and morbidity in patients because of surgical failure or post-operative complications.[1] Apart from the reduction of technical errors, the selection of appropriate orthopaedic implants may improve clinical outcomes.[2, 3] For example, current traditional inert orthopaedic implants such as stainless steel, titanium alloy or cobalt-chromium alloy have much higher mechanical strength and Young's modulus than human bone. The huge gap in mechanical properties between bone and the metallic implants provides sufficient support strength, but may cause stress shielding and radiographic artefacts.[3, 4] More importantly, a second surgery for removal of these implants is often required after healing is complete.[5, 6] Consequently, biodegradable polymer materials such as polylactic acid (PLA), polyglycolic acid, and copolymers with much lower mechanical modulus were developed as alternatives to the aforementioned metals in orthopaedics.[7] However, the released degradation products from these absorbable polymers may cause a non-infectious inflammatory response,[8] thereby eventually leading to pathological bone resorption. In addition, the traditional metals or polymers are not considered as "bioactive materials", so an increasing demand to favour tissue healing via modulation of the biological interaction between the host tissue and the implants in orthopaedics has attracted a lot of attention in recent years.

Among the various biodegradable materials, magnesium (Mg) or its alloys has shown superior properties over its counterparts in biocompatibility, mechanical modulus, and bioactivity in regulation of new bone formation.[8] Consequently, more and more surgeons and researchers have made great efforts to explore the

potential of Mg-based implants in orthopaedics. This review covers four parts including the preclinical models, the repair mechanism of biodegradable Mg metal, clinical studies, and challenges and strategies of Mg-based orthopaedic implants.

Literature Search

The literature reviewed was retrieved from four databases, and 1108 related citations were retrieved (**Figure 1**). First, 818 articles were excluded because of their irrelevance to our topic in orthopaedics, and then 243 of the remaining 290 articles were further excluded due to the lack of cellular, animal and clinical information. Thus, the final 47 articles focusing on the translational work of Mg-based orthopaedic implants were considered in this review.

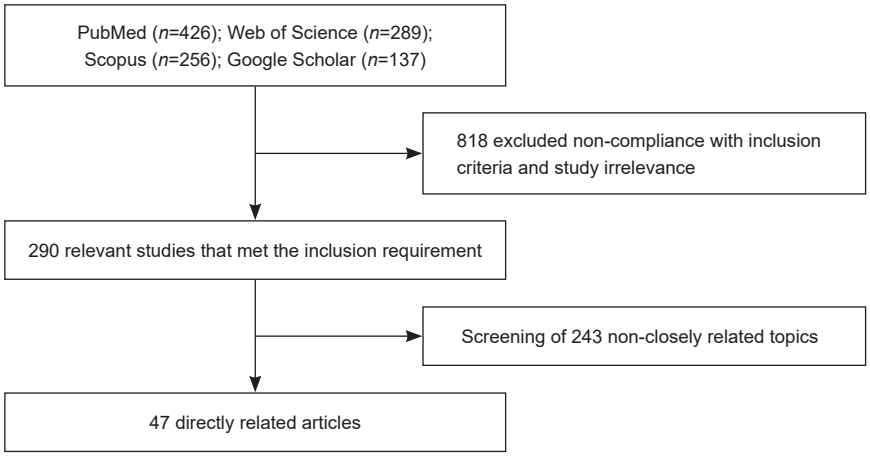

Figure 1. Flowchart of the literature search process.

