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Current status and outlook on the clinical translation of biodegradable metals

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During the last decade, translational research on biodegradable metallic materials has shown the feasibility of these novel materials for use in the fields of cardiology and orthopedics. Implants prepared with biodegradable metals are significantly stronger than their polymer counterparts, and there is now convincing evidence demonstrating that these materials fully biodegrade *in vivo*, thus reducing the need for secondary surgery. Clinical trials of such novel materials show significant potential, with the prospect of a paradigm shift in the way musculoskeletal and cardiovascular conditions are treated. This work provides an overview of the rapidly advancing technology of biodegradable metals, as well as defining some challenges in the application of these new biodegradable materials in the medical field.

Introduction

The use of biomaterials in medical applications has risen exponentially in recent years. Improving medical treatments and a better understanding of chronic medical conditions has led to an aging population that is more active than a generation ago. While this demographic shift has transformed the treatment of many life-threatening conditions, an increasingly active aging population places significant demands on healthcare resources at a time when budgets are constrained. Consequently, healthcare professionals and commissioners are placing greater emphasis on the early treatment of disease and improving the efficacy of existing treatment strategies.

Conventionally, inert metals such as titanium, stainless steel, and cobalt alloys have been used to fabricate orthopedic and cardiovascular implants due to their excellent corrosion resistant characteristics and adequate mechanical properties relative to local biological tissues [1]. Current metallic implants produced from inert materials are designed to remain in the body permanently and replace the original tissues. This concept of complete tissue replacement, however, does not consider instances that only require temporary supporting function until complete tissue healing has occurred. The usage of permanent inert materials to fulfill the temporary supporting function has caused several complications such as stress-shielding over time, leading to the weakening of bone, distortion of diagnostic images, and secondary surgery to remove the implant [2].

As an alternative, biodegradable synthetic polymer compounds such as poly(glycolic acid) (PGA), poly(l-lactic acid) (PLLA), and poly(lactic acid-co-glycolic acid)(PLGA) have been

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developed and approved by the Food and Drug Administration (FDA) for use in clinical settings [3]. Degradable implants have the advantage of complete tissue healing with restoration of function. A permanent implant will restore function, but complete restoration of the tissue cannot be obtained since the implant stays in place permanently. Studies have shown that removing permanent implants contributes up to 30% of all elective procedures performed in orthopedics [4]. In 2010, a total of 180,000 additional surgeries to remove permanent fixtures were performed in Germany, making it the fourth most commonly performed surgical procedure in orthopedic surgery following surgical fracture fixation, arthroscopies, and intervertebral disk interventions [5]. Consequently, usage of degradable implants could eliminate additional surgery to remove permanent fixtures, which benefits the patient by reducing surgery time and ultimately provides cost savings to the entire healthcare system. However, both inflammation resulting from the acidification of the tissue surrounding the degrading synthetic polymers and early fracture of the implant caused by its weak mechanical properties have limited their practical use [6]. Only a few applications of natural polymers such as collagen, keratin, and chitosan have been reported as suitable degradable implant materials because most mechanical properties of such polymers are inadequate to withstand loading while undergoing degradation [7].

Recent advances in biodegradable metallic material technology have demonstrated the potential to revolutionize the treatment of broken bones and heart disease [8–10]. Implants made with biodegradable metals are significantly stronger than their polymer counterparts, and the degraded metal particles are fully dissolvable in body fluids. Phagocytic cells like macrophages can dissolve the excess amount of degraded metal particles, which are known to be safely excreted [9,11,12]. The degradation of biodegradable metals in physiological settings occurs through a series of anodic and cathodic reactions (herein, the terms "degradation" and "corrosion" convey the same meaning). In general, the degradation of a metal occurs through corrosion involving conversion of the metallic material to a more stable ion. As depicted in Fig. 1, contact with body fluid results in oxidization of the metal, with the generated electrons being consumed by cathodic reactions. These reactions lead to the release of hydrogen gas along with hydroxide, resulting in the formation of a protective metal oxide layer on the surface. For magnesium alloys, the high concentration of chloride ions in body fluid weakens this protective oxide layer and accelerates the degradation process. As this process proceeds, saturated calcium and phosphate in the body fluid and local alkalization lead to calcium phosphate deposition on the metal oxide layer, which allows cells to adhere on the surface to form tissues.

The first application of biodegradable implant materials in humans dates back to over a century ago. Although performed without knowledge of its unique biodegradable properties, Edward C. Huse reported the first successful usage of pure magnesium wire ligature to stop bleeding in 1878 [13]. A series of clinical trials using Mg-based implants followed, but they failed prematurely due to the lack of metallurgical technology to control the fast degradability (Fig. 2). Over the past half-century, however, improvements in metal purification technology and various alloying techniques revived interest in the application of biodegradable metals. Following nearly two decades of laboratory and early translational research [14–17], these new metals now demonstrate significant clinical potential with the ability to create a paradigm shift in the way musculoskeletal [18,19] and cardiovascular conditions [20–24] are treated.

In this review, we describe the state-of-the-art technology in the field of biodegradable metals. We focus on the developments in the context of clinical translation and define potential

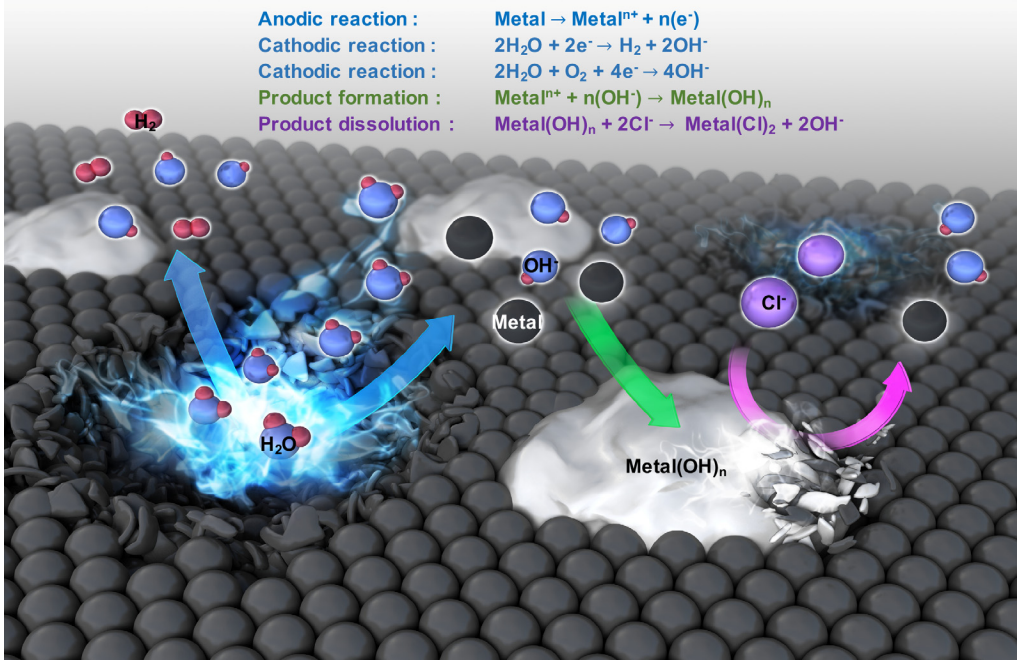

FIGURE 1

Biodegradation mechanism of metals.

