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Review

Current Status and Outlook of Temporary Implants (Magnesium/Zinc) in Cardiovascular Applications

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Abstract: Medical application materials must meet multiple requirements, and the designed material must mimic the structure, shape. and support the formation of the replacing tissue. Magnesium (Mg) and Zinc alloys (Zn), as a "smart" biodegradable material and as "the green engineering material in the 21st century", have become an outstanding implant material due to their natural degradability, smart biocompatibility, and desirable mechanical properties. Magnesium and Zinc are recognized as the next generation of cardiovascular stents and bioresorbable scaffolds. At the same time, improving the properties and corrosion resistance of these alloys is an urgent challenge. particularly to promote the application of magnesium alloys. A relatively fast deterioration rate of magnesium-based materials generally results in premature mechanical integrity compromise and local hydrogen build-up, resulting in restricted applicability. This review article aims to give a comprehensive comparison between Zn-based alloys and Mg-based alloys, focusing primarily on degradation and biocompatibility for cardiovascular applications. The recent clinical trials using these biodegradable metals have also been addressed.

Keywords: zinc; magnesium; biodegradable implants; cardiovascular stents; functional materials

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1. Introduction

Over recent years, there has been an exponential rise in the usage of biomaterials in medicine-based applications [1]. Healthcare professionals and commissioners have been emphasizing early diagnosis and treatment of diseases and enhancing the efficiency of the available treatment strategies. This has been due to the more active lifestyle of the population, which significantly transformed the treatment of fatal diseases and conditions. However, there exists a requirement of affordable healthcare resources for the active aging generation. The longevity of an implanted biomaterial depends on the anchorage and integration between the implant and the living bone [2]. There are various factors that determine the success of an implanted biomaterial, namely the form and structural characterization, stability, mechanical-loading, material property, location of the implanted site, and host response [3,4]. The key outcome is to finally derive a matrix that matches the bone in composition, structure, and properties [5]. Biocompatibility and mechanical strength are the essential pre-requisite characteristics of any implanted biomaterial to be employed for biomedical, orthopedic, and dental applications [6–10].

The inert metals, such as stainless steel, titanium, and cobalt alloys, having superior corrosion resistance and mechanical properties (concerning biological tissues) have been traditionally used as implant materials for cardiovascular and orthopedic applications [11–13].

Liu et al. [14] constructed a novel stromal cell-derived factor-1α (SDF-1α)/laminin-loaded nanocoating on the 316 L stainless steel (SS) surface to provide improved function in the modulation of vascular remodeling. The modified surface was found to control the delivery of biomolecules and exhibit promising potential to provide stage-adjusted treatment after injury. Furthermore, an in vitro biocompatibility study suggested that the constructed layer may effectively prevent thrombosis formation by inhibiting platelet adhesion and activation, while accelerating endothelium regeneration by inducing endothelial cell (EC) migration and endothelial progenitor cell (EPC) aggregation. An in vivo animal test further demonstrated that the nanocoating may prevent thrombus and neointimal hyperplasia after implantation for 3 months [14]. Presently, these metallic implants are mainly designed for permanent tissue replacement, but they do not account for cases where only temporary support is required. There have been numerous difficulties involved, some of which are the stress-shielding effect over a while, which then leads to bone-weakening and distortion of diagnostic images. Finally, additional surgery is required for removal of the implant when these permanent metallic implants are used [15,16]. Extensive research efforts are ongoing to develop materials that can be used as temporary implants in the human body to perform multiple functions, depending on the nature of the ailment. Among the metals, Zinc (Zn)- and Magnesium (Mg)-based materials have garnered significant attention in recent years to serve as temporary implants [17]. Magnesium and its alloys exhibit superior strength, ductility, and degradability compared to its biodegradable counterparts, Zinc and Iron [17]. The elastic modulus (∼45 GPa) of magnesium is close to that of human bone (∼10–20 GPa), and this helps to avoid stress shielding effects compared to other metallic biomaterials [18,19]. The magnesium in plasma exists as Mg^{2+} in a concentration of 1.2–1.4 mM and is excreted in urine [20,21]. Increased local degradation of Mg (and its alloys) causes increased hydrogen gas release from the implanted site, leading to an increase in pH [20]. This increase in hydrogen gas evolution and pH causes localized cell death and cytotoxic reactions, which further leads to failure [22–24]. For implanted devices, such as in orthopedics, where it is poorly vascularized, the accumulation of hydrogen gas is a safety concern as a gas embolism may potentially block the bloodstream, causing fatalities [25]. For coronary stents, the gas generated is of not a large concern, as it can be removed by convective transport phenomena due to a high amount of blood flow at the implantation site [26]. Nevertheless, it has been reported that the addition of Zn to Mg can significantly decrease the amount of hydrogen generated.

The favorable degradation behavior of Zn has led to the emergence and development of Zn-based alloys in recent years [22,27]. Being an essential element, Zn is involved in various biological processes, including being a metabolite for nucleic acid, signal transduction, and gene expression, and it takes part in interactions with a range of organic ligands and apoptosis coordination [28]. Zn does not corrode as quickly as Mg and the corrosion of pure Zn is known to be moderate [29]. However, Zn on its own has inferior mechanical properties with a tensile strength as low as 20 MPa, Vicker hardness of 3.7 and elongation of 0.2%. and these translate to relatively lower material strength as compared to its metallic counterparts [22]. Thus, alloying of Zn is crucial for its application in load-bearing implants. There have been several new opportunities and difficulties in the development of Mg and Zn alloys for cardiovascular applications and to overcome the drawbacks of hydrogen gas evolution [29].