Preclinical Research on Magnesium Orthopaedic Implants

Anterior cruciate ligament reconstruction

In recent years, biodegradable Mg-based interference screws and a Mg-based endobutton suture fixation system have been developed and tested for anterior cruciate ligament (ACL) reconstruction to accelerate the healing of the tendon–bone interface.[9] Recently, Mg-based interference screws with and without coatings were implanted in the femoral condyle of the hind leg of a merino sheep to test the degradation behaviour and the peri-screw tissue response over one year period.[10] In this study, the rapid corrosion of the Mg-based interference screws seriously impaired their mechanical integrity at the early stage due to fast degradation, and also caused the accumulation of gas cavities around the peri-screw tissue, thereby leading to potential fixation failure of the tendon graft. Diekmann et al.[11] reported the first animal study of ACL reconstruction using Mg alloy interference screws with CE certification, and found no inflammation or necrosis of the tendon graft. More importantly, all the screws remained in close connection with the surrounding tendon and bone tunnel surface, thus resulting in sufficient osseous integration at 24 weeks post-surgery.[11] As high-purity (HP) Mg (99.99 wt.%) possesses much higher corrosion resistance than Mg alloys due to the absence of a second phase, Wang et al.[12] developed HP Mg interference screws for ACL reconstruction in rabbits (**Figure 2A**). Compared to Ti or PLA interference screws, the HP Mg interference screws significantly promoted tendon–bone healing by increasing fibrocartilage formation and attenuated graft degradation.[13,14] However, the detailed repair mechanism of the Mg-based screws in promoting tendon–bone healing remains to be investigated. The enhancement of migration, adhesion, and osteogenic differentiation ability of progenitor cells in the presence of the released Mg ions may contribute to the improved graft healing.[15] Although pre-screening information about the potential use of Mg-based interference screws has been provided in animal models of ACL reconstruction, there is a huge gap between animal and human samples. Therefore, a cadaver study of ACL reconstruction was performed by comparing HP Mg with commercially-available PLA interference screws (**Figure 2B**).[16] In this study, the HP Mg interference screws showed similar mechanical stability to the PLA interference screws. In addition to the Mg-based interference screws, a Mg ring for a cadaveric goat model while a Mg-based endo-button for a beagle model of ACL reconstruction were also studied (**Figure 2C** and **D**).[17,18] The Mg ring provided stable fixation of the transected ACL while the Mg-based endobutton showed sufficient mechanical strength to support graft healing.

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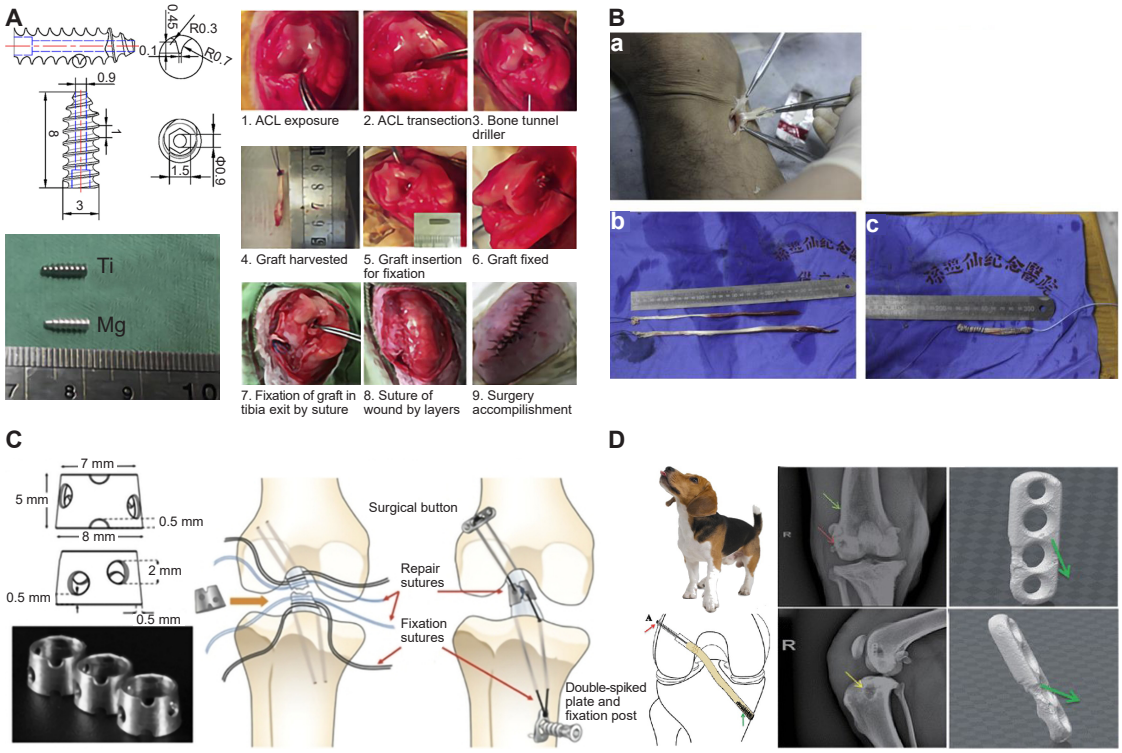

