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Bioceramic Coatings on Magnesium Alloys

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Abstract Magnesium (Mg)-based materials have attracted interest as for its use as a biodegradable metallic implant material. However, one of the main challenges in the use of magnesium and its alloys for biomedical applications is its poor corrosion resistance in physiological environments. Surface coatings to control biodegradation of magnesium offer the flexibility to be easily modified for specific applications and have significantly less investment. Hydroxyapatite-based bioceramic coatings on metallic implants have been favorably viewed because of its excellent bioactivity and biocompatibility and the fact that the composition of hydroxyapatite is similar to that of natural bone. In this manuscript, we discuss the context of magnesium as biodegradable metal, current challenges on use of magnesium-based materials for biomedical applications. Focusing specifically on orthopedic applications, we elaborate on calcium phosphate-based bioceramic coatings. Recent work on hydroxyapatite coatings on magnesium, fabrication process and the biological response of the coatings are highlighted.

Keywords Magnesium alloy · Biodegradable metals · Bioceramic coatings · Hydroxyapatite

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1 Introduction

Metallic biomaterials are widely used in load-bearing biomedical applications because they possess a good combination of high mechanical properties and fracture toughness [1, 2]. Metallic implants have found various applications and have been used in cardiovascular, orthopedics, dental and other biomedical device applications [3–6]. Clinical concerns related to permanent metallic implants include toxic metal ions released by corrosion or mechanical wear which could cause harmful effects on bone and tissue response such as reducing biocompatibility and causing tissue loss [7–10]. Also for orthopedic devices the stress-shielding effect is induced due to a higher elastic modulus of metal in-service in comparison with natural bone. These phenomena result in unbalanced load supported by the metal instead of surrounding bone contributing to accelerated reabsorption of bone in vicinity of the implant leading to implant failure [10]. Biodegradable polymers and resorbable ceramics have widely been developed as a substitution to permanent metallic implants; however, limitations exist in their mechanical properties which have restricted their use and they are thus not suitable for load-bearing applications as encountered in orthopedic devices [11–17]. There is therefore a need for development of alternatives to polymeric and ceramic biodegradable implant materials leading to an increased interest in biodegradable metallic materials. Biodegradable metals have an advantage over existing biodegradable materials such as polymers, ceramics or bioactive glasses in load-bearing applications that require a higher tensile strength and a Young's modulus [18–21].

Some current metals that are being explored for biodegradable metal applications include magnesium, iron and zinc with magnesium being the most studied of

these metals [22–26]. For orthopedic bone contact applications, iron does not seem to be an excellent alternative for bone fixation because of the prominent deviation of its properties from those of natural bone [27, 28]. Mg and Mg alloys offer several advantages such as (1) when alloyed, magnesium has the highest strength-to-weight ratio of all the structural metals [29, 30], (2) the high specific strength of magnesium is greater than ceramic biomaterials such as hydroxyapatite, while the elastic modulus and compressive yield strength of magnesium alloys are closer to those of natural bone [31, 32]. These properties are important since matching the mechanical strength and elastic modulus can alleviate the stress-shielding effects between the bone and the implant [31], (3) magnesium is an essential mineral for human metabolism, and it is the fourth most abundant cation in the human body with approximately half of the total content stored in bone tissue [33, 34]. Hence, magnesium has been explored as a possible biodegradable material for orthopedic applications. The biomedical implant based on magnesium and its alloys offers a new alternative for orthopedic bone fixation applications. The physiological concentration of magnesium ions discharged by corrosion and wear leads to sustaining and/or alleviating the storage of Mg in bone, while the excess magnesium ions are excreted through the kidney [33]. Furthermore, through the corrosion process of magnesium–calcium alloys, the protective layer which consists of the precipitated calcium phosphates (the result of calcium from the alloy interacting the surrounding physiological environment) and corrosion products like magnesium hydroxides and magnesium oxides formed on the surface of the implants enhances the osteoconductivity in vivo [35] [10, 36, 37]. However, the fast evolution of hydrogen gas produced by rapid corrosion of magnesium in the physiological condition results in subcutaneous formation of gas cavities which could cause localized toxicity and tissue loss [19]. Thus, substantial research in controlling biodegradation via coatings of magnesium and enhancing its bone integration has been carried out in the last decade [19]. This manuscript aims to review magnesium-based materials and bioceramic coatings on magnesium for its bone contact-related applications.