Therefore, there is a need to summarize the findings of the researchers in this area in comparison to recently published reviews. Specifically, the use of biodegradable Mg and Zn alloys in cardiovascular applications as temporary implants has not been addressed so far and, hence, is the primary objective of this paper. In the present paper, we have reviewed the properties and the in vitro and in vivo biological performance of Mg and Zn alloys in context for use as cardiovascular stents. Novel insights that were gained in clinical translation of biomedical Mg and Zn have also been discussed.

2. Driving Force for Temporary Implants

There are broadly two types of implants that are used in the body: permanent implants and temporary implants. Permanent implants refer to implants that are intended to stay in the body throughout life, such as the one used for hip and knee replacement sand artificial tooths and their fixation. Then, there are temporary implants, which are not required in the body after a certain period when the injury is healed. This is applicable for orthopedics fixation purposes (plates and screws) and in cardiovascular (stents) application. The use of temporary implants helps in:

1. Avoiding revision surgery for the patient.
2. Minimizing medical costs for the patient.
3. Minimizing patient trauma inflicted during the second surgery.
4. Saving the doctor's time.
5. Avoid long-term toxicity effects if a permanent implant material is used instead.

Commonly used implant materials used in the past as both temporary and permanent implant applications are [30]

1. Titanium-based materials.
2. Steels.
3. Co-Cr based alloys.
4. Tantalum.
5. Nitinol [31].

Given the disadvantages associated with using permanent implants for temporary functionality required by the human body, extensive research has been carried out to develop Magnesium- and Zinc-based materials in recent years. For any biodegradable materials to serve as a temporary implant, it must meet the following requirements [30–32]

1. Biocompatible with acceptable or zero cytotoxicity.
2. No chronic deleterious effect.
3. To maintain mechanical integrity during the healing time.
4. Minimal stress-shielding effect.
5. Acceptable degradation time, synchronized closely with healing time.

The body should be able to metabolize or excrete corrosion products arising from temporary implants.

3. Magnesium and Zinc in the Human Body

Both Zinc and Magnesium are nutritionally essential elements for the human body and are hence non-toxic [33,34]. The human body is capable of metabolizing them and excreting the excess of them if they need to be excreted. Some of the significant roles that these two elements play in the human body are summarized in Table 1 and are instrumental for researchers to use them for making temporary implants. One must note that the daily requirement of Zinc and its serum concentration in the human body is an order of magnitude lower when compared to magnesium. Moreover, an excess amount of magnesium does not affect bone development as against Zinc. This suggests that the body exhibits more tolerance to magnesium than for excess Zinc in the physiological environment.

Table 1. Importance of Zinc and Magnesium to the human body [31,35,36].

Application	Zinc	Magnesium
Function in Human Body	• Stimulates beneficial osteogenesis in bone. • A component of 300 enzymes. • A component of almost 1200 proteins. • Required for optimal nucleic acid and protein metabolism. • Required for cell growth, division, and function. • Assists in physiological systems, including the immune, sexual, and neurosensory. • Daily requirement: ~15 mg/day. • Serum concentration: 0.012–0.017 $mmolL^{-1}$ • At a high concentration, hinders bone development and damages vital organs.	• Promotes the growth of new bone tissues. • Assists in the synthesis of proteins. • Activates a variety of enzymes. • Regulates the activities of the neuromuscular and central nervous system. • Involved in more than 300 chemical reactions in the body. • Assists in good cardiovascular health. • Mostly stored in bones. • Daily requirement varies from 250–400 mg/day. • Serum concentration: 0.73–1.06 $mmolL^{-1}$ • At a high concentration, does not affect bone development.

4. Material Requirements for Fully-Bioresorbable Vascular Stents

The material properties that are essential for designing the implants are based on the clinical requirements. Age-related issues, such as clogging of blood vessels due to clots, are of immense importance [37–39]. Antithrombotic therapy was one of the earliest treatments for the clogging caused by blood clots. However, sufficient time was necessary for the clot to dissolve. Later, vascular stents were employed to keep the blood vessels unblocked. It proved to be a better technique regardless of the consideration that treatment often had to be delayed, avoiding the patient's death. Another technique, balloon angioplasty [40] has been routinely carried out. This technique requires minimally invasive surgery. In this method, a tiny, folded stent over a balloon present on the tip of the catheter is operated along the blood vessels to reach the restricted site. Stents can present as a confusing artefact on the X-ray and can mimic a foreign body if the index of suspicion is not high, and they should be kept high on the list of differentials in such X-rays. Radiopaque metal markers are required to improve the density of the X-ray absorption to enable precise stent placement. These stents with radiopaque markers are called X-ray-dense stents. An X-ray-dense stent can prove to be very useful, as the stent can be easily positioned by the X-ray camera. The balloon is inflated to unfold the stent once the region is reached. The over-extension of the stents can prevent migration by permitting a firm attachment in the blood vessel, and elastic recoil of the stent upon deflation of the balloon can be compensated [40–42]. The thin stent material should possess sufficient strength to curtail the recoil and tolerate the pressure caused by the tissues upon body movement [43]. The overextension of the stent and the mechanical stress stimulates the smooth muscle cell growth along the walls of the vessels. The obstruction of the stented vessel can be caused by restenosis, where a growing mass of proliferating smooth muscle cells blocks the blood vessels. The insertion of the second stent or surgical bypass can restore the blood flow, but it leads to more discomfort and risks. The restenosis issue has been successfully overcome by drug-loaded polymer-coated stents [44,45]. These stents release immuno-suppressive agents, such as sirolimus, or the antiproliferative drug paclitaxel. However, these drugs can have serious effects, such as delayed healing, inflammation, and thrombosis, resulting in regular expensive and prolonged antiplatelet treatments [46–51]. Hence, each patient must

