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Bioresorbable metallic implants: surface functionalization with nanoparticles and nanostructures

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Outline

Introduction

Musculoskeletal disorders and cardiovascular diseases are the most prevalent health problems in human that seriously affect the life quality of patients. Due to demographic changes, the number of elderly suffering from musculoskeletal disorders and cardiovascular diseases are growing phenomena that will persist in the near future [1]. Currently, permanent metallic implants with appropriated mechanical strengths and biocompatibility, including stainless steel, titanium alloys and cobalt-chromium alloys have been widely used in medical devices. However, their limitations include stress shielding, which induces re-fracture and may compromise the bio-efficacy of these inert metallic materials [1]. Biodegradable materials, working as temporary implants will avoid a second surgery, reducing costs and patients' pain. To overcome the mentioned disadvantages of permanent devices in transient wound-healing processes, such as prolonged physical irritation and chronic inflammation [2], a new generation of medical biodegradable metallic materials has been proposed by several researchers [3-5]. Until now magnesium, iron and zinc are the three main metals with biodegradable properties compatible with medical devices applications. These metals, upon degradation, are described to release biological relevant ions with important physiological functions in the human body.

These metallic biodegradable metals are design to degrade gradually *in vivo*, with an appropriate host response elicited by released corrosion products, then completely dissolving upon fulfilling the mission to assist tissue healing with no implant residues. In this dissolution process the major components of these biodegradable metals should ideally be essential elements that can be metabolized by the human body. In same specific cases, the presence of such ions can even aid the wound-healing process [3, 6]. Temporary implants made of magnesium and its alloys have been the most studied, developed and had already reached clinical trials in humans. Pioneer medical application for magnesium as orthopaedic implant materials is dated from the beginning of last century [7] and recently in 2016, Biotronik's Magmaris developed a magnesium bioabsorbable scaffolds approved for commercialized in the European market. Followed by magnesium comes those biodegradable metal made of iron, which have reached *in vivo* studies in animals. Finally zinc has just been recently proposed as a bioabsorbable metal with only few studies reported [6]. Although the increasing interest in magnesium-based alloys the poor mechanical properties, fast degradation rate in physiological environments and significant hydrogen evolution during the corrosion process limits their applications [8].

From a structural point of view iron mechanical properties are closer to those of stainless steel (316L SS), which brings advantageous in several medical devices. Nevertheless iron has a slow degradation rate, which is not suitable for most of the clinical cases, where a faster degradation rate is desirable. Indeed, some reports refereed that large portions of biodegradable iron implants remained intact after a long period of time [9]. Zinc and zinc-based alloys have been recently reported to exhibit a corrosion rate between the other two metals (magnesium and iron) compatible with that of wound-healing processes, but suffer from very low radial strength compared with other alloys [10].

Another important aspect that needs to be considered for all biodegradable metals is the total amount of metallic ions released in the body during the biodegradation process. While magnesium (Mg^{2+}) as a recommended dietary allowance that can reach 420 mg per day, iron (Fe^{2+}, Fe^{3+}) and zinc (Zn^{2+}) have a recommended dietary allowance that should not go up to 14 and 11 mg per day, respectively [11]. Although the degradation of these metallic materials is ultimately releasing non-toxic amounts of ions into the organism, the possible occurrence of local toxicity cannot be ignored. Another quite important aspect in the particular case of the alloys is the release of the

alloying elements (e.g. Al or rare earths), which may have important deleterious effects in human health. To overcome these problems (high corrosion rate, loss of mechanic integrity, formation of hydrogen pockets near the implant site, alkalinisation, de-adhesion, release of debris, etc.), several researchers have proposed new design strategies that aim a surface modification and functionalization, which improve the performance of the biodegradable implant.
This book chapter presents a focused review on limitations of biodegradable metals: pure Mg, Fe and Zn as well as their alloys, and on their surface functionalization aiming medical applications.

Potentialities and limitations of the principal bioabsorbable metallic implants

Metallic biodegradable materials, compared to polymeric and ceramic materials are particularly attractive due to their higher mechanical performance and easier translation to a clinical environment. Their greater mechanical strength and better elastic properties allow a greater flexibility in the design of medical pieces with a wider range of applicable parameters during deployment. In the development of novel and effective biomaterials it is important to have in mind the targeted physiological parameters required for the successful application of the implantable device, as for instance in orthopaedic applications where a more static environment is expected when compared with the constant blood flow exerted in a stent (Table 10.1).

