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Review

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A review on Mg-based metallic glasses for biomedical scaffolds: experimental and computational modeling

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Abstract

Magnesium (Mg)-based metallic glasses have emerged as a promising class of biomaterials for various biomedical applications due to their unique properties, such as high strength-to-weight ratio, good biocompatibility and biodegradability. The development of Mg-based metallic glass scaffolds is of particular interest for tissue engineering and regenerative medicine applications. However, the rate of biodegradability of the materials is not well controlled and requires extensive research for efficient tissue/bone regeneration. This review provides a comprehensive overview of the recent advancements in the development of Mg-based metallic glass scaffolds and their tuneable biodegradability with different compositions and thin film coatings. It discusses the structural and biological properties, mechanical and biodegradation behavior, and various fabrication techniques employed to produce Mg-based bulk metallic glass scaffolds. Furthermore, the review explores surface modification of permanent implants with Mg-based thin film biodegradable metallic glasses to simulate tissue regeneration on the implants. Optimization of scaffold design to increase tissue growth and healing by understanding the complex interactions between the scaffold and biological tissues and predicting the long-term implant behavior using computational models are reviewed. The challenges and future research directions in this field are also discussed, providing insights into the potential of Mg-based metallic glass scaffolds for various biomedical applications, including bone tissue engineering, wound healing, and cardiovascular implants.

Keywords: Metallic glasses, Mg-based metallic glasses, biocompatible, biodegradation, scaffolds, bone and tissue regeneration

INTRODUCTION

Scaffolds are biomaterials and bioimplants that stimulate tissue growth and facilitate the repair or reconstruction of diseased body parts[1]. In bone tissue engineering (BTE), scaffolds made of conventional materials such as metals, polymers, ceramics, or natural materials are introduced into the site of a bone defect to promote repair and regrowth[2,3]. While polymer or ceramic scaffolds are common in orthopedics, their limitations are significant[4-6]. These implants can trigger a foreign body reaction and deter integration with bone tissue, hindering successful repair[7-9].

Magnesium (Mg)-mediated calcitonin gene-related peptide (CGRP) mechanisms are promising to enhance bone regeneration by integrating the osteoinductive properties of Mg with the regulatory effects of CGRP on bone remodeling[10]. As a biodegradable material, Mg releases magnesium ions (Mg^{2+}) during its degradation, which stimulate osteoblast differentiation, enhance extracellular matrix production, and promote angiogenesis, thereby improving oxygen and nutrient delivery to regenerating bone tissue[11]. It also activates key signaling pathways that contribute to bone mineralization and formation, establishing its role as a potent material for BTE[12]. Furthermore, Mg implants can induce localized CGRP release, enhancing vascularization and immune regulation at the injury site to optimize bone healing[13]. CGRP, a neuropeptide released by sensory nerves, complements the effects of Mg by promoting osteoblast proliferation, enhancing bone formation, and inhibiting osteoclast activity to reduce bone resorption[14]. It also modulates the inflammatory response, creating a balanced microenvironment conducive to tissue repair[15]. Integrated Mg and CGRP synergistically enhance bone regeneration by amplifying vascularization, stimulating osteoblast activity, and preventing excessive bone resorption[14]. This dual-action mechanism ensures efficient and balanced bone remodeling, offering a robust strategy for treating fractures, bone defects, and other skeletal injuries[16]. Mg and CGRP provide a powerful foundation for advancing BTE and regenerative medicine[17-20].

Some biodegradable metals such as Fe and Zn possess much higher Young's modulus (higher stiffness) compared to bone which could lead to or contribute to stress shielding if the scaffold is not appropriately designed[21-23]. As a result, the implant bears most of the load, weakening the surrounding bone and suffering from poor plasticity, making it unsuitable for most medical (orthopedic) applications[24-26]. Mg is a vital mineral in the human body, essential for various physiological processes and a promising biodegradable implant scaffold material due to its biocompatibility, osteoconductivity, and mechanical properties that are more similar to natural bone that contributes less to stress shielding than many other metals[27-29]. Since its first use as wire ligature in 1878, magnesium has been proposed for biomedical applications[30].

As a biomaterial, it offers clinical advantages by dissolving in a controlled manner within the body post-surgery[31]. Its corrosion products are non-toxic, eliminating the need for additional surgeries to remove the implant once it has fulfilled its purpose[31]. Magnesium occurs naturally in the body, playing crucial roles in various metabolic functions, making it highly biocompatible. An average adult weighing 70 kg carries approximately 25 g of magnesium, primarily in bone tissue[32]. However, Mg has significant limitations, including a rapid degradation rate that can lead to premature loss of structural integrity, excessive hydrogen gas release, and local increase in pH that can damage surrounding tissues[33]. Additionally, its relatively low mechanical strength makes it less suitable for load-bearing applications, and controlling its degradation rate to match tissue healing remains challenging[33].

To address these limitations, magnesium alloys have been developed by adding elements such as aluminum (Al), zinc (Zn), calcium (Ca), or rare earth metals to the pure metal[33-35]. These alloys typically exhibit

improved mechanical strength, corrosion resistance, and more controlled degradation rates, making them more suitable for load-bearing applications[33]. However, the biocompatibility of these alloys can vary depending on the added elements, and there is a risk that some alloying elements could introduce toxicity or unwanted side effects[33]. Furthermore, while alloying can improve the properties of Mg, it may still not fully address issues such as stress shielding or the precise control of the degradation rate, which are critical for matching the performance of scaffolds to the tissue healing process[33].

Bulk metallic glasses (BMGs) represent an advanced class of materials explored as load-bearing implants in biomedical applications due to their exceptional strength, flexibility, and corrosion resistance[33]. They exhibit an amorphous structure, lacking the regular atomic arrangement found in crystalline metallic alloys[36]. Mg-based BMGs (Mg-BMGs) are particularly attractive for load-bearing biodegradable implant scaffolds, offering the mechanical characteristics of bone[37-39]. The lower modulus of the Mg-BMGs provides a better match to the modulus of cortical bone and helps reduce stress shielding, a beneficial feature for hard-tissue prostheses[40]. In addition, Mg-based metallic glass has an improved corrosion resistance compared to crystalline Mg and its alloys[41,42]. These properties make Mg-BMGs particularly attractive for scaffolds with tailored properties including degradation rates[33]. Tissue growth and cell infiltration that are crucial for osseointegration and the fusion of implant and bone can be enhanced through the coating of porous materials that require further studies[39]. This includes surface engineering of implants with an interlayer of Mg-based thin film metallic glass (TFMGs) coatings to simulate tissue regeneration on desired permanent implant substrates[43-45] and thin film.

BMGs are advanced materials with an amorphous atomic structure, formed by rapidly cooling metal alloys to prevent crystallization. They offer exceptional properties such as high strength, elasticity, corrosion and wear resistance, and ease of processing in their supercooled liquid state. Common BMG systems include Zr-, Pd-, Fe-, Ti-, Cu-, and Mg-based alloys [Figure 1], each tailored for specific properties such as biocompatibility, lightweight, or cost-effectiveness[46]. These materials are widely used in biomedical implants, aerospace, automotive, consumer electronics, sporting goods, and industrial tools due to their superior performance and versatility.

The discovery of BMGs sparked significant scientific and technological interest due to their potential application[47]. Since the mid-20th century, scientists and engineers have been researching suitable properties of metallic glasses through diverse manufacturing techniques to overcome their limitations[48-50]. BMGs are formed from rapidly cooled molten alloys that inhibit the formation of crystalline nuclei, resulting in amorphous materials[46]. The cooling process for the formation of amorphous material includes water quenching[46,51], melt spinning[52], gas atomization[53], *etc.* In 1960, Klement *et al.* reported the first BMG[54] by rapidly cooling specific combinations of multi-elements (primarily metals) below the glass transition temperature (T_g) to prevent the formation of crystalline materials[44]. Figure 2 describes this phenomenon, illustrating the supercooled liquid region between the melting temperatures (T_m) and T_g over periods not more than the time required for crystal nucleation. These multicomponent (> 4 elements) metallic glasses are commonly based on Zn, Au, Mg, Fe, Zr, Ti, *etc.*[46]. However, ternary component metallic glass from Pd-Cu-Si was created, using a quenching rate below 10^3 Ks^{-1}[55]. BMGs can be molded by applying slight force through processes including forming, extrusion, hot rolling, injection, and blow molding, followed by fast cooling to solidify the material[56-60].

BMGs appear as atomically frozen (solidified) liquid due to no long-range atomic order[47,61]. They can also be fabricated using various casting techniques designed for rapid cooling of molten alloys to prevent crystallization, maintaining an amorphous structure[61]. Techniques include suction casting, which rapidly

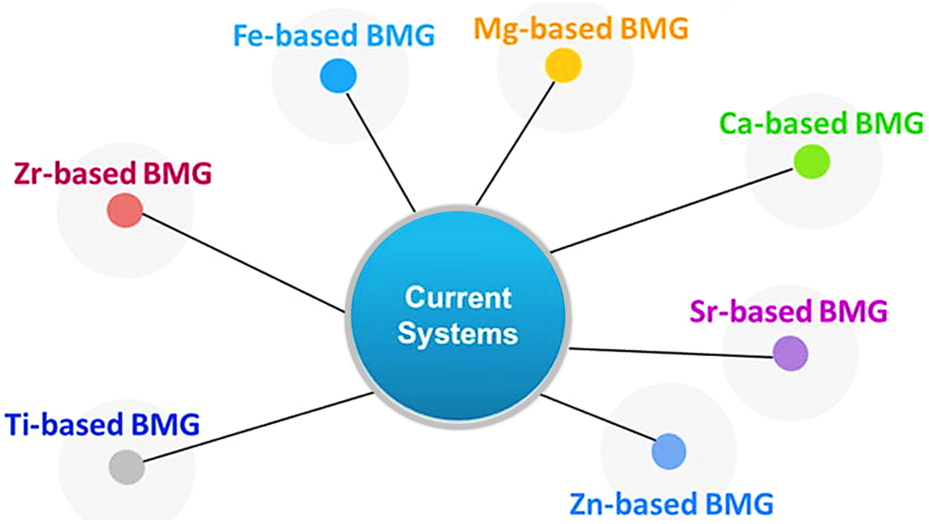

Figure 1. BMGs, including Ti-, Zr-, Fe-, Mg-, Zn-, Ca- and Sr-based alloying systems. Reproduced with permission from ref.[46] © 2016 Acta Materialia Inc. Published by Elsevier Ltd. All rights reserved. BMGs: Bulk metallic glasses.