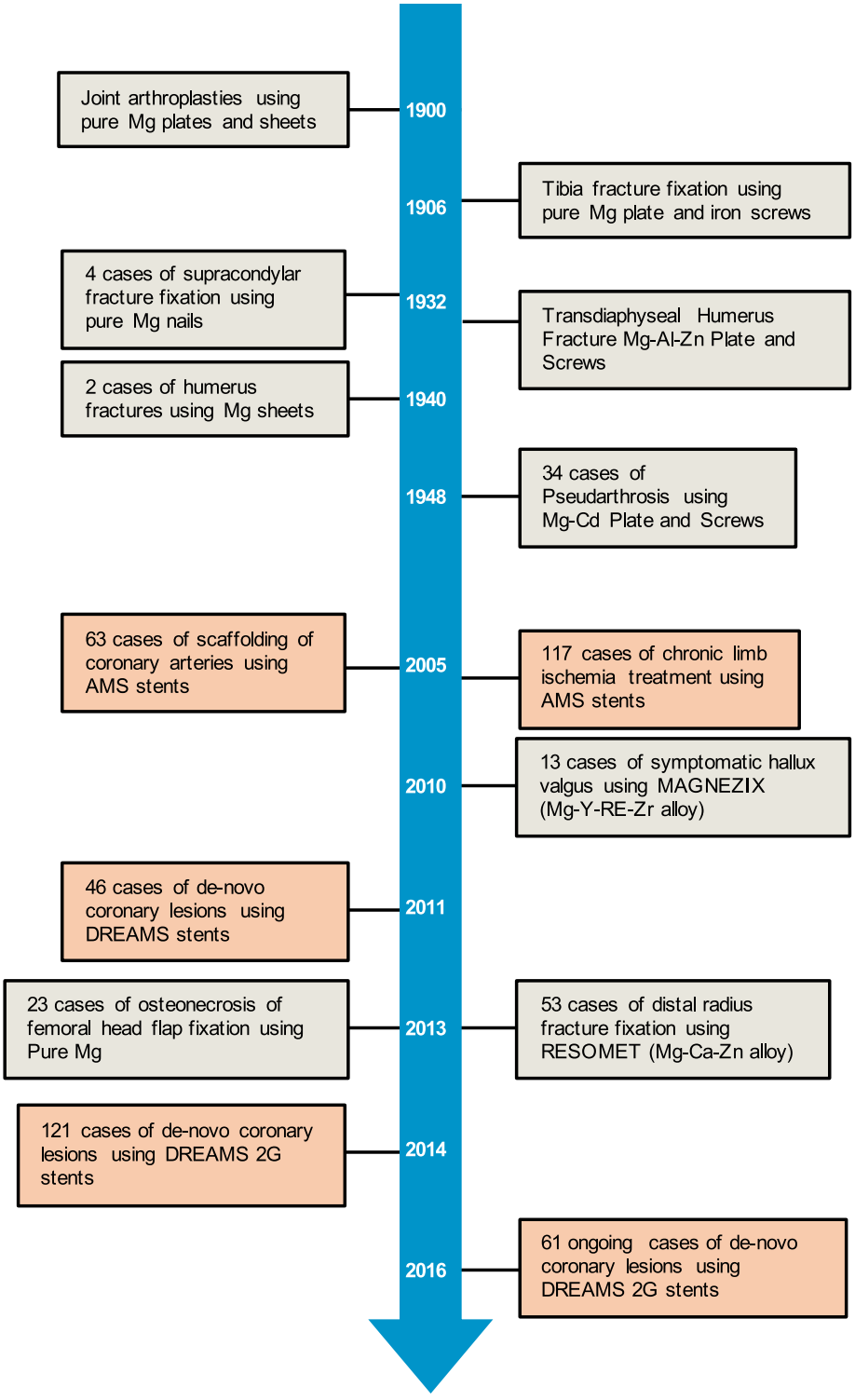

FIGURE 2

Timeline of representative clinical trials of biodegradable metals in cardiology (red) and orthopedics (gray).

advances and applications of new biodegradable materials in medicine.

Orthopedic application of biodegradable metals

The finding of replacement materials in skull and teeth of ancient human skeletons indicates that the use of metallic implants has occurred over several millennia [25]. The concept of bone replacement has been the central factor in the development of orthopedic implants, and conventional biometals such as stainless steel, cobalt alloy, and titanium have been used to treat trauma in the human body for nearly a century without significant changes [2,26]. Despite their clinically proven biocompatibilities, these foreign materials remain in the body indefinitely and may eventually cause problems or generate com-

plications once their expected working life has been reached. These limitations have stimulated researchers to investigate biodegradable materials that will provide sufficient initial mechanical integrity and degrade over time to provide a latticework for new tissue formation before being completely replaced by natural healthy tissue [27]. The benefit of such implant materials is enormous when applied in pediatrics, where the patient's tissue often continues to grow after implantation.

Over time, orthopedic implants designed with biodegradable metals (mostly magnesium) have been found to display similar elastic modulus to bone and biodegrade safely by reacting with chloride ions once implanted into physiological surroundings. Combined with advanced metallurgy techniques, biodegradable metallic alloys can now be designed to match the bone healing and remodeling process, thereby transferring load gradually from the implant to the tissue [27]. In general, the initial healing of fractured bone requires the implant to maintain structural integrity. Carefully designed alloy systems provide sufficient load support at this early stage while degrading at an optimal rate for complete bone healing [28]. Zhang et al. (2016) recently reported the calcitonin gene-related polypeptide-α mediated osteogenic differentiation promoted by magnesium, demonstrating the therapeutic potential of biodegradable metals in orthopedics [17].

Translational research on biodegradable metals

Research on the development of biodegradable orthopedic metals has focused mostly on magnesium (Mg) and its alloys due to their excellent biocompatibility and mechanical properties. As an essential mineral in the human body, a considerably large amount of Mg is present in bones and teeth [29]. The rapid ionization process involving the active degradation of magnesium implants showed a positive effect on the surrounding hard tissues, and excess amounts of Mg are known to be secreted by the kidneys [30]. The elastic modulus of Mg-based alloys is close to that of human bones, which prevents stress shielding by allowing a natural load transfer to the surrounding bones to stimulate the bone remodeling process.

Initial attempts to utilize magnesium as an implantable orthopedic device date to the early 1900s [31]. However, the lack of refinement technology resulted in excessive corrosion of Mg in the human body, which limited its widespread usage until much later. In 1999, scientists from the University of Hannover in Germany began basic research to exploit the bioactive properties of Mg alloys and proposed a new concept of biodegradable metallic materials. A German implant manufacturing company pursued the idea by developing a Mg alloy stent in 2003, and after 2005, the United States, Japan, Korea, and China also began intensive studies on biodegradable metallic materials. A decade later, a road map for the next generation of magnesium implants with the addition of different elements can now be envisioned (Fig. 3). Several literature reviews have covered the developmental process of these alloy systems, the details of which will not be included in this review [27,28,32]. Instead, this section will provide an overview of systems that are either very near or currently in the clinical stage, including their general degradation behavior, state-of-the-art *in vivo* performances, and translation efforts, with a particular focus on their clinical benefits.

