Biomaterials Translational

Advances and perspective on the translational medicine of biodegradable metals

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Key Words:
biodegradable metals; cardiovascular applications; clinical translation; degradation mechanism; orthopaedic applications

From the Contents

ABSTRACT

Biodegradable metals, designed to be safely degraded and absorbed by the body after fulfil the intended functions, are of particular interest in the 21st century. The marriage of advanced biodegradable metals with clinical needs have yield unprecedented possibility. Magnesium, iron, and zinc-based materials constitute the main components of temporary, implantable metallic medical devices. A burgeoning number of studies on biodegradable metals have driven the clinical translation of biodegradable metallic devices in the fields of cardiology and orthopaedics over the last decade. Their ability to degrade as well as their beneficial biological functions elicited during degradation endow this type of material with the potential to shift the paradigm in the treatment of musculoskeletal and cardiovascular diseases. This review provides an insight into the degradation mechanism of these metallic devices in specific application sites and introduces state-of-the-art translational research in the field of biodegradable metals, as well as highlighting some challenges for materials design strategies in the context of mechanical and biological compatibility.

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http://doi.org/10.12336/biomatertransl.2021.03.002

How to cite this article:
Yang, H.; Lin, W.; Zheng, Y. Advances and perspective on the translational medicine of biodegradable metals. *Biomater Transl.* **2021**, *2*(3), 177-187.

Introduction

The pace of population aging around the world is increasing dramatically. The World Health Organization has estimated that the population over 60 years of age will nearly double from 12% to 22% from 2015 to 2050,[1] while recent census data (May, 2021) announced by the National Bureau of Statistics of China reported that the population aged 60 years and above accounts for 18.7% of the total population, an increase of 5.44% compared with 2010.[1] As a result, it is a major challenge to ensure that healthcare resources are ready to cope with this demographic shift.

Biomaterials are widely used in various applications such as orthopaedics, cardiovascular medicine, ophthalmics, dentistry, wound healing, and drug-delivery systems. Innovations in biomaterials can drive advances in medicine and provide patients with better treatments. Metallic biomaterials have played a leading role in the development of medical devices due to their excellent corrosion resistance and adequate mechanical properties relative to local biological tissues.[2] Conventional metallic devices are designed to stay in the body permanently. However, demands for temporary mechanical support until tissue healing is achieved has risen greatly in orthopaedic and cardiovascular applications in recent years.[3] The use of permanent metallic devices for treatment in cases where temporary support is required has caused complications in the long term. For orthopaedics, stress shielding effects due to the high Young's modulus of metals like cobalt-chromium (Co-Cr), stainless steel, and titanium alloys may cause peri-implant bone loss over time.[4] Second surgery for implant removal is required after bone healing or impaired function.[5] For cardiovascular applications, there is evidence that the existence of a permanent metallic cage may abolish vascular reactivity, alter flow dynamics and limit the potential for maximal vasodilation.[6]

Recent advances in biodegradable metals (BMs) provide promising solutions to fulfil the above demands and may revolutionize the treatment of bone fractures and coronary artery diseases. Biodegradable magnesium (Mg)-based materials have been extensively studied in the past decade. The accumulation of a large amount of research data has effectively promoted Mg from the scientific research stage to the innovative medical device product research and development stage.[7, 8] Research on iron (Fe)-based materials has also driven the first-in-human clinical trial of a biodegradable Fe-based scaffold. Meanwhile zinc (Zn), with a favourable degradation profile, is quickly emerging as the new research frontier in the field of BMs.[9]

The articles about the definition, criteria, and classifications of BMs were retrieved by the search terms: Biodegradable metals (MeSH Terms) OR Bioabsorbable metals (MeSH Terms) OR Bioresorbable metals AND Definition (MeSH Terms) AND Criteria AND Classifications. Then, the articles about biodegradation mechanisms were retrieved by the search terms: Degradation (MeSH Terms) OR Corrosion (MeSH Terms) AND *In vivo* (MeSH Terms) AND Animal study (MeSH Terms) AND Magnesium (MeSH Terms) OR Iron (MeSH Terms) OR Zinc (MeSH Terms). Then, the articles about clinical translation of biodegradation implants were retrieved by the search terms: Biodegradable (MeSH Terms) OR Bioabsorbable (MeSH Terms) OR Bioresorbable (MeSH Terms) AND Orthopedic implants (MeSH Terms) OR Cardiovascular stents (MeSH Terms) OR Wound closure applications (MeSH Terms). All these searches were performed on Web of Science and Google Scholar databases prior to May, 2021. Results were further screened by title and abstract, irrelevant research were excluded. Finally, 75 articles were included in this review. In this review, we discussed the latest definition, criteria, and classifications of BMs. We focused on the biodegradation mechanism of Mg, Fe, and Zn in specific physiological environments. Finally, we introduced the developments in the context of clinical translation and discussed challenges and directions for materials design strategies to improve the clinical outcomes for biodegradable metallic devices.

Definition, Criteria, and Classifications

Definition

The traditional idea for metallic implants was to "*achieve a suitable combination of physical properties to match those of the replaced tissue with a minimal toxic response by the host*".[10] Therefore, materials like stainless steel, Co-Cr-based alloys, and titanium (Ti)-based alloys were chosen because they exhibit superior mechanical properties and corrosion resistance. The evolution from bioinert materials to the new generation of BMs has offered an alternative to biomedical metallic implants. The definition of BMs is "metals expected to corrode gradually *in vivo*, with an appropriate host response elicited by released corrosion products, which can pass through or be metabolized or assimilated by cells and/or tissue, and then dissolve completely upon fulfilling the mission to assist with tissue healing leaving no implant residues",[11] indicating the intrinsic degradable feature and corresponding biological effects of this new class of metals. Therefore, biodegradability and biocompatibility can be set as necessary and sufficient criteria according to the definition of BMs.

Biodegradability

The term "biodegradation" is used to describe "the process as a deleterious change in the chemical structure, physical properties, or appearance of a material" according to the American Society for Testing and Materials.[12] However, the detailed process represented by "biodegradation" in biodegradable polymers, ceramics, and metals is different. The "biodegradation" of biodegradable polymers was interpreted as "cleavage of hydrolytically- or enzymatically-sensitive bonds in the polymer leading to polymer erosion."[13] In contrast, the meaning of "biodegradation" in bioceramics is interpreted as "decomposition to small particles as well as dissolved ions, which participate in the enzyme/cell-mediated reaction and new tissue forms."[14] For BMs, biodegradation is a chemical reaction process, in other words, corrosion of metals in a physiologic environment. Therefore, parameters used to describe metallic corrosion including "electrode potential," "reactivity series," "galvanic series," "Pilling-Bedworth ratio" as well as "Pourbaix diagram" can be adopted to characterize the biodegradability of BMs. In general, metallic elements with standard electrode potential lower than zero exhibit the potential to initiate biodegradation in a neutral physiological environment. Additionally, metals with an electrode potential slightly higher than zero may be degradable in certain physiological microenvironments. Nevertheless, electrode potential only tells us the thermodynamic tendency of metallic corrosion, and corrosion kinetics depend on factors such as properties of a surface film and microenvironmental parameters.

Biocompatibility

The most critical feature of biomaterials is that they will not cause any unacceptable harm when present in contact with tissues of the human body. The concept of biocompatibility has evolved in the past few decades. During the years between 1940 and 1980, biocompatibility has traditionally been concerned with long-term implantable devices, and the sole requirement is that the materials shall not harm tissues, achieved through chemical and biological inertness. As a result, metallic materials with the least reactivity are preferred as they would be non-toxic, non-immunogenic, non-thrombogenic, non-carcinogenic, non-irritant, and so on. With the development of biomaterials science and the clinical need for materials to react with tissues specifically, the basic edict that was equated with biological safety was no longer a sufficient pre-requisite. Therefore, biocompatibility has been re-defined as follows:

1 School of Materials Science and Engineering, Peking University, Beijing, China; 2 School of Engineering Medicine, Beihang University, Beijing, China; 3 College of Materials Science and Chemical Engineering, Harbin Engineering University, Harbin, Heilongjiang Province, China; 4 Biotyx Medical (Shenzhen) Co., Ltd., Shenzhen, Guangdong Province, China

"*Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimizing the clinically-relevant performance of that therapy.*"[15] To evaluate the biocompatibility of a metal, at least three levels of consideration should be included. The first level is cellular biocompatibility. IC50 (half maximal inhibitory concentration) is a typical parameter used to quantitatively measure the potency of an element in inhibiting a specific cell type.[16] The second level is tissue biocompatibility. LD50 (median lethal dose) is commonly adopted to reflect the lethal dose of a metallic element.[17] Thus, it can serve as the upper limit for BMs. The third and the most important one is human/clinical-related biocompatibility. Clinical data, without doubt, provide the most authoritative and convincing evidence to prove the biocompatibility of a BM. However, a lack of clinical data is normal for materials under development. In light of this, other criteria such as whether the element exists in the human body, the recommended daily intake, and the serum concentration of an element can be used as a reference as well.