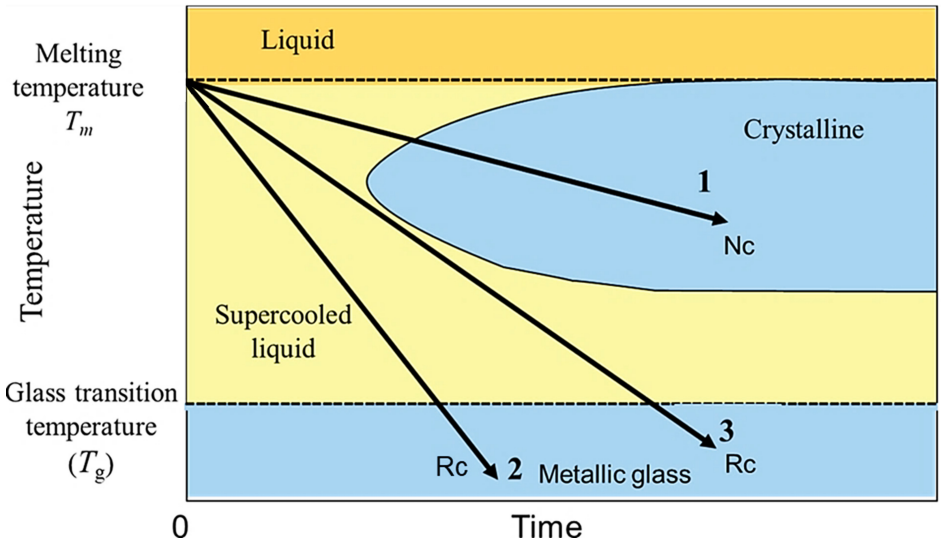

Figure 2. Fabrication concept of metallic glass: Schematic of continuous cooling transformation (CCT) curve diagram for the onset of crystallization of a glass-forming liquid. Between T_m and T_g, (arrow 1; normal cooling Nc) depicts the crystallization phase which can be avoided with the cooling rate (Rc; arrow 2) ≥ critical cooling rate (Rc; arrow 3) to conserve the macroscopically disordered structure of the liquid at the T_g. This image is licensed under Creative Commons Attribution and reproduced from ref.[61] © 2024 Onyeagba C. Raphael. All rights reserved.

draws molten alloy into a pre-cooled mold under vacuum[47]; injection casting, where molten metal is injected under high pressure to form complex shapes[53]; and copper mold casting, which uses a copper mold to quickly extract heat and solidify the alloy[52,62-65]. These methods are constrained by the cooling rates (Rc) shown in Figure 2. To form a fully amorphous structure, BMGs require extremely high Rc, typically between 10^3 and 10^6 K/s, beyond the *Tg* [Figure 2] to prevent crystallization[66]. Conventional casting methods achieve Rc of only up to 10^2 K/s, often insufficient to avoid crystalline phase formation[66]. While techniques, such as melt spinning and splat quenching, can reach Rc of 10^4 to 10^6 K/s, they are limited to producing thin ribbons or flakes[66]. Alternative fabrication methods, such as 3D printing and laser processing, can achieve the necessary high Rc and avail the benefit of complex geometries and tailored

properties[67]. In 3D printing, techniques such as selective laser melting (SLM) or laser powder bed fusion (LPBF) are employed, where a laser selectively melts and fuses layers of metallic powder, allowing the creation of intricate BMG structures layer by layer[68,69]. This method provides precise control over the design and material distribution, making it ideal for custom applications[51,70]. However, 3D printing of crack-free BMG components remains a challenge due to the generation of structural heterogeneity and crystallization during the rapid solidification process[71-73]. Ultimately, the choice of fabrication techniques depends on the desired size, shape, and properties of the component.

Research on the reliability, rigidity, and dynamic mechanical characteristics of BMGs dates to the early 1970s, with most early examples being low-dimensional, such as amorphous ribbons and wires[44]. The toughness of some BMGs approaches the values of crystalline metals, significantly exceeding that of ceramics. Composite BMGs, which consist of crystals embedded in an amorphous matrix, can rival the toughness of their crystalline counterparts while retaining the benefits of the glassy structure[44,45]. Additionally, their unique thermal properties, such as a distinct T_g, allow for precision shaping and molding without crystallization [Figure 2].

Figure 3 shows the fracture toughness and yield strength of a range of BMGs from the literature in comparison to polymers, ceramics, steel, and titanium alloys[74]. BMGs occupy a distinctive region in the Ashby maps, characterized by their exceptionally high yield strength and moderate fracture toughness that were not achievable from the other materials.

The development of BMG matrix composites (BMGMCs) has been a key focus, which involves incorporating ductile phases into the brittle BMG matrix to improve their mechanical properties[75]. BMGs are expected to see widespread applications in consumer electronics, jewelry, fuel cells, coatings, and nano/microtechnology due to an enhanced understanding of their properties and processing potential[74]. Ashby maps for fracture toughness versus density [Figure 3A] and yield strength [Figure 3B] highlight that these amorphous alloys and composites compare favorably with other engineering materials, although the plastic zone size (1-10 μm) limits BMG applications as the deformation is not spread evenly in thicker (> 1mm) BMGs and leads to brittle failure under stress[76,77].

BMGs typically have moderate fracture toughness compared to more ductile materials (e.g., metals) due to their lack of plastic deformation mechanisms that can lead to brittle fracture under certain conditions[78,79]. Despite this, some BMGs demonstrate a good balance between strength and toughness, making them suitable for applications requiring high strength and moderate toughness[79]. Their position on the Ashby map [Figure 3B] highlights their role as materials that provide high strength with adequate toughness, bridging the gap between brittle ceramics and ductile crystalline metals[79]. Mg-BMGs can be categorized under new BMGs and exhibit a unique combination of properties on the Ashby map, particularly in terms of their high yield strength and moderate fracture toughness, making them competitive with other lightweight structural materials[80].

This review focuses on the latest research on bulk Mg-based metallic glasses (Mg-MGs) as tailored scaffolds or thin films as tissue regenerative interlayers on permanent implants, focusing on their Experimental aspects (synthesis, structural/mechanical properties, biocompatibility, biodegradability) and Computational Modeling of Mg-MGs in both thin films and bulk properties for biomedical scaffolds with an emphasis on controlling corrosion rate for tissue regeneration. The challenges and future directions in this field are also discussed.

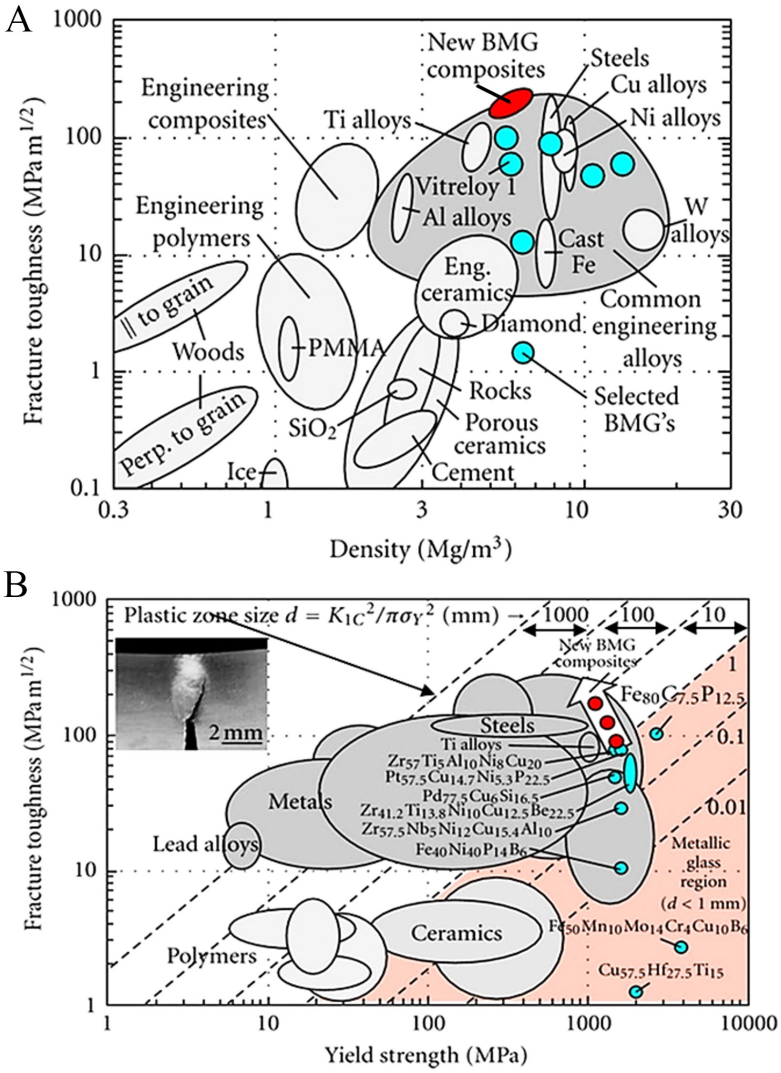

Figure 3. (A) Ashby map of fracture toughness versus density of materials including the location of select bulk metallic glasses and Zr-Ti-Nb-Cu-Be bulk metallic glass matrix composites; Composite alloys have among the highest fracture toughness (B) Ashby map of fracture toughness versus yield strength of materials including selected metallic glasses and composites. Contour lines indicate plastic zone size, and the shaded region signifies the diameter (d) < 1 mm region that typically confines monolithic metallic glasses. The plastic zone size of the toughened composites is shown in the inset. This image is reproduced from ref.[74]

MG-BASED BULK METALLIC GLASSES

Processing and Properties of Mg-based BMG

Research has demonstrated that magnesium is hypoallergenic and promotes the generation of new bone as evidenced by both in vitro and *in vivo* experiments[81]. It is one of the few load-bearing light metals having a density of 1.74 g/cm^3 and modulus of elasticity (45 GPa) closest to bone (23 GPa). However, magnesium has limited solubility for other elements, which limits processing methods. Its crystal structure [hexagonal close-packed (HCP)] restricts deformation and affects the toughness required in biomedical implants. Extensive research has been conducted to create Mg-based scaffolds for temporary implants such as screws, pins, and stents by incorporating well-known biocompatible alloying elements (Ti, Ca, Zn, *etc.*)[46].

Figure 4 shows steps for manufacturing porous Mg-based alloy for scaffolds in animal bone implants. Fabricating materials as a porous scaffold facilitates cell/tissue regrowth which makes them more suitable for biomedical implants[82].

However, traditional alloying methods are not very effective in improving properties such as elasticity and chemical behavior in magnesium[83]. This is because magnesium has limited solubility for other elements and a crystal structure that restricts its ability to deform (ductility). Adding fibers as reinforcement was found to overcome these limitations [Figure 5A][83]. As shown in Figure 3, BMGs have limited ductility[48,84], and require improved fabrication and processing techniques to enhance their properties. The structure of the Mg-based binary or ternary alloys can be modified by introducing and substituting elements in matrix systems, as shown in Figure 5B[85,86].

Mg-MGs can be processed using commonly known manufacturing methods[87,88]. Table 1 displays the production of various Mg-BMGs throughout time, utilizing diverse processes. Combining Mg-based metallic glass with mesoporous silica nanocomposites boosts biocompatibility and BTE capabilities[89]. Alloying Mg with elements such as Zn, Ni, and Ca enhances glass-forming ability and mechanical properties, making the material more suitable for biomedical applications[90-94]. For instance, the addition of a small amount of Ni could improve the glass-forming ability of an Mg-Cu-Y matrix[86]. Manufacturing Mg-BMGs with critical diameters [Table 1] provided the ability to manipulate material characteristics to mitigate brittle failure[83].

As previously emphasized, Mg-BMGs are highly significant due to their exceptional properties. This amorphous nature of BMG allows for a broad range of glassy compositions without specific stoichiometric requirements, facilitating microscopic property adjustments within a defined range through optimization of the glass transition composition[95-99]. The atomic structures of five types of Mg-BMGs using neutron diffraction and classical molecular simulation methods were explored by Gulenko *et al.*[100] and the findings indicated that bond lengths remained relatively stable despite changes in composition. A similar study investigated the structure of multicomponent Mg-MGs using techniques such as high-resolution transmission electron microscopy, and reverse Monte Carlo modeling[101]. They focused on the $Mg_{65}Cu_{20}Y_{10}N_{i5}$ alloy, revealing a randomly packed structure with some observable ordered regions [Figure 6]. Their analysis, which included peak values, coordination numbers, and correlation functions [Figure 6A-B], suggested structural clustering [Figure 6C-D][101]. The primary objective of their research was to investigate the structural effects of annealing on Mg-BMG structure, specifically $Mg_{65}Cu_{25}Y_{10}$, integrating experimental findings with Monte Carlo modeling results[101].