Pure Mg

Pure Mg is the simplest form of a material system available for Mg-based orthopedic devices. The mechanical strength of pure Mg is relatively low for its effective utilization as a heavy load-bearing implant, but its usage eliminates the concern for toxicity of other alloying elements. Moreover, exceptionally high-purity magnesium (>99.99%) has been shown to degrade slower than most of the alloying systems available, thus making it an attractive target for low load-bearing applications in orthopedics, for example. One of the greatest challenges of pure Mg is controlling the amount of impurities. Local degradation processes could be initiated by a trace amount of impurities in pure Mg and cause rapid total erosion through pitting corrosion processes [33]. Such an outcome leads to the generation of a significant amount of hydrogen gas at the early stage of implantation that exceeds the local saturation level of hydrogen in blood and tissue, resulting in the formation of gas cavities. An excessive amount of hydrogen gas within these cavities results in the formation of callus by creating pressure, which causes mechanical disturbances at the implantation site [34]. Studies have shown that the presence of gas cavities disturbs the balance of blood cell parameters and causes massive subcutaneous emphysema in tested rats, leadings to a decreased survival rate [35]. Therefore, the development of pure Mg implants has focused on advanced purification techniques to reduce the degradation rate, and its current preclinical application ranges from bone screws, plate and screw systems, and interference screws [36–41]. Apart from the bone screw system, which will be discussed in the subsequent clinical trial section, there have been meaningful efforts to develop interference screws for anterior cruciate ligament (ACL) reconstruction.

Recent studies have shown that the Mg ions released from high-purity Mg interference screws in ACL reconstruction rabbit models lead to an accumulation of bone morphogenetic protein-2 and vascular endothelial growth factor, which facilitate early phase healing of the tendon-bone [41]. Furthermore, reduction in the expression of matrix metalloproteinase-13 by Mg interference screws resulted in an inhibitory effect on tendon graft degradation at the remodeling phase, providing a larger quantity of collagen fibers in the tendon graft to attach to the bone for better preclinical outcomes [42]. Most recently, a comparative study of high-purity Mg and Ti screws on tendon graft healing in rabbits with ACL reconstruction has confirmed excellent bone formation of Mg screws at the early healing stage without bone tunnel widening, implying its potential application in clinical settings [39].

Mg–Al alloys

Due to excellent castability, mechanical properties, corrosion resistance, and high maximum solubility of 12.7 wt.% in Mg, aluminum has been one of the most commonly studied alloying elements for Mg-alloy systems in the early development stage of biodegradable orthopedic implants [28]. Mg–Al alloy systems such as AM and AZ alloys, which were previously developed for industrial applications, are readily available for further optimization. In general, an increased Al content in Mg alloys increases the ultimate tensile strength (UTS) and elongation up to 6 wt.% while decreasing the degradation rate by forming an aluminum oxide film [27]. Although aluminum is a well-known

FIGURE 3

Current state-of-the-art applications of biodegradable metals. Devices at developmental stages – (a) Mg operative clip mounted on the clip applier, (b) MgF_2 coated Mg-2 wt%Nd alloy nasal stent, (c) Loaded Mg microclip in microlaryngeal forcep, (d) Mg stent for neurological application, (e) Mg-based intramedullary nail. Devices at clinical stages – (f) Resomet orthopaedic devices (Courtesy of U&I Corporation), (g) DREAMS 2nd generation stent, (h) Magnezix screw and pin (Courtesy of Syntellix), (i) Iron-based suture anchor (Courtesy of Fraunhofer IFAM), (j) Velox CD vascular closure device (Courtesy of Transluminal Technologies), (k) Pure Mg Screws. Figure adapted with permission from: Refs. [38,80,103,129,131–133].

neurotoxicant linked with Alzheimer's disease and dementia [43], researchers argue that the amount of aluminum released from such alloy systems with less than 5 wt.% aluminum is well below the weekly intake limits, and long-term *in vivo* studies have shown no direct detrimental effect [44]. In 2016, Angrisani et al. reported degradation of aluminum-containing LAE442-based alloys up to 3.5 years post-implantation in a rabbit model, demonstrating the safety of the implanted material in rabbits. Although the exact neurological state of the animals was not reported in this study, accumulation of degrading particles in brain, liver, spleen, and kidney after 3.5 years of implantation showed no remarkable changes [44]. Such a non-toxicity result, however, could be largely due to the relatively small content of aluminum (4 wt.%) in the LAE442 alloy system. Recent applications of Mg–Al systems range from the development of intramedullary nail systems to craniofacial screws [45–47].

Mg-rare earth alloys

Rare earth elements (REEs) can be classified into two categories depending on their solubility in Mg. The high solid-solubility group includes Y, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu, whereas the limited solid-solubility group includes Nd, La, Ce, Pr, Sm,

and Eu [27]. Initially, the addition of these REEs was performed to drastically increase the creep and corrosion resistance of Mg at both room and elevated temperatures [48,49]. Experimenting with various elemental compositions, remarkable progress has been made in the development of Mg-REE alloy systems with different mechanical and corrosion characteristics [16,18,50–57]. The most advanced system in Mg-REE alloys is the MgYREZr alloy, which is already in clinical use. From a material perspective, the MgYREZr alloy is very similar to WE43. The system contains >90 wt.% of magnesium with an average grain size of <5 μm. Further, its tensile strength and elongation is estimated at 275 MPa and 10%, respectively. Following its approval from the Conformité Européene (CE) for human application in 2013, a wide range of implants using this alloy system is currently being developed. To further optimize its degradation properties, various surface treatment techniques are also being tested in *in vivo* models. For example, direct comparisons of anodized WE43 screws and PLLA screws in a canine fracture model have proven the superior mechanical strength of WE43 at load-bearing sites (all PLLA screws were broken after 4 weeks), and anodized treatment of WE43 showed a further reduction in the inflammatory response from hydrogen gas [52].

Their possible application of MG-REE alloys in ACL reconstruction was tested in a recent pilot study; similar results to a titanium control were reported, suggesting their potential applicability [51]. Furthermore, excellent mechanical and corrosion properties of WE43 have allowed testing of human standard-sized plate and screw implants in a miniature pig model [54].

Mg–Zn alloys

Found in cells throughout the human body, zinc is an essential element that plays a role in cellular interactions, the immune system, and the catabolism of carbohydrates. With 6.2 wt.% solubility in Mg, Mg–Zn alloys reach a maximum UTS of 216.8 MPa and an elongation of 15.8% at 4 wt.% [58]. The addition of various elements including Ca, Zr, Sr, Y, Mn, and Si has been extensively studied, leading to the development of systems such as ZK alloys and ZX alloys, which have superior mechanical properties than the clinically approved WE alloys [59]. However, the degradation rate of Mg–Zn alloys is generally higher than that of Mg-REE alloys, and recent long-term animal studies using Sprague–Dawley rats have confirmed a similar degradation pattern *in vivo* after 24 months. Recently, a unique application of a Mg-6Zn alloy system as a pin stapler to treat intestinal anastomosis has been reported [60]. In direct comparison, the Mg-6Zn alloy outperformed a titanium alloy by stimulating the accumulation of the extra cellular matrix to promote better healing of intestinal anastomosis.