2 Magnesium and Its Alloys

Experiments utilizing pure Mg metal as a potential biodegradable implants date back to 1878 when Edward Huse successfully used pure Mg wire ligature to stop hemorrhaging blood vessels [38]. Magnesium is one of the alkaline earth metals and possesses excellent electrical and thermal conductivity and has a high chemical reactivity [39]. Mg is the lightest of all structural metals which are used in the automobile and building industry [40], and it has been explored extensively in the automotive and aerospace industry for weight reduction in the vehicles. Pure magnesium possesses a hexagonal closed-packed (h.c.p.) crystal structure. Representative mechanical properties of magnesium are illustrated in Table 1 [41]. To enhance and tailor the properties of Mg for specific applications, different elements such as zinc, aluminum, cerium, zirconium and yttrium are alloyed in commercial magnesium alloys [21]. A large quantity of commercial magnesium alloys contains aluminum. Mg–Al–Zn alloys are known as AZ series alloys such as AZ31, AZ61 and AZ91, which are commonly used in industrial applications [42]. These alloys contain aluminum and zinc as the major alloying elements which contain 1% zinc and 3, 6 and 9%, respectively, of aluminum. Increasing the % content of aluminum results in improved strength and hardness [43]. In addition, AJ62 and AM60 are other available Mg alloys, which contain approximately 6.0 wt% Al, and are also widely used in some engineering applications [42]. Most of the current magnesium alloys available were not developed for its use as a biodegradable implant material [30]. The development of new alloys requires substantial investment [44], and an alloy developed for one particular application such as cardiovascular stent may not be suitable for other applications such as orthopedic fracture management device. Phase diagrams are used to determine intermetallic miscibility and help in development of new alloys. For example, a representative phase diagram of binary Mg–ZN alloy is shown schematically in Fig. 1 [45]. Based on Fig. 1, the maximum solid solubility of Zn in Mg is approximately 0.25 mol fraction) at 615 °K. As temperature falls below 594 °K, the intermetallic particles can spontaneously precipitate from the magnesium matrix and the eutectic phase forms [45].

3 Corrosion Behavior of Magnesium

One of the main challenges in the use of magnesium and its alloys for biomedical applications is its poor corrosion resistance in physiological environments [46, 47]. Unfortunately, as pure magnesium corrodes too quickly in physiological pH (7.4–7.6), it loses mechanical integrity before the tissue has sufficiently healed and produces hydrogen gas at a rate that is too fast to be dealt with by the

Table 1 Mechanical properties of metallic biomaterials as compared to bone and synthetic hydroxyapatite [21]

	Mg alloy	Pure iron	Co–Cr alloy	Ti alloy	Stainless steel	Natural bone	Synthetic hydroxyapatite
Tensile strength (MPa)	250	180–210	951–1220	760	586	42–109	–
Yield strength (MPa)	162	120–150	448–648	485	331	77–114	–
Modulus of elasticity (GPa)	44	211.4	210	110	190	3–20	77–117
Density	1.84	7.87	9.2	4.5	7.9	1.8–2.1	3.1