Figure 2. Research status of ACL reconstruction. (A) HP Mg screws were applied for ACL reconstruction in a rabbit model. Reprinted from Wang et al.[12] Copyright 2018, with permission from Elsevier. (B) ACL reconstruction conducted in fresh cadaveric knee joints using HP Mg interference screws. Reprinted from Song et al.[16] (C) A bioabsorbable monocrystalline Mg ring device used to repair the ruptured ACL of goats. Reprinted from Farraro et al.[17] Copyright 2016, with permission from the Orthopaedic Research Society. (D) A WE43 Mg alloy stretch plate used for ACL reconstruction in Beagle dogs to support ligament grafts at the femoral ends (green arrowheads). Reprinted from Mao et al.[18] Copyright 2018, with permission from American Chemical Society. ACL: anterior cruciate ligament; HP: high-purity; Mg: magnesium; Ti: titanium.

Fracture model

Bone fracture is very common in patients with osteoporosis. However, the clinically commonly-used inert metallic and degradable polymeric devices show some drawbacks including high mechanical modulus or excessive acidic intermediate products, thereby impairing the fracture healing. Mg or its alloys have been considered as competitive alternatives to those internal fixators in weight-bearing skeletal sites. For example, HP Mg screws were used in fixation of the bony flap at the distal femora of rabbits after intracondylar longitudinal osteotomy, and significantly promoted fracture healing when compared to commercial PLA screws (**Figure 3A**).[19] Large animal models, such as goats with femoral condyle fractures,[20] were also used to test the safety and efficacy of the Mg-based screws. Histological and radiographic results provided solid evidence that a new type of Mg alloy screws, named JDBM with the composition of Mg-Nd-Zn-Zr, may be an alternative to currently-used polymer screws in fixation of bone fractures which are not subjected to heavy loads (**Figure 3B**).[20] In addition to their use at low weight-bearing sites, pure Mg fixation plates and screws were also tested for fixation of ulnar shaft fractures in a rabbit model and exhibited sufficient strength to support ulnar healing, with promotion of callus formation around the Mg devices when compared to the Ti devices (**Figure 3C**).[21] Most recently, Chow et al.[22] reported the treatment outcomes in a rabbit model of patellar fracture treated with stainless steel or Mg pin fixation, and they found that Mg pins favoured new bone formation and promoted fracture healing. As the mechanical strength of Mg or its alloys is much lower than that of titanium or stainless steel, researchers and clinicians have concerns over using them in heavy weight-bearing fracture sites.

Recently, WE43 (Mg-Y-Re-Zr) screws have been developed for fixation of tibial fractures in beagle dogs, and these showed sufficient mechanical strength to support fracture healing without inducing systemic inflammatory reactions (**Figure 4A**).[23] Although the HP Mg metals showed even lower mechanical strength than its alloys, the increase in size and the change of structure design may facilitate support of heavy loads at the fracture sites due to the optimised stress distribution in the implants. For instance, Huang et al.[24] reported for the first time that large-size HP Mg weight-bearing screws were used to fix fractures of the femoral neck in goats and found that these biodegradable HP Mg screws supported fracture healing over the degradation time (**Figure 4B**). Femoral shaft fracture is a huge challenge for the clinical application of Mg or its alloys as fixators due to the high demand for mechanical support at the heavy load-bearing site. Most recently, an