Another intriguing aspect of Zn-containing Mg systems is the involvement of metallic glass materials. Conventional metallic materials have a particular atomic arrangement that forms specific crystalline structures. However, by utilizing a secondary process such as extremely rapid cooling, ion irradiation, or physical vapor deposition, non-crystalline amorphous metals with glass-like structures could be obtained. Solidification of metallic glass is completed before the crystallization occurs, and it can be casted into shaped functional bulk materials using molds. Derived from their unique irregular atomic arrangement, metallic glasses have, in general, low elasticity, high strength, and excellent corrosion resistance characteristics due to the absence of crystal grain boundaries. In 2009, Zberg et al. developed a biodegradable $Mg_{60+x}Zn_{35-x}Ca_5$ ($0 \leq x \leq 7$) metallic glass material with exceptionally high strength (maximum 854 MPa in compression and 894 MPa in tension) that was 2–3 times higher than that of common crystalline Mg alloy systems. The lack of crystalline structure resulted in low elongation (less than 2%), but a significantly lower corrosion rate with hardly any hydrogen evolution was observed [14]. Additionally, formation of a protective ZnO and $ZnCO_3$ film layer also dramatically prevented further corrosion of the Mg glass with more favorable clinical outcomes being realized on account of a lower amount of hydrogen gas being produced. Usually, alloying different elements in pure Mg mostly results in the formation of secondary or tertiary phases, which lead to galvanic corrosion. The rapid and non-uniform progression of such corrosion in physiological systems could cause deterioration in mechanical integrity of biodegradable implant devices, and from this perspective, usage of metallic glass systems without clinically observable hydrogen evolution offers an alternative solution. The main obstacle that must be overcome for possible clinical application is the brittleness of the metallic glasses, which would result in a shattered implant under severe loading.

Mg–Ca alloys

Mostly stored in bone and teeth, calcium plays a critical role in cell signaling and maintaining the structure and function of skeletal tissues. The release of Ca ions into local cellular environments has been reported to have a positive effect in bone healing, and various studies have been conducted to develop clinically relevant Mg–Ca alloy systems. However, the solubility of Ca in Mg is very limited at 1.34 wt.%, and Ca saturation results in a secondary Mg_2Ca phase with the potential to cause accelerated degradation [61]. In 2010, Cha et al. reported the development of a clinically applicable system with the addition of 5 wt.% Ca [15]. In addition to the presence of Ca, the degradation rate was controlled by selectively doping Zn into Mg_2Ca in order to synchronize the corrosion potentials of two constituent phases (i.e., Mg and Mg_2Ca). Optimized mechanical extrusion broke the connectivity of the Mg_2Ca phases to prevent continuous corrosion and form a galvanic circuit, which causes severe corrosion of the Mg–Ca alloy. Further, a reduction in hydrogen gas formation and increased bone deposition at the implantation site were observed in long-term animal tests (Fig. 4). In 2015, the Korea government approved this alloy system for clinical applications. Recent studies have also revealed that the addition of Sr into Mg–Ca alloys has a stimulatory effect on osteogenesis by regulating the activation of extracellular signal-regulated kinases, and more advanced application in load-bearing orthopedic implants such as spinal cages, bone plates, k-wires, and scaffolds are currently being developed [19,62].

Fe-based alloys

Iron is one of the most abundant metal elements in the body. Owing to its good machinability and mechanical reliability, ferrous-based alloys have been frequently used as a structural material [63]. Degradation of Fe is a well-known phenomenon;

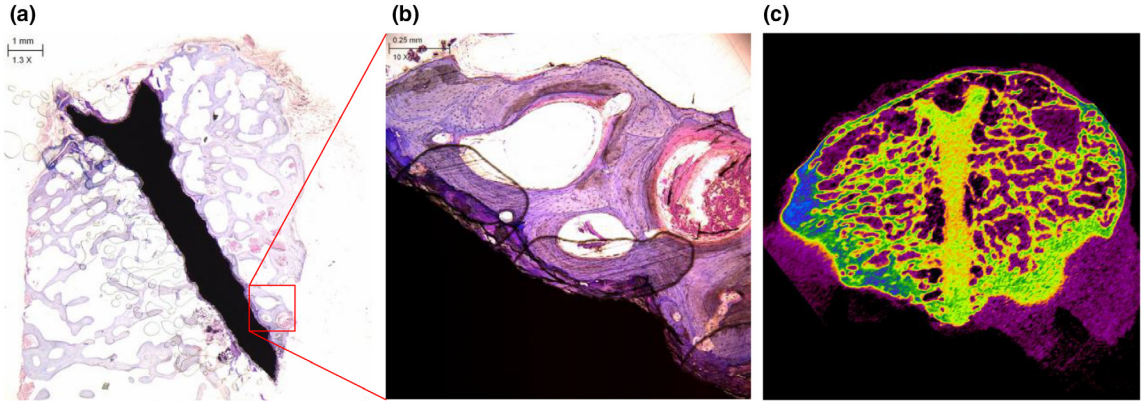

FIGURE 4

in vivo evaluation of Mg-5 wt.%Ca-1 wt.%Zn alloy bone screw in femoral condyle of New Zealand white rabbit at 24 weeks after operation. (a) histological analysis showing new bone formation around the degrading implant site without notable immune response and hydrogen gas bubble formation. (b) magnified image showing the degrading implant interface and abundance of new bone deposition. (c) micro-computed tomographic image confirming the significant direct bone deposition and new bone formation around the degrading bone screw. Figure adapted with permission from: Ref. [15].

OH^- and Fe^{2+} ions are produced when it is immersed in body fluid, leading to the oxidation of Fe^{2+} ions. Although the degradation products of Fe and Fe-based alloys are biocompatible, they have been found to cause delays of oxygen transport required for the continuous degradation of iron [64]. Thus, the degradation rate of Fe is considerately slower than the rate of tissue healing, and research on the development of Fe alloys as biodegradable materials is heavily focused on accelerating the corrosion rate [63–66]. However, several attempts to accelerate the corrosion rate of Fe-based alloys by alloying with different elements to induce galvanic corrosion have failed to achieve sufficiently fast degradation rates, requiring more than a decade for the implant to degrade completely in the physiological environment [67,68]. To overcome such slow degradation rates, the provision of local acidity from the hydrolysis of polymers to accelerate dissolution of the degradation products has been suggested. Combined with a porous Fe structure, polymer-infiltrated porous iron materials have shown accelerated iron degradation rates without detrimental cellular effects when tested on human skin fibroblast cells for 72 h [69]. However, further *in vivo* biocompatibility and degradation study is required to determine the practicality and usability of such method in clinical practice.

Zn-based alloys

In addition to Zn-rich Mg glasses, Vojtech et al. reported the possibility of biodegradable metallic materials based on Zn following the successful implementation of Mg as a biodegradable material [70]. The degradation rate of Zn-based alloys is 1/4 slower than that of pure Mg when immersed in simulated body fluid (pH = 7.4), and its excellent biocompatibility could provide a new alternative for overcoming the challenges of Mg alloy systems [71,72]. Implantation of three different Zn-based binary materials in mouse has shown corrosion rates of 0.17 mm/year, 0.19 mm/year, and 0.22 mm/year for Zn-1wt.%Mg, Zn-1wt.% Ca, and Zn-1wt.%Sr pins, respectively [73]. This study also reported a threefold increase in the compressive yield strength relative to pure Zn, which persisted after 8 weeks of *in vitro* corrosion. Currently, research on Zn-based alloys has focused mostly on cardiovascular applications, but applications in orthopedics are expected to progress rapidly in the near future.

Clinical trials of biodegradable metallic screws

Three compositions of Mg-based systems have been granted clinical approval from governing agencies in their respective countries for orthopedic applications (Table 1).