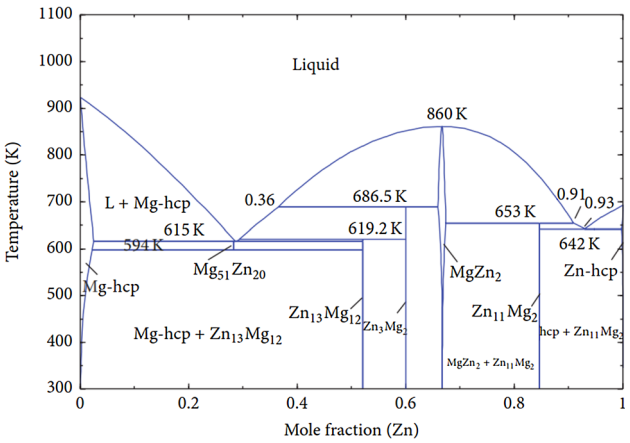

Fig. 1 Mg–Zn phase diagram. Adapted from ref [45]. Open access article distributed under the Creative Commons Attribution License

host tissue [48, 49]. The corrosion products generally observed are magnesium hydroxide and hydrogen. The complete corrosion equation of magnesium in aqueous solution is elaborated as follows.

$$\mathrm{Mg\,(s) + 2\,H_2O\,(aq) \leftrightarrow Mg\,(OH)_2(s) + H_2(g)}$$

This reaction can be separated in three partial equations

$$\mathrm{Mg\,(s) \leftrightarrow Mg^{2+}(aq) + 2\,e^-\,(anodic\ reaction)}$$

$$\mathrm{2\,H_2O\,(aq) + 2\,e^- \leftrightarrow H_2(g) + 2\,OH^-(aq)\,(cathodic\ reaction)}$$

$$\mathrm{Mg_2 + (aq) + 2\,OH^-(aq) \leftrightarrow Mg(OH)_2(s)\,(product\ formation)}$$

The Mg (OH) 2 film obtained on the surface on Mg could temporarily retard the corrosion to some extent, and it, however, becomes susceptible to breakdown when the concentration of aggressive chloride ions increases above 30 mmol/l and eventually transform the Mg(OH)2 into $MgCl_2$ with high solubility [49]. A large number of researchers have investigated the degradation mechanism of different magnesium alloys on the bone–implant interface and its effect on the surrounding bone [50–52]. It has been reported that a basic pH could improve the stable protective hydroxide layer on the Mg alloys implants surface, while a low acidic pH could enhance the corrosion of magnesium [49]. Hence, the corrosion of magnesium alloy implants increases under low pH which is critical due to acidosis after the surgery resulting in low pH. Comparing degradation process occurring on the bone–magnesium alloy (AZ31, AZ91, LAE 442, WE43) interface with currently degradable polymers (SR-PLA96), it was seen that a better osteoblast activity was observed in the neighborhood of degradable Mg implants relative to a degradable polymer implant [47]. Researchers hypothesized that magnesium ions positively influenced the synthesis of biological nucleic acids and the translation of protein for the extracellular matrix production such as collagen type 1 was noticed due to the presence of high Mg ion concentration [53].

4 Bioceramic Coatings

Magnesium alloys are excessively susceptible to the physiological pH (7.4–7.6) and environments comprising of high concentration of chloride ions [54]. Negative outcomes of rapid magnesium degradation include large amount of hydrogen release and relatively loss of mechanical integrity before the tissue has sufficiently healed [55]. New alloy development could be viewed a possible solution to prolong degradation of magnesium. However, most of the current magnesium alloys available were not developed for its use as a biodegradable implant material and they still lack the required biodegradation behavior [30]. The development of new alloys requires substantial investment and will have to undergo significant testing to obtain regulatory approvals [44]. Also a new alloy developed for a particular application may not necessarily meet the application requirements for a different application. For example, a biodegradable staple may have a different degradation requirement as compared to a bone screw although both of these devices may be classified under devices for fracture fixation. Surface coatings to control biodegradation of magnesium offer the flexibility to be easily modified for specific applications and have significantly less investment [21, 56]. Representative coating

materials that have been used on magnesium include metals [57], ceramics [58], organic materials [46], polymers [1] and composites [59]. Several reports have indicated that corrosion resistance of pure magnesium may be controlled by appropriate surface modification processes [21, 60]. These include electrochemical plating, conversion coating, anodizing, hydride coatings and vapor-phase processes [61]. In recent years, bioceramic coatings based on calcium phosphate materials have gained significant attention due to their chemical similarity to calcified tissue (teeth and bones) [62]. Calcium phosphate-based materials have been in medicine and dentistry for over thirty years