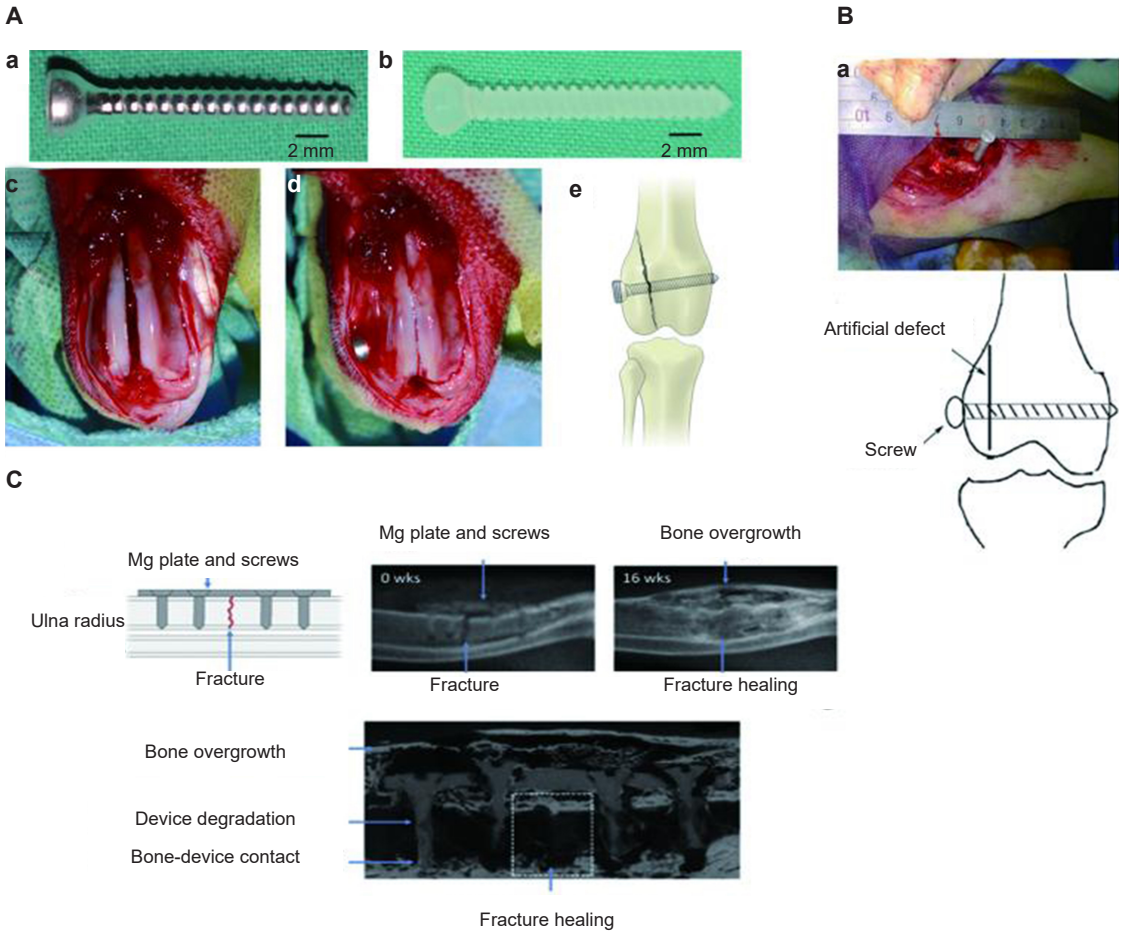

Figure 3. Research and development of Mg-based orthopaedic implants for fixation of fractures at low weight-bearing skeletal sites in different animal models. (A) High-purity Mg (HPM) screws used to fix femoral condylar fractures in rabbits. a: HPM screw; b: polymer screw; c: femoral condyle fracture; d: fixation of the fracture; e: schematic diagram showing the surgery. Scale bars: 2 mm. Reprinted from Han et al.[19] Copyright 2015, with permission from Elsevier. (B) A Mg-Nd-Zn-Zr alloy screw for fixation of a femoral condyle fracture in a goat model. Reprinted from Kong et al.[20] Copyright 2018, with permission from Elsevier. (C) Pure Mg screws and plates used to fix ulnar fractures in rabbits. Reprinted from Chaya et al.[21] Copyright 2015, with permission from Elsevier. Mg: magnesium.

intramedullary nail composed of Mg alloy containing 2% silver (Mg2Ag) was developed to fix femoral shaft fractures in mice and showed beneficial effects on callus formation and sufficient mechanical support to facilitate fracture healing without the necessity for a second removal surgery (**Figure 4C**).[25] Although Mg-based orthopaedic implants have shown their potential to support fractures at heavy weight-bearing sites, their mechanical integrity cannot be guaranteed during the degradation time before complete healing. Therefore, Tian et al.[26] designed an innovative Mg/Ti hybrid device for long-bone fracture models in rabbits. The Mg-containing hybrid implants not only showed sufficient mechanical strength, but also improved fracture healing by up-regulating the local secretion of calcitonin gene-related peptide[27] (**Figure 4D**).