TABLE 10.1
Summary of material criteria for different bioabsorbable metals

Constrains	**Orthopaedics [12]**	**Stents [12, 13]**
Mechanical integrity	2 weeks to 1 year	3 to 6 months
Mechanical properties		
Tensile strength	1.5-280 MPa	0.5-1.7 MPa
Yield strength	-	>200 MPa
Ultimate tensile strength	-	>300 MPa
Elongation to failure	1.1-2.1%	> 15-18%
Biocompatibility	Preferential precipitation of bone analogues	No retention or accumulation of particles

The study of different metallic biodegradable materials and deep characterization will allow physicians to choose adequate biomaterials according to wound-healing and patient physiological requirements. Healing rates can vary from to 2-3 weeks for a finger bone healing in younger patients to 1 year for femoral healing in elderly patients. This wide range of healing time requires the deep characterization of the degradation rate of the biomaterial, with the different chemical elements involved playing an additional role when providing physiological relevant effects (Table 10.2). For instance, both magnesium and zinc when dissolving can have a positive role in bone healing processes, with zinc additionally inhibiting the inflammatory processes inherent to medical surgeries (Table 10.2). Iron on the other hand can have a beneficial effect for coping with the bleeding caused by the surgical interventions and/or in patients suffering from anaemia-related pathologies (Table 10.2). While the beneficial effects can bring advantageous in wound-healing processes, the existence of local toxicity effects has to be considered. For iron, the possible suppression of the immune system can potentiate the dissemination of an infection, which can be

particularly problematic in suppressed immune patients. The beneficial inhibitory effect that zinc can have in the early beginning of the inflammatory processes triggered upon implantation, can render an altered immune function afterwards (Table 10.2).

TABLE 10.2
Physiological effects of magnesium, iron and zinc in the organism

	Physiological Function	**Beneficial effects**	**Toxic effects**	**Refs**
Magnesium	Co-factor of enzymes and participates in calcium the regulation.	Incorporation of calcium in bones.		[11, 14]
Iron	Essential for haemoglobin and myoglobin and participate in redox reactions of various cytochromes.	Aid in anaemia prevention.	Suppression of immune cell functioning, damage of gastrointestinal, hepatic, pancreatic and cardiovascular structures.	[11]
Zinc	Catalytic, structural and regulatory roles for many enzymes.	Anti-inflammatory and antioxidant potential.	Hypocupraemia, leucopaenia, neutropaenia, sideroblastic anaemia, altered lipoprotein metabolism and impaired immune function.	[11, 15, 16]

Pure Magnesium and Magnesium alloys

When looking deeper into the roles of magnesium in the human body, it is well known that after sodium, potassium and calcium, magnesium is the most important and abundant cation in the human body, with about 21-35 g stored in a 70 kg body of a healthy adult. Magnesium can be mainly found in bones (about 50%) and in soft tissues (about 35-40%), where it plays key roles in several enzymatic and cellular reactions among which protein and nucleic acid synthesis, ion channel modulation, mitochondrial activity, plasma membrane stabilization and translational processes can be highlighted (Table 10.2) [14]. When magnesium is below 10 mM no decrease in cell viability is reported whereas when increased until 15 mM, a decrease of 25% in cells viability occurs [17]. When translating to the human body, magnesium can hardly reach toxic concentrations, as excessive amounts of Mg can be readily excreted through urine and faeces [18].
Apart from initial detrimental formation of gas cavities originate from Mg rapid corrosion, satisfactory functional results have been reported [7], as Mg and its alloys can retain advantage properties, like density and elastic modulus similar to those of cortical bone. Indeed during several decades treatments using pins made of spindle-shaped Mg sheets have been reported to fix humeral fractures in adults [7]. Apart from initial detrimental formation of gas cavities originate from Mg rapid corrosion, satisfactory functional results have been reported [7]. A plate and a screw of Mg-Cd alloy have been also applied in several successful treatments of pseudarthrosis [7].
Making use of the Mg rapid degradation rates in body fluids, the first implanting of a Mg stent in a pulmonary artery of a baby has been reported, with stent degradation up to 5 months and no in-stent obstruction or neointimal hypertrophy [19]. In last decade, ultra-pure Mg (HP Mg) and new developed Mg alloys emerge as implants material in clinical studies for bone fixation function, using