be thoroughly investigated before the usage of drug-eluting stents. The fully biodegradable stents are an effective alternative to the drug-eluting stents. These stents provide essential support during the healing process and then completely vanish [52–56]. The materials that are involved in fabrication should have excellent corrosion resistance, biocompatibility, high elasticity, and the strength required to prevent the collapse. The implant material should be biocompatible to prevent inflammation [57]. Therefore, a strong, biocompatible temporary implant, minimizing the stress shielding and prevention of secondary surgery for implant removal, is required. The permanent implants, such as strong, inert, and resorbable polymers and corrosive metals, have distinct biological characteristics.

5. Cardiovascular Applications of Biodegradable Magnesium and Zinc Based Materials

5.1. Criteria for Biodegradable Vascular Stents

Stents are the most common cardiovascular application of biodegradable metals. The three significant conditions that need to be satisfied by a bioresorbable vascular scaffold (BVS) are mechanical properties, vascular biocompatibility, and degradation [58]. The stent should not fail during service, and elastic recoil on expansion must be avoided from the mechanical outlook [59]. Biocompatibility is also dependent on the solubility of the material in bio-fluids and the toxicity of the degradation products. The stent must also be conducive to cell attachment while simultaneously inhibiting excessive cell growth. This might cause in-stent restenosis (ISR). Furthermore, there should not be any release of toxic ions from the implant surface, as these toxic ions lead to severe inflammatory reactions. Ideally, the stent must degrade by less than 0.2 mm/yr to avoid the excessive release of degradation products, which may have long-term effects [60].

5.1.1. Traditional Stents

From a purely mechanical standpoint, traditional materials such as 316 L stainless steel, Co-Cr alloys are ideal choices for stent materials. However, when these metallic systems were uncoated, it was reported that it could lead to ISR [61] due to the release of Ni ions, leading to the inflammatory response [62]. This scenario was commonly observed where repeated procedures were conducted [63]. To reduce the occurrence of ISR, drug-eluting stents (DES) were designed, which eluted an antiproliferative drug from its surface. Despite the coating, incidences of late stent thrombosis were reported [64]. The mechanical support in the artery may not be essential for more extended periods, as the remodeling of the artery takes place six months after implantation [65]. A device which can assure mechanical support during the initial six months after implantation and get absorbed by the body [66] will significantly reduce any post-operative complications.

5.1.2. Required Mechanical Properties

The essential mechanical criteria for qualifying a stent for favorable clinical results are biocompatibility, flexibility, easy deployability, greater radial strength, minimal crossing profile, low metallic surface area, and acceptable tractability. In the case of metallic stents, the following decisive factors are to be considered: construction, geometry, and strut thickness. The construction of metallic stents is of three types: (a) the coil type, (b) the tubular mesh type, and (c) the plain tubular type. The plain tubular type can be a modular tube or a slotted tube. On the other hand, coil stents are made of metallic stripes wound in a coil-like shape. Finally, the tubular mesh stent is made using a mesh in a tubular shape employing metallic wires. Slotted tube stents are made using metal tubes with a laser-cut design. Among the above-mentioned stent construction types, the slotted tube stent construction shows better radial strength and clinical outcomes compared to coil and mesh type stents. The modular stent construction is also suitable, as it possesses the optimum characteristics of the flexibility of coil type and the radial strength of the slotted tube design [67,68].

The geometry and physical construction of the stent plays a vital role in restenosis. The greater the number of strut-strut intersections, the greater is the rise in the neointimal

region. Hence a lower number of intersections is preferred to minimize vascular injuries. In addition to these considerations, the stents also are designed considering restenosis for better clinical results. The thickness of the stent strut is an essential parameter in the stent design. The stents are categorized based on thickness as (a) thick (>120 µm), (b) intermediate (101–120 µm), (c) thin (81–100 µm), and (d) ultrathin (60–80 µm). Among them, the thinner struts have lower restenosis rates and better deliverability. To improve radial strength, arterial wall support, and radio-visibility, the intermediate thickness struts can be chosen. However, this would cause more intimal hyperplasia and vascular injuries resulting in a higher risk of restenosis when compared to thinner struts. For optimum radial strength and radio-visibility with better scaffolding properties, new materials and processes are needed [67,68].

The standard vascular stent is made of Stainless Steel (SS) 316 L, which gives optimum performance. The permanent SS-316L stent lasts for 10 years, with about 400 million cycles. The BVS requirements are satisfied by a biodegradable stent that retains its mechanical properties for six months, with 20 million cycles before failure [69–71]. The mechanical characteristics of the candidate stent material should be comparable to that of SS 316 L, which includes Young's modulus (YM), ultimate tensile strength (UTS), yield strength (YS), and elongation. These basic mechanical properties manifest into radial strength, axial and radial flexibility, acute and chronic recoil, profile, deliverability, and integrity during its lifetime [72]. Materials having a lower YS and higher UTS are preferred for cardiovascular stents. Low yield strength is required to allow the balloon to expand at lower pressures, while a higher yield strength with high elastic deformation may result in acute recoil during the balloon expansion. Usually, materials having a high UTS also have a high YS. There have also been no criteria set thus far for cyclic fatigue for BVS materials [73].