Table 2 Calcium phosphate-based bioceramics. Adapted from Ref. [63] Copyright Springer

Ion ratio Ca: P	Calcium orthophosphate [2, 4]	Chemical formula	Solubility, $-\log(K_s)$, at temperature		pH range for stability in water solutions at temperature 25 °C
			25 °C	37 °C	
	Monocalcium phosphate:				
0.5	Monohydrate (MCPM)	$Ca(H_2PO_4)_2{\cdot}H_2O$	1.14	No found	0.0–2.0
0.5	Anhydride (MCPA)	$Ca(H_2PO_4)_2$	1.14	Same	Unstable[a]
	Dicalcium phosphate:				
1.0	Dehydrate (DCPD), mineral brushite	$CaHPO_4{\cdot}2H_2O$	6.59	6.63	2.0–6.0
1.0	Anhydride (DCPA), mineral monetite	$CaHPO_4$	6.90	7.02	Unstable[a]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$	96.6	95.9	5.5–7.0
1.5	α-Tricalcium phosphate (α-TCP)	α-$Ca_3(PO_4)_2$	25.5	25.5	No data[b]
1.5	β-Tricalcium phosphate (β-TCP)	β-$Ca_3(PO_4)_2$	28.9	29.5	Same[b]
1.2–2.2	Amorphous calcium phosphate (ACP)	$Ca_xH_y(PO_4)_z{\cdot}nH_2O$ (n = 3.0–4.5, 15–20% H_2O)	No data[c]		~5–12[d]
1.5–1.67	Calcium-deficient hydroxyapatite (CDHA)	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$	~85.1	~85.1	6.5–9.5
1.67	Hydroxyapatite (HA or HAP)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	117.2	9.5–12
1.67	Fluorapatite (FA or FAP)	$Ca_{10}(PO_4)_6F_2$	120.0	119.2	7–12
2.0	Tetracalcium phosphate (TTKP or tetcp), mineral hilgenstokite	$Ca_4(PO_4)_2O$	38–44	37–42	No data[b]

[a] Stable at temperatures above 100 °C

[b] Data on calcium orthophosphates cannot be obtained by crystallization from water solutions

[c] Not amenable to accurate measurements. The comparative solubility in an acidic buffer decreases in the following order: ACP > _-TCP > _-TCP > CDHA > HA > FA

[d] Always metastable

Table 3 Comparison of different fabrication methods for depositing hydroxyapatite coatings. Adapted from Ref. [81] Copyright Wiley

Method	Characteristics
Dip coating/sintering	The high-temperature sintering (1000°) can degrade mechanical properties of metal implants and lead to low bond strength and impurity of HA
Electrophoretic deposition	Same problems as dip coating/sintering, also leads to nonuniform thickness of HA
Immersion coating	The high-temperature process (1500°) results in a coating of non-HA compound mixture and very poor adherence
Hot isostatic pressing	The encapsulating materials react to the HA coating. Difficult to seal borders on implants with complex shapes
Solution deposition	A low-temperature precipitation process resulting in a pure, highly crystalline, firmly adherent HA coating. Good for coating evenly for porous and beaded surfaces. Maximum thickness of 20 m limits its use as a primary mode of fixation
Sputter coating	Too slow and has a low deposition rate. Ca/P ratio of the coating is higher than that of synthetic HA if RF magnetron sputtering is used
Thermal spraying	High deposition rate. Good chemical and microstructure control, biocorrosion resistance, and substrate fatigue resistance of the coating. Can obtain various coating thickness and be used for complex shapes