Classifications

By screening according to the dual criteria of "biodegradability" and "biocompatibility", elements suitable for BMs are listed in descending order of content in the human body: calcium (Ca), potassium (K), sodium (Na), Mg, Fe, Zn, rubidium (Rb), strontium (Sr), tin (Sn), barium (Ba), manganese (Mn), lithium (Li), caesium (Cs), molybdenum (Mo), yttrium (Y), scandium (Sc), rare earth elements, and tungsten (W)[18] (**Figure 1**). Ca presents the highest content in the human body, however, only amorphous Ca-based metallic glasses[19] have been reported as BMs and none of the pure metallic forms of Ca has been studied yet. Na and K are unstable in air due to their high reactivity, thus, there are no reports on Na- or K-based BMs yet. Considering the high concentrations and tolerances of Ca, Na, and K in the human body, the amounts alloyed with other metals can be high. Mg, Fe, and Zn are commonly accepted as elements for BM matrix due to their appropriate reactivity in physiological environments. The remaining elements present relatively low contents in the human body. Therefore, they are usually used as potential elements for alloying with other BMs. In principle, the lower the content of an element in the human body, the greater must be the consideration when using it, and less content should be added into BMs.

Three major categories of BMs are proposed concerning their compositions and crystallization.

1) Biodegradable pure metals: Metals consisting of single elements are included in this category. Pure Mg, Fe, and Zn are the major BMs that have been widely studied. Impurity is the most critical factor that impacts the biodegradability and biocompatibility of pure metals.[20] Thus, the purity of Mg, Fe, and Zn is recommended to be higher than 99.99%, 99.99%, and 99.999% (wt.) for biomedical applications.

2) Biodegradable crystalline alloys: Alloying is one of the most common methods used to adjust the mechanical, chemical and biological properties of BMs. Generally, the type and quantity of elements that are added into the matrix are based on phase diagrams, electrode potentials, and biological effects. Detailed progress of biodegradable crystalline Mg-,[8] Fe-,[21] and Zn-based alloys[9] can be found elsewhere.

3) BM matrix composites: Incorporating BMs into composites is an effective way to integrate the advantages of metals, ceramics, and polymers. Various phases such as hydroxyapatite,[22, 23] tricalcium phosphate,[24] polycaprolactone,[25] MgO,[26] and ZnO[27] have been added into Mg, Fe or Zn to form BM-matrix composites.

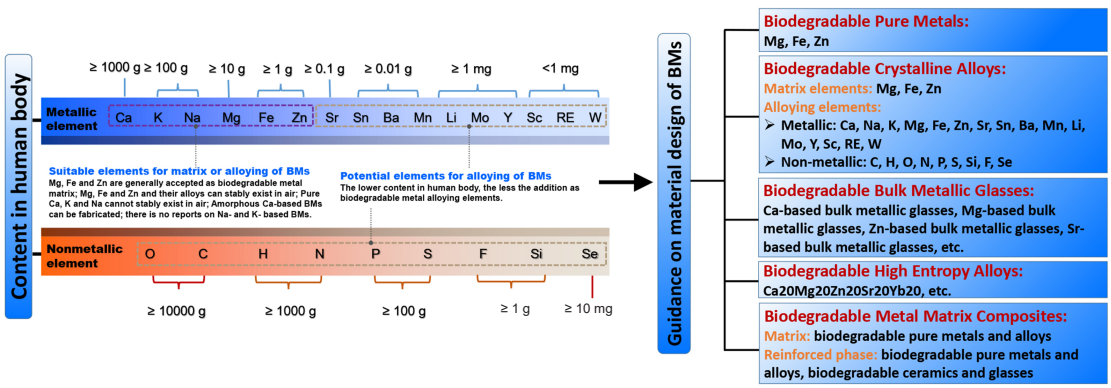

Figure 1. Design of biodegradable metals based on the criteria of "biodegradability" and "biocompatibility". BM: biodegradable metal. Reprinted with permission from Liu et al.[11] Copyright 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Biodegradation Mechanisms

Magnesium-based implants

Generalities of magnesium corrosion

Under the physiological environment, which can be simplified as a NaCl-based aqueous solution buffered to pH 7.4, Mg-based materials readily corrode in the presence of body fluids, thereby releasing H_2 gas. Two major factors lead to the degradability of Mg and its alloys: (i) the highly electronegative potential of Mg allows the cathodic water reduction reaction to predominate, whereby the corrosion of Mg proceeds even without oxygen and (ii) the surface film formed on Mg is poorly protective in the presence of aggressive anions such as chloride ions in body fluid.[28] The corrosion of Mg is an electrochemical process that occurs by electron transfer due to the interaction between the

metal and the environment, i.e., body fluid. The oxidation half-reaction for Mg is:

$Mg \rightarrow Mg^{2+} + 2e^-$ (1)

Considering the neutral biological environment, water reduction is the dominant cathodic reaction:

$2H_2O + 2e^- \rightarrow H_2 + 2OH^-$ (2)

Consequently, the overall corrosion reaction for Mg is:

$Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$ (3)

The major clinical applications of Mg-based implants focus on bone and vascular environments. Therefore, it will be more clinically meaningful to discuss the degradation of Mg-based implants in the specific biological environment.

Degradation of magnesium-based screws in the bone environment

The detailed degradation process and related chemical reactions of biodegradable Mg-5Ca-1Zn alloy screws have been reported by Lee et al.[29] Corrosion of Mg within the bone environment enables a series of reactions. First, an increase in the pH and Mg ion concentrations leads to the precipitation of $Mg(OH)_2$ on degrading Mg surfaces. Then, increased pH triggers the formation of calcium phosphate (CaP) compounds near the implant site. Across the bone–implant interface, Mg ion concentrations decrease according to the diffusing feature as they move away from the Mg implant surface toward the native bone while Ca shows the opposite trend. CaP compounds are composed of both an amorphous phase and a crystalline phase. The preferential formation of amorphous CaP can be explained by its lower kinetic energy barrier or the stabilizing effect of Mg ions. After maturation, crystallized CaP, which exhibits a similar chemical composition to that of native bone, will form. The physiological buffering system will continuously drive the formation of CaP from $Mg(OH)_2$ and move the degrading interface towards the Mg implant. Finally, the crystallized CaP will be resorbed by osteoclasts to induce bone formation by osteoblasts.

Degradation of magnesium-based scaffolds in the vascular environment

The degradation of a Mg alloy scaffold is described as a two-stage process starting at the scaffold surface and moving inward until the metallic backbone is replaced by amorphous CaP.[30,31] In the first stage, water penetrates the polymer coating and reacts with the Mg scaffold to form $Mg(OH)_2$. In the second stage, $Mg(OH)_2$ is slowly converted to an amorphous CaP with high water content. The entire degradation process takes about 12 months. It is interesting to note that regardless of the different physiological environments, the degradation process and products of Mg alloy screws and scaffolds are similar ($Mg(OH)_2$ and CaP), indicating the uniformity of the underlying mechanism.

Iron-based implants

Generalities of iron corrosion

The corrosion mechanism of Fe has been amply studied and demonstrated.[32] When exposed to a neutral aqueous medium, the anodic reaction is:

$Fe \rightarrow Fe^{2+} + 2e^-$ (4)

At the cathodic areas, an oxygen reduction reaction takes place:

$O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$ (5)

The hydroxide ions react with the Fe^{2+} ions:

$Fe^{2+} + 2OH^- \rightarrow Fe(OH)_2$ (6)

In an oxygen-rich environment, $Fe(OH)_2$ oxidizes to $Fe(OH)_3$:

$4Fe(OH)_2 + O_2 + 2H_2O \rightarrow 4Fe(OH)_3$ (7)

When there is limited oxygen to access, $Fe(OH)_2$ is oxidized by water to form magnetite:

$3Fe(OH)_2 \rightarrow Fe_3O_4 + H_2 + 2H_2O$ (8)

Due to the excessively slow degradation rate of Fe in bone environments, most research on biodegradable Fe-based materials has focused on cardiovascular environments.