Mg-BMGs are promising candidates for temporary implants such as orthopedic implants and cardiovascular stents owing to the following properties and advantages compared to their crystalline counterparts and other bioabsorbable implants. Mg-BMGs combine their lightweight nature and biodegradability with tailored elastic properties compared to pure magnesium, enhancing their toughness[32,102]. While Mg-BMGs generally have superior mechanical properties, such as compressive strength, compared to conventional cast magnesium alloys, their performance can be influenced by factors such as sample size, casting defects, and alloying elements which can improve glass-forming ability and plasticity[103,104]. Tuning the properties makes such materials ideal for temporary implant devices, such as bone fixation screws or stents, to gradually dissolve in the body, eliminating the need for secondary surgeries to remove them. Engineering of the Mg-BMGs to degrade at controlled rates and matching the healing process of tissues remains challenging. Thus, fine-tuning the characteristics of these materials as scaffolds and ensuring long-term clinical use requires further research and optimization. This section

Table 1. Various fabrication methods and critical size of different Mg-based BMGs

Mg-based BMGs composition	Fabrication method	Critical diameter	Post-production condition	Ref.
Mg-Zn-Ca	Induction furnace under an inert atmosphere, cast in copper mold	5 mm rod	Fully amorphous phase	[92]
Mg-Zn-Ca-Sr	Copper mold casting	4-6 mm rod	Fully amorphous phase after 5hr of milling	[93]
Mg-Ca-Zn	Induction furnace under an inert atmosphere	3-4 mm rod	Mixture of crystalline and amorphous phase	[94]
Mg-Cu-Ag-Er	Copper mold casting	8-10 mm rod	Fully amorphous phase	[95]
Mg-Y-Cu-Ag-Pd	Water quenching	12 mm rod	Fully amorphous phase	[96]
Mg-Ni-Nd	Chill-block melt-spinning	1 mm ribbons	Fully amorphous phase	[97]
Mg-Cu-Ni-Ag-Zn-Y-Gd	Copper mold casting method	14 mm ribbons	Fully amorphous phase	[98]
Mg-Cu-Y-Zn	Induction furnace under an inert atmosphere	3 mm rod	Fully amorphous phase	[85]
Mg-Cu-Ni-Gd	Copper mold casting	25-50 mm rod	Fully amorphous phase	[102]

BMGs: Bulk metallic glasses.

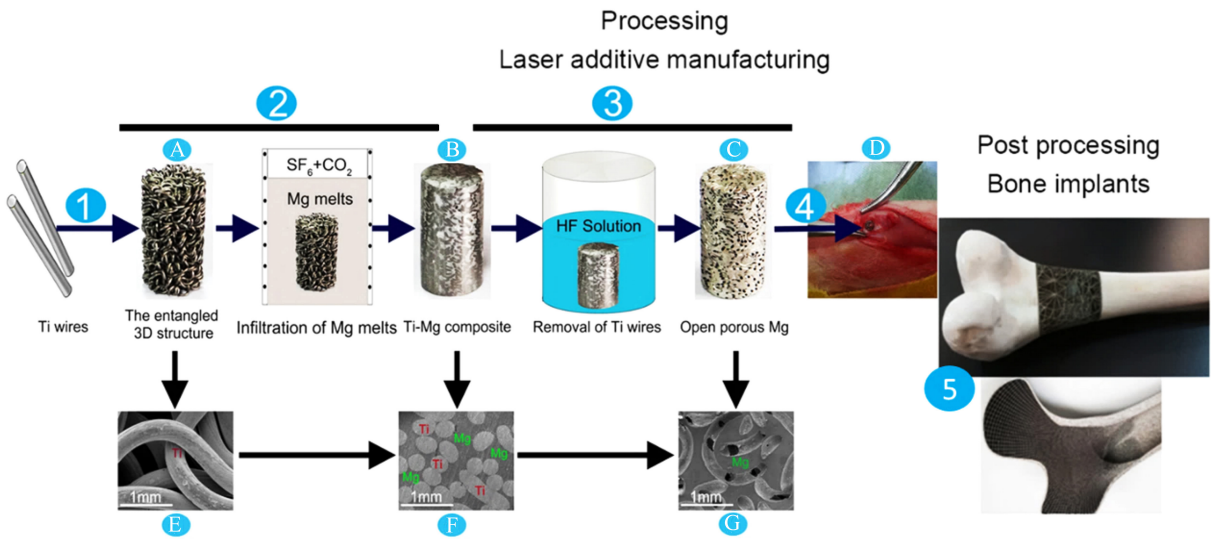

Figure 4. Step 1: the 3D entangled titanium wire material (A and E) was prepared with Ti wires. Step 2: the Ti-Mg composite (B and F) was prepared with high-purity Mg melts. Step 3: Ti wires were removed by HF solution and an open-porous magnesium scaffold (C and G) was successfully manufactured. Step4:open-porous magnesium scaffolds were implanted into the lateral epicondyle of rabbits (D). Image reproduced from ref.[82] licensed under a Creative Commons Attribution 3.0 unported license, Copyright © 2016, Meng-qi Cheng.

systematically analyses the requisite attributes of Mg-MGs, such as biocompatibility, biodegradability, mechanical properties, and other attributes, that make them excellent for stimulating tissue regeneration and scaffolding.

Biocompatibility: Mg is an essential element for human health. Mg-BMGs exhibit excellent biocompatibility, minimizing the risk of adverse tissue reactions. Due to the intrinsic biocompatibility, metallic glass of Mg attracts significant interest in the biomedical field[105,106]. It has garnered considerable

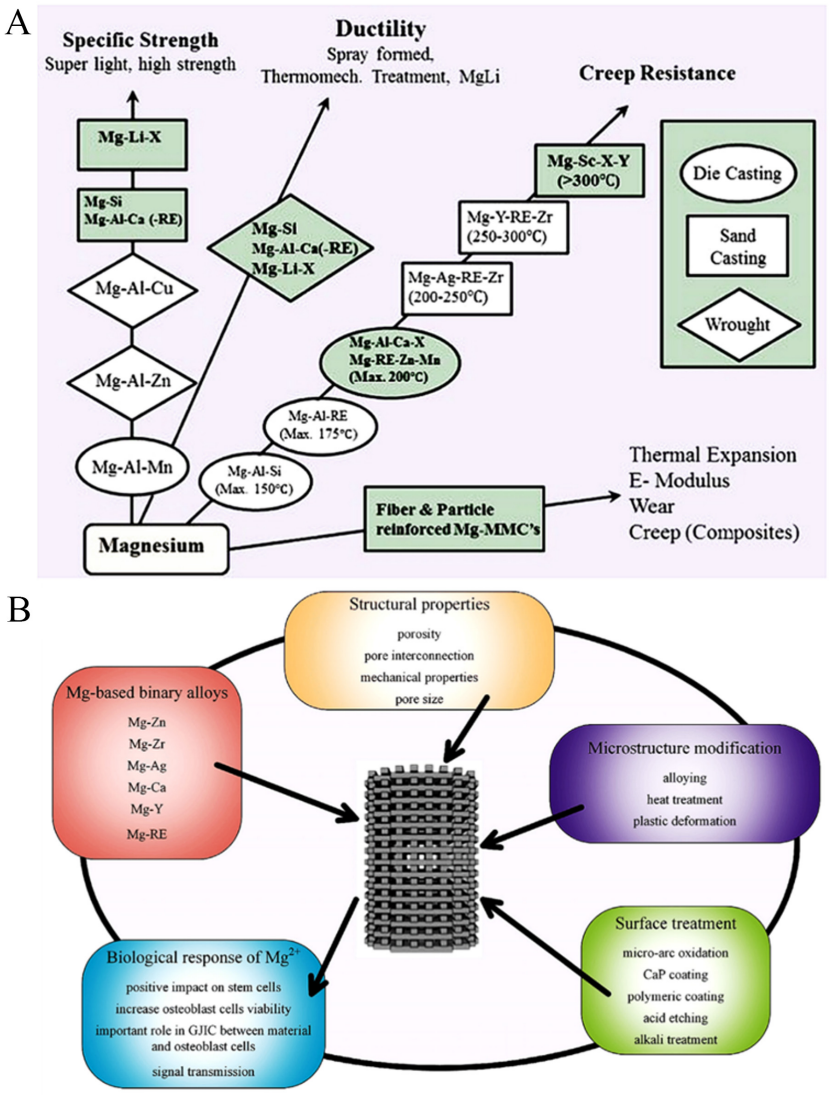

Figure 5. (A) Directions of metallic glass matrix/alloy development; (B) Type of alloys, microstructure modifications, surface treatments, and biological effects of Mg-based scaffolds. The figure is licensed under CC-BY 4.0 and reproduced from ref.[88] with permission © 2022 by the authors. Licensee MDPI, Basel, Switzerland.

attention in the biomedical field, primarily because of magnesium's indispensable function in the human body, specifically with bone health[105,107,108]. *In-vivo* and *in-vitro* research on Mg-Zn-Ca BMGs resulted in good biocompatibility no toxicity to cells and minimal bio-destruction[109].

Biodegradability: Unlike permanent implants, Mg-based scaffolds degrade over time, allowing the diseased body part to regrow in its place[110,111]. Magnesium implants degrade slowly in dry air but relatively quickly in biological fluids, with pure magnesium corroding at rates of 0.5 mm to 1 mm per month[112-119]. Magnesium alloys, such as AZ91D, WE43, and AM60, exhibit slower degradation rates, approximately 0.1 mm to 0.5 mm per month due to their alloying elements such as aluminium, Zn, and rare earth elements, which enhance corrosion resistance[120-122]. However, the bio-incompatible nature of the alloying components limited their scaffold use. Most research on creating biodegradable magnesium alloys for use as biomaterials has focused on crystalline alloys[25]. However, Mg-MGs for stimulating tissue regeneration and scaffolding

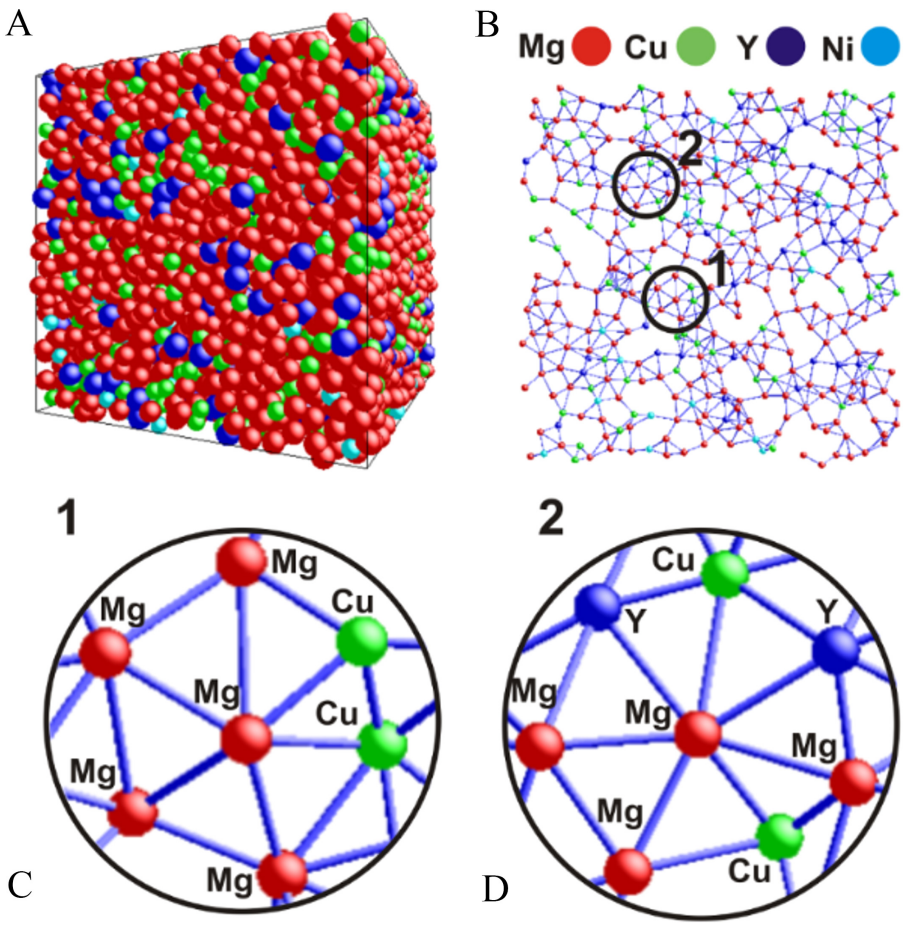

Figure 6. Schematic illustration of the Mg-based BMGs ($Mg_{65}Cu_{20}Y_{10}Ni_5$) developed using the reverse Monte Carlo modeling shows (A) simulation box; (B) elemental distribution; and (C and D) short-range-order (SRO) region formation because of clustering. The figure is licensed under CC-BY 4.0 and reproduced from ref.[101] © 2017 Babilas *et al.*; licensee Beilstein-Institute.

are gaining much interest. The degradation of the materials releases Mg^{2+} which are beneficial for the body as they are involved in various enzyme functions[123]. This eliminates the need for a second surgery to remove the implant as it gradually dissolves into the body providing stronger bones, good metabolism energy and nutrients for overall health and well-being[124-126]. However, rapid degradation of Mg-based implants can lead to toxicity and other negative biological reactions, so it is important to design the material with controllable degradation rates[117-121].