Osteopromotive Mechanisms of Biodegradable Magnesium-based Orthopaedic Implants

Mg-based orthopaedic implants exert their osteopromotive properties by promoting osteogenesis and/or angiogenesis to directly or indirectly modulate new bone formation. An *in vitro* study confirmed that Mg ions significantly upregulated gene and protein expression levels of collagen type X and vascular endothelial growth factor through regulation of hypoxia-inducible factor-2α in undifferentiated mesenchymal stem cells (MSCs) and promoted the production of vascular endothelial growth factor via peroxisome proliferator-activated receptor-γ coactivator-1α in the differentiated MSCs.[28] The Wnt/β-catenin and Notch signalling pathways are closely involved in bone development. Recently, Hung et al.[29] found that the addition of 10 mM Mg ions to the medium activated the canonical Wnt/β-catenin pathway in bone marrow stromal cells and detected increased expression levels of lymphoid enhancer-binding factor 1 and Dickkopf 1 genes. In addition, it was shown that Mg^{2+} directly promoted osteogenesis through Notch 1 signalling activation in MSCs.[30] Animal models were also used to explore and verify the proposed repair mechanism of the Mg-based implants. Hedgehog-alternative Wnt signalling was activated by Mg ions released from the Mg pins

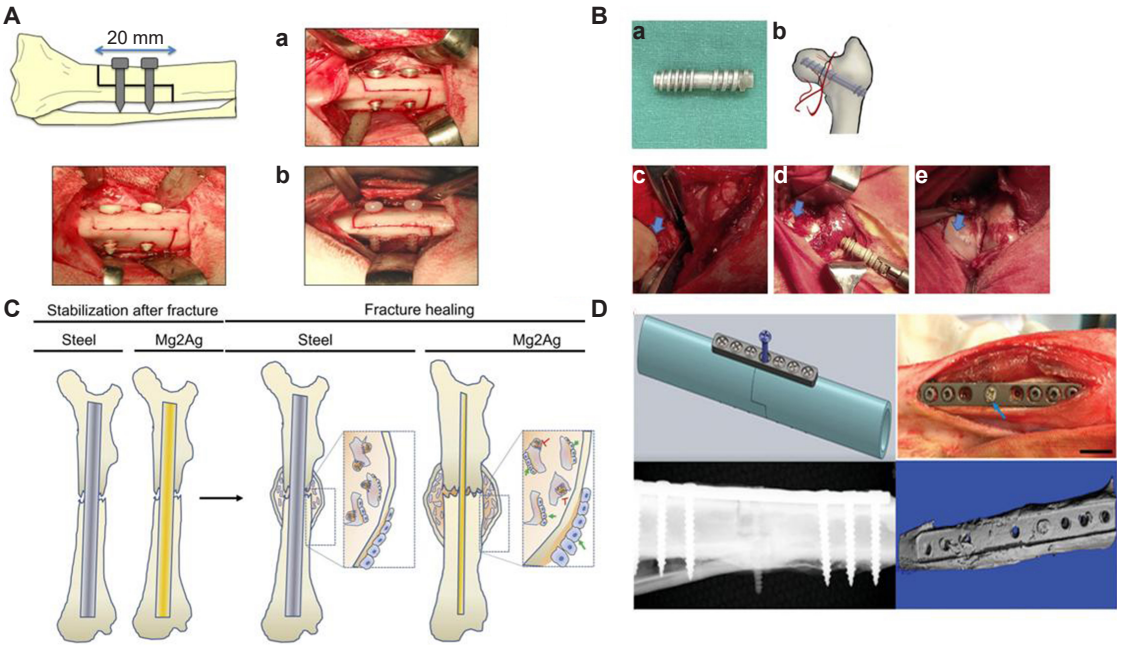

Figure 4. Research and development of Mg-based orthopaedic devices for fixation of fractures at high weight-bearing sites in various animal models. (A) The WE43 alloy screw used in the tibia fracture model of beagle dogs.[23] Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reprinted with permission. (B) The HP Mg screw used to fix goat femoral neck fractures. The blue arrow indicates the femoral head. Reprinted from Huang et al.[24] Copyright 2020, with permission from Elsevier. (C) The Mg2Ag intramedullary nails for femoral fractures in mice. Reprinted from Jähn et al.[25] Copyright 2016, with permission from Elsevier. (D) The innovative Mg/Ti hybrid fixation device (blue arrow) to fix tibial fractures in rabbits. Scale bar: 10 mm. Adapted from Hou et al.[26] Copyright 2018, with permission from Elsevier. Mg: magnesium; Ti: titanium.