5.2. Magnesium Stents

Magnesium plays a crucial role in the functioning of the human body, as it is involved in various regulatory mechanisms [74]. The poor mechanical properties of pure Mg relative to pure iron and its poor corrosion resistance make it a less favorable candidate [58,75]. The studies on AE21 and WE43 alloys showed that these alloys degrade in vivo and in pre-clinical studies very rapidly. as they exhibit localized corrosion caused by the disintegration of the passive protective film [76]

5.2.1. Mechanical Properties

Magnesium alloys are mechanically inferior to 316L SS. Consequently, processing methodologies, such as deformation and alloying, must be used to enhance the mechanical characteristics. Alloying elements like Nd, Zr, Y, Zn, Al, and Ca can be used in small amounts for improving mechanical behavior. Mg alloys typically exhibit a hexagonal close-packed (HCP) structure with three slip planes and, hence, are difficult to deform. However, once deformed, they exhibit better mechanical properties. Hence, deformation techniques, such as extrusion and drawing, have also been explored (Figure 1, Table 2) [68].

5.2.2. Biocompatibility and Degradation

Since Mg alloys have a higher rate of degradation, coatings with poly(carbonate urethane) urea (PCUU), poly(ester urethane) urea (PEUU), and poly(lactic-co-glycolic acid) (PLGA) are effective in controlling the degradation rate. Magnesium itself is an essential element for human metabolism, with a tolerance level of up to 121 mg/L in blood [68]. Gao et al. [77] evaluated the corrosion and biocompatibility of magnesium alloys by depositing a Chitosan-Functionalized Graphene Oxide/Heparin (GOCS) bioactive multilayer coating on the magnesium alloy surface layer-by-layer to construct the positively charged GOCS and negatively charged heparin. The results showed that the corrosion resistance of the magnesium alloy was significantly improved by GOCS/Heparin multilayers. The GOCS/Heparin multilayer coating had good blood compatibility and significantly reduced the homolysis rate of magnesium alloy [77]. Zhang et al. [78] surface-modified magnesium

alloys by treating them with NaOH to form a passive chemical conversion layer followed by 16-Phosphonohexadecanoic acid (16-Pho) introduction on the modified surface to improve the acute corrosion resistance. Further, the biocompatibility of the magnesium alloys was improved by Poly (ethylene glycol) (PEG), fibronectin (Fn), and fibronectin/heparin (FH). The results of the study showed improvement in corrosion resistance and hydrophilicity by alkali heat treatment. Better corrosion resistance was clearly observed after the following immobilization of the molecules. Surface modifications with Fn and FH effectively enhanced cell attachment and growth and showed good cytocompatibility to endothelial cells [78]. Pan et al. [79] surface-modified a magnesium alloy (AZ31B) modified by the alkali heating treatment followed by the self-assembly of 3-phosphonopropionic acid, 3-aminopropyltrimethoxysilane (APTMS), and dopamine representatives to control the corrosion rate of Mg-based alloys and to enhance the biocompatibility. The results showed excellent hydrophilic surface, and the water contact angle increased to some degree after the self-assembly of dopamine, APTMS, and 3-phosphonopropionic acid. The alkali heating treatment formed a passivation layer, thereby forming the corrosion resistance of the magnesium [79].