Mechanical Properties: Mg-BMGs possess mechanical properties comparable to bone that reduce the risk of stress shielding, a complication observed with stiffer implant materials[127]. Most research on the creation of biodegradable magnesium alloys for use as biomaterials has focused on crystalline alloys[25]. The amorphous biodegradable magnesium structure provides superior mechanical properties: low density, high strength and elasticity, which are crucial for biomedical applications with respect to the regulation of the degradation rate and stress shielding[128-130].

The composition of this biocompatible Mg-BMG can be adjusted to achieve desired degradation rates and mechanical properties[131]. The degradation rate of Mg-BMGs is controllable through compositional changes and surface treatments, allowing for gradual scaffold dissolution that aligns with tissue regeneration

timelines[132,133]. Porosity and pore structure can be finely tuned to enhance cell infiltration and vascularization, crucial for effective tissue integration[133-135]. Surface properties, including chemistry and wettability, can be modified to promote better cell adhesion and bioactivity[136,137]. Additionally, scaffolds can be functionalized with bioactive agents such as growth factors or antibiotics to support specific healing processes and reduce infection risks[120,121,138,139]. Overall, these tailorable properties enable Mg-BMG scaffolds to be engineered for optimal performance across a range of medical applications, from bone regeneration to wound healing and cardiovascular implants.

Figure 7 shows an anticipated 10-year progression and demand for magnesium based on their history[83,140]. Researchers have explored various Mg-based alloy scaffolds created using laser-based additive manufacturing techniques. Li *et al.*[141] examined WE43 Mg alloy scaffolds produced via LPBF, finding that increasing the strut diameter to 800 μm enhanced the elastic modulus from 0.2 GPa to 0.8 GPa. They also found that plasma electrolytic oxidation treatments reduced the corrosion rate to approximately 0.1 mm/year and achieved favorable biocompatibility. Wu *et al.*[142] fabricated ZK60 Mg alloy scaffolds using SLM, leading to a refined grain size of 7.3 μm compared to 56.4 μm in cast ZK60 and increased hardness and improved corrosion resistance.

In another set of studies, researchers investigated Mg-based composites created through laser additive manufacturing. Yang *et al.*[143] developed bioglass-reinforced Mg-based composites that showed a refined and homogenized structure, an enhanced corrosion rate, and good biocompatibility. Yao *et al.*[144] used SLM to produce binary and ternary Mg alloys, improving microhardness and corrosion resistance. Xu *et al.*[145] enhanced the biodegradation resistance of ZK30 + Cu alloys through grain refinement, which also imparted antibacterial properties due to the copper content. Yin *et al.*[146] studied ZK30/bioactive glass composites, concluding that the addition of bioactive glass improved corrosion resistance, microhardness, and biocompatibility. Shuai *et al.*[147] created an antibacterial ZK60-Cu(x) alloy, finding that increasing the Cu content boosted antibacterial properties while maintaining good cytocompatibility. In recent years, advancements have been made in producing large quantities of metallic glasses. A key strategy for creating BMGs involves selecting elements with significant differences in atomic size. This complex atomic structure hinders crystallization during cooling, allowing for the formation of thicker, amorphous materials. BMGs come in a diverse range of chemical compositions, offering the potential to tailor their mechanical, magnetic, chemical, and biological properties for specific applications[52].

Applications of Mg-based BMG

Table 2 describes several critical design criteria that metallic implants must meet to be suitable for biomedical applications, especially cardiovascular, orthopedic, and dental applications.

Magnesium alloys are considered for load-bearing implant devices such as plates, screws, and pins for bone fracture repair, as their elastic modulus is closer to natural bone compared to other metals used for implants[148,149]. Firstly, the corrosion rate and associated hydrogen evolution must be carefully controlled, with a degradation target value typically less than 10 μL/cm^2/day to avoid complications[150]. The penetration rate of the corrosion process should also be limited to less than 20 μm/year to maintain the mechanical integrity of the implant over the required service life[151]. Additionally, the biodegradation products released during the corrosion process must be biocompatible and not elicit adverse biological responses.

The mechanical properties of the biodegradable metal, such as strength, ductility, and fatigue resistance, need to be tailored to match the specific requirements of the target application, whether for load-bearing orthopedic devices or flexible cardiovascular stents[152,153]. Surface modifications further enhance the

Table 2. Design criteria for biodegradable metallic implant devices in cardiovascular and orthopedic applications achievable by new BMGs according to Ashby map

Criteria	Orthopedic internal fixation device	Cardiovascular stent	Ref.
Mechanical properties	Tensile strength > 300 MPa Yield strength > 230 MPa Elongation to failure > 15%-18% Elastic modulus approx. to that of cortical bone (10-20 GPa)	Tensile strength > 300 MPa Yield strength > 200 MPa Elongation to failure > 15%-18%	[127, 130,152, 153]
Biocompatibility	Non-inflammatory, non-toxic, hypoallergenic. No particle retention or harmful release. Promotes osteoclast and osteoblast attachment. Prevent fibrous encapsulation	Non-toxic hypoallergenic. No retention of particles or harmful release. Avoid smooth muscle cell attachment and promote endothelial cell attachment	[154]
Corrosion behavior	Hydrogen evolution < 10 μL/cm^2/day Screws and plates (0.2-0.5 mm year^{-1})	Hydrogen evolution < 10 μL/cm^2/day Penetration rate < 20 μm year^{-1}	[131,150]
Mechanical integrity and resorption	Osteotomy staples < 3 months Full absorption 1-2 years Screws and Plates < 6 months	Mechanical integrity (UTS) 3-6 months Full absorption 1-2 years	[151,155]

BMGs: Bulk metallic glasses.

Figure 7. Increasing the capacity and demand for magnesium. This image is reproduced from ref.[140]

corrosion resistance, biocompatibility, and osseointegration of the implant[154]. Meeting these multifaceted design criteria is crucial to developing safe and effective biodegradable metallic implants for use in the human body.

Mg-alloys possess light weight, strength, biodegradability, and biocompatibility, making them excellent interfaces for orthopedic implants as they minimize stress shielding and associated effects[155,156]. However, the rapid degradation and hydrogen gas evolution of Mg-based implants in the physiological environment is a major obstacle, leading to rapid loss of mechanical integrity and potential adverse effects such as local gas cavities, alkalization, and Mg^{2+} enrichment[157-159]. By-products such as Mg^{2+}, hydrogen gas (H_2), and hydroxide ions (OH^-), can disrupt the surrounding microenvironment[80]. Excessive Mg^{2+} release may cause local ion overload, pH shifts, and cytotoxicity, while hydrogen gas accumulation can form cavities that hinder tissue integration[160]. These effects can impair cellular activity, bone regeneration, and scaffold biocompatibility. Strategies such as surface coatings, pH-buffering materials, and alloying with elements such as Ca and Zn are being explored to control the corrosion rate and reduce toxicity[11,161,162]. The low corrosion resistance of Mg alloys is also related to heavy metal contamination and the formation of galvanic couples[163]. The position of Mg-BMGs on the Ashby map [Figure 3B] highlights their balance of strength, toughness, and low density, making them suitable for biomedical and lightweight structural applications[164]. However, their fracture toughness is generally lower than some crystalline metals, which can limit their use in more demanding structural applications[80,165,166]. Corrosion-induced defects, such as pitting and stress corrosion cracking, compromise the load-bearing capability of the scaffold, particularly under physiological stress[167,168]. Optimized scaffold designs with hierarchical porosity, mechanical reinforcement, and corrosion-resistant alloys are essential to improve structural stability and prolong functional performance during the critical healing period[151].

There are also technical barriers and challenges in adopting Mg-based scaffolds, such as improved manufacturing methods, high cost, and a better understanding of their performance[169]. To address these issues, the design of new metallic glass composites and surface modification of magnesium and its alloys with biocompatible nanostructured thin film protective coatings and treatments help slow degradation and

improve their hemocompatibility and cytocompatibility[170-172]. Fabricating the material as a porous scaffold facilitates cell growth, and using Mg-based metallic glass as a thin film coating on permanent implants can improve tissue regeneration and growth. Alternatively, a protective thin film coating from biodegradable materials on an Mg-based scaffold can improve its corrosion resistance.

MG-BASED THIN FILM METALLIC GLASSES

TFMGs are a separate category of metallic glasses with a much smaller scale (micrometers or nanometres) and present controllable properties compared to bulk materials, making them a promising candidate for tuneable biodegradable implants[43]. Metallurgical modification including microstructure and composition optimization through alloying and thin film processes can be used to control Mg degradation with respect to its specific application[156,173]. Mg-based TFMGs avail improved surface bioactivity, greater tissue integration, and regulated degradation rates[174-176], thereby controlling the hydrogen gas evolution[177,178]. The surface of conventional implants can be modified with Mg-based TFMG coating to enhance tissue regrowth[156] through the biodegradability of the thin film. TFMG can be fabricated with techniques such as sol-gel, dip coating, chemical vapor deposition (CVD), Physical Vapor Deposition (PVD), and pulsed laser deposition (PLD)[179].

The PVD-sputter system [Figure 7] is a robust and flexible technique for TFMG fabrication. It involves a vacuum deposition where the material is transferred from a solid state to a vapor or atomic state before depositing it onto a substrate. Sputtering is an effective and cost-efficient PVD method for depositing thin films[180]. It is a flexible and high-throughput deposition process that can produce high-quality thin films[181]. Sputtering is scalable and can be used for large-area depositions, making it cost-effective for industrial production[182,183]. The deposition rate in sputtering can be easily controlled and optimized for high efficiency with a wide range of material options, including metals, alloys, and compounds, allowing for the fabrication of diverse thin film structures[184,185,186]. Thin films deposited by sputtering can help reduce costs and miniaturize devices, providing effective protection and functionalization of materials, and making them useful for various applications[187,188].

PVD co-sputtering excels in thin film fabrication due to its versatility and precision. It allows simultaneous sputtering of multiple targets, enabling the deposition of complex multicomponent films [Figure 8] including metallic and polymorphic metallic glasses from a wide range of materials[44,189,190]. This technique provides fine control over film composition, thickness, and uniformity, ensuring high-quality, defect-free films with excellent adhesion[44]. Co-sputtering is efficient and scalable, suitable for large-scale production, and adaptable to various temperatures and integration with other processes. The method operates in a vacuum, minimizing contamination, and generating minimal waste, offering both environmental and economic benefits[191].

Table 3 shows a comparison between Mg-based implant scaffolds and those scaffolds coated with TFMGs. From Table 3, we can see the role of the thin film in improving the attributes and performance of the scaffolds. TFMG coatings improve the degradability and microstructure of Mg-based implant surfaces by hindering the subcutaneous gas pockets during the healing period[192,193]. The amorphous nature of the metallic glasses offers better resistance to localized corrosion and stress corrosion cracking, which are common issues in biomedical environments.