via regulation of Patched protein, contributing to enhanced bone consolidation in a distraction osteogenesis model of rats.[31]

In recent years, modulation of cell-cell crosstalk by Mg ions was investigated to elaborate the potential mechanism of the Mg-based orthopaedic implants in promoting bone formation. For instance, it was found that Mg ions exerted osteoimmunomodulatory effects by inducing M2 phenotype changes of macrophages, thereby favouring osteogenic differentiation of MSCs via activation of the bone morphogenetic protein/small mother against decapentaplegic (SMAD) signalling pathway.[32] Most recently, the effects of Mg ions on their osteoimmunomodulatory environment were delineated. For example, the influx of Mg ions initiated an immune microenvironment favouring osteogenic differentiation of stem cells during the early inflammation phase, while the prolonged release of Mg ions overactivated nuclear factor kappa B signalling, thereby resulting in more tartrate-resistant acid phosphatase-positive cells and consequent impaired bone formation in the later remodelling phase.[33] The crosstalk between bone and nerves has become a hot topic in recent years. The release of calcitonin gene-related peptide, as one of the important neurotransmitters regulating bone formation,[34] can be significantly promoted from the sensory nerve fibre endings of the dorsal root ganglion induced by Mg ions. This leads to enhanced osteogenic differentiation ability of MSCs by initiating calcitonin receptor-like receptor and receptor activity-modifying protein 1-dependent activation of cyclic adenosine monophosphate-responsive element binding protein 1 and specificity protein-7.[35] Increasing evidence shows that bone formation processes are coupled with the formation of blood vessels.[36] Mg-based orthopaedic implants facilitate both angiogenesis and osteogenesis leading to improved bone healing in a bone defect model,[37] which may be ascribed to the upregulated expression of MagT1, a major Mg transporter, which activates the downstream mitogen-activated protein kinases/extracellular signal-regulated kinases pathway.[38] Wang et al.[15] found that HP Mg implants significantly increased the secreted concentrations of platelet-derived growth factor BB, a pro-angiogenic factor, in the peri-implant bone tissue, which may contribute to bony ingrowth towards the interzone structure between the tendon graft and the bone tunnel surface in rabbits after ACL reconstruction.

Current Status of Clinical studies of Magnesium-based Implants in Orthopaedics

The clinical application of Mg-based devices in orthopaedics can be traced back to over one century ago,[39] but they have not been widely applied clinically because of the rapid corrosion rate of Mg or its alloys. In recent years, tremendous efforts have been made to promote clinical translation of Mg-based orthopaedic implants, where successful clinical trials for product registration with the approval of special clinical indications are essential. Through searching the current Web of Science database, we found that Mg-based orthopaedic implants have been reported for a number of applications, including hallux valgus surgery in Germany, fixation of vascularised bone flaps in femoral heads and malleolar

fractures in China, and distal radius fractures in Korea.[7] The first commercial Mg screw, called MAGNEZIX, was made of MgYReZr alloy and received CE mark approval in 2013 for the treatment of hallux valgus surgery (**Figure 5A**).[40] The MAGNEZIX series compression screws produced by Syntellix AG company in Germany have been successfully registered in 58 countries or regions for more fracture types around the world by 2021 (**Figure 5B**).[41, 42] In 2015, the K-MET screw with the composition of Mg-Ca-Zn alloy produced by the U&I company in South Korea successfully obtained approval from the Korea Food and Drug Administration to fix distal radius fractures (**Figure 5C**).[43] In 2019, HP Mg screws developed by E-Ande Technology Co., Ltd. in China received approval from the National Medical Products Administration for a multi-centre clinical trial for fixation of autologous vascularised bone flaps to treat patients with femoral head vascular necrosis based on a published clinical study (**Figure 5D**).[44] Most recently, another clinical study was reported to discuss the use potential of JDBM screws with a Ca-P coating in the treatment of medial malleolus fractures in China.[45] The results showed that all patients achieved good medial malleolus fracture alignment without observation of breakage of the JDBM screws prior to complete fracture healing (**Figure 5E**). In summary, based on the establishment of sound indications, clinical translational research into Mg-based orthopaedic implant devices or implants will make great breakthroughs in the coming decades towards wide clinical applications.