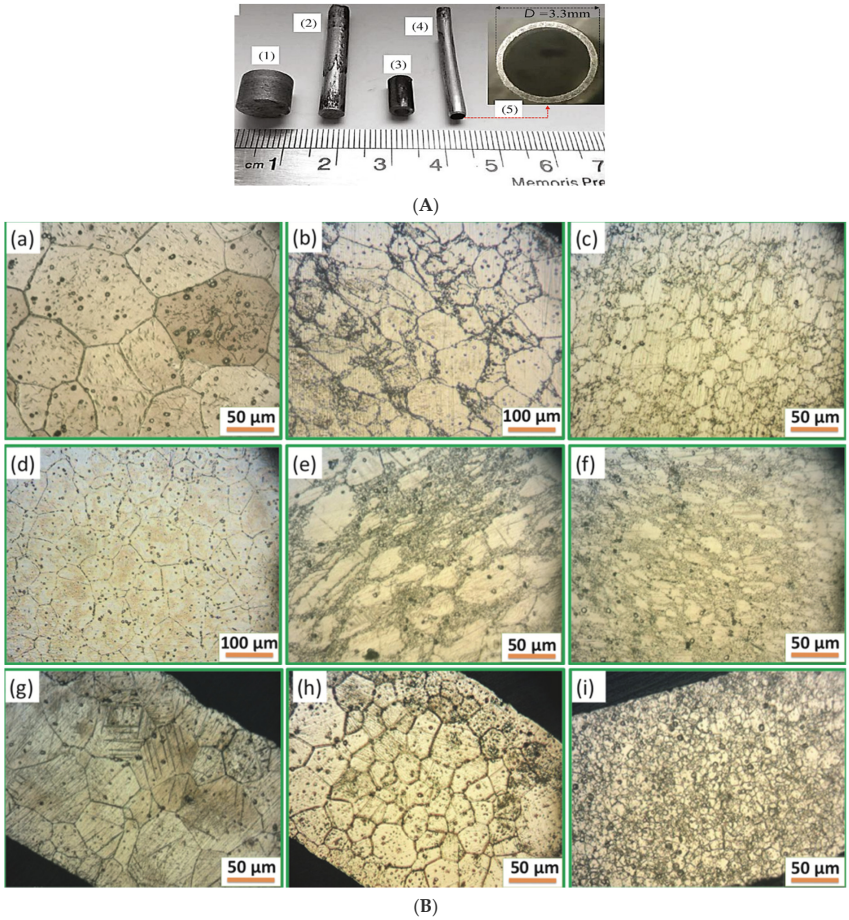


Figure 1. (**A**) Tube morphologies obtained by different processes: (1) CEE; (2) DE; (3) drilling; (4) MTE; (5) cross-section of final microtube. (**B**) Microstructures of WE43 alloys: (**a**) as-received; (**b**) 1P CEE; (**c**) 2P CEE; (**d**) 0P + DE; (**e**) 1P + DE; (**f**) 2P + DE; (**g**) 0P + DE + MTE; (**h**) 1P + DE +MTE; (**i**) 2P + DE + MTE. Copyright [68,80]. Magnification: 10 and 20×. (DE—Direct Extrusion, CEE—Cyclic Expansion Extrusion, MTE—Micro-tube Extrusion).

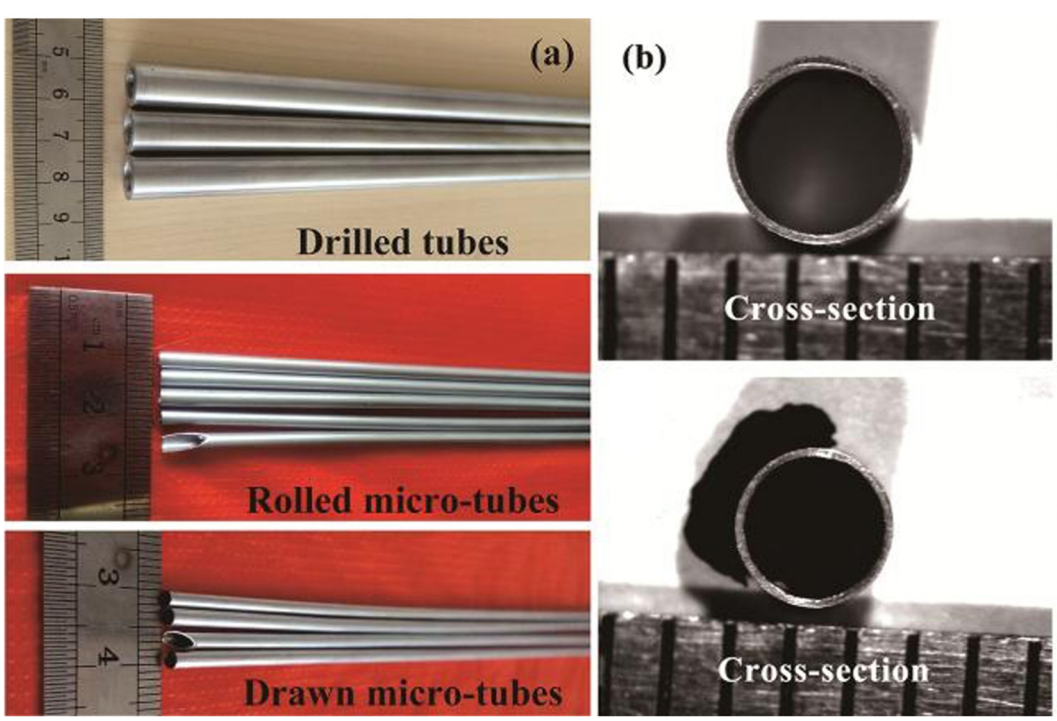
5.3. Zinc Stents

5.3.1. Degradation

The research interest of Zinc alloys as a suitable cardiovascular stent material is relatively recent, compared to Mg and Fe. The degradation behavior of Zinc alloys is highly favorable. In a study, the abdominal aorta of rats was implanted with Zinc wires. The wires exhibited increasing degradation with time, as is required [81]. For up to 20 months, the cross-sectional area of the wire decreased steadily [82]. A new experiment revealed that in adult rabbits, the degradation of Zn stents was about 42 ± 30% over 12 months [83]. Despite such promising degradation data, the mechanical properties of pure Zinc are not suitable for use as cardiovascular stents [84,85] (Figure 2).

5.3.2. Mechanical Properties

The strength of pure Zinc is unfavorable for use as a cardiovascular stent. Since Zn has a hexagonal close-packed (HCP) structure, it is hard to deform. Consequently, the addition of alloying elements is a suitable strengthening method for Zn. The addition of several alloying elements like Mg [86–88], Ca and Sr [89,90], Al [85], and Mn [91] to Zn was investigated to overcome the mechanical deficiencies. However, the main drawback of these systems is the strain-softening exhibited within the plastic range. This is a well-known occurrence in Zn and its alloys [92]. The residual strength of alloys is reduced due to strain softening, which can increase the chances of late recoil in the implants. Ag is a possible candidate for an alloying element in Zinc, as it has been reported to increase both ductility and strength, with a reduction in strain-softening [88]. There are avenues for further research with regards to hemocompatibility and cytocompatibility to check the effects of Ag [88].