Table 4 shows Mg-based thin films including metallic glasses with improved corrosion resistance and other properties compared to pure metal[194-196]. One of the promising scaffolds with great biocompatibility and less toxicity to tissue cells is Mg-Zn-Ca metallic glass. The addition of Ca forms fine Mg_2Ca precipitates,

Table 3. Comparison of Magnesium-based BMG scaffolds and TFMG coated scaffolds[43]

Aspect	Magnesium-based scaffolds	TFMG-coated Magnesium-based scaffolds
Material	Pure magnesium is biomaterial and biodegradable	Material selection of the TFMG composition is challenging (e.g., MgZnCa, MgZnZr, Mg-Zr-Ca-Sr-Sn, *etc.*)
Corrosion resistance	Scaffold corrodes relatively quickly in physiological environments	Improved corrosion resistance of scaffold due to the protective TFMG layer
Mechanical properties	Good for load-bearing scaffolds but properties affected by rapid degradation	Thin film coating maintained the base metal's mechanical properties for the scaffold's life
Cell growth	May require additional surface treatments before the implantation of scaffolds for optimal cell growth	Generally engineered surface morphology during coating suitable for cell adhesion and growth
Degradation control	Design of the degradation rate to match tissue healing is challenging	The TFMG coating maintains its protective qualities throughout the degradation process
Toxicity	The rapid degradation of Mg can lead to localized high pH environments affecting surrounding tissues	The slow degradation rate of the TFMG coating reduces tissue reaction and release of toxic elements
Manufacturing complexity	It is a relatively straightforward manufacturing process but may require post-processing	Increased complexity due to the need for precise control over the coating surface morphology and process to ensure film uniformity and adherence with the base metal

TFMG: Thin film metallic glasses; BMG: bulk metallic glasses.

Table 4. Potential and current density of Mg-based thin films deduced from polarization curves

Sample	E_{corr} (V)	*Icorr* (A/cm^2)	Electrolyte	Ref.
Pure Mg	-1.886	86.06×10^{-6}	SBF	[199]
Mg-Nd-Zn-Zr	-1.659	1.718×10^{-6}	SBF	[200]
Mg-Zn-Ca	-0.07	0.26×10^{-6}	NaCl	[201]
Mg-Zr-O	1.43	0.71×10^{-6}	K_2ZrF_6	[202]
Mg-Zr-Ca	-1.89	0.51×10^{-6}	SBF	[203]
Mg-Zr-Ca-Sr-Sn	-1.78	0.04×10^{-6}	SBF	[203]
Mg-Zn-Yb-Ag	-1186	5.43×10^{-6}	SBF	[204]
Mg-Cu-Gd-Ag	-1.06	0.54×10^{-6}	NaCl	[205]

SBF: Simulated body fluid

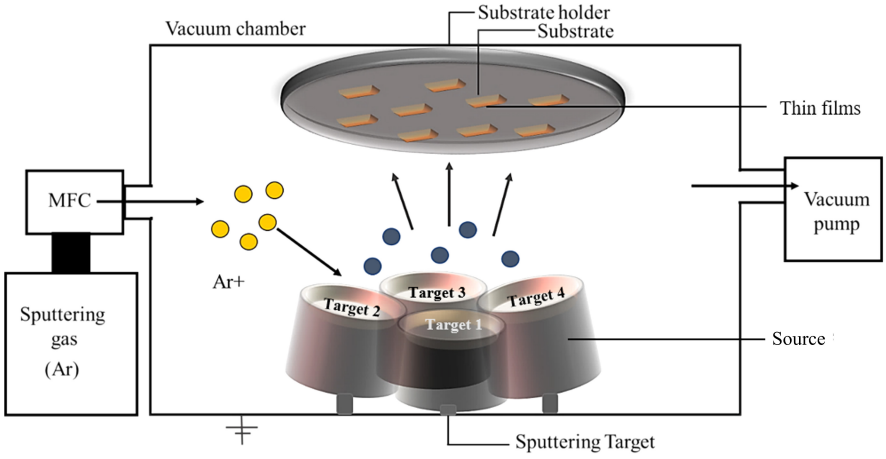

Figure 8. Schematic illustration of the magnetron sputtering process revealing the bombardment of the substrate surface with sputtered atoms from the target to create a thin film. The figure is licensed under CC-BY 4.0 and reproduced from ref.[44] © 2023 C.R. Onyeagba,M. Valashani,H. Wang,C. Brown,P. Yarlagadda,T. Tesfamichael. Published by Elsevier B.V.

enhancing the mechanical properties through precipitation hardening[197,198]. Moreover, as shown in Table 4 the corrosion resistance of Mg (Ecorr -1.886, Icorr 86.06 × 10^{-6})[199] improved significantly after alloying with other elements (Nd, Zn, Zr, Ca, Sr, Sn, Yb, Ag, Cu, Gd, Ag)[200-205], for example, Mg-Zn-Ca with higher Ecorr -0.07 and lower Icorr 0.26 × 10^{-6})[201].

The inclusion of Zn in Mg improves tensile and creep strength, reduces grain size, and enhances the alloy's castability[198]. Zn is solubilized up to 2 wt% in Mg at room temperature in the equilibrium state. When the Ca and Zn concentrations are optimized in the Mg-Ca-Zn system, they exhibit a favorable combination of degradation mitigation/control, mechanical properties, and biocompatibility. Figure 9 shows the corrosion characteristics of Mg TFMGs (Mg-Zn-Ca) with different Zn compositions studied by Li *et al.*[206]. Mg-Zn-Ca TFMGs exhibited better corrosion resistance than pure crystalline Mg, and when the Zn content exceeded 50%, the films showed passivation behavior for $Mg_{49.3}Ca_{8.5}Zn_{42.2}$ [Figure 9].

Polarization studies were conducted in simulated body fluid (SBF), NaCl, K_2ZrF_6 solution electrolyte at room temperature and show that a thin film coating can improve the corrosion/degradability of Mg-BMG composite[179,201,202].

Figure 10 shows the scanning electron microscopy (SEM) before and after the corrosion tests of the Mg-based samples reported by Olugbade *et al.*[201]. The result shows improved electrochemical properties of Mg-Zn-Ca hard coating with different thicknesses (4 mm and 6 mm). The uncoated sample [Figure 10A] exhibited rougher surfaces and retention of corrosion products after testing [Figure 10Ai-Aii], depicting more corrosion attacks while the coated samples [Figure 10B] and [Figure 10C] are observed with smoother surfaces before and after testing [Figure 10Bi-Bii and Ci-Cii], depicting lesser corrosion attacks. The polarization curves obtained for the uncoated and coated samples within the potential range of -100 to +120 mV (Ag/AgCl) are shown in Figure 10D where the 6 mm coated sample performed better than the rest[201]. Mg-based TFMGs can viably decrease the degradation rate of Mg-based materials, making them suitable for bioimplants[179]. Moreover, TFMGs reduce the rate of hydrogen gas formation which affects their mechanical performance and biological compatibility by slowing down the degradation process, addressing one of the critical challenges in Mg-based implants[132], thereby increasing the alloy application prospects.

The interplay between coating thickness, process parameters, and degradation rate is complex, and a systematic approach is required to understand and optimize the performance of Mg-based thin films for biomedical applications. Zhao *et al.*[207] provide a comprehensive review of the mechanisms, classification, modeling, and experimental testing of Mg corrosion in bio-applications. The coating thickness plays a crucial role in the degradation rate of Mg-based materials. Thinner coatings may be more effective in controlling the degradation rate, as Tong *et al.*[208] demonstrated that the corrosion rate of bulk Mg alloy samples accelerated with increasing layer thickness. The coating process parameters can significantly influence the microstructure, mechanical properties, and corrosion resistance of Mg-based thin films. Moreover, the layer thickness was found to influence the formation quality, microstructure, and mechanical properties of the Mg alloy samples[208]. The various coating techniques have been explored to control the degradation rate of Mg-based materials, including sol-gel TiO_2 coatings[209], biomimetic silk coatings[210], chemical conversion coatings such as MgF_2 and MgF_2-$MgPO_4$[211], and PVD coatings such as TiO_2/MgO[207]. Optimizing the coating composition, microstructure, and thickness can tailor the degradation rate. To illustrate, Kania *et al.*[209] showed that nano-porous titanate coatings can control the degradation rate of Mg implants.

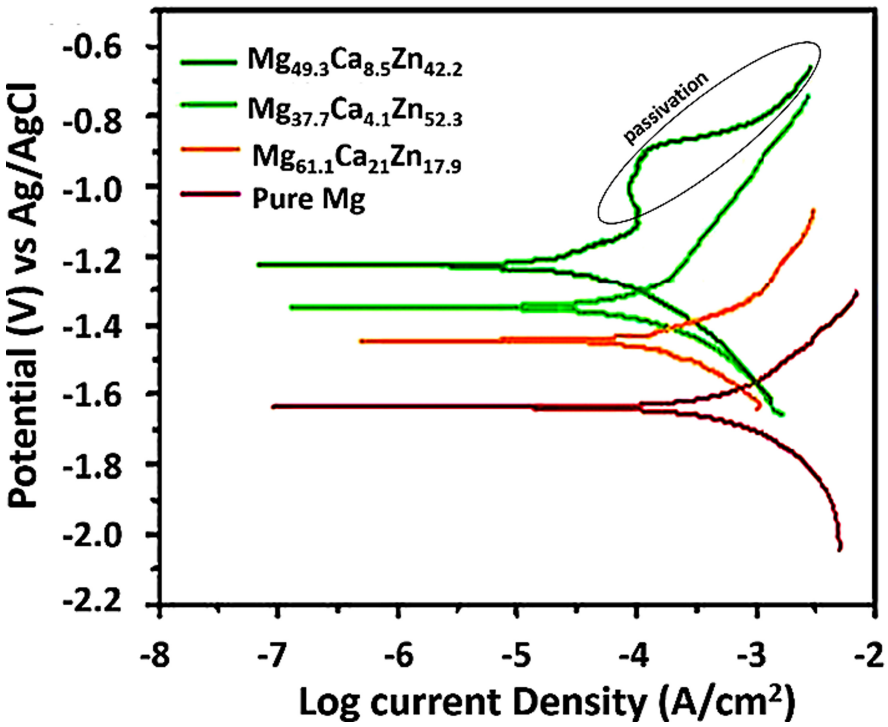

Figure 9. Tafel plot of Mg-Ca-Zn TFMG and pure Mg. reproduced with permission from reference[206] © Copyright Royal Society of Chemistry 2024. TFMGs: Thin film metallic glass.

COMPUTATIONAL MODELS FOR SIMULATION OF TISSUE GROWTH IN MG-BASED BMG SCAFFOLDS

The integration of Mg-BMGs into biomedical scaffolds presents a promising avenue for enhancing tissue regeneration and implant performance.

Mechano-driven models have successfully predicted variations in bone ingrowth distribution based on scaffold implantation sites, emphasizing the importance of the mechanobiological environment for scaffold-guided bone regeneration[212,213]. These computational approaches can be integrated into optimization frameworks to design scaffolds that maximize bone formation, with results guiding additive manufacturing parameters[214]. To fully capture the regenerative process, models must incorporate dynamic changes in the mechanobiological environment, achievable with biodegradable scaffolds[215].