Degradation of iron-based scaffold in the vascular environment

Lin et al.[33,34] evaluated the degradation behaviour of Fe-based scaffolds in rabbit abdominal aorta and porcine coronary artery and proposed a potential bioresorption pathway for its degradation products (**Figure 2A**). They speculated that magnetic Fe_3O_4 is generated adjacent to the Fe struts while $Ca_3(PO_4)_2$ distributes in the outermost areas. Nonmagnetic $Fe(OH)_3$ and its dehydration products (FeOOH and Fe_2O_3) and $Fe_3(PO_4)_2$ are formed in between. The released Fe ions could be easily utilized by cells and tissues, whereas the clearance of solid products through dissolution is more difficult due to their extremely low solubility, e.g. the solubility of $Fe(OH)_3$ is 1×10^{-17} M at pH 7.0. Instead, they found that an increasing number of macrophages surrounded the scaffold struts to engulf the insoluble particles (**Figure 2B**). These macrophages then migrated from the strut sites to the adventitia. Consequently, they hypothesized that the hemosiderin-laden macrophages could finally enter the lymphatics and travel to the adjacent lymph nodes to fulfil the bioresorption of Fe degradation products.

Generalities of zinc corrosion

Zn and its alloys have been widely used as a sacrificial coating for steel for a long time, but the use of Zn for biomedical applications has only emerged recently due to its favourable degradable characteristics in physiologic environments. The anode reaction (equation (9)) is the dissolution of Zn and the dominant cathode reaction (equation (5)) in a neutral aqueous medium is the oxygen reduction reaction. Solid $Zn(OH)_2$ and ZnO are formed due to the release of Zn ions and the increased pH of the material surface (equations (10) and (11)). However, the surface oxides and hydroxides are unable to protect the underlying Zn in the pH range from 7 to 10, which enables the continuous degradation of Zn.[35] The potential clinical applications of Zn and its alloys include, but are not limited to, biodegradable vascular scaffolds and bone implants due to their satisfactory combination of mechanical properties, degradation behaviour, and biocompatibility.

$Zn \rightarrow Zn^{2+} + 2e^-$ (9)

$Zn^{2+} + 2OH^- \rightarrow Zn(OH)_2$ (10)

$Zn(OH)_2 \rightarrow ZnO + H_2O$ (11)

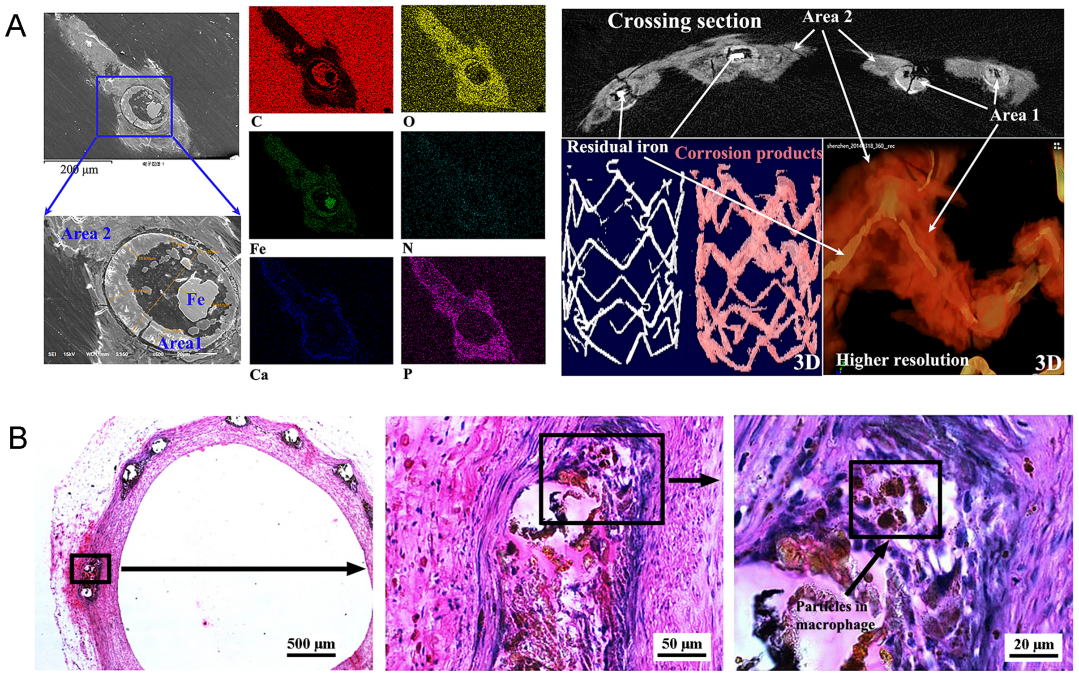

Figure 2. (A) Scanning electron microscopic images and corresponding chemical element distribution of one iron strut, and micro-computed tomographic image of a representative iron-based scaffold with residual iron backbone and corrosion products at 6 months after implantation in the rabbit abdominal aorta. Scale bars: 200 μm (scanning electron microscopic images). 3D: three-dimensional. Reprinted from Lin et al.[33] Copyright 2016, with permission from Elsevier. (B) Macrophages engulf the insoluble corrosion products of an iron-based scaffold in rabbit abdominal aorta within 12 months. Right images are magnifications of black rectangles in left images. Scale bars: 500 μm (left), 50 μm (middle), 20 μm (right). Reprinted Lin et al.[34] Copyright 2017, with permission from Elsevier.

Degradation of zinc-based implants in the bone environment

The potential applications of Zn-based materials for bone fixation have been proposed since 2011, so far there have been about 20 publications reporting *in vivo* studies. Generally, *in vivo* degradation rates of Zn alloy bulk implants are around 13–25 μm/year,[36] which can provide bone tissue healing with sufficient mechanical support for at least 3–6 months. However, complete degradation of Zn-based materials in the bone environment has not been reported yet, and the degradation of these implants was insignificant when characterized by micro-computed tomography. Roughly, degradation products of Zn alloy implants consist of three categories. The first type consists of Zn, oxygen (O), and carbon (C), which are usually generated close to the implant.[37] Transmission electron microscopy analysis identified the products as predominantly equiaxed nanocrystalline ZnO with a small amount of dispersed $ZnCO_3$.[38] Ca and P were detected in the second type of products in addition to Zn, O, and C.[36] These products are distributed closer to the adjacent tissue, and $Ca_3(PO_4)_2$ and ZnO are found inside. The third type of product exhibits similar chemical composition to that of new bone, and usually plays the role of a transition zone to the new bone tissue.[39] The exact chemical formula of this product has not yet been revealed.

Degradation of zinc-based scaffold in the vascular environment

The degradation behaviour of Zn in vascular tissue was first revealed by Bowen et al.[40] using a Zn wire in a rat model. They found that the Zn wire retained about 70% of its original cross-sectional area at 4 months followed by accelerated corrosion, indicating an appropriate degradation rate for cardiovascular scaffold application. The presumed degradation products include Zn oxide, Zn carbonate, and Ca/P. A subsequent 20-month *in vivo* study revealed that the Zn wire exhibited a steady corrosion rate of around 25 μm/year without local toxicity.[41] A more comprehensive degradation mechanism was proposed by Yang et al.[42] considering the interaction between vascular healing and scaffold degradation (**Figure 3**). Before endothelialisation, the corrosion microenvironment for pure Zn scaffold is dynamic blood flow, in which convection is the major method of mass transfer. In addition, blood is an oxygen-rich medium and has a strong buffering capability. As a result, the degradation rate of the pure Zn scaffold reached 30 μm/year with a uniform corrosion model. ZnO and $Zn(OH)_2$ were speculated to form preferentially due to kinetic factors whereas $Zn_3(PO_4)_2 \cdot 4H_2O$ formed later as a more thermodynamically-stable phase. After endothelialisation, the corrosion microenvironment switches to the neointima where diffusion leads to mass transfer. The oxygen partial pressure in the artery wall decreases compared to that of blood. Accordingly, the degradation rate of pure Zn scaffold decreases (< 20 μm/year) and nonuniform corrosion becomes dominant. Degradation products transform to ZnO and Ca/P phase as the local pH adjacent to the scaffold surface increases. After one year of implantation, 41.75% of the scaffold volume is degraded, given an estimated complete degradation of about 2 to 3 years. Zhou et al.[43] reported the longer-term degradation behaviour of Zn-0.8Cu scaffold, in which approximately 28% by volume of the scaffold remained after 24-month degradation, which further confirms the satisfactory degradation behaviour of Zn-based scaffolds.