(**A**)

Figure 2. *Cont.*

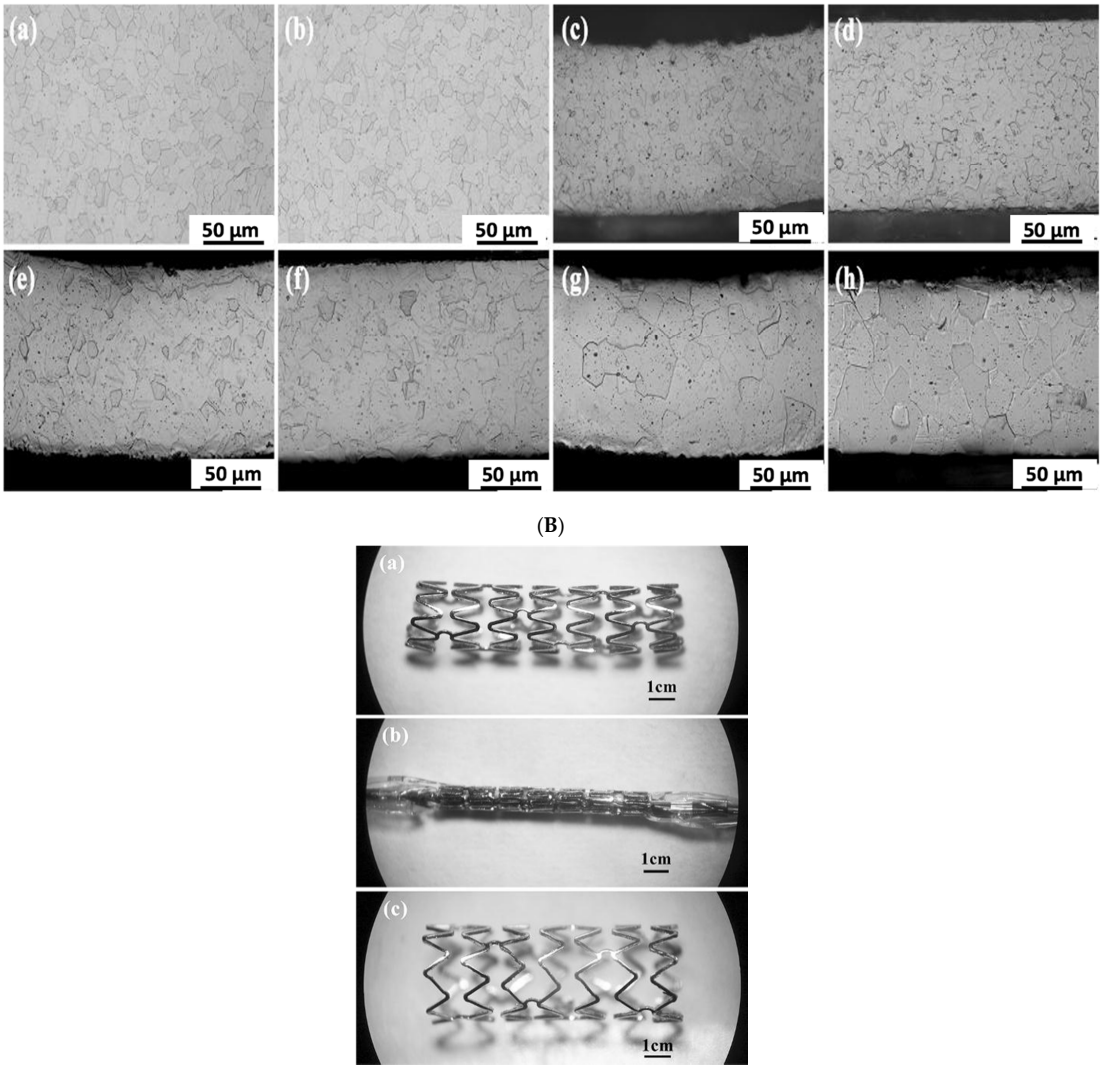


Figure 2. (**A**) Microtube of Zn—0.05 and Mg—0.01 Fe alloy fabricated by drilling, rolling, and drawing: (**a**) microtube; (**b**) cross-section of the microtube. (**B**) Microstructure of Zn microtubes: drilling, (**a**) cross-section, and (**b**) longitudinal section; rolling, (**c**) cross-section and (**d**) longitudinal section; drawing, (**e**) cross-section and (**f**) longitudinal section; annealing, (**g**) cross-section and (**h**) longitudinal section. (**C**) Zn-based vascular stents fabricated by laser etching and electrochemical polishing: (**a**) Zn-based stent with a diameter of 2.5 mm; (**b**) first crimp to a diameter of 1.3 mm; (**c**) balloon expansion to a diameter of 3.5 mm Copyright [68,93].

5.3.3. Biocompatibility

Zn has a lower rate of degradation as compared to Mg- and Fe-based stents. Studies have demonstrated that the degradation of Zn in six months is less than 50 µm/year. Similar to Mg, Zn, too, is an essential element for humans and is suitable for muscles, skin, liver, and bones. The recommended dose of Zinc per day in adults is 6.5–15 mg/day [94]. Generally, a zinc alloy-based stent may contain about 50 mg of Zn, which will degrade over 6–12 months. Therefore, the amount of Zinc is not high enough to cause any side-effects [81]. Claudia et al. [95] investigated the mechanical properties, biodegradability, and biocompatibility of Zn–Mg and Zn–Cu alloys. The addition of Mg or Cu alloying elements refined the microstructure of Zn and enhanced yield strength (YS) and ultimate tensile strength (UTS) proportional to the volume fraction of secondary phases. Zn–1Mg showed the higher YS and UTS and better performance in terms of degradation stability

in Hanks' solution. Zn–Cu alloys presented an antibacterial effect for S. aureus controlled by diffusion mechanisms and by contact [95]. Bowen et al. [81] revealed no necrosis or rejection Zn wires when implanted in the abdominal aorta of Sprague–Dawley rats during six months. However, Sherier et al. [96] suggested that free Zn^{2+} ions might hinder cell mobility and adhesion. Kubasek et al. [97] reported a maximum safe Zn^{2+} ion concentration for U2OS and L929 cell lines. Differences in the in vitro response depend on the studied alloy, selected cell line and cell culture medium, and the obtained products of corrosion. The Zn alloys bacterial response is of interest, since stent infection is a rare complication with high mortality (32%), in which the S. Aureus and the P. Aeruginosa bacteria are responsible for over 80% of the cases [98].