Computational models are pivotal in understanding and predicting the complex interactions between Mg-BMG implants and biological tissues[216,217]. These models facilitate the optimization of scaffold design [Figure 11], assess the impact of material properties on tissue growth, and predict long-term implant behavior under physiological conditions[217-219]. This section delves into the various computational approaches employed to simulate tissue growth stimulated by Mg-BMG implant scaffolds, highlighting their methodologies, applications, and the challenges they address. Computational modeling in the context of tissue-implant interactions encompasses a range of techniques aimed at simulating biological processes and mechanical responses[220,221]. These models integrate biological, chemical, and mechanical factors to provide a holistic understanding of how tissues respond to implants. Specifically, for Mg-BMG scaffolds, models must account for the biodegradation of the material, the release of Mg^{2+}, mechanical stability, and the subsequent effects on cellular activities and tissue formation. Finite Element Analysis (FEA), Agent-based

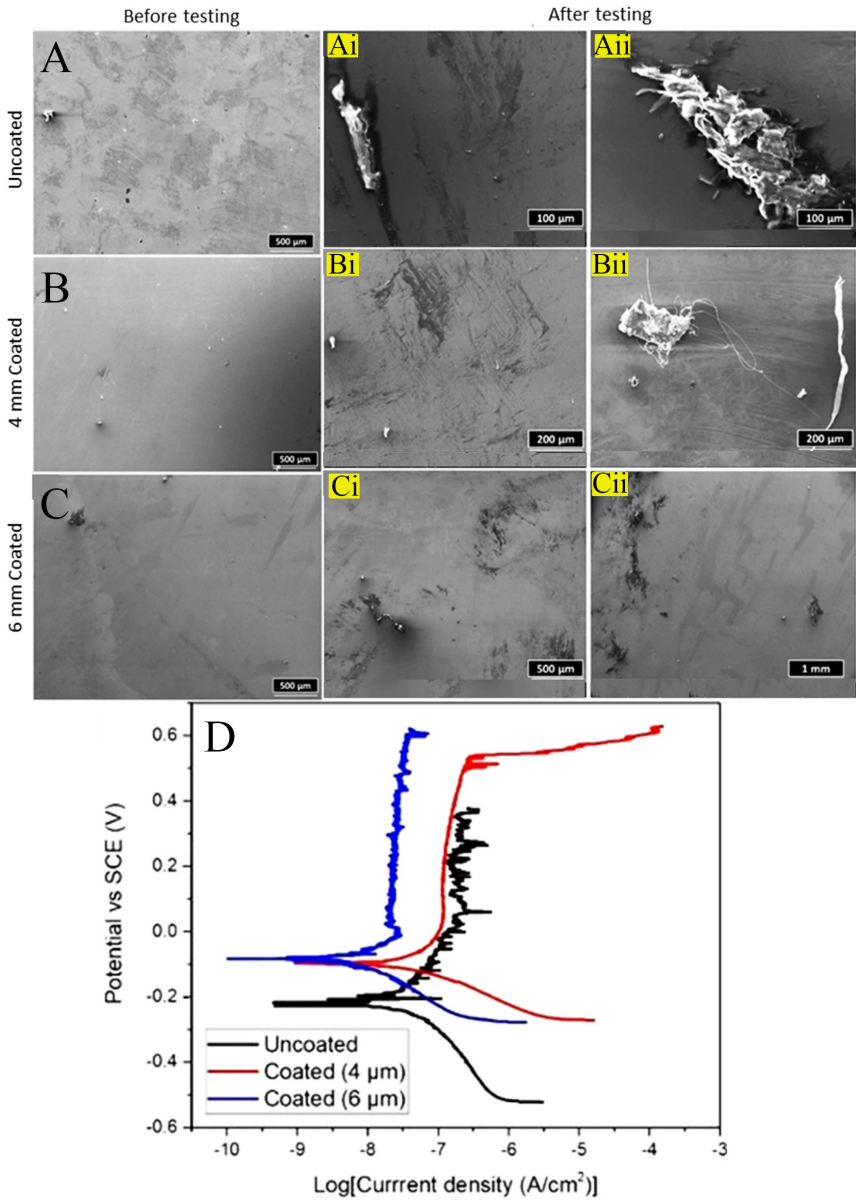

Figure 10. Scanning electron microscopic images for the uncoated and 4 and 6 mm Mg-Zn-Ca TFMG-coated Mg samples fabricated via magnetron sputtering process before and after polarization: (A) uncoated with (i) magnification by 600 × and (ii) magnification by 500 ×; (B) 4 mm coated with (i) magnification by 270 × and (ii) magnification by 290 ×; and (C) 6 mm coated with (i) magnification by 90 × and (ii) magnification by 50 × (D) Tafel plot of uncoated pure Mg and coated Mg with Mg-based TFMG. Reproduced with permission from reference[201]

modeling (ABM), Computational Fluid Dynamics (CFD), Molecular Dynamics (MD) simulations, Density Functional Theory (DFT), Phase Field Modeling, Corrosion Simulations, Multiscale Modeling, Machine Learning and Artificial Intelligence are commonly applied computational models for the understanding and optimization of scaffold design using biological, chemical, and material properties.

FEA

FEA is a widely used computational tool in biomedical engineering for assessing the mechanical behavior of implant scaffolds and predicting tissue responses[222,223]. In the context of Mg-BMG scaffolds, FEA models

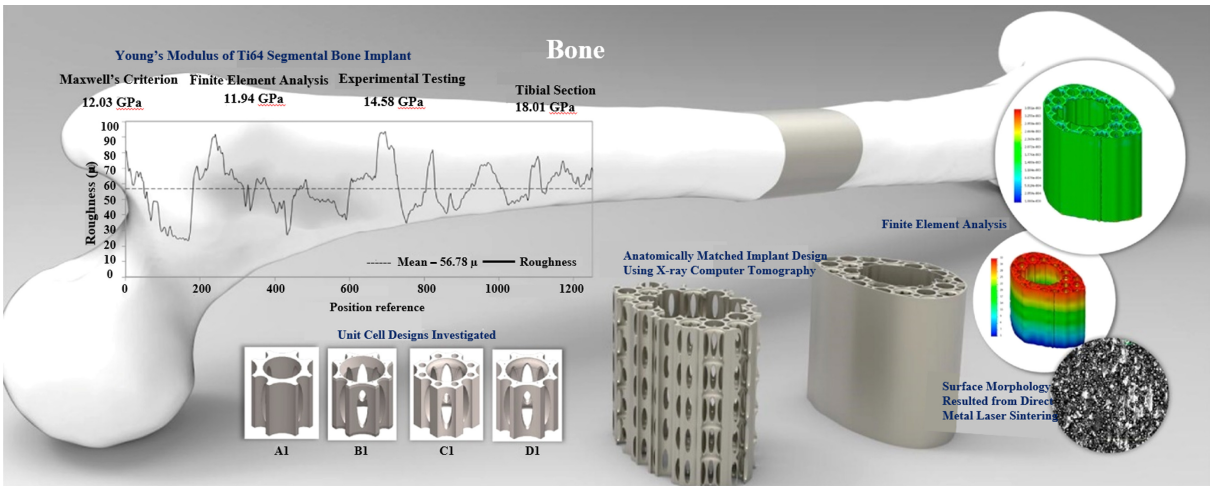

Figure 11. Computer-based methods, such as Finite Element Analysis (FEM)-based Bilinear Isotropic Stress-Strain (BISO) elastoplastic model prediction of scaffolds for tibial bone defect repair. Reproduced with permission from ref.[212], CC BY-NC-ND 4.0 © 2018 Elsevier Ltd.

can simulate the distribution of mechanical stresses within the scaffold and surrounding tissues under various loading conditions[224,225]. This is crucial for ensuring the scaffold provides adequate support without causing excessive stress that could impede tissue growth or lead to implant failure. FEA can incorporate the gradual degradation of Mg-BMGs due to corrosion. By modeling the reduction in scaffold mass and structural integrity over time, FEA helps predict how the scaffold's mechanical properties evolve, thereby influencing tissue regeneration dynamics[226].

Figure 12 compares the stress distribution in bone when using solid versus porous scaffolds [Figure 12A-B], highlighting the benefits of porous scaffolds in reducing stress shielding. The analysis reveals that stress transmission through bone is significantly higher (325 MPa) [Figure 12C-E] with a porous scaffold, while a solid scaffold reduces this to 76.204 MPa [Figure 12D-F], indicating a 76% reduction due to a modulus mismatch with the bone[227]. Porous scaffolds, however, offer a better modulus match, leading to a more even distribution of stress and promoting bone regeneration and stronger implant interfaces, thus reducing stress shielding and implant loosening. The study also notes the importance of considering manufacturing errors and surface roughness in FEA to predict scaffold performance, particularly in patient-specific applications accurately. FEA was used to select the unit cell and indicate the implant's performance, which was then validated through compression testing with an anatomical stiffness-matched design that may be suitable for segmental bone defect repair, with mitigated stress shielding[212].

The stress distribution in solid and porous magnesium scaffolds can have different impacts on BTE for segmental femur defects[227]. Solid magnesium scaffolds tend to exhibit higher stress concentrations at the scaffold-bone interface, which can lead to:

(1) Increased risk of scaffold failure, as high-stress concentrations can cause the scaffold to fracture or degrade prematurely, compromising the BTE process[228].

(2) Reduced bone regeneration, since high-stress concentrations can inhibit bone cell growth and differentiation, resulting in impaired bone regeneration and reduced integration with the scaffold[228,229].

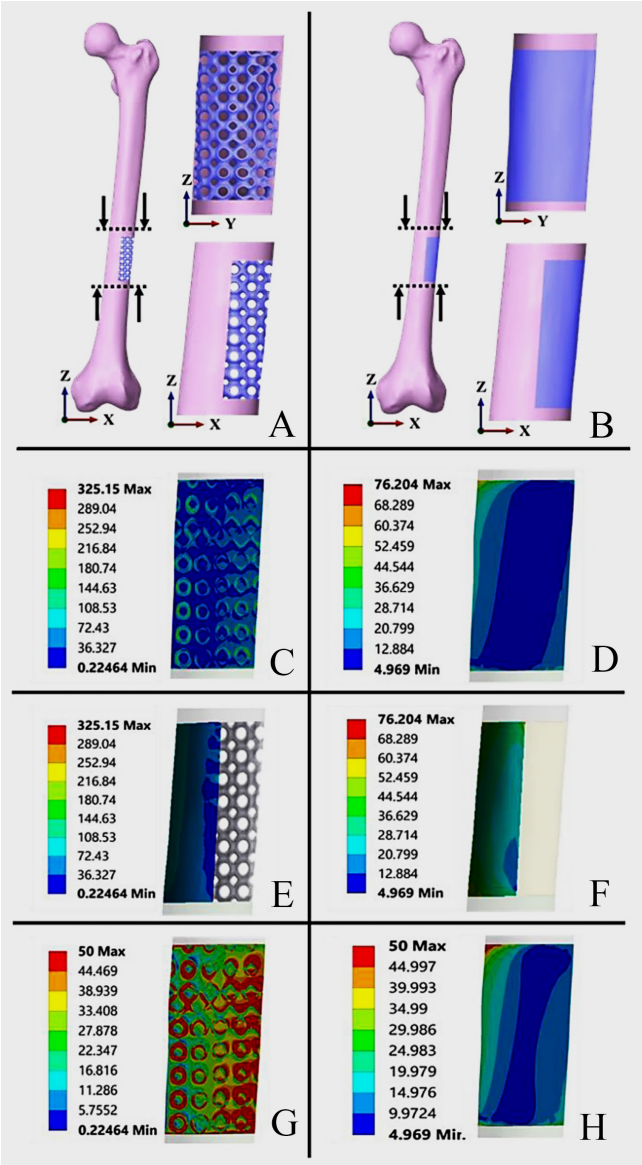

Figure 12. FEA of solid and porous scaffolds based on segmental femur defect for BTE and its related stress distributions (units in MPa): (A and B) Implantation of porous and solid scaffolds; (C and D) stress distribution contours on the bone; (E and F) von Mises stress contours of porous and solid scaffolds; (G and H) stress distribution contours for porous and solid scaffolds at 50 MPa. This figure is licensed under CC-BY 4.0 and reproduced from ref.[227] © 1996-2024 MDPI (Basel, Switzerland). FEA: Finite element analysis.

On the other hand, porous magnesium scaffolds tend to exhibit lower stress concentrations and more uniform stress distributions, which can lead to improved scaffold stability with lower stress concentrations that can reduce the risk of scaffold failure and improve its stability, allowing for more effective BTE[230,231]. They also enhance bone regeneration where the porous structure can provide a more favorable environment for bone cell growth and differentiation, leading to improved bone regeneration and integration with the scaffold[230,232]. However, the optimal porosity and pore size of the scaffold can vary depending on the specific BTE application and the desired mechanical and biological properties [Figure 12G-H][228,233]. Additionally, the degradation rate of the magnesium scaffold can also influence the BTE process, as it can affect the release of Mg^{2+} and the subsequent bone cell response making it more favorable for BTE applications[229,231].