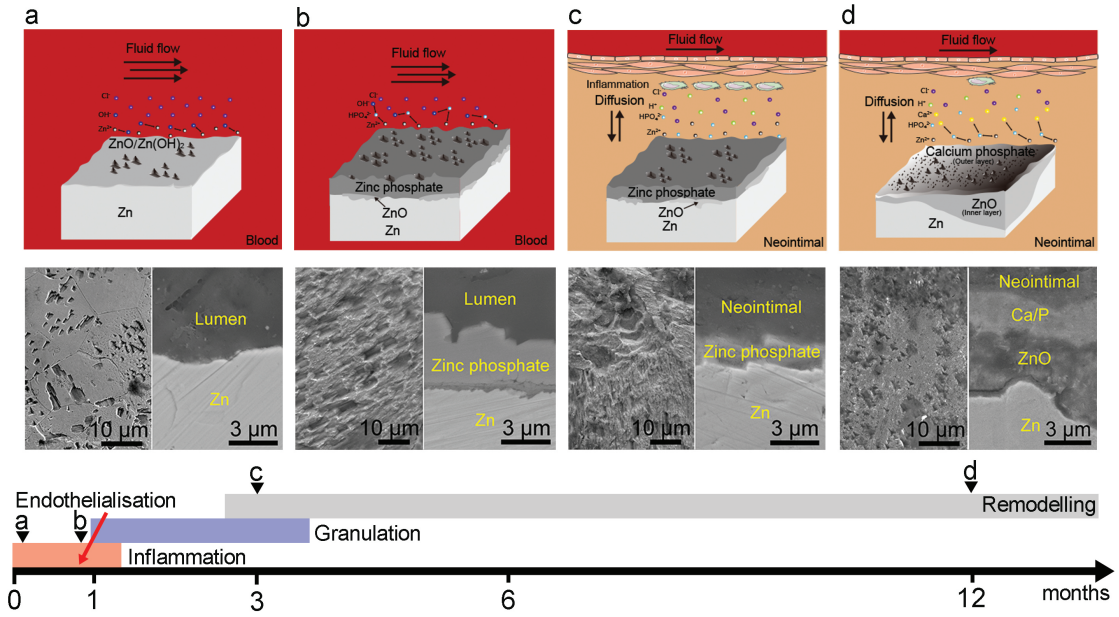

Figure 3. Schematic diagrams showing evolution of the degradation mechanism of a zinc (Zn) stent associated with the conversion of degradation microenvironments during the healing process. a–d indicates representative time points during vascular healing, which are described by images above from left to right. Scale bars: 10 μm or 3 μm. Reprinted from Yang et al.[42] Copyright 2017, with permission from Elsevier.

Clinical Translation

The pioneering study of biodegradable implants in humans dates back over a century to 1878 when Edward C. Huse[44] used pure Mg wire ligatures to stop bleeding. However, clinical applications of Mg-based implants were subject to metallurgical technology as they corroded rapidly and formed hydrogen gas in the human body. Over the past decades, developments in purification technology, material design, and fabrication techniques have rekindled people's interest in the clinical use of BMs. As a result, translational research on biodegradable devices is creating a progressive shift in paradigm in the treatment of musculoskeletal and cardiovascular diseases.

Orthopaedic applications

The advantage of Mg ions in promoting osteogenic differentiation and the similar modulus of Mg to bone tissue has enabled it to become a promising candidate for hard tissue repair. Three compositions of Mg-based systems have been granted clinical approval for orthopaedic applications from governing agencies in Germany,[45] South Korea,[29] and China.[8] MAGNEAIX® CS, a fracture compression screw researched and developed by a German company (Syntellix AG) was the first biodegradable bone implant to receive CE approval in early 2013 (**Figure 4**). A MgYReZr alloy system was optimized to reduce hydrogen generation while providing sufficient mechanical support for tissue healing. A clinical prospective-randomized and controlled approval study[45] verified the non-inferiority of the MAGNEAIX® screws compared to Ti implants in Hallux valgus operations. Currently, MAGNEAIX® CS has been used in particular for Hallux valgus surgery and treatment of bone fractures of the hand. K-MET screws composed of MgCaZn alloy have been developed by the U&I corporation, Korea, for distal radius fracture repair. In a clinical trial,[29] hand fractures in all 53 cases recovered in ~4–6 weeks, and the range of motion of the hand was restored to almost the same level as the contralateral hand after 6 months. The gas cavities formed due to the corrosion of MgZnCa screws reached their maximum size at 2–3 months and then gradually reduced over time, and no adverse side effects were reported. To avoid the potential impact of alloying elements, high purity Mg screws

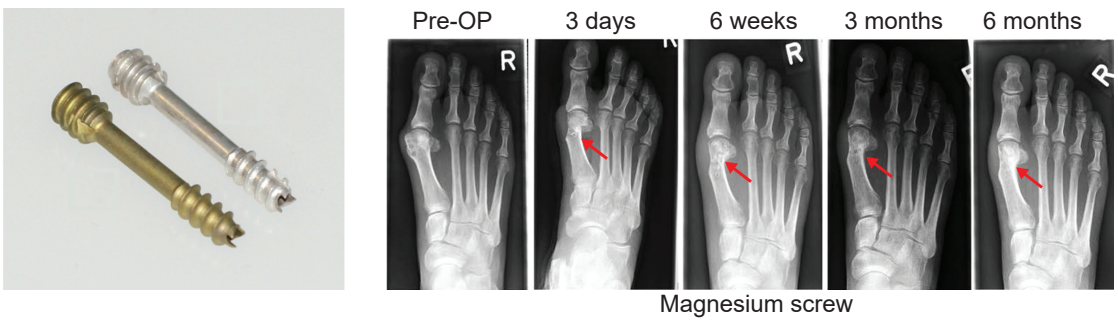

Figure 4. MAGNEAIX® compression screws for Hallux valgus surgery. Red arrows indicate implantation sites. OP: operative; R: right. Reprinted from Windhagen et al.[45]; licensee BioMed Central Ltd.

were used in patients suffering from Association Research Circulation Osseous stage II/III osteonecrosis in the femoral head to fix vascularized bone flaps.[8] Significantly more satisfactory therapeutic results in the Harris hip score and bone flap displacement were found in the Mg screws group compared to the control group. High-purity Mg screws were further used for fixation of femoral neck fracture, metatarsal fracture, diaphyseal defect, acetabular defect, and femoral head fracture. In 2019, the high purity Mg screw was approved by the China National Medical Products Administration for multicentre clinical trials of the treatment of steroid-induced osteonecrosis, and gained CE approval in 2020.