for applications comprising dental applications, alveolar ridge augmentation, periodontal treatment, orthopedics, maxillofacial surgery and otolaryngology [62]. There are various distinct calcium phosphate compounds such as dicalcium phosphate, octacalcium phosphate and hydroxyapatite. Table 2 details the various representative calcium phosphate materials available [63]. Of all the calcium phosphate ceramics, hydroxyapatite (HA) has gained the most attention. The unit cell of hydroxyapatite comprises a closely packed hexagonal unit cell containing Ca^{2+}, PO_4^{3-} and OH^- groups [64, 65]. The six $PO4^{3-}$ groups have tetrahedral symmetry and are accountable for the stability of the apatite structure [64, 65]. Alterations in the properties of Ca^- hydroxyapatite can occur as a result of ionic substitutions of Ca^{2+}, PO_4^{3-} and OH^- groups within the apatite structure. The alterations in properties include lattice parameters, morphology and solubility; however, they can take place without significantly altering the hexagonal symmetry [64, 65].

4.1 Hydroxyapatite Coatings

Hydroxyapatite (HA) has been widely regarded as a biomedical material because of its excellent bioactivity and biocompatibility, with the composition of HA similar to that of natural bone [66]. Hydroxyapatite has a great biocompatibility but poor fracture toughness and bending strength [67] and hence not suitable for applications requiring significant load bearing. For a higher strength and fatigue resistance, HA is applied as a coating strategy on a stronger substrate, such as a metal. HA can be used for medical applications such as bone repair, augmentation, substitution and coatings of metals used as dental and orthopedic implants [68, 69]. Bone is a specialized connective tissue composed of an extracellular matrix that is partly organic and partly inorganic, embedded within which are osteocytes (bone cells) [70]; 35% constitutes the organic part of bone, and of that 95% is made up of mainly type I collagen fibers and the rest consists of non-collagen proteins of bone, such as osteocalcin, osteonectin and osteopontin, plasma proteins, lipids and glycosaminoglycans [71]. The inorganic mineral component of bone makes up 6% of the bone matrix and consists of crystalline salts that are mainly calcium and phosphate based. A well-known form of crystalline salt that is a constituent of bone is hydroxyapatite $[(Ca)_{10}(PO4)_6(OH)_2]$ [72–74].

Biological HA, such as that present in teeth and bones, comprises many impurities. Biological HA is typically calcium deficient and carbon substituted [75]. The minor elements connected with biological apatites are magnesium (Mg^{2+}), carbonate (CO_3^{2-}), sodium (Na^+), chloride (Cl^-), potassium (K^+), fluoride (F^-) and acid phosphate (HPO_4). Trace elements include strontium (Sr^{2+}), barium (Ba^{2+}) and lead (Pb^{2+}). The biocompatibility of synthetic HA is not only due to its similar composition to that of biological HA but also experimentally validated by results from in vivo implantation which showed no local systemic toxicity, no inflammation and no foreign response [51, 75, 76]. The biocompatibility of the HA surface permits the cell attachment and cell proliferation of a variety of cell types; these include macrophages,