screws for treatment of osteonecrosis of femoral head [20] Mg-Y-Re-Zr alloy screws in hallux valgus surgery [21], HP Mg screws for treatment of osteonecrosis of femoral head [20], and Mg-Ca-Zn screws to fix radius fractures [22]. A screw and a plate of Mg-Cd alloy have been also applied in several successful treatments of pseudarthrosis [7]. Overall, the rapid corrosion rate of Mg and Mg alloys could be useful to avoid a second surgery for remove the implants, in fast wound-healing processes, but premature degradation may provoke loss of implant mechanical integrity, limiting its application for longer periods.

From an electrochemical point of view, Mg suffers an intense corrosion in aqueous media owing to its low standard electrode potential of -2.372 V versus normal hydrogen electrode (NHE). The dissolution of Mg in aqueous medium originates Mg cations release leading to the formation of magnesium hydroxide $Mg(OH)_2$ and an equivalent mole of hydrogen H_2 [23] (Eq. 1).

$$Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2 \quad \text{(Eq. 1)}$$

Magnesium hydroxide $Mg(OH)_2$ precipitates on Mg surface as a non-efficient protective film. In the presence of a very low concentration of aggressive halogens anions, like above 30 mM chloride, the chloride will react with $Mg(OH)_2$ leading to the formation of the highly soluble magnesium chloride ($MgCl_2$)[24] (Eq. 2)

$$Mg(OH)_2 + 2Cl^- \rightarrow MgCl_2 + 2OH^- \quad \text{(Eq. 2)}$$

In vivo Mg degradation studies have reported the continuous corrosion of Mg only for chloride content of about 150 mM in body fluid [25]. The inevitable presence of metal impurities such as Fe, Ni, Cu, and Co in pure Mg reduces the corrosion resistance of pure Mg even when present in ppm concentrations. So, the corrosion rate of pure Mg is highly influenced by the amount of impurities especially when exceeding the tolerance limit: 0.005 wt.% for Fe or Ni, and 0.05 wt.% for Cu. Indeed, when Fe concentration increase to 26 to 48 ppm the corrosion rate of pure Mg is accelerated by 3 to 60 times [26]. Not only the presence of impurities are determinative for the corrosion rate of pure Mg, but also particular combinations of these metal impurities. In particular, the Fe/Mn ratio increases the formation of anodic precipitates containing Fe and Fe-Mn increasing the corrosion rate of pure Mg [27]. Besides the influence of the composition, alloying elements and impurities in the corrosion resistance of Mg, the microstructure, secondary phases and production processing are other important parameters that influence corrosion rate. In order to optimize these factors an intense research have been focus in the development of new alloys for degradable implants, namely binary Mg alloys (Mg-Re, Mg-Ag, Mg-Ca, Mg-Zn, Mg-Li), ternary Mg alloys (Mg-Al-Zn, Mg-Ca-Zn, Mg-Zn-Mn, Mg-Zn-Zr) and quaternary Mg alloys (Mg-Y-Re-Zr, Mg-Nd-Zn-Zr) [21, 22, 28-33].

Summarizing, new design of biomedical Mg alloys aims at regulating the degradation rate by *in-situ* formation of a uniform and stable alloying-element protective film. Contrary to $Mg(OH)_2$ non-protective film, those protective films could precipitate and act as efficient natural protective barriers. An example has been published in a recent study that attributes the alloy enhanced corrosion resistance to the formation of a stable protective carbonate Li_2CO_3 film over a compact Li_2O/MgO layer on Mg-Li alloy [31]. Instead of this indirect surface modification, a direct surface modification and functionalization could represent an expedite strategy to achieve an improved corrosion and mechanical resistance of Mg and its alloys. This approach is a promising route to guarantee an adequate integrity of Mg bioabsorbable implants, which would degrade upon service.