Advanced FEA models integrate multiple physical phenomena, such as mechanical loading, chemical corrosion, and biological tissue growth[234-236]. These coupled simulations provide a more comprehensive understanding of the interplay between scaffold degradation and tissue development-a study by Liu *et al.*[237] utilized FEA to model the mechanical stability of Mg-based scaffolds during degradation. The model incorporated corrosion rates and assessed how the loss of material affected stress distribution, providing insights into scaffold design parameters that optimize mechanical support while facilitating tissue ingrowth.

Figure 13 illustrates a biomechanical analysis of a femur via FEA to study bone properties and structural behavior. The left panel depicts the Bone Mineral Density (BMD) distribution of a bone, with a color gradient indicating varying density levels crucial for simulating mechanical strength and stress distribution. The right panel shows a 3D femur model with specific regions marked, likely for evaluating stress concentration, fracture risk, or load response under physiological conditions. Such analyses are vital in orthopedic research, implant design, and understanding bone adaptation to mechanical loads[238].

Biomechanical performance design method of joint prosthesis for medical rehabilitation via Generative Structure Optimization (GSO). The method involves 3D reconstruction of hard bone and cartilage structures from heterogeneous medical images such as computed tomography (CT) and magnetic resonance imaging (MRI), followed by FEA to verify the reconstructed structure and multi-objective optimization to design the 3D printing parameters, including adaptive layer thickness, infill patterns, and infill trajectories[239]. The GSO approach covers various stages from personalized CT imaging to 3D reconstruction, finite element analysis, and structural parameter optimization. The physical experiment of additive manufacturing shows that the proposed method can improve the relative density, surface topography, and wear-resistance performance of the joint prosthesis, thereby enhancing its biomechanical performance in terms of kinematics and dynamics[239]. This method aims to promote high-end customization and improve the well-being of patients requiring prosthetic rehabilitation.

ABM

ABM simulates the interactions between cells, such as osteoblasts and osteoclasts, and the scaffold environment in BTE. It models the behavior of osteoblasts, osteoclasts, and other relevant cell types in response to the scaffold environment, including factors such as Mg^{2+} concentration, pH changes, and mechanical cues[240-242]. ABM allows for the simulation of spatial distributions and temporal evolution of cell populations around the implant, which is essential for understanding how cells migrate, adhere, and form new tissue structures in response to scaffold degradation[240,241]. A study employed ABM to investigate how varying Mg^{2+} concentrations from degrading Mg-BMG scaffolds affect osteoblast proliferation and bone matrix deposition, providing predictions on optimal degradation rates that balance scaffold support with favorable cellular responses[240]. ABM has also been used to study the complex interactions between different cell types and chemical components in the context of bone regeneration and mechanobiology[242-246]. Computational modeling and simulation of porous scaffolds, including Mg-based trabecular bone implants, is an important tool in BTE applications to restore and treat bone defects[247]. ABM is a powerful computational approach for simulating the complex interactions between cells and the scaffold environment in BTE, allowing researchers to predict optimal scaffold properties and cellular responses.

CFD

CFD is used to model the transport of fluids and solutes around and within the scaffold. CFD models can simulate the release of Mg^{2+} from the scaffold and their subsequent diffusion through surrounding tissues[248,249]. Understanding the concentration gradients of Mg^{2+} is crucial, as excessive concentrations can lead to cytotoxicity, while optimal levels can enhance bone regeneration. CFD helps in assessing how scaffold degradation influences the transport of nutrients and waste products, which are vital for cell

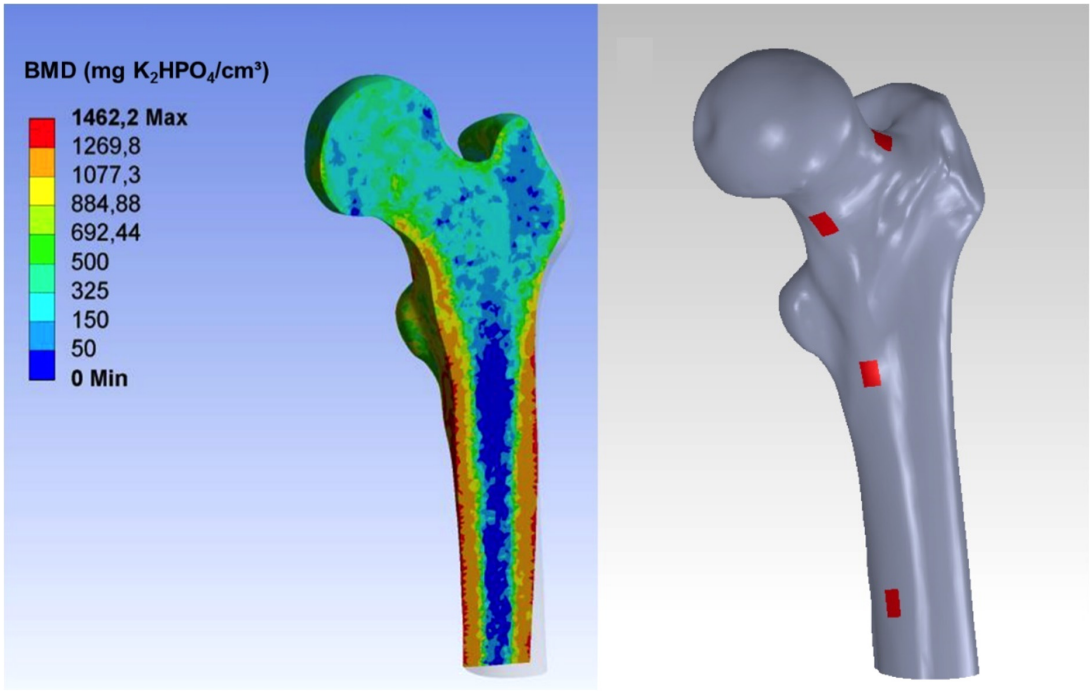

Figure 13. Representation of the bone mineral density distribution within the bone (left) and location of the string gauges at the femur specimen (right). This figure is licensed under CC-BY 4.0 Reproduced from ref.[238] © 2015 Liebl Hans.

survival and tissue health[250-252]. A recent study by Manescu *et al.*[253] utilized CFD to model the diffusion of Mg^{2+} from a degrading Mg-BMG scaffold within a bone defect. The results highlighted regions of potential Mg^{2+} accumulation and informed scaffold porosity designs that promote even ion distribution, thereby mitigating cytotoxic risks[253].

Multiscale modeling integrates processes occurring at different spatial and temporal scales, from molecular interactions to macroscopic tissue behavior. This approach is particularly beneficial for Mg-BMG scaffolds due to the complex interplay between material degradation and biological responses[254]. Models at the molecular scale can simulate the corrosion mechanisms of Mg-BMGs, including electrochemical reactions and ion release rates[46,255,256]. Cellular scale models focus on how individual cells respond to changes in their microenvironment, such as alterations in pH and ion concentration due to scaffold degradation[257,258]. Tissue and organ scale models assess the overall tissue regeneration, mechanical integration with the host bone, and long-term implant stability[254]. Researchers have developed a multiscale model that linked molecular corrosion processes of Mg-BMGs with cellular responses and tissue-level bone regeneration[259-262]. The model successfully predicted scaffold performance over 12 months, providing valuable insights for long-term implant viability[254].

MD simulations

MD simulations are invaluable for understanding the behavior of Mg-BMG scaffolds used in tissue growth applications. These simulations provide atomic-scale insights into key processes such as biodegradation, protein adsorption, and ion release[89,132,263]. MD models scaffold degradation in physiological environments, revealing the mechanisms of corrosion, ion diffusion, and by-product formation [e.g., $Mg(OH)_2$], which influence local pH and tissue compatibility[89,177]. They also simulate protein-surface interactions, helping optimize scaffold surfaces for better cell adhesion, while tracking ion release to predict its role in promoting osteogenesis and bone mineralization[89].

Additionally, MD predicts the mechanical integrity of scaffolds under physiological loads, ensuring their structural stability during tissue regeneration[264,265]. Immersion and electrochemical tests validate corrosion models, while surface characterization techniques such as AFM confirm protein adsorption prediction[135,177]. Compression and tensile tests ensure the accuracy of mechanical property simulations, and in vitro cell culture studies validate biological responses such as ion concentration effects on osteoblast activity[88,135]. Although MD is limited by scale and biological complexity, its integration with other methods such as finite element analysis and machine learning (ML) offers a path toward comprehensive scaffold design and optimization for biomedical applications[266].

DFT

DFT has been extensively used to study the electronic structure and atomic-scale properties of Mg-based metallic glass (BMG) scaffolds for tissue engineering applications. It provides critical insights into the biodegradation mechanisms, protein adsorption, ion release, and mechanical properties of these scaffolds, which are crucial for their performance in tissue engineering. Specifically, DFT models the surface interactions of Mg-BMG scaffolds with water and ions, allowing the prediction of corrosion rates and the effects of alloying elements such as Zn, Ca, and Y on corrosion resistance[267,268]. DFT also examines how proteins or amino acids bind to the scaffold surfaces, aiding in the optimization of biocompatibility[269,270]. Additionally, it simulates the dissolution of Mg^{2+}, which is critical for promoting osteogenesis and calculates the elastic constants of the scaffolds to predict their stiffness and load-bearing capacity[268,271]. The validation of DFT predictions is achieved through comparisons with experimental data, and the integration of DFT with larger-scale models, such as MD or finite element analysis, can provide multiscale insights[269,270]. Moving forward, the combination of DFT with ML and functionalized surface simulations will further enhance its potential in optimizing Mg-BMG scaffolds for tissue engineering applications[270].

Phase field modeling

Phase field modeling (PFM) is a powerful computational technique that can simulate the evolution of microstructures in Mg-MGs during various processes such as solidification, crystallization, and corrosion[272]. This approach is particularly valuable for investigating the glass-to-crystal transition, which affects the stability and degradation of metallic glasses in biological environments[132,263]. By simulating these microstructural changes, phase field modeling provides a deeper understanding of how Mg-MGs behave under various conditions relevant to their biomedical applications[132,263]. For instance, the model can determine the conditions that minimize crystallization and maintain the amorphous structure, which is critical for ensuring mechanical stability and corrosion resistance in biological environments[90,273]. The predictions from phase field modelling are validated through experimental techniques such as SEM and X-ray diffraction (XRD)[38,273]. These methods provide detailed information on the microstructure and crystallization behavior of Mg-MGs, allowing researchers to compare experimental observations with model predictions and ensure the reliability of phase-field modeling in guiding the design and processing of Mg-MGs for biomedical applications[38,273]. Phase field modeling is a valuable computational tool for studying the evolution of microstructures in Mg-MGs and optimizing their properties for biomedical applications, such as in the development of metallic glass-based biomedical scaffolds[90,273].

Corrosion simulations

The corrosion behavior of Mg-MGs is a key aspect when considering their use in biomedical applications, especially for bone scaffolds that are designed to degrade over time. Computational methods such as MD, DFT, and electrochemical simulations are used to predict how Mg-MGs will behave in physiological environments[38,263,274]. To illustrate, electrochemical simulations can predict the corrosion rate of Mg-MGs in SBFs, considering factors such as pH, ion concentration, and temperature[267,274,275]. These computational predictions can then be validated by comparing them with experimental results obtained from immersion

tests or electrochemical measurements (e.g., potentiodynamic polarization tests or electrochemical impedance spectroscopy) to assess the accuracy of the computational models[258,274,276].

Mg-MGs generally exhibit better corrosion resistance compared to their crystalline counterparts, due to their amorphous structure[263,276]. This improved corrosion resistance is a key advantage for their use in biomedical applications, as it can help ensure the mechanical stability and degradation behavior of Mg-based metallic glass-based implants or scaffolds in biological environments[90,267,275].