Table 2. Properties of Mg and Zn Microtubes (Copyright [68]).

References	Alloys	Processes	Dimensions	Mechanical Properties		
				YS (MPa)	UTS (MPa)	EL (%)
-			**Zn alloys**			
[87]	Zn–0.15Mg	DE + TE	Tube: outer diameter of 4 mm; inner diameter of 1.5 mm	114	250	22
	Zn–0.5Mg			159	297	13
	Zn–1Mg			180	340	6
	Zn–3Mg			291	399	1
[28]	Zn–1Mg–1Ca	HR	-	210	260	5.5
	Zn–1Mg–1Sr	HE	-	200	250	7.5
	Zn–1Mg–1Sr			215	265	6.8
[99]	Zn–1Ca–0.1Sr	HR	Sheet metal: thickness of 2.1	196	300	22.49
[100]	Zn–1Mg–0.1Mn	-	Sheet metal: thickness of 2.1	195	299	26.07
[89]	Zn–1Ca	HE	Rod: diameter of 10 mm	195	240	7.5
	Zn–1Sr			220	260	10.8
	Zn–1Mg			205	265	8.5
[87]	Zn–0.5Al	DE + TE	Tube: outer diamter of 4 mm; inner diameter of 1.5 mm	119	203	33
	Zn–1Al			134	223	24
[101]	Zn–1Cu	HE	Rod: diameter of 20 mm	149	186	21
	Zn–2Cu			199	240	46.8
	Zn–3Cu			213	257	47.2
-	Zn–4Cu			227	270	50.6
[102]	Zn–3Cu–0.1Mg	HE	Rod: diameter of 20 mm	340	375	5
	Zn–3Cu–0.5Mg			400	425	2
	Zn–3Cu–1Mg			425	450	1
[88]	Zn–2.5Ag	HE	Rod: extrusion ratio 14:1	155	205	35
	Zn–5.0Ag			210	260	38
	Zn–7.0Ag			240	290	32
			Mg alloys			
[103]	AZ31	DE + CD + CD	Outer diameter of 3 mm, Thickness of 0.18 mm	172	-	16
[104]		Dieless drawing	Outer diameter of 3.35 mm, Thickness of 0.69 mm	-	-	-
[103]	JDBM	DE + CD + CD	Outer diameter of 3 mm, Thickness of 0.18 mm	123	-	26
[74]	-	Double Extrusion	Outer diameter of 3.5 mm, Thickness of 0.18 mm	220	267	48.8
[103]	WE43	DE + CD + CD	Outer diameter of 3 mm, Thickness of 0.18 mm	113	-	10
[80]		CEE + DE + MTE	Outer diameter of 3.3 mm, Thickness of 0.22 mm	-	410	18.5
[105]		CEE	-	-	440 at highest	21 at highest
[105]	Mg–Zn–Y–Nd	ECAE + DE + MTE	Outer diameter of 3.3 mm, Thickness of 0.22 mm	-	340	20
[60]		DE + CD annealing	Outer diameter of 2 mm, Thickness of 0.15 mm	196	298	20
[106]	ZM21	DE + drilling + HIDE + CD	Outer diameter of 2.9 mm, Thickness of 0.2 mm	-	-	-
[107]		DE + drilling + IDE + CD	Outer diameter of 2.9 mm, Thickness of 0.217 mm	-	-	-
[108]	Mg–4Zn–1Y	DE + ECAE	Outer diameter of 2.4 mm, Thickness of 0.4 mm	340	353	11.5
		HDE + annealing	-	240	330	20.4

DE—Direct Extrusion, IDE—Indirect Extrusion, TE–, HR—Hot Rolling, HE—Hot Extrusion, CD—Drawing, CEE—Cyclic Expansion Extrusion, MTE—Micro-tube Extrusion, ECAE—Equal Channel Angular Extrusion, CR—Cold rolling.

6. Translational Research on Cardiovascular Applications

Currently, academia and industry have been studying mainly three alloy systems for the synthesis of biodegradable stents, which are Mg-based, Zn-based, and Fe-based alloy systems. Compared to the other alloy systems, the Mg-based system has been studied the most for clinical translation [67,109]. On the other hand, clinical trial reports for Fe-based and Zn-based alloys are currently unavailable, although translational studies are ongoing. In 2016, a bioresorbable stents composed of Mg alloy received the CE mark after a successful clinical trial [67].

Clinical Trials of Stents

Many other alloying elements were added to pure Mg to improve the mechanical properties for use in Mg-based cardiovascular stents [110–113]. Usually, rare earth elements (REEs) are added to reduce the grain-size in the alloy. As per the Hall–Petch relation, smaller grain sizes improve mechanical characteristics. Contrary to the addition of Gd and Nd [111], the corrosion resistance of Mg alloys is improved by the addition of REEs. This is because they suppress the micro-galvanic coupling that occurs with Mg and other elements by precipitating the secondary phases, which have electrochemical potentials similar to the matrix. Zr is also commonly used as a grain refiner [111]. Many patents have been filed by both academic institutions and companies regarding the development of REEs-added bioabsorbable alloys for stents [114–117].