Cardiovascular applications

The biodegradable feature of Mg also inspired people to apply it as a temporary scaffold to facilitate vessel healing after which it will fully degrade without impairing the restoration of normal vascular function. The first version of biodegradable Mg scaffold designed for human coronary arteries was known as the absorbable metal stent (AMS-1), which was made of a WE43 alloy containing 93 wt.% Mg and 7 wt.% rare earth elements. AMS-1 was a bare metal scaffold, designed with struts 80 μm wide × 165 μm thick, which degraded within 1 month.[46] A significant vessel recoil caused by radial strength loss and neointimal proliferation due to fast degradation and the absence of anti-proliferation drugs was revealed in the first prospective, multicenter non-randomized clinical trial (PROGRESS-AMS, 63 patients).[46] To improve the performance of AMS-1, AMS-2.1 was developed with a refined alloy composition to lower the degradation rate, a modified strut design (130 × 120 μm) to preserve radial strength, and an optimized scaffold cell design to improve collapse pressure. Poly lactic-co-glycolic acid coating-loaded paclitaxel was added to AMS-2.1 to make it AMS-3 (DREAMS-1G) to address the neointimal proliferation.[31] Meanwhile, the degradation time was extended to 6 months. A further improvement was implemented to generate the DREAMS-2G, commercially distributed as Magmaris. Modifications included a cross-sectional profile of 150 μm × 150 μm to slow down fracture and resorption time, a 7 μm sirolimus-eluting poly-L-lactic acid coating to better inhibit the neointimal proliferation and tantalum radiopaque edge markers to add X-ray visibility.[47] More importantly, Magmaris doubled its scaffolding time, and the degradation time was prolonged to 12 months. Magmaris received CE marking for release in the European Union in 2016 as the first biodegradable drug-eluting metal scaffold. The multicentre prospective non-randomized trials BIOSOLVE-II,[48, 49] -III,[50] and -IV[30] have been carried out to evaluate the clinical performance of Magmaris. Results from BIOSOLVE-II (123 patients) and III (61 patients) reported a target lesion failure rate of 3.4%, 5.9%, and 6.8% at 12, 24, and 36 months with no definite or probable scaffold thrombosis, target-vessel myocardial infraction, or cardiac deaths. The 1-year outcome from BIOSOLVE-IV(400 patients) reported a target lesion failure rate of 4.3%, and one definite case of scaffold thrombosis in a patient 10 days after implantation. All the clinical trials confirmed the safety of the Magmaris scaffold. The iteration of the next generation RMS DREAMS 3G includes a thinner strut (99–147 μm), a longer scaffolding time (> 3 months), higher radial strength, and superior deliverability.[30]

Fe-based scaffolds have been considered as a biodegradable metallic scaffold due to their excellent mechanical properties that are similar to durable stents. Early animal studies found no local or systemic toxicity during short- or long-term implantation of Fe stents in the porcine descending aorta.[51, 52] However, the degradation of Fe scaffolds was insignificant after 12 months. To address the problem, an intercalated structure, created by introducing a nanoscale Zn sacrificial layer between the nitride Fe platform and sirolimus-carrying poly (D, L-lactide) drug coating was proposed and developed (**Figure 5**).[34, 53] This novel design created a multistage biodegradation behaviour, maintained mechanical integrity

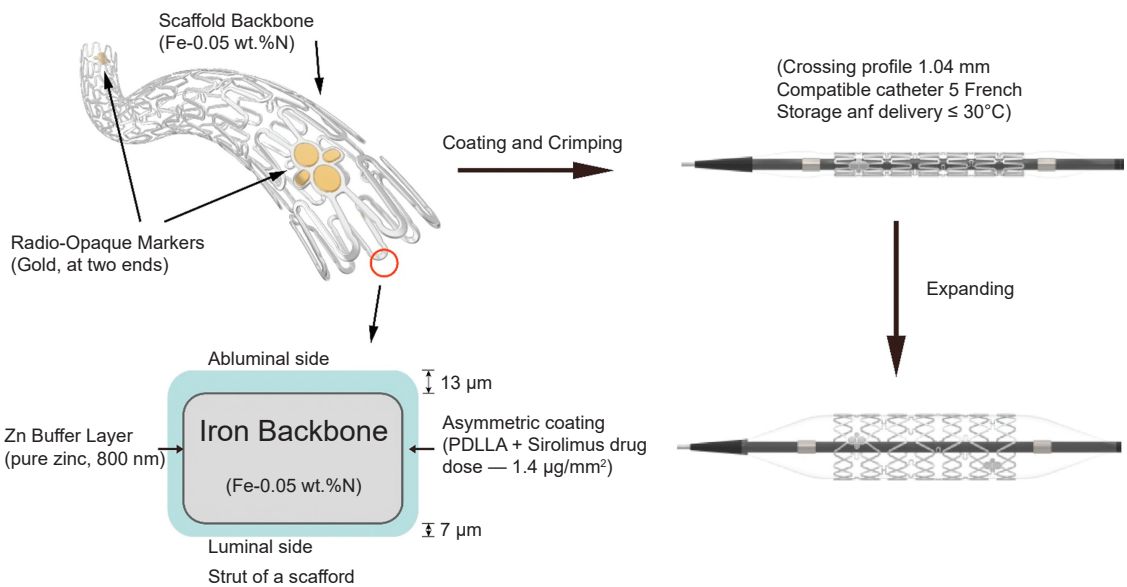

Figure 5. Biodegradable nitride iron scaffold with intercalated structure design. PDLLA: poly (D, L-lactide). Reprinted from Lin et al.[55]

at the early stage while accelerating the degradation at the subsequent stage. The first-in-human study of the poly (D, L-lactide)-Zn-nitrided Fe biodegradable scaffold reported no intimal hyperplasia at 6-month follow-up, and much of the scaffold degraded after 26 months. The insoluble degradation products produced by the corrosion of Fe scaffolds *in vivo* have long been regarded as a potential biosafety issue. Recent studies reveal a possible bioresorption mechanism of these products via phagocytosis by macrophages in rabbit abdominal aorta, and further clearance through the lymph nodes.[34] In addition, evaluation of magnetic resonance safety and compatibility revealed that Fe-based scaffolds are MR conditional until fully biodegraded.[54]

Wound closure applications

A biodegradable vascular closure device (Velox CDTM), which is made of AZ31 alloy, has been developed to quickly achieve stable mechanical vascular closure following percutaneous catheterization for diagnostic or interventional procedures. The implant includes a plug and footplate system. A first-in-human study reported unimpaired healing of the tissue tract and indirect evidence for arterial healing without inflammation at 30 days post-surgery.[56] Another biodegradable Mg clip received special approval for innovative medical devices from the Centre for Medical Device Evaluation in China, and a corresponding clinical trial is in progress.

Challenges and Perspectives

Biodegradability is the most important feature that distinguishes Mg, Fe, and Zn, etc. from traditional durable metals. Therefore, a proper and thorough understanding of biodegradability is essential for us to take advantage of BMs for biomedical applications. Biodegradation is an interpretation of the corrosion process of metals taking place under a specific physiological environment. In other words, materials and biological environments are equally important factors to consider when unravelling the biodegradation mechanism. We should always bear in mind that tissue healing is a dynamic biological process, which means the corrosive microenvironment is changing over time. For example, blood flow is the corrosive microenvironment for biodegradable vascular scaffolds right after implantation. However, after endothelialisation, the neointima takes the place of blood flow and becomes the major corrosive environment for the scaffold for the remainder of the implantation time.[42] As a result, key factors affecting degradation include stress,[57] mass transfer,[58] buffering capability,[59] local pH,[32] oxygen content,[60] changes in cells/tissues,[40] etc. as well. After drawing a complete picture of dynamic interactions between the material and biological microenvironment, a further step is to build up mechanical and biological compatibility between the device and the host tissue during biodegradation.

Mechanical compatibility describes the adaptation of the loss of mechanical integrity of implants to the dynamic tissue healing process. Generally, biodegradable devices are designed to provide temporary mechanical support for the tissue-reconstruction process, after which the device should degrade completely at an appropriate rate tolerable to the human body and be absorbed by cells/tissues or safely excreted. The time frame of a device's function depends on its specific applications. For orthopaedic implants, mechanical support for 3–6 months is considered necessary to assist with hard tissue reconstruction. For a cardiovascular scaffold, adequate radial support for the first 3–6 months is needed to allow vessel remodelling.[61] However, challenges in the three aspects listed below need to be overcome before achieving optimal mechanical compatibility.

(1) The commonly-used time frame for degradation is roughly estimated from the biological process and evaluated mostly in healthy animal models. We should never ignore the impact of interspecies differences. For example, Lin et al.[55] reported a significant difference in the degradation of Fe scaffolds between rabbit abdominal aorta and porcine coronary artery. The most accurate data come from clinical trials. The degradation frame of the current iteration of the Magmaris scaffold is based on a series of clinical studies (BIOSOLVE I–IV),[30] and scaffold performance will improve as the clinical data available increase.