Pure Mg

Screws designed with high purity (99.99%) magnesium have been used in China to repair the vascularized bone flaps of patients with osteonecrosis of the femoral head (ONFH) [38]. In a prospective and randomized pilot clinical trial registered in the Chinese Clinical Trial Registry (ChiCTR-TRC-13003238), 48 patients aged 18 years to 55 years suffering from association of research circulation osseous (ARCO) stage II/III were recruited and divided into two groups. Out of those 48 patients, 23 received the Mg screw fixation of the bone flaps during ONFH and the remaining 25 patients received the vascularized bone grafting without fixation. Computed tomography (CT) analysis showed higher mineral density around the Mg screws, and degradation of the Mg screw after implantation at 1, 3, 6, and 12 months has been reported to be 3.7 ± 0.4%, 9.3 ± 0.8%, 13.7 ± 0.4%, and 25.2 ± 1.8%, respectively. Additionally, Mg serum levels in patients after screw implantation did not exceed the normal physiological range. For the Mg screw group, two patients suffered from collapse of the femoral head, whereas the control group had six patients suffering from femoral head collapse. After 12 months, the Mg screw group scored a considerably higher number in the Harris hip score than the control group, indicating the high potential of using pure magnesium for medical applications. The Chinese FDA (CFDA) recently approved high purity Mg screws as a medical device, and various applications for fractures of the femoral neck, femoral head, and metatarsals are currently being developed.

MgYREZr alloy (Magnezix)

Clinical application of the MgYREZr alloy system was first reported in Germany, where it was investigated as a fixture to

TABLE 1

Summary of recent clinical trials of orthopedic devices.

Device	Type of study	No patients	Conditions	Total duration	Outcomes	Identifier[#]
MAGNEZIX® [18]	Prospective and randomized controlled (according to EN ISO 14155–1:2009 and EN ISO 14155–2:2009)	26	Mild hallux valgus	6 months	Outstanding results for ROM, MTPJ, AOFAS. Equivalent performance to titanium screws for treatment of mild hallux valgus deformities.	
RESOMET® (K-MET) [19]	Prospective, single center, single group, open (KFDA clinical trial approval for medical device No. 362)	53	Hand fractures	12 months	Normal range of grip power. No change in ROM, DASH. At 12 months, screws were completely replaced by new bones.	NCT02456415
Pure Magnesium [38]	Prospective and randomized pilot (Registered in the Chinese Clinical Trial registry)	48	Osteonecrosis of the femoral head	12 months	Increased bone flap stability. Serum levels were normal. Two patients suffered collapse of the femoral head. At 12 months, higher Harris hip score than control.	ChiCTR-TRC-13003238

[#] Clinical trial identifiers retrieved on www.clinicaltrials.gov where available.

treat patients with mild hallux valgus [18]. In this prospective and randomized controlled study, chevron osteotomy was performed to compare the clinical performance of the MgYREZr alloy screw to that of a titanium screw. A total of 26 patients were randomly assigned to two groups to receive the treatment using either the titanium or MgYREZr alloy screws. There were no complications during the 6-month follow-up period but one patient from each group dropped out of the study after surgery for personal reasons. In general, both groups displayed outstanding results in terms of their range of motion (ROM) of the first metatarsophalangeal joint (MTPJ), visual analog scale for pain assessment, and the postoperative American Orthopaedic Foot and Ankle Society (AOFAS) score for hallux, demonstrating the equivalent performance of MgYREZr alloy screws to conventional titanium screws [18]. In 2013, the MgYREZr alloy system received the CE mark and a modified chevron osteotomy study with a larger group of patients (44 total) has been performed, yielding similar results [56]. Recent case studies have reported the application of MgYREZr alloy systems in fixation of distal fibular fractures and intra-articular fractures [55,57].

MgCaZn alloy (Resomet)

Following its approval for clinical trial by the Korea Food and Drug Administration (KFDA Clinical Trial Approval for Medical Device No. 362), the Mg–Ca–Zn alloy system was tested in a prospective, single center, single group, open clinical trial to evaluate its performance in the treatment of hand fractures [19]. A total of 53 cases revealed a normal healing rate with continuity of the cortical bone and a reduced diameter of the Mg–Ca–Zn alloy screws after implantation without a single failure at 6- and 12-month post-implantation (Fig. 5). None of the patients presented any indication of pain and reported recovery of their normal range of grip power. Their ROM did not decrease, and the disability of their arm, shoulder, and hand ranging from 0 to 100 indicating no disability to extreme disability, respectively, was reported to be 29.82 ± 4.4 after 6 months. Furthermore, the Mg–Ca–Zn screws were completely replaced by new bone after 1 year of implantation, clearly showing genuine clinical benefits of biodegradable metals in orthopedics. Mg–Ca–Zn screws were approved by the KFDA for clinical use in 2015, and various prototypes are currently being developed to utilize this newly approved system.

Cardiovascular applications of biodegradable metals

Most of the applications envisaged in cardiovascular system involve stents. The following are the required design criteria, mostly concerning mechanical properties and vascular biocompatibility, when designing cardiovascular stents. From a mechanical point of view, elastic recoil upon expansion and device failure during service life must be avoided [74]. Further, the device surface should favor cell attachment while avoiding excessive cell proliferation, which may lead to in-stent restenosis (ISR). In addition, no potentially toxic ions can be released from the implant surface so as to avoid severe inflammatory reactions. Conventional inert materials used to manufacture bare metal stents (BMS) (e.g., 316L stainless steel, Co–Cr alloys, and Ni–Ti alloys) excel from a mechanical viewpoint. If uncoated, however, a high incidence of ISR was observed [75]. This was also caused by the release of Ni ions, which can stimulate an inflammatory response [76], especially after repeated procedures [77]. Drug-eluting stents (DES) are aimed at reducing the ISR incidence by eluting an antiproliferative drug from their surface. Nonetheless, an increased incidence of late stent thrombosis was reported [78]. It must be noted that artery remodeling occurs after 6 months post-implantation [79], thus eliminating the need to have mechanical support in the artery for longer time periods. These design features suggest that a device that guarantees mechanical integrity for the first 6 months post-surgery and that can become absorbed by the body [21] would be of great value for limiting post-operative complications.

Translational research on cardiovascular applications

At present, three alloying systems have been studied by academia and industry for manufacturing biodegradable stents: Mg-based, Fe-based, and Zn-based alloys. By far, the highest number of studies related to the clinical translation of cardiovascular stents

FIGURE 5

Clinical translation of biodegradable metallic implant materials in orthopedics. X-ray images showing fixation of the distal radius fracture with conventional stainless-steel pin implant and the scaphoid nonunion with RESOMET screws at pre-operative, post-operative, 6-month follow-up and 12-month follow-up. Complete degradation of screw and bone healing was observed at 12-month follow-up. Figure adapted with permission from: Ref. [19].

involves Mg-based devices [80]. In this regard, a bioresorbable scaffold made from a Mg alloy has received the CE mark in 2016 [81] following a successful clinical trial [23,82] (Table 2). For the Fe- and Zn-based alloys, however, no reports of clinical trials are currently available, though the translational research on these two systems is very active.

Magnesium-based stents

Magnesium is known to be an essential element of the human body, being involved in several regulation mechanisms [27]. When cardiovascular applications are considered, the main drawback of pure Mg is its mechanical properties, which are much less favorable than those of pure iron [83]. In addition, its electrochemical behavior in physiological environments suggests that Mg and its alloys can suffer from significant localized corrosion stemming from the breaking of the passive film [84], pure Mg is heavily corrodible. Indeed, degradation processes were considered as too fast in the first *in vivo* and pre-clinical studies involving the use of AE21 and WE43 alloys [8,85].

In order to improve the mechanical properties of Mg for cardiovascular stents, different elements have been tested as alloying elements in pure Mg. The two aforementioned alloys contain REEs that aim to promote grain refinement upon thermo-mechanical treatment. The effect of small grain sizes on mechanical performance is dictated by the Hall–Petch relation. Furthermore, REEs can improve the corrosion resistance of Mg alloys by precipitating secondary phases with similar electrochemical potentials with respect to the matrix, thus suppressing micro-galvanic coupling between Mg and impurities, such as in the case of Nd and Gd [28]. Another element that is commonly added as a grain refiner is Zr [28]. Patents concerning the development of new alloys for bioabsorbable stents comprising several REEs have been filed by both companies and academic institutions [86–89].