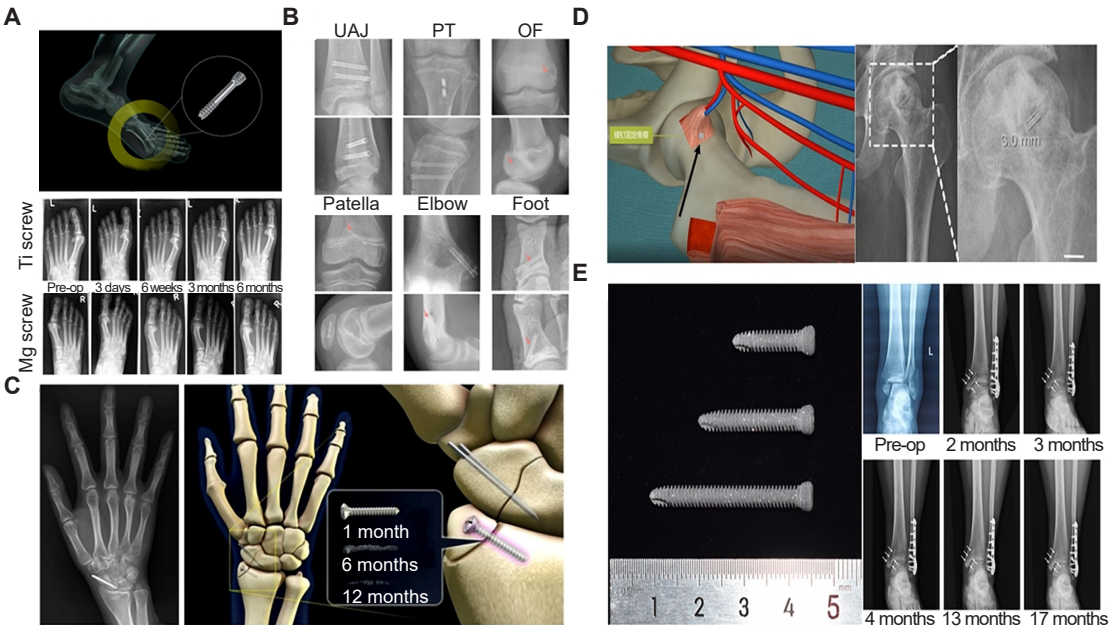

Figure 5. Clinical studies of Mg-based screws in orthopaedics. (A) MAGNEZIX screws produced in Germany for the treatment of mild hallux valgus fractures. Reprinted from Windhagen et al.[40] licensee BioMed Central Ltd. (B) Representative images of the MAGNEZIX screws applied for fixation of fractures at skeletal sites in children and adolescents. Red arrows indicate implants. Reprinted from Stürznickel et al.[41] Copyright 2021, with permission from Elsevier. (C) Mg-based alloy screws composed of Mg-Ca-Zn alloy made in Korea for fixation of distal radius fractures. (D) HP Mg screws for fixation of vascularised autogenous bone flaps to treat vascular necrosis of the femoral head in China. Reprinted from Zhao et al.[44] Copyright 2016, with permission from Elsevier. (E) JDBM screws (white arrows) for fixation of medial malleolar fractures in China. Reprinted from Xie et al.[45] DF: distal femur; HP: high-purity; JDBM: Mg-Nd-Zn-Zr alloy; Mg: magnesium; PT: proximal tibia; UAJ: upper ankle joint.

Challenges and Strategies of the use of Magnesium-based Devices in Orthopaedics

Degradable Mg-based orthopaedic implants are now widely regarded as the next generation of alternatives to current orthopaedic devices, but there are still technical or technological challenges to maintaining appropriate or controlled degradation behaviour and desirable mechanical properties over the entire treatment period to support tissue healing, especially for heavy weight-bearing skeletal sites, prior to larger-scale clinical studies. Alloying and surface modification have been extensively studied to address the aforementioned concerns.[5] However, the bonding strength of the coatings and the impairment of corrosion resistance caused by the second phase in Mg alloys still limit their further use in Mg-based orthopaedic implants. A recent study suggested that changing the structural design of a screw, such as the thread geometry and the shape of the screw head, favoured improvement of the mechanical properties of Mg-based screws.[46] Therefore, optimising the structure design of Mg-based orthopaedic devices may be a promising direction to overcome the drawbacks of the mechanical properties (**Figure 6A**).[8] Most recently, Luo et al.[8] re-designed HP Mg interference screws and predicted their optimal structural design through finite element analysis. Experimental testing was then applied to ascertain the best design which favoured improved torque properties. As only quadrupedal animal models have been applied so far to test the use potential of Mg-based orthopaedic implants in bone fractures, there are still clinical concerns