The use of Mg–REE alloy stents in babies with congenital heart diseases has also been investigated. It is suggested that using biodegradable stents in children can be significantly beneficial compared to that in adults. This is rationalized on the notion that as the patient ages, arterial growth would not be hindered, as opposed to a permanent stent. The trials have reported mixed success. In one study, a bioabsorbable stent (AMS, Biotronik) was implanted in the pulmonary artery of a preterm baby, and clinical success was reported [118]. Unfortunately, the baby died due to unrelated reasons five months later. It was revealed by the histopathology that some calcium compounds were observed near the strut sites. The stent had also degraded completely without any foreign-body reaction [119]. In contrast, heavy restenosis was reported in two studies on newborns [120,121] three and four months after surgery. Similar results were observed in an animal study [122], where segments with AMS implants exhibited a considerable reduction in lumen area compared to BMS and DES after three months. Similarly, in other animal studies, reabsorption occurred within three months. Efforts were made to increase the absorption time to accommodate artery remodeling completely. PLGA coating, in which paclitaxel was present as an antiproliferative agent, was done on stents, which resulted in a similar intimal area and late lumen loss compared to permanent methods [123]. Another study [124] demonstrated that an Mg-based cardiovascular stent (Magmaris, Biotronik) has significantly less thrombogenicity compared to a commercial polymeric resorbable stent (Absorb, Abbott Vascular) [124] (Table 3).

Mg–2.5Nd–0.2Zn–0.4Zr (JBDM) is another alloy system that has been thoroughly tested in vivo [125]. It is expected that this composition would cause micro-pitting corrosion rather than macroscopic pitting corrosion seen in other Mg alloys [125]. Good biodegradation of the stents made with this alloy was demonstrated in in vivo tests on rabbits and mini pigs, both in the drug-eluting [126] and bare versions [125,126]. In the coated variant, some late lumen loss was observable, while this was not so in the case of bare stents. However, no quantitative data were provided by this study. A study based on the modified version of the alloy (JBDM-2) exhibited slight neointimal hyperplasia in rabbits after four months of introduction [127]. A new stent made of a Mg–2Nd–0.2Zn–0.5Zr alloy to treat the construction of a lateral aneurysm present in the common carotid of rabbits showed significant benefits, like an increase in diameter and lumen area after 12 months [128]. A study revealed that a Mg–2Zn–0.5Y–0.5Nd alloy stent, having an APTES coating with a top layer of PLGA embedded with rapamycin, in the arteries of mini pigs

had a comparable lumen area to that of 316L DES. It was seen that the struts had undergone partial degradation in six months [128].

Table 3. Clinical Translated Stents for cardiovascular Applications.

References	Device	No. of patients	Total Duration (Months)	Outcomes	Identifier
[129–131]	AMS–PROGRESS	63	28 months	Stent totally absorbed after four months. 47% of patients suffered restenosis. No myocardial infarction or late thrombosis occurred.	-
[129–131]	AMS–INSIGHT	117	12 months	Three patients with one-month complications. Lower patency rate for AMS (31.8%) versus PTA (58.0%).	NCT00572494
[132,133]	DREAMS–BIOSOLVE-I	46	36 months	One myocardial infarction occurred (not stentrelated). No late thrombosis. Late lumen loss was higher than inert drug-eluting stents. LLL lower at 36 months	NCT01168830
[134,135]	DREAMS-2G (Magmaris©)–BIOSOLVEII	121	36 months	No thrombosis after 24 months. Late lumen loss reduced vs. DREAMS. The device was absorbed at 95% after 12 months.	NCT01960504
[135]	DREAMS-2G (Magmaris©)–BIOSOLVEIII	61	36 months	No thrombosis detected. One post-intervention death (not procedure-related)	NCT02716220
[136]	MAGNEZIX©	26	6 months	Outstanding results for ROM, MTPJ, and AOFAS. Equivalent performance to titanium screws for the treatment of mild hallux valgus deformities.	-
[137]	RESOMET© (K-MET)	53	12 months	The normal range of grip power. No change in ROM and DASH. At 12 months, screws were completely replaced by new bones.	NCT02456415
[138]	Pure Magnesium	48	12 months	Increased bone flap stability. Serum levels were normal. Two patients suffered collapse of the femoral head. At 12 months, there was a higher Harris hip score than control.	ChiCTR-TRC-13003238

7. Conclusions and Future Perspective

There has been a significant expansion in the research on biodegradable metals after their successful application in orthopedic implants, such as bone replacement, and cardiovascular applications, such as vascular stents. With the development of material science, biodegradable metals like magnesium and zinc have been fabricated into biodegradable medical stents to circumvent potential side effects from permanent implants. Stenting a biodegradable metal 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. Moving forward, the challenges facing Zn-based stent development are largely the same as those facing Mg-based stents. Primarily, no material has yet been reproducibly shown to possess ideal mechanical, corrosion and biocompatibility properties that will enable stenting with degradable biomaterials. This is the grand pursuit in the study of degradable biomaterials for stents, but straightforward "melt-and-corrode" methodologies currently pervasive in the literature are not sufficient to advance the field towards this end goal. In summary, the development of biodegradable metallic stents is still in its infancy stage. It is expected that more innovative technologies will be applied in developing new biodegradable stents. These technologies may include new biodegradable materials, novel stent structure designs, and advanced stent fabrication methods.

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