The applicability of Mg-REE alloys in newborns with congenital heart diseases has also been reported. It was claimed that the main advantage of using biodegradable stents in children would be even more evident than in the case of adults, since artery

TABLE 2

Summary of recent clinical trials of stents.

Device	Trial	No patients	Regulatory stage	Primary endpoint	Total duration	Outcomes	Identifier[#]
AMS	PROGRESS [20,126]	63	FIM	Cardiac death, non-fatal myocardial infarction, or clinically driven target lesion revascularization at 4 months	28 months	Stent totally absorbed after 4 months. 47% patients suffered restenosis. No myocardial infarction or late thrombosis occurred.	
	INSIGHT [124,125]	117	FIM	Patients with chronical limb ischemia. Absence of clinical complications at 1 month. Compare the patency rate between AMS and PTA at 6 months.	12 months	3 patients with 1-month complications. Lower patency rate for AMS (31.8%) versus PTA (58.0%).	NCT00572494
DREAMS	BIOSOLVE-I [22,127]	46	FIM	Target lesion failure, a composite of cardiac death, target vessel myocardial infarction, and clinically driven target lesion revascularization, at 6 and 12 months	36 months	One myocardial infarction occurred (not stent-related). No late thrombosis. Late lumen loss is higher than inert drug-eluting stents. LLL lower at 36 months	NCT01168830
DREAMS-2G (Magmaris®)	BIOSOLVE-II [23,24,82][*]	121	FIM	In- segment late lumen loss at 6 months	36 months	No thrombosis after 24 months. Late lumen loss reduced vs DREAMS. Device absorbed at 95% after 12 months.	NCT01960504
	BIOSOLVE-III [24][*,^]	61	Pivotal Trial	Procedure success	36 months	No thrombosis detected. One post-intervention death (not procedure-related)	NCT02716220

[*] Ongoing trial. Outcomes are referred to the results published at the time this review was written.
[^] Available results at the time this review was written were pooled with BIOSOLVE-II.
[#] Clinical trial identifiers retrieved on www.clinicaltrials.gov where available.

growth would not be hindered as the patient ages, such as when a permanent stent would be used. Overall, the results from these reports are mixed. One study [90] reported the clinical success of implantation of an absorbable metal stent (AMS, Biotronik) in the pulmonary artery of a preterm baby. However, the baby died 5 months after surgery due to multiple organ failure related to a previously developed pneumonia. Histopathology showed that the stent fully degraded without causing foreign body reaction; calcium compounds were detected at the strut sites [91]. On the contrary, two different studies on newborns [92,93] reported heavy restenosis 3 and 4 months post-surgery, respectively. These findings were further supported by an animal study [94] where, after 3-month implantation in pigs, segments with an AMS implantation showed significantly reduced lumen area versus control BMS and DES. Stent absorption was completed in 3 months, as seen in other animal investigations [95,96]. Successive efforts were directed toward increasing the absorption time in order to fully support artery remodeling. Coating a stent with PLGA, in which paclitaxel is embedded as antiproliferative agent, led to a similar late lumen loss and intimal area with respect to the permanent controls [97]. Other data [98] demonstrated that a Mg-based stent (Magmaris®, Biotronik) has a much lower thrombogenicity relative to a commercial polymeric resorbable stent (Absorb®, Abbott Vascular).

Another alloying system extensively investigated *in vivo* is Mg-2.5Nd-0.2Zn-0.4Zr (JBDM) [89]. Such a composition should promote micro pitting corrosion, in contrast to the macroscopic pitting observed in other commercial Mg alloys [99]. *In vivo* tests in rabbits and mini pigs showed biosafety and good degradation of stents made from this material, both in its bare [99,100] and drug-eluting versions [101]. No neointimal hyperplasia was observed for the bare stents, whereas some late lumen loss was observed for the coated variant. It must be noted, however, that no quantitative data were reported. A variant of this alloy (JBDM-2) showed mild neointimal hyperplasia after 4 months in a New Zealand rabbit model, which was associated with an inflammatory response [102]. A recent study, which evaluated the effectiveness of the Mg-2Nd-0.2Zn-0.5Zr alloy stent for the occlusion of a lateral aneurysm in the common carotid artery of rabbits, reported distinct advantages in terms of increased diameter and lumen area of the stented arteries after 12-month follow-up (Fig. 6) [103]. An aneurysm was artificially induced in the carotid artery and the endoprosthesis was implanted in 12 rabbits after 1 month. Increased lumen area at months 6 and 12 versus immediate post-implantation was observed, whereas the lumen area decreased in the control group [103].

Finally, a Mg-2Zn-0.5Y-0.5Nd alloy coated with APTES and an upper layer of PLGA with embedded rapamycin was evaluated in mini pig arteries [103]. The struts were partially degraded after 6 months and showed comparable lumen area with respect to a 316L DES control.

Iron-based stents

Pure iron possesses significant advantages over magnesium and zinc for cardiovascular stents in terms of mechanical properties. In fact, pure iron possesses the best combination of strength and ductility compared with the aforementioned metals, thus

allowing, in principle, fabrication of devices with thinner struts. In addition, Fe controls smooth muscle cell proliferation, thus preventing excessive neointimal growth [104]. The first translational research focused on animal tests of pure Fe bare stents in a porcine model [105,106]. These studies showed the biosafety of iron inside arteries for up to 18 months. A short-term follow-up study [107] also demonstrated the absence of excess inflammatory reactions or thrombotic events, as observed with Co–Cr stents. However, the devices remained mostly intact even after 18 months. In order to accelerate the degradation process, new alloys have been designed by either adding soluble elements with lower electrochemical potentials than iron or precipitating noble secondary phases, which can enhance corrosion by galvanic coupling [63]. Manganese possesses a lower electrochemical potential than iron; moreover, it can enhance the mechanical performance of iron by stabilizing its more ductile phase [108]. In addition, this phase promotes antiferromagnetic behavior, thus favoring imaging using magnetic-based techniques such as magnetic resonance imaging [27]. The addition of C to Fe–Mn alloys can lead to mechanical properties close to those of Co–Cr alloys [109]. Manganese is known to be neurotoxic in high amounts, however, which has led to the development of Mn-free alloys, though such alloys have inferior mechanical properties than alloys with Mn [110]. It is also known that the transport path influences the incidence of Mn neurotoxicity, the main one being inhalation [111]. Although many papers have reported the development of alloys for cardiovascular stents, only one *in vivo* test on Fe–Mn alloys in soft tissues has been reported [112]. The authors implanted disks in the subcutaneous region of mice for 9 months. The implants remained mostly intact due to the formation of Mn phosphates on the surface, which acted as a passivation layer.

Surface modification was also explored to accelerate the degradation of iron. Plasma nitriding was performed on Fe tubes in order to precipitate Fe_4N particles, which can create a galvanic couple with the iron matrix [113]. *In vivo* tests in mini pigs showed that, while the *in vitro* corrosion rate doubled for the nitrided material, a significant portion of the stent remained intact after 12 months. By reducing the strut thickness from 120 μm to 70 μm, the same material degraded more effectively in a rabbit model after 1 year [114]. However, porcine experiments up to 53 months showed only selective degradation, with a portion of the struts remaining mostly intact. Further reduction in the strut thickness to 53 μm, together with coating a 600 nm Zn layer and a 12 μm poly(dl-lactic acid) (PDLLA) drug-eluting layer, resulted in a stent degradation of 95% after 13 months in a rabbit model [115]. The absence of the Zn layer for such a thin strut resulted in loss of structural integrity after 3 months.