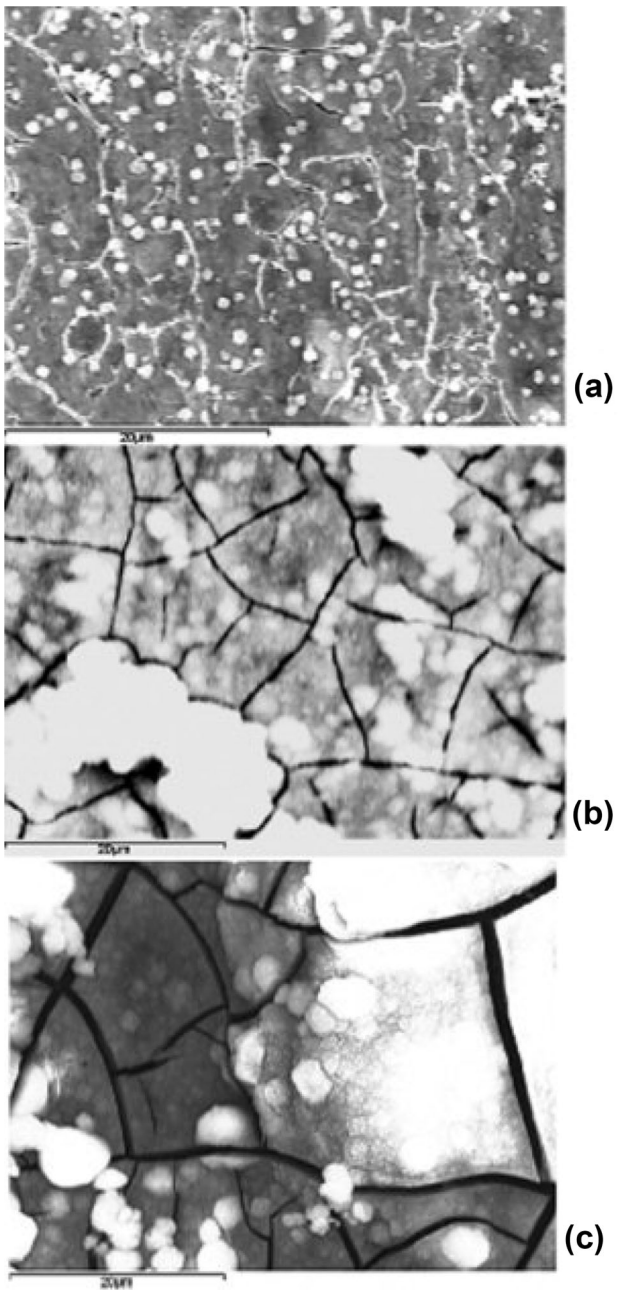

Fig. 2 Scanning electron microscopy images of calcium phosphate coatings on magnesium AZ31 substrates at various deposition times. **a** 3 h, **b** 24 h, **c** 96 h. Adapted from Ref. [83] copyright Wiley

fibroblasts, osteoclasts, osteoblasts and periodontal ligament cells [77]. Dissolution of HA crystals from the surface of the ceramic takes place as a result of cellular interactions. This process is carried out in two ways: (a) intracellular—phagocytosis and (b) extracellular—producing an acid environment for dissolution. Bone cells that attach and proliferate on HA and on bone surfaces do not appear to distinguish between the two surfaces, indicating that the surface chemistry of HA and bone exhibits similarities. The ability of dense HA to boost the attachment and proliferation of matrix producing bone cells on a CO_3– apatite surface is indicative of a material which provides the right surface chemistry and surface charges and in many respects is considered osteoconductive in nature [77].

For the production of hydroxyapatite coatings, a wide number of coating strategies have been used [78–80]. Table 3 lists the different fabrication methods for forming hydroxyapatite coatings using different methods [81]. The thermal spray process consists of passing the deposition material, in this case HA powder, and melting it over a heating zone, after which the molten materials are propelled toward the substrate. The history of thermal spraying process dates back to late 1800s. Coatings have been applied on tin and lead to metal surfaces through flame spraying to increase corrosion resistance performance [82]. Presently, there are a wide range of thermal spray processes [82].