regarding the risks associated with mechanical support of Mg-based fixators at heavy load-bearing skeletal sites in patients. The combination of Mg-based devices and their traditional metallic counterparts may be another feasible strategy to avoid the limitations of Mg-based implants alone. Tian et al.[47] reported a novel hybrid device composed of Mg screws and Ti plates/screws for the fixation of tibial fractures in rabbits (**Figure 6B**). Such a Mg-containing hybrid system could be used for a wide range of clinical indications at both low and high load-bearing skeletal sites.

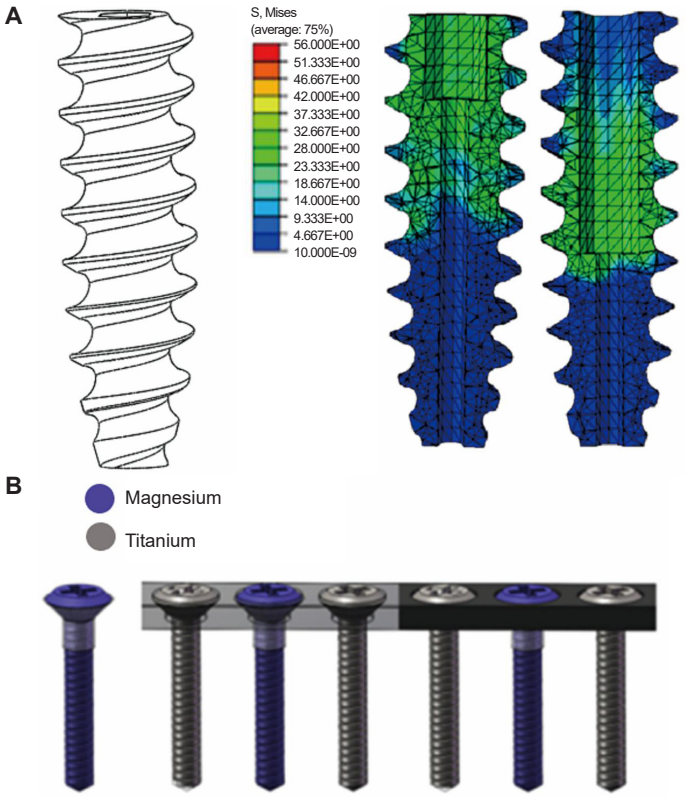

Figure 6. The research and development strategies of novel magnesium-based implants and hybrid systems in orthopaedics. (A) Novel design of the structure of a magnesium-based interference screw for improved maximal torque. Reprinted from Luo et al.[8] (B) Mg-containing hybrid devices for fixation of fractures at high weight-bearing skeletal sites. Adapted from Tian et al.[47]

Conclusions

Mg-based and clinical indication-based orthopaedic implants have been widely investigated and used in extensive pre-clinical models and clinical studies or trials, such as fracture fixation and ACL reconstruction, due to their excellent biocompatibility, appropriate Young's modulus, biodegradability and beneficial effects on bone formation. Mg-based orthopaedic implants promote bone formation through direct modulation of the osteogenic differentiation of osteoprogenitor cells and indirect regulation of osteogenesis by affecting cell–cell crosstalk. Encouraging progress has been made in clinical trials of Mg-based orthopaedic implants used for the fixation of hallux valgus, vascularised bone flaps and malleolus fractures, distal radius fractures, and medial malleolar fractures, providing solid evidence for the use of Mg-based orthopaedic implants as a revolutionary fixator. Although there are still huge challenges to be overcome for the large scale clinical application of Mg-based orthopaedic implants at the current stage, the adoption of new strategies including new structure designs and hybrid systems may facilitate addressing these clinical concerns regarding the degradation performance and mechanical strength of Mg-based fixators in orthopaedics especially at high weight-bearing skeletal sites.

Author contributions
YL, JW, JW, and LQ drafted the manuscript; MTYO and PSY gave comments during the preparation of the manuscript. All authors approved the final version of this manuscript.
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