Zinc-based stents

Compared with Mg and Fe, interest toward Zn for cardiovascular stents is rather recent. Nonetheless, Zn wires implanted in the abdominal aorta of rats showed an increasing degradation rate with time, which is close to ideal for application [116]. It was also found that the cross-sectional area of a wire decreased steadily with implantation time up to 20 months [117]. A more recent study observed that pure Zn stents degraded by 42 ± 30% after 12-month implantation in adult rabbits while maintaining their mechanical integrity for the first 6 months [118]. Although such degradation data are very promising, the mechanical properties of pure Zn are insufficient for producing cardiovascular stents [83]. Several alloying elements have been explored to improve the mechanical behavior of Zn, such as Mg [119], Al [120], Ca and Sr [73], and Mn [121]. A shortcoming of such systems, however, is the resultant strain softening behavior in the plastic range, which is a well-documented phenomenon for zinc [122]. Plastic strain softening reduces the residual strength of the implant once deployed, possibly increasing the risk of late recoil. A promising alloying element for Zn is Ag, since it was shown to enhance both strength and ductility while partly eliminating strain softening [123]. However, cyto- and hemocompatibility tests must be performed in the future to determine whether the release of Ag causes adverse reactions in the arteries.

Clinical trials of biodegradable metallic stents

INSIGHT and PROGRESS trials

The AMS INSIGHT [124,125] and PROGRESS-AMS [20,126] trials involved first-in-men studies of the AMS device (Biotronik). INSIGHT discussed the safety and feasibility of implanting such a stent in patients with chronical limb ischemia, while PROGRESS focused on *de novo* native coronary artery lesions. INSIGHT showed that the device is safe, with a 5% complication rate both in the AMS group and the control group (which underwent plain balloon angioplasty) after 30 days from intervention. However, the restenosis rate after 6 months was seen to be much higher in the AMS group (68.2%) relative to the control group (42.0%), suggesting that AMS is not capable of supporting artery remodeling. PROGRESS identified recoil (negative vessel remodeling) as the main mechanism for in-stent restenosis at the 4-month follow-up; moreover, the struts were almost completely degraded at this time. The safety of the material was confirmed by the absence of adverse effects even after 28 months from implantation, and no thrombosis was detected in either trial. These findings confirm the observations made in the animal model and demonstrate that further improvement to the material is required to ensure longer degradation times.

BIOSOLVE trials

The BIOSOLVE trials are designed to study the safety and efficacy of the drug-eluting evolution of the AMS stent, called DREAMS (Biotronik); the base alloy was also improved and evaluated. Four trials have been reported: BIOSOLVE-I (clinicaltrials.gov number NCT01168830), BIOSOLVE-II (NCT01960504), BIOSOLVE-III (NCT02716220), and BIOSOLVE-IV (NCT02817802). Among these, only number I has been completed, numbers II and III are currently active, and number IV was at the recruitment stage when this review was written.

BIOSOLVE-I data up to 12 months [22] showed good device clinical safety without any cardiac death or thrombosis. The device was fully absorbed after 12 months, and it outperformed AMS in all clinical parameters including angiographic measures of late lumen loss and rate of clinically drive target lesion revascularization [22]. However, late lumen loss was still higher than that observed for permanent stents. The 36-month follow-up [127] confirmed the safety of the device. In addition, late lumen loss was reduced from the 12-month observation.

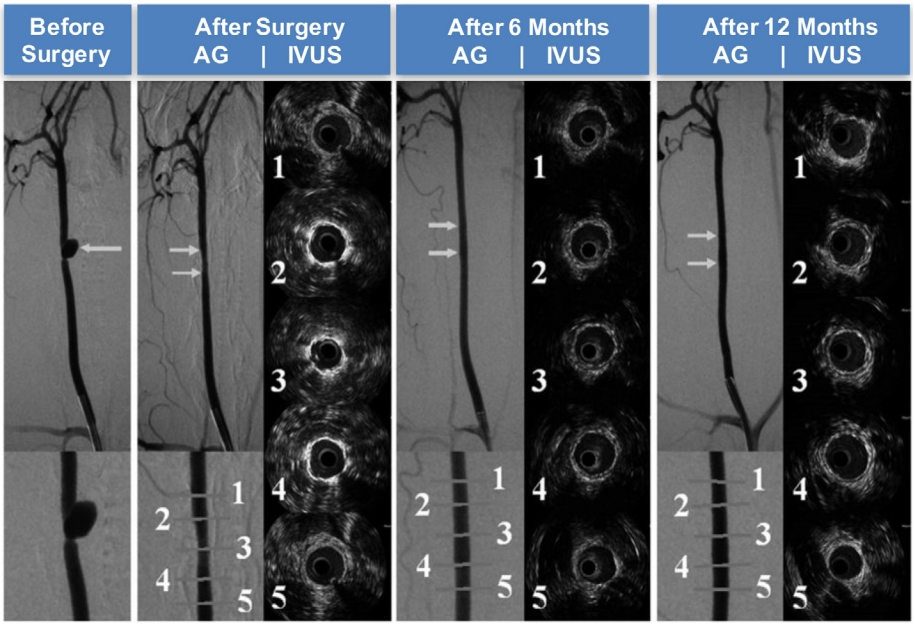

FIGURE 6

1-Year follow-up of magnesium alloy covered stent using the angiography (AG) and intravascular ultrasound (IVUS) grayscale results in rabbit right common carotid artery (CCA) model. Angiography results (indicated by the arrows) show the significantly greater diameter of Mg stented CCA at 6 and 12 months compare to diameter immediately after surgery. Numbers represent the corresponding IVUS examination sites showing significantly greater mean lumen area at 6 and 12 months. Figure adapted with permission from: Ref. [103].

BIOSOLVE-II introduced a modified version of the device, named DREAMS 2G (commercial name Magmaris®). The differences with DREAMS include the base alloy and the coating system. Specifically, while the first generation employed a PLGA coating with paclitaxel embedded as the antiproliferative agent, the coating in the 2G variant is made of PLLA and sirolimus is used as the antiproliferative agent instead of paclitaxel. After 6 months [23], late lumen loss and neointimal hyperplasia were significantly reduced with respect to the first generation, yielding levels similar to commercial polymeric resorbable scaffolds (Fig. 7). In addition, the struts appeared to be mostly absorbed, as evidenced by optical coherence tomography (OCT) measurements. Data at 12 months [82] and 24 months [24] confirmed the findings reported after 6 months. The incidence of target lesion failure was found to be lower than that reported for the ABSORB scaffold. Moreover, no sign of restenosis was observed up to 36 months [24], as visible from Fig. 7. Only data pooled with BIOSOLVE-II are available for BIOSOLVE-III. In this case, the safety of the device was further confirmed over a period of 6 months.

Planned clinical trials

BIOSOLVE-IV is expected to provide a 5-year follow-up on a large number of patients (>1000). Subjects were being recruited as this review was written, with completion of this trial expected by the end of 2023.