4.2 Bioceramic Coatings on Magnesium

Bioceramic coatings including hydroxyapatite coatings have gained significant attention recently as a strategy to control the biodegradation of magnesium while simultaneous attempting to enhance bone intergradation due to the osteoconductive properties of hydroxyapatite. Munro and coworkers [83] demonstrated the deposition of hydroxyapatite coatings on Mg–Zn foil using solution emersion method. Figure 2 shows SEM images of the coatings that they obtained at various time intervals. Characterization of the coatings revealed that the primary phase formed was a poorly crystalline calcium magnesium hydroxyapatite material [83]. Another report demonstrated the formation of calcium phosphate-based coatings on magnesium alloy by electrodeposition [84] which resulted in a layer consisting of dicalcium phosphate dehydrate (DCPD) and β-tricalcium phosphate (β-TCP) which converted into hydroxyapatite after immersion into alkali solution indicating that DCPD and β-TCP were precursors for the formation of HA. Pre-treatment and post-treatment processes were carried out at certain temperatures on the HA-coated implant materials to enhance the coating formed. Pre-treatment process helped in removing the impurities form

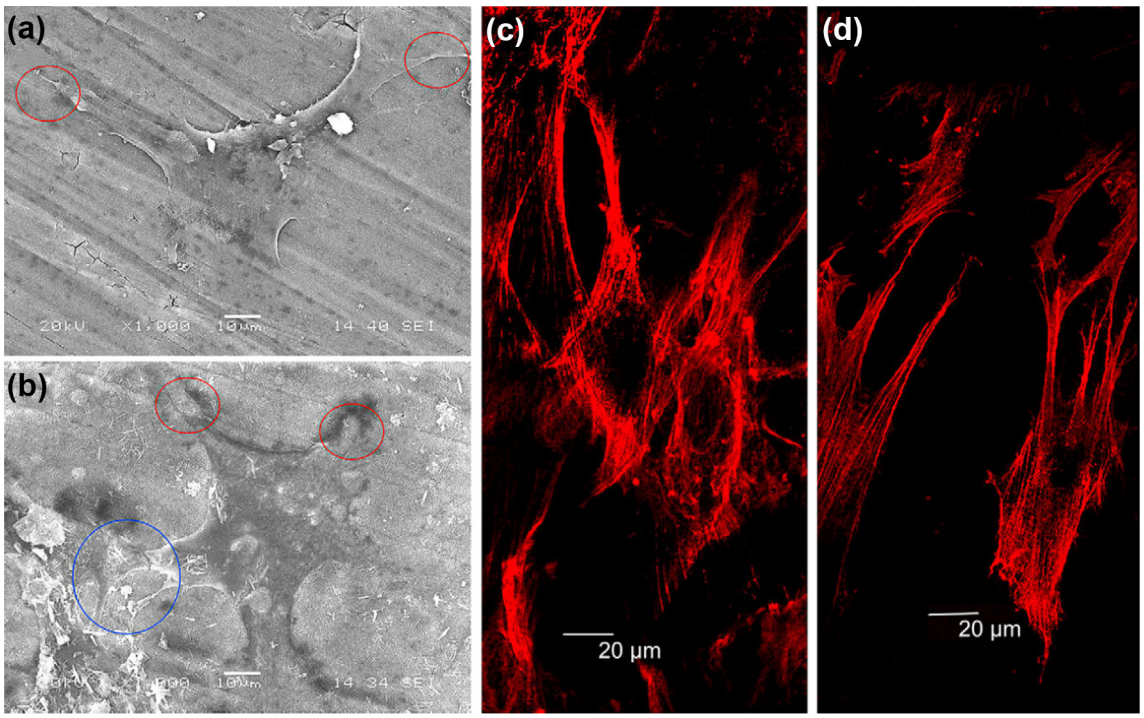

Fig. 3 The typical SEM image of Mg-6 wt%Zn alloy. *Scale bar* = 10 µm. **b** The typical SEM image of FHA-coated Mg-6 wt%Zn alloy. *Scale bar* = 10 µm. **c** The typical LSCM image of Mg-6 wt%Zn alloy. *Scale bar* = 20 µm. **d** The typical LSCM image of FHA-coated Mg-6 wt%Zn alloy. *Scale bar* = 20 µm. Adapted from Ref. [88] copyright Elsevier