(2) The loss of mechanical integrity of the device should not simply be equal to the volume or weight loss. Commonly-used methods to characterize *in vivo* degradation rates include micro-computed tomography, weight loss, and scanning electron microscopy. However, degradation rates calculated from data obtained by these methods are based on an assumption that the corrosion of the device is uniform, which is rare for BMs. Therefore, it is necessary to establish the relationship between available characterisation methods and the real mechanical loss of devices.

(3) Effective means to regulate the degradation remain to be developed. Alloying,[36, 62, 63] structure design,[64, 65] and surface modification[66, 67] have been widely used to accelerate or inhibit the degradation of Mg, Fe or Zn. Recently, a novel intercalated structure containing a nanoscale Zn sacrificial layer and a biodegradable polymer drug coating was applied to a biodegradable Fe-based scaffold to achieve multistage biodegradable behaviour.[53] The scaffold maintained mechanical integrity at the initial stage and exhibiting accelerated biodegradation at the subsequent stage in both animal and human arteries. However, all these methods are "passive" as they lose control of the degradation behaviour of devices once they are implanted. Developments of novel implant designs that enable *in vitro* "active" regulation of implant degradation are more capable of achieving multistage control.

Biological compatibility requires the degradation products of implants to be at least biosafe, and better to exhibit biological functions which promote tissue healing. In light of this, an in-depth and mechanistic understanding of the dynamic host response is critical for designing biodegradable devices. For example, the major biological stages in bone fracture healing are the inflammatory stage, the endochondral stage, and the remodelling stage.[68] Traditional strategies have focused on stimulating osteogenic differentiation directly to promote bone healing. In recent years, osteoimmunomodulation has been proposed after the vital role of immune cells in regulating bone dynamics was revealed.[69] Strategies to control inflammatory response include tailoring protein adsorption,[70] biomimetic

coating,[71] surface topographical patterns,[72] drug delivery,[73] macrophage polarization,[74] and nitric oxide regulation.[75] Further, a better understanding of the interaction mechanism between the degradation profile of implants and corresponding immune responses is necessary to tune material performance to induce a favourable healing environment. Additionally, integration of biosensors to biodegradable devices to monitor physiological signals such as local temperature and blood flow enable more possibilities for biodegradable devices.

Author contributions

YZ and HY designed and wrote the manuscript. WL revised and supplemented the manuscript. All authors approved the final version of this manuscript.

Financial support

This work was supported by the National Natural Science Foundation of China (No. 5193000081).

Acknowledgement

None.

Conflicts of interest statement

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1. National Bureau of Statistics. The main data of the seventh national census, National Bureau of Statistics of China. http://www.stats.gov.cn/tjsj/zxfb/202105/t20210510_1817176.html. Accessed by May, 2021.
2. Navarro, M.; Michiardi, A.; Castaño, O.; Planell, J. A. Biomaterials in orthopaedics. *J R Soc Interface*. **2008**, *5*, 1137-1158.
3. Li, C.; Guo, C.; Fitzpatrick, V.; Ibrahim, A.; Zwierstra, M. J.; Hanna, P.; Lechtig, A.; Nazarian, A.; Lin, S. J.; Kaplan, D. L. Design of biodegradable, implantable devices towards clinical translation. *Nat Rev Mater*. **2020**, *5*, 61-81.
4. Haseeb, M.; Butt, M. F.; Altaf, T.; Muzaffar, K.; Gupta, A.; Jallu, A. Indications of implant removal: A study of 83 cases. *Int J Health Sci (Qassim)*. **2017**, *11*, 1-7.
5. Reith, G.; Schmitz-Greven, V.; Hensel, K. O.; Schneider, M. M.; Tinschmann, T.; Bouillon, B.; Probst, C. Metal implant removal: benefits and drawbacks--a patient survey. *BMC Surg*. **2015**, *15*, 96.
6. Wentzel, J. J.; Whelan, D. M.; van der Giessen, W. J.; van Beusekom, H. M.; Andhyiswara, I.; Serruys, P. W.; Slager, C. J.; Krams, R. Coronary stent implantation changes 3-D vessel geometry and 3-D shear stress distribution. *J Biomech*. **2000**, *33*, 1287-1295.
7. Han, H. S.; Loffredo, S.; Jun, I.; Edwards, J.; Kim, Y. C.; Seok, H. K.; Witte, F.; Mantovani, D.; Glyn-Jones, S. Current status and outlook on the clinical translation of biodegradable metals. *Mater Today*. **2019**, *23*, 57-71.
8. Zhao, D.; Witte, F.; Lu, F.; Wang, J.; Li, J.; Qin, L. Current status on clinical applications of magnesium-based orthopaedic implants: A review from clinical translational perspective. *Biomaterials*. **2017**, *112*, 287-302.
9. Venezuela, J.; Dargusch, M. S. The influence of alloying and fabrication techniques on the mechanical properties, biodegradability and biocompatibility of zinc: a comprehensive review. *Acta Biomater*. **2019**, *87*, 1-40.
10. Hench, L. L.; Polak, J. M. Third-generation biomedical materials. *Science*. **2002**, *295*, 1014-1017.
11. Liu, Y.; Zheng, Y.; Chen, X. H.; Yang, J. A.; Pan, H.; Chen, D.; Wang, L.; Zhang, J.; Zhu, D.; Wu, S.; Yeung, K. W. K.; Zeng, R. C.; Han, Y.; Guan, S. Fundamental theory of biodegradable metals—definition, criteria, and design. *Adv Funct Mater*. **2019**, *29*, 1805402.
12. Williams, D. The williams dictionary of biomaterials. Liverpool University Press: 1999.
13. Tamada, J. A.; Langer, R. Erosion kinetics of hydrolytically degradable polymers. *Proc Natl Acad Sci U S A*. **1993**, *90*, 552-556.
14. Hench, L. L. The future of bioactive ceramics. *J Mater Sci Mater Med*. **2015**, *26*, 86.
15. Williams, D. F. On the mechanisms of biocompatibility. *Biomaterials*. **2008**, *29*, 2941-2953.
16. Aykul, S.; Martinez-Hackert, E. Determination of half-maximal inhibitory concentration using biosensor-based protein interaction analysis. *Anal Biochem*. **2016**, *508*, 97-103.
17. Zbinden, G.; Flury-Roversi, M. Significance of the LD50-test for the toxicological evaluation of chemical substances. *Arch Toxicol*. **1981**, *47*, 77-99.
18. Zoroddu, M. A.; Aaseth, J.; Crisponi, G.; Medici, S.; Peana, M.; Nurchi, V. M. The essential metals for humans: a brief overview. *J Inorg Biochem*. **2019**, *195*, 120-129.
19. Li, H. F.; Zheng, Y. F. Recent advances in bulk metallic glasses for biomedical applications. *Acta Biomater*. **2016**, *36*, 1-20.
20. Virtanen, S. Biodegradable Mg and Mg alloys: corrosion and biocompatibility. *Mater Sci Eng B*. **2011**, *176*, 1600-1608.
21. Hermawan, H. Updates on the research and development of absorbable metals for biomedical applications. *Prog Biomater*. **2018**, *7*, 93-110.
22. Ye, X.; Chen, M.; Yang, M.; Wei, J.; Liu, D. In vitro corrosion resistance and cytocompatibility of nano-hydroxyapatite reinforced Mg-Zn-Zr composites. *J Mater Sci Mater Med*. **2010**, *21*, 1321-1328.
23. Witte, F.; Feyerabend, F.; Maier, P.; Fischer, J.; Störmer, M.; Blawert, C.; Dietzel, W.; Hort, N. Biodegradable magnesium-hydroxyapatite metal matrix composites. *Biomaterials*. **2007**, *28*, 2163-2174.
24. Narita, K.; Tian, Q.; Johnson, I.; Zhang, C.; Kobayashi, E.; Liu, H. Degradation behaviors and cytocompatibility of Mg/β-tricalcium phosphate composites produced by spark plasma sintering. *J Biomed Mater Res B Appl Biomater*. **2019**, *107*, 2238-2253.
25. Wong, H. M.; Wu, S.; Chu, P. K.; Cheng, S. H.; Luk, K. D.; Cheung, K. M.; Yeung, K. W. Low-modulus Mg/PCL hybrid bone substitute for osteoporotic fracture fixation. *Biomaterials*. **2013**, *34*, 7016-7032.
26. Lei, T.; Tang, W.; Cai, S. H.; Feng, F. F.; Li, N. F. On the corrosion behaviour of newly developed biodegradable Mg-based metal matrix composites produced by in situ reaction. *Corros Sci*. **2012**, *54*, 270-277.
27. Yang, H. T.; Wang, Z. H.; Li, H. F.; Zheng, Y. F.; Li, Y. W.; Li, R. In vitro study on novel Zn-ZnO composites with tunable degradation rate. *Eur Cell Mater*. **2014**, *25*, S5.
28. Esmaily, M.; Svensson, J. E.; Fajardo, S.; Birbilis, N.; Frankel, G. S.; Virtanen, S.; Arrabal, R.; Thomas, S.; Johansson, L. G. Fundamentals and advances in magnesium alloy corrosion. *Prog Mater Sci*. **2017**, *89*, 92-193.
29. Lee, J. W.; Han, H. S.; Han, K. J.; Park, J.; Jeon, H.; Ok, M. R.; Seok, H. K.; Ahn, J. P.; Lee, K. E.; Lee, D. H.; Yang, S. J.; Cho, S. Y.; Cha, P. R.; Kwon, H.; Nam, T. H.; Han, J. H.; Rho, H. J.; Lee, K. S.; Kim, Y. C.; Mantovani, D. Long-term clinical study and multiscale analysis of in vivo biodegradation mechanism of Mg alloy. *Proc Natl Acad Sci U S A*. **2016**, *113*, 716-721.
30. Bennett, J.; De Hemptinne, Q.; McCutcheon, K. Magmaris resorbable magnesium scaffold for the treatment of coronary heart disease:

overview of its safety and efficacy. *Expert Rev Med Devices*. **2019**, *16*, 757-769.

31. Wittchow, E.; Adden, N.; Riedmüller, J.; Savard, C.; Waksman, R.; Braune, M. Bioresorbable drug-eluting magnesium-alloy scaffold: design and feasibility in a porcine coronary model. *EuroIntervention*. **2013**, *8*, 1441-1450.
32. Ahmad, Z. Principles of corrosion engineering and corrosion control. Elsevier: 2006.
33. Lin, W. J.; Zhang, D. Y.; Zhang, G.; Sun, H. T.; Qi, H. P.; Chen, L. P.; Liu, Z. Q.; Gao, R. L.; Zheng, W. Design and characterization of a novel biocorrodible iron-based drug-eluting coronary scaffold. *Mater Des*. **2016**, *91*, 72-79.
34. Lin, W.; Qin, L.; Qi, H.; Zhang, D.; Zhang, G.; Gao, R.; Qiu, H.; Xia, Y.; Cao, P.; Wang, X.; Zheng, W. Long-term in vivo corrosion behavior, biocompatibility and bioresorption mechanism of a bioresorbable nitrided iron scaffold. *Acta Biomater*. **2017**, *54*, 454-468.
35. Thomas, S.; Birbilis, N.; Venkatraman, M. S.; Cole, I. S. Corrosion of zinc as a function of pH. *Corrosion*. **2012**, *68*:015009-1-015009-9.
36. Yang, H.; Jia, B.; Zhang, Z.; Qu, X.; Li, G.; Lin, W.; Zhu, D.; Dai, K.; Zheng, Y. Alloying design of biodegradable zinc as promising bone implants for load-bearing applications. *Nat Commun*. **2020**, *11*, 401.
37. Yang, H.; Qu, X.; Wang, M.; Cheng, H.; Jia, B.; Nie, J.; Dai, K.; Zheng, Y. Zn-0.4Li alloy shows great potential for the fixation and healing of bone fractures at load-bearing sites. *Chem Eng J*. **2021**, *417*, 129317.
38. He, J.; Fang, J.; Wei, P.; Li, Y.; Guo, H.; Mei, Q.; Ren, F. Cancellous bone-like porous Fe@Zn scaffolds with core-shell-structured skeletons for biodegradable bone implants. *Acta Biomater*. **2021**, *121*, 665-681.
39. Yang, H.; Qu, X.; Lin, W.; Chen, D.; Zhu, D.; Dai, K.; Zheng, Y. Enhanced osseointegration of Zn-Mg composites by tuning the release of Zn ions with sacrificial Mg-rich anode design. *ACS Biomater Sci Eng*. **2019**, *5*, 453-467.
40. Bowen, P. K.; Drelich, J.; Goldman, J. Zinc exhibits ideal physiological corrosion behavior for bioabsorbable stents. *Adv Mater*. **2013**, *25*, 2577-2582.
41. Drelich, A. J.; Zhao, S.; Guillory, R. J., 2nd; Drelich, J. W.; Goldman, J. Long-term surveillance of zinc implant in murine artery: Surprisingly steady biocorrosion rate. *Acta Biomater*. **2017**, *58*, 539-549.
42. Yang, H.; Wang, C.; Liu, C.; Chen, H.; Wu, Y.; Han, J.; Jia, Z.; Lin, W.; Zhang, D.; Li, W.; Yuan, W.; Guo, H.; Li, H.; Yang, G.; Kong, D.; Zhu, D.; Takashima, K.; Ruan, L.; Nie, J.; Li, X.; Zheng, Y. Evolution of the degradation mechanism of pure zinc stent in the one-year study of rabbit abdominal aorta model. *Biomaterials*. **2017**, *145*, 92-105.
43. Zhou, C.; Li, H. F.; Yin, Y. X.; Shi, Z. Z.; Li, T.; Feng, X. Y.; Zhang, J. W.; Song, C. X.; Cui, X. S.; Xu, K. L.; Zhao, Y. W.; Hou, W. B.; Lu, S. T.; Liu, G.; Li, M. Q.; Ma, J. Y.; Toft, E.; Volinsky, A. A.; Wan, M.; Yao, X. J.; Wang, C. B.; Yao, K.; Xu, S. K.; Lu, H.; Chang, S. F.; Ge, J. B.; Wang, L. N.; Zhang, H. J. Long-term in vivo study of biodegradable Zn-Cu stent: A 2-year implantation evaluation in porcine coronary artery. *Acta Biomater*. **2019**, *97*, 657-670.
44. Huse, E. C. A new ligature? *Chicago Med J Exam*. **1878**, *172*, 11.
45. Windhagen, H.; Radtke, K.; Weizbauer, A.; Diekmann, J.; Noll, Y.; Kreimeyer, U.; Schavan, R.; Stukenborg-Colsman, C.; Waizy, H. Biodegradable magnesium-based screw clinically equivalent to titanium screw in hallux valgus surgery: short term results of the first prospective, randomized, controlled clinical pilot study. *Biomed Eng Online*. **2013**, *12*, 62.
46. Erbel, R.; Di Mario, C.; Bartunek, J.; Bonnier, J.; de Bruyne, B.; Eberli, F. R.; Erne, P.; Haude, M.; Heublein, B.; Horrigan, M.; Ilsley, C.; Böse, D.; Koolen, J.; Lüscher, T. F.; Weissman, N.; Waksman, R.; PROGRESS-AMS (Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents) Investigators. Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. *Lancet*. **2007**, *369*, 1869-1875.
47. Campos, C. M.; Muramatsu, T.; Iqbal, J.; Zhang, Y. J.; Onuma, Y.; Garcia-Garcia, H. M.; Haude, M.; Lemos, P. A.; Warnack, B.; Serruys, P. W. Bioresorbable drug-eluting magnesium-alloy scaffold for treatment of coronary artery disease. *Int J Mol Sci*. **2013**, *14*, 24492-24500.
48. Haude, M.; Ince, H.; Abizaid, A.; Toelg, R.; Lemos, P. A.; von Birgelen, C.; Christiansen, E. H.; Wijns, W.; Neumann, F. J.; Kaiser, C.; Eeckhout, E.; Lim, S. T.; Escaned, J.; Onuma, Y.; Garcia-Garcia, H. M.; Waksman, R. Sustained safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de novo coronary lesions: 12-month clinical results and angiographic findings of the BIOSOLVE-II first-in-man trial. *Eur Heart J*. **2016**, *37*, 2701-2709.
49. Haude, M.; Ince, H.; Abizaid, A.; Toelg, R.; Lemos, P. A.; von Birgelen, C.; Christiansen, E. H.; Wijns, W.; Neumann, F. J.; Kaiser, C.; Eeckhout, E.; Lim, S. T.; Escaned, J.; Garcia-Garcia, H. M.; Waksman, R. Safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de-novo coronary artery lesions (BIOSOLVE-II): 6 month results of a prospective, multicentre, non-randomised, first-in-man trial. *Lancet*. **2016**, *387*, 31-39.
50. Haude, M.; Ince, H.; Kische, S.; Abizaid, A.; Tölg, R.; Alves Lemos, P.; Van Mieghem, N. M.; Verheye, S.; von Birgelen, C.; Christiansen, E. H.; Barbato, E.; Garcia-Garcia, H. M.; Waksman, R. Safety and clinical performance of a drug eluting absorbable metal scaffold in the treatment of subjects with de novo lesions in native coronary arteries: Pooled 12-month outcomes of BIOSOLVE-II and BIOSOLVE-III. *Catheter Cardiovasc Interv*. **2018**, *92*, E502-E511.
51. Peuster, M.; Hesse, C.; Schloo, T.; Fink, C.; Beerbaum, P.; von Schnakenburg, C. Long-term biocompatibility of a corrodible peripheral iron stent in the porcine descending aorta. *Biomaterials*. **2006**, *27*, 4955-4962.
52. Waksman, R.; Pakala, R.; Baffour, R.; Seabron, R.; Hellinga, D.; Tio, F. O. Short-term effects of biocorrodible iron stents in porcine coronary arteries. *J Interv Cardiol*. **2008**, *21*, 15-20.
53. Shen, D.; Qi, H.; Lin, W.; Zhang, W.; Bian, D.; Shi, X.; Qin, L.; Zhang, G.; Fu, W.; Dou, K.; Xu, B.; Yin, Z.; Rao, J.; Alwi, M.; Wang, S.; Zheng, Y.; Zhang, D.; Gao, R. PDLLA-Zn-nitrided Fe bioresorbable scaffold with 53-μm-thick metallic struts and tunable multistage biodegradation function. *Sci Adv*. **2021**, *7*, eabf0614.
54. Bian, D.; Qin, L.; Lin, W.; Shen, D.; Qi, H.; Shi, X.; Zhang, G.; Liu, H.; Yang, H.; Wang, J.; Zhang, D.; Zheng, Y. Magnetic resonance (MR) safety and compatibility of a novel iron bioresorbable scaffold. *Bioact Mater*. **2020**, *5*, 260-274.
55. Lin, W.; Zhang, H.; Zhang, W.; Qi, H.; Zhang, G.; Qian, J.; Li, X.; Qin, L.; Li, H.; Wang, X.; Qiu, H.; Shi, X.; Zheng, W.; Zhang, D.; Gao, R.; Ding, J. In vivo degradation and endothelialization of an iron bioresorbable scaffold. *Bioact Mater*. **2021**, *6*, 1028-1039.
56. Caputo, R.; Kirwan, J.; Green, S.; Ebner, A. TCT-233 first in man experience with a large bore (≥14 FR) bio-corrodable vascular closure device. *J Am Coll Cardiol*. **2017**, *70*, B97.
57. Jafari, S.; Raman, R. K. S.; Davies, C. H. J.; Hofstetter, J.; Uggowitzer, P. J.; Löffler, J. F. Stress corrosion cracking and corrosion fatigue