Other clinical trials involving the Magmaris scaffold were recruiting participants at the time this review was written. In one trial (MAGSTEMI, NCT03234348), the efficacy of Magmaris in treating myocardial infarction will be tested against a DES with a degradable polymer coating. The HONEST trial (NCT03016624) will assess whether using OCT as guide for the deployment of a Magmaris stent can improve coronary artery healing at 6 months versus standard angiography. Finally, the BIFSORB P-II trial (NCT03027856) will assess if the Magmaris scaffold can be used safely for treating coronary bifurcation lesions.

Concluding remarks and perspective

Successful application of biodegradable metals in orthopedic and cardiology had led to the recent expansion of research to other feasible applications. Stenting a cylindrical cavity inside the human body for a limited time represents a valid, non-invasive, low-cost alternative to conventional surgical operation. Therefore, it is clear that surgeons and clinicians must consider adapting to this technology in the treatment of a wide range of diseases. At present, much of this technology remains in the design and development stage.

Stenting a ureteral conduit is considered a low-risk treatment today [128]. Mg-based alloys (i.e., Mg-4Y) have been investigated *in vitro* for ureteral stenting. The challenge is to predict the behavior of the material in the repeated presence of urine in a very humid environment where bacterial contamination can easily develop. The formation of a thermal MgO layer on the surface of a MgY alloy suppressed bacterial activity at day 3, whereas the control alloys (i.e., AZ31 and pure Mg) showed bacterial proliferation at this time.

Nasal cavities, especially when re-opening an occluded sinus is required, can also benefit from biodegradable stent technology [129]. Studies over a 6-month period involving 16 mini pigs aged 24 months (36 ± 4 kg) have been reported. The geometry of the devices was akin to tubes with slotted ends (i.e., an L-geometry) rather than a stent. Two groups were compared: those

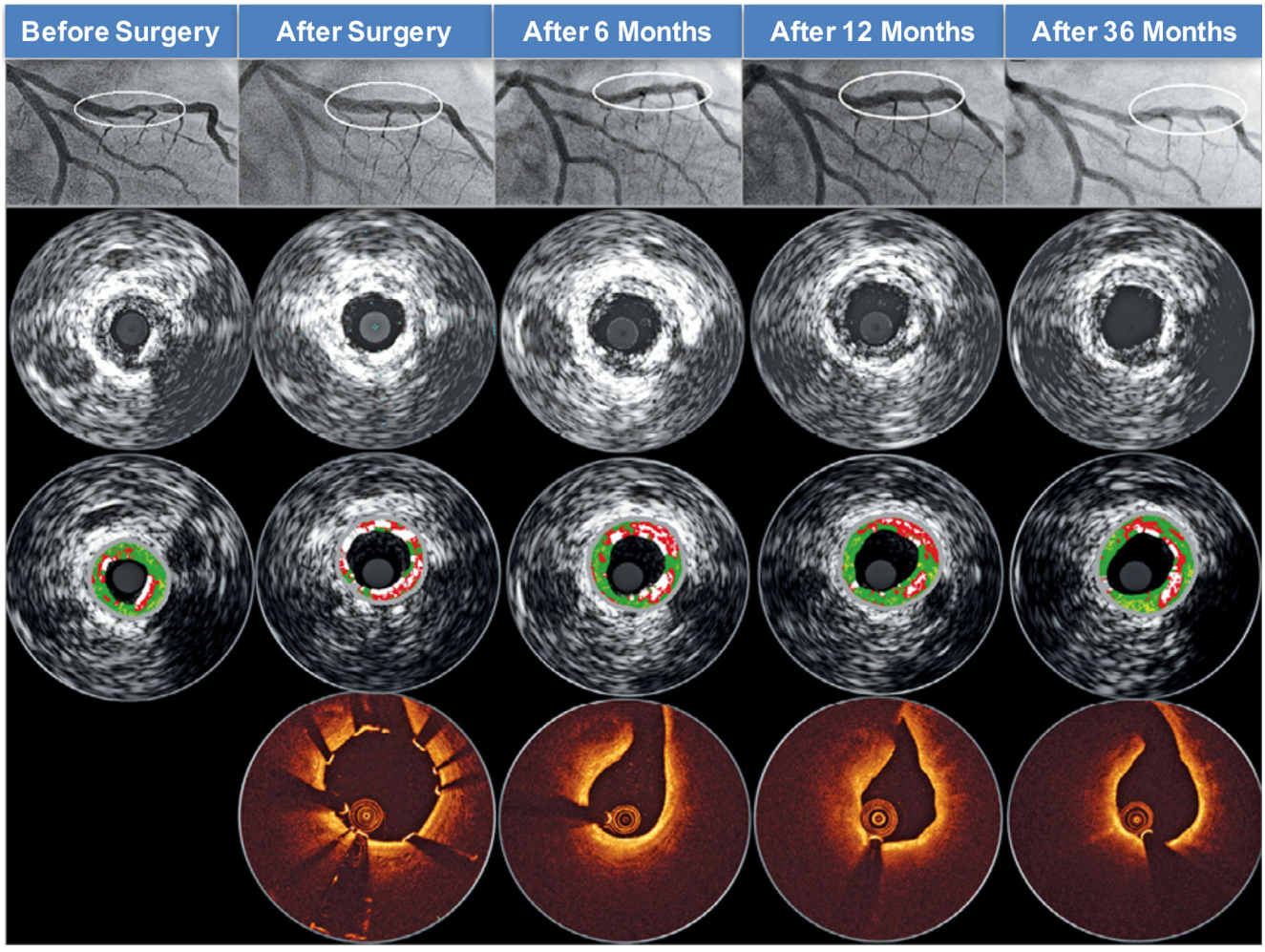

FIGURE 7

Clinical translation of biodegradable metallic implant materials in cardiology. Observation of DREAMS 2G implantation in a patient through serial angiography, intravascular ultrasound, virtual histology intravascular ultrasound and optical coherence tomography. IVUS and OCT observation confirms the metallic appearance of DREAMS 2G and good conformability to the vessels following the surgery. The degrading scaffold is visible at six month and OCT shows homogeneous neointima formation after 12 months. At 36 months follow-up, approximately 95% degradation of magnesium without late lumen loss was observed. Figure adapted with permission from: Ref. [24].

euthanized at: (1) day 90 ($n = 8$) and (2) day 180 ($n = 8$), with follow-up studies every 45 days. μCT at day 90 showed that some wings became degraded; most of the device became corroded with visible pitting at day 180. Magnesium was still mostly detectable after 90 days, whereas it was barely detectable after 180 days, and Nd was barely detectable at either time. Ventilation may have favored air removal of particles. Stent degradation may promote device displacement, and this possibility requires further study. For nasal applications, the device fixation technology across the entire degradation time must be developed further, as moderate tissue formation around the implant was found to occur.

The millennia-old concept of an inert device that replaces the missing or damaged tissue dates back nearly four thousand years to ancient Egypt where a functional wooden toe was used to replace a missing right big toe [130]. With the advancements in metallurgy, countless studies in the last decade have provided a robust foundation for the successful application of biodegradable metals in tissue replacement by controlling their mechanical and corrosion properties. Notably, these devices degrade in the physiological environments once their purpose is realized, and they overcome the flaws of the inert implant materials, thereby shifting the very dated paradigm of conventional cardiovascular and orthopedic devices. Still, a series of hurdles persists that must be addressed before these materials can be safely deployed in a clinical setting. Compared with conventional inert materials, research on biodegradable metals has just completed its infancy phase, with wide scope for innovation. Overall, we firmly believe that the ongoing development and refinement of biodegradable metals will act as a portal technology to revolutionize a myriad of clinical applications in the near future.

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Competing interests statement

The authors declare no competing interests.

Data availability

The authors declare no data availability.

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