ML and artificial intelligence

The integration of ML and artificial intelligence (AI) in computational modeling offers enhanced predictive capabilities and optimization of scaffold designs[277,278]. ML algorithms can analyze large datasets from experimental and simulation studies to identify patterns and predict outcomes related to tissue growth and scaffold performance. AI-driven optimization techniques can determine the optimal combination of scaffold properties (e.g., porosity and alloy composition) that maximize tissue regeneration while minimizing adverse effects[279,280]. Recent studies applied machine-learning models to predict bone regeneration outcomes based on various scaffold design parameters and degradation rates[281,282]. The model facilitated the identification of design strategies that enhance tissue integration and mechanical stability.

Figure 14 summarizes a framework of a Machine Learning Regression model that can predict the performance of nanofibrous scaffolds for skin tissue engineering.

The framework comprises two key stages: Model Preparation and Model Deployment. In the preparation stage, transformer loading estimation involves data preprocessing, ML model fitting, and evaluation to identify the most relevant smart meters (SMs) and the optimal regression algorithm[283]. Regression techniques, including random forest, decision tree, AdaBoost, and gradient boosting, can be applied to datasets featuring four numerical parameters-water contact angle, fiber diameter, Young's modulus, and pore diameter-to predict cell number[278]. In the deployment stage, data from the selected SMs is input into the trained and tuned model to estimate transformer loading and identify congestion, with performance results[283]. Among the techniques, AdaBoost has been reported to demonstrate the highest accuracy, with a mean absolute percentage error of 1.41% and a coefficient of determination (R^2) of 0.999, indicating a strong correlation between predicted and actual values[278]. These results offer a valuable tool for estimating cell generation based on scaffold physicochemical properties, aiding physicians in the design and optimization of scaffolds for skin tissue engineering.

ML can help identify new alloy compositions with optimized mechanical properties and biodegradation rates for use in biomedical scaffolds. ML can be used to analyze the relationship between alloy composition, processing conditions, and the mechanical and degradation properties of Mg-MGs[283]. Computational models have been used to design new Mg-based MG compositions, such as Mg-Zn-Ca and Mg-Zn-Ag, predicting their amorphous forming ability, mechanical properties, and corrosion behavior[284-286]. These models, combined with experimental validation through techniques such as magnetron sputtering and additive manufacturing, accelerate the development of Mg-based MGs for biomedical scaffolds by optimizing their properties for biocompatibility, biodegradability, and mechanical performance[284,285].

Limitations of existing computational models

Key limitations of existing computational models for simulating tissue growth in Mg-BMG scaffolds are:

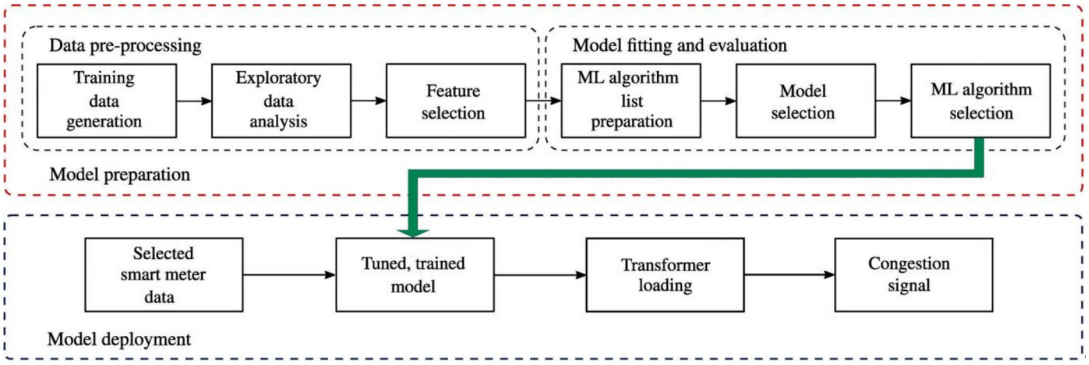

Figure 14. Development of Machine Learning Regression Models to understand the problem and the data to select the most appropriate analytic technique for predicting performance. The figure is licensed under CC-BY 4.0. Reproduced from ref.[283] © Copyright (2024) The Institution of Engineering and Technology.

• Limitations in accurately simulating the complex interactions between different tissue types (e.g., cartilage and bone) and the Mg-based biomaterial scaffold[240].

• Challenges in accurately modeling the parameters involved in tissue healing and cell seeding procedures in perfusion bioreactors to achieve optimal bone tissue growth[287].

• Difficulties in accurately predicting the *in vivo* service life and degradation rate of Mg-based biomedical devices, which should match the rate of bone/tissue growth[236].

• Limitations in accurately modeling the antibacterial and cell response properties of Mg-based scaffolds coated with materials such as alginate and magnesium oxide[288].

• Challenges in computationally modeling the 3D printing and fabrication processes of Mg-based metallic glass scaffolds, including issues related to fluid dynamics and structural integrity[68,289].

• Limitations in fully recreating the tissue heterogeneity and accurately reflecting human pharmacokinetics in computational models[290].

• Difficulties in computationally modeling the disordered structure and reduced mechanical properties of metallic glasses, which can lead to potential tissue damage[291].

• Exploring computational approaches to model the disordered structure and mechanical properties of metallic glasses to minimize the risk of tissue damage[291].

FUTURE DIRECTIONS AND CHALLENGES TO PROMOTE MG-BASED METALLIC GLASS SCAFFOLDS

To advance Mg-based metallic glass scaffolds in biomedical applications, future focus should entail optimization of porosity, pore structure, and interconnectivity for better cell infiltration and tissue growth. Incorporating bioactive agents such as growth factors enhances tissue regenerative properties and evaluates long-term performance and integration with host tissues. For wound healing, developing scaffolds or coatings with antimicrobial properties and exploring the combined effects of Mg^{2+} released are practical future challenges. In cardiovascular applications, it is critical to design scaffolds with improved mechanical

properties and biocompatibility for long-term performance. The overall challenges in biomedical scaffolds include balancing mechanical properties, biodegradability, biocompatibility, and manufacturability addressing potential cytotoxicity and materials stability. Continued research is essential to address these challenges and fully exploit the potential of Mg-based metallic glass scaffolds.

Scaling up the production of TFMG-coated implants from laboratory to commercial scale remains challenging. Substrate effects and contamination can be a problem in the production process of TFMG-coated implants[292,293]. Optimized and improved preparation processes, matrix systems, and structural modelings should be developed to address the challenges in commercialized TFMG production. More long-term studies are needed to fully understand the performance and potential side effects of Mg-based TFMG coatings in clinical settings[294]. Accessing and testing the biocompatibility of TFMG coatings *in vivo* remains a challenge. Advancements in computational methodologies and interdisciplinary collaboration are poised to overcome existing challenges and enhance the utility of models in Mg-BMG scaffold development. Incorporating genomic, proteomic, and metabolomic data can provide deeper insights into cellular responses and improve model accuracy. Developing models that can update in real time with experimental data will enable dynamic simulations that better reflect ongoing biological processes. Refining multiscale models to seamlessly integrate molecular, cellular, and tissue-level processes will provide more holistic predictions of scaffold performance. Leveraging big data and advanced AI techniques can enhance model training, reduce uncertainty, and enable the discovery of novel scaffold design principles. Tailoring scaffold designs based on patient-specific data through computational models can lead to personalized implants that optimize tissue regeneration and implant integration.

Successful translation of Mg-based scaffold implants to clinical practice will require continued research to address and control corrosion, biocompatibility and biodegradation. Surface modification of Mg-MGs as discussed here is promising and needs more input such as bioactive surface modification of the material for efficient biomedical applications. The economic viability of surface modification of Mg-based scaffolds is critical as the high cost of TFMG materials and deposition techniques will deter the clinical translation of these scaffolds; thus, optimized composition and process are paramount to make them commercially viable products for widespread use.

While computational models offer significant advantages in understanding and optimizing Mg-BMG scaffolds, several challenges persist. Accurately capturing the multifaceted interactions between scaffold degradation, ion release, and biological responses remains a formidable task[295]. Simplifications and assumptions in models can limit their predictive accuracy, and many model parameters, such as corrosion rates and cellular response thresholds, are derived from experimental data that may exhibit variability, which can affect the reliability of model predictions[295]. This uncertainty can affect the reliability of model predictions. High-fidelity models, especially multiscale and coupled simulations, demand substantial computational power and time, which can be a barrier to their widespread application. Combining data from various sources (e.g., mechanical testing, biological assays, imaging) into cohesive models is challenging but necessary for comprehensive simulations[296,297].

Moreover, potential solutions to address the limitations of existing computational models include:

• Developing more sophisticated multiscale models that can capture the complex interactions between different tissue types and the Mg-based scaffold.

• Improving computational models to better simulate the parameters involved in tissue healing and cell seeding in bioreactors.

• Enhancing computational models to accurately predict the *in vivo* degradation and absorption of Mg-based devices.

• Incorporating advanced computational techniques, such as finite element analysis and computational fluid dynamics, to model the 3D printing and fabrication processes of Mg-based metallic glass scaffolds.

• Advancing computational models to better reflect tissue heterogeneity and human pharmacokinetics.

CONCLUSION

The development of Mg-based metallic glass scaffolds represents a promising frontier in biomedical applications, offering significant advancements in tissue engineering, wound healing, and cardiovascular implants. By optimizing scaffold characteristics such as pore structure, porosity, and interconnectivity, and incorporating bioactive agents, researchers can enhance cell infiltration, proliferation, and tissue regeneration. The Mg^{2+} release with other therapeutic agents can further improve wound healing outcomes. For cardiovascular applications, the focus on improving mechanical properties, corrosion resistance, and biocompatibility, alongside evaluating long-term *in vivo* performance, is crucial. However, challenges remain, including balancing mechanical strength with degradation rates, developing scalable manufacturing techniques, ensuring long-term stability, and addressing potential cytotoxicity. Addressing these challenges through surface modification with TFMGs and continued research and innovation will be essential to realizing the full potential of Mg-based metallic glass scaffolds and advancing their application in various medical fields. Moreover, computational models provide a powerful tool for simulating tissue growth around Mg-based implant scaffolds. By combining different approaches such as finite element analysis for mechanical interactions, agent-based models for cellular dynamics, and diffusion-reaction models for nutrient supply researchers can gain valuable insights into the behavior of these biodegradable materials *in vivo*. These models enhance our understanding of how Mg-based scaffolds perform and offer the potential to optimize scaffold design and predict long-term outcomes, ultimately improving their application in regenerative medicine and permanent implants.

Future research on Mg-MGs (Mg-BMGs) for biomedical scaffolds should focus on enhancing glass-forming ability, optimizing biodegradability and corrosion control, and tailoring mechanical properties to match natural bone. Advanced computational modeling (e.g., MD, DFT, and FEA) can accelerate alloy design and predict degradation behavior, while bioactive surface modifications and 3D printing can improve biocompatibility and scaffold customization. Long-term *in-vivo* studies are needed to evaluate clinical performance, and sustainable production methods can facilitate cost-effective manufacturing. These advancements aim to establish Mg-BMGs as a leading material for biodegradable, bioactive scaffolds in regenerative medicine.

Moreover, their ability to degrade naturally aligns with tissue healing, reducing the need for surgical removal. Realizing these applications requires interdisciplinary collaboration among materials scientists, engineers, computational modelers, and clinicians to optimize alloy properties, predict performance, and design effective bioactive surfaces. Such collaboration is key to advancing Mg-BMGs as a revolutionary material in regenerative medicine.

Fabrication techniques must overcome the low glass-forming ability of Mg alloys to produce large, defect-free amorphous structures suitable for medical applications. Cost control remains a hurdle, as current manufacturing processes and alloying elements can be expensive, limiting scalability. Additionally, ensuring long-term biocompatibility is crucial, requiring detailed studies to address potential cytotoxicity, inflammatory responses, and the controlled release of degradation products. Tackling these challenges demands innovation in processing methods, alloy design, and interdisciplinary collaboration to unlock the full potential of Mg-BMGs in biomedical applications.

DECLARATIONS

Authors' contributions

Manuscript writing, data analysis, methodology, investigation, formal analysis, visualization, data curation, and conceptualization: Onyeagba, C. R.

Validation, methodology, funding acquisition, conceptualization. Manuscript review and editing: Tesfamichael, T.

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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