characterisation of MgZn1Ca0.3 (ZX10) in a simulated physiological environment. *J Mech Behav Biomed Mater.* **2017**, *65*, 634-643.
58. Khakpour, M.; Vafai, K. Critical assessment of arterial transport models. *Int J Heat Mass Transfer.* **2008**, *51*, 807-822.
59. Liu, X.; Yang, H.; Xiong, P.; Li, W.; Huang, H. H.; Zheng, Y. Comparative studies of Tris-HCl, HEPES and NaHCO3/CO2 buffer systems on the biodegradation behaviour of pure Zn in NaCl and SBF solutions. *Corros Sci.* **2019**, *157*, 205-219.
60. Yadav, A. P.; Nishikata, A.; Tsuru, T. Oxygen reduction mechanism on corroded zinc. *J Electroanal Chem.* **2005**, *585*, 142-149.
61. Zheng, Y. F.; Gu, X. N.; Witte, F. Biodegradable metals. *Mater Sci Eng R Rep.* **2014**, *77*, 1-34.
62. Li, Z.; Gu, X.; Lou, S.; Zheng, Y. The development of binary Mg-Ca alloys for use as biodegradable materials within bone. *Biomaterials.* **2008**, *29*, 1329-1344.
63. Liu, X.; Sun, J.; Zhou, F.; Yang, Y.; Chang, R.; Qiu, K.; Pu, Z.; Li, L.; Zheng, Y. Micro-alloying with Mn in Zn–Mg alloy for future biodegradable metals application. *Mater Des.* **2016**, *94*, 95-104.
64. Li, Y.; Pavanram, P.; Zhou, J.; Lietaert, K.; Bobbert, F. S. L.; Kubo, Y.; Leeflang, M. A.; Jahr, H.; Zadpoor, A. A. Additively manufactured functionally graded biodegradable porous zinc. *Biomater Sci.* **2020**, *8*, 2404-2419.
65. Gu, X. N.; Zhou, W. R.; Zheng, Y. F.; Liu, Y.; Li, Y. X. Degradation and cytotoxicity of lotus-type porous pure magnesium as potential tissue engineering scaffold material. *Mater Lett.* **2010**, *64*, 1871-1874.
66. Yan, T.; Tan, L.; Xiong, D.; Liu, X.; Zhang, B.; Yang, K. Fluoride treatment and in vitro corrosion behavior of an AZ31B magnesium alloy. *Mater Sci Eng C.* **2010**, *30*, 740-748.
67. Xu, X.; Lu, P.; Guo, M.; Fang, M. Cross-linked gelatin/nanoparticles composite coating on micro-arc oxidation film for corrosion and drug release. *Appl Surf Sci.* **2010**, *256*, 2367-2371.
68. Einhorn, T. A.; Gerstenfeld, L. C. Fracture healing: mechanisms and interventions. *Nat Rev Rheumatol.* **2015**, *11*, 45-54.
69. Chen, Z.; Klein, T.; Murray, R. Z.; Crawford, R.; Chang, J.; Wu, C.; Xiao, Y. Osteoimmunomodulation for the development of advanced bone biomaterials. *Mater Today.* **2016**, *19*, 304-321.
70. Kim, S. E.; Song, S. H.; Yun, Y. P.; Choi, B. J.; Kwon, I. K.; Bae, M. S.; Moon, H. J.; Kwon, Y. D. The effect of immobilization of heparin and bone morphogenic protein-2 (BMP-2) to titanium surfaces on inflammation and osteoblast function. *Biomaterials.* **2011**, *32*, 366-373.
71. Zhou, L.; Lin, Z.; Ding, J.; Huang, W.; Chen, J.; Wu, D. Inflammatory and biocompatibility evaluation of antimicrobial peptide GL13K immobilized onto titanium by silanization. *Colloids Surf B Biointerfaces.* **2017**, *160*, 581-588.
72. Luu, T. U.; Gott, S. C.; Woo, B. W.; Rao, M. P.; Liu, W. F. Micro- and nanopatterned topographical cues for regulating macrophage cell shape and phenotype. *ACS Appl Mater Interfaces.* **2015**, *7*, 28665-28672.
73. Jayant, R. D.; McShane, M. J.; Srivastava, R. In vitro and in vivo evaluation of anti-inflammatory agents using nanoengineered alginate carriers: towards localized implant inflammation suppression. *Int J Pharm.* **2011**, *403*, 268-275.
74. Kzhyshkowska, J.; Gudima, A.; Riabov, V.; Dollinger, C.; Lavalle, P.; Vrana, N. E. Macrophage responses to implants: prospects for personalized medicine. *J Leukoc Biol.* **2015**, *98*, 953-962.
75. Simon-Walker, R.; Romero, R.; Staver, J. M.; Zang, Y.; Reynolds, M. M.; Popat, K. C.; Kipper, M. J. Glycocalyx-inspired nitric oxide-releasing surfaces reduce platelet adhesion and activation on titanium. *ACS Biomater Sci Eng.* **2017**, *3*, 68-77.

Received: May 30, 2021
Revised: July 16, 2021
Accepted: July 21, 2021
Available online: September 28, 2021