the magnesium substrate and enhanced the rate of coating process. Post-treatment process eliminated the formation of some amorphous phases such as tricalcium phosphate and dicalcium phosphate dehydrate [85]. Rojaee and coworkers exploited the use of micro-arc oxidation (MAO) and MgF_2 conversion coating as a surface pre-treatment method for AZ91 magnesium alloy to generate a nanostructured hydroxyapatite (n-HAp) coating via electrophoretic deposition (EPD) method [86]. Their results showed that the MAO/n-HAp-coated AZ91 Mg alloy samples had a rough topography and resulted in lower corrosion current density leading to a lower Mg degradation rate accompanied by high bioactivity [86]. Thermal spraying has been used to effectively coat hydroxyapatite on magnesium. Cheang and coworkers reported the preparation and characterization of HA powders and coating by plasma spray process and concluded that the state of the starting powder adversely affects the coating characteristics [87]. Their results indicated that particle cohesion, size range and thermal treatment during thermal spray processing affected the phase and structure of the coatings and post-spray treatments were suggested to produce a dense and adherent coating having the desired biocompatible properties [87].

In vitro and in vivo results have shown the effectiveness of bioceramic coatings on magnesium. Li and coworkers reported the fabrication of bone-like fluoridated hydroxyapatite (FHA) coatings on Mg-6 wt%Zn substrates using electrochemical methods. They utilized human bone marrow stromal cells (hBMSCs) to investigate the cellular biocompatibility of Mg-6 wt%Zn alloy [88]. Their in vitro results indicated that the bioactive FHA coating improved the interfacial bioactivity of Mg-6 wt%Zn substrate, specifically, both on biodegradation behavior control and good cellular proliferation and differentiation (Fig. 3) [88]. Xu and coworkers coated a calcium phosphate coating on magnesium alloy by a phosphating process [89]. They carried out the in vivo implantations of the Ca–P-coated rods and compared them with the naked alloy rods to investigate the bone response at the early stage post-implantation (Fig. 4) [89]. Their results via routine pathological examination and immunohistochemical analysis demonstrated that the Ca–P coating provided magnesium with a significantly good surface bioactivity ($p < 0.05$) and promoted early bone growth at the implant–bone interface [89].

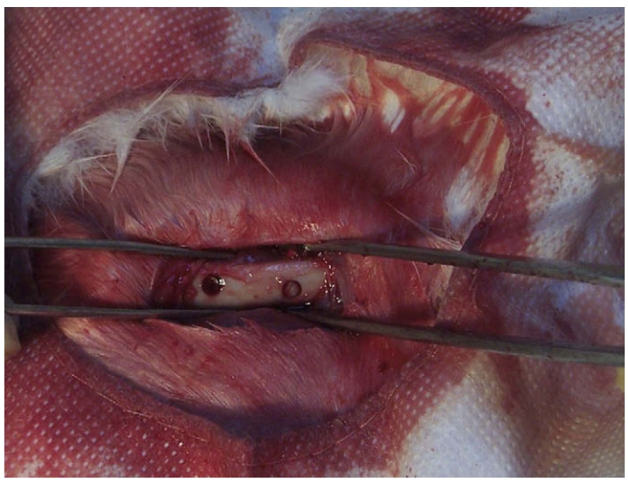

Fig. 4 Implantation of magnesium rod samples with one uncoated sample and one Ca–P-coated sample in one femora of a rabbit. Adapted from Ref. [89] copyright Elsevier

5 Summary and Conclusions

Magnesium (Mg)-based materials have attracted interest as for its use as a biodegradable metallic implant material. However, one of the main challenges in the use of magnesium and its alloys for biomedical applications is its poor corrosion resistance in physiological environments. Hydroxyapatite coatings on magnesium have shown its effectiveness in controlling the degradation of magnesium as well as enhancing its biocompatibility and bioactivity. Much research is still needed to develop various coating technologies to provide device manufacturer the flexibility in selecting the coating process and well as to ensure viability of this technology as a biodegradable metallic system.

Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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