Pure Iron and Iron alloys

Iron, another essential element for the human body, is able to transport oxygen and electrons. With this role iron has relevant biological functions, as for example, in the formation of hemoglobin, myoglobin, and numerous enzyme groups (Table 10.2). Adults typically have 3 to 5 g of iron in total, and the majority is circulating in the hemoglobin of the red blood cell. About 0.5–2 mg of dietary iron is absorbed each day through the proximal small intestine [34]. Figure 10.1 shows a scheme with distribution of the iron in the human body. Although being an essential element, excessive amount of iron in the body (> 50 μg/ml) can generate lesions in the gastrointestinal tract, cause abdominal pain, fatigue and liver damage [3, 35].

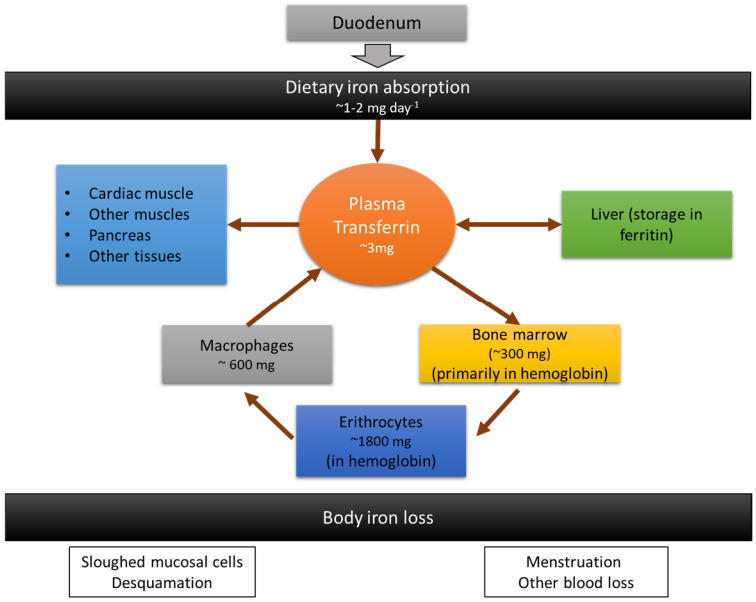

FIGURE 10.1
Distribution of iron in human body (adapted from [34, 36])

Due to the overall positive effect of iron in the human body, it can be considered to be an alternative interesting candidate for use as biodegradable implant material. As mentioned, there are fewer studies for Fe and its alloys than for Mg. Despite this, the earliest record of Fe use as biomaterial was a dental implant found in Europe that dated back to 200 A.D. [37]. Later in the 17th century Hieronymus Fabricius used Fe wires as sutures [37]. In 1775, Fe wires were used for fracture fixations, but concomitant infections were observed [3]. Afterwards, in 1906 Lambotte used Fe plates and screws for repair bone fracture fixation in human, nevertheless, this treatment was a clinical failure due to loosely attached fractured ends four months after surgery [1, 3]. In 1924, A. Zierold reported a study on tissue reaction to various metals in dogs. Iron was found to corrode rapidly leading to the resorption of adjacent bone [38, 39]. More recently, the suitability of iron as a degradable implant material has been verified *in vivo* studies, in which developed stents from pure iron were studied in animal models. The authors verified that no local or systemic toxicity, no early restenosis due to thrombotic processes, and no pronounced inflammation reactions were observed. Additionally, the neointimal proliferation was found to be similar with

that obtain for stainless steel 316L and Co-Cr alloys [3, 40-42]. However, the animal tests have revealed a slow degradation rate *in vivo*, with iron remaining relatively intact up to 1 year. This was considered to cause a reaction similar to those found in permanent applications [3, 42]. In an almost ironic circumstance, pure iron, has a degradation rate in osteogenic environments excessively slow to be used as bioresorbable metal although, possesses satisfactory mechanical properties, close to those of 316L stainless steel. The elastic modulus of pure iron is 200GPa slightly higher than that of 316L stainless steel (190 GPa) [3]. Furthermore, pure iron has good ductility and can provide high radius strength to blood vessels. To overcome several obstacles concerning the optimization of the degradation rate and depletion of any toxic effects, elements such as manganese are usually added in an effort to increase iron's corrosion rate trough the creation of microgalvanic corrosion sites [9, 43].

When a biodegradable metal, as iron, is implanted it comes into contact with soft or hard tissues and is continuously exposed to corrosive body fluid. This will expose the iron implant to dissolved oxygen, sodium chloride, phosphate, carbonates, calcium, other salts, and complex organic compounds such as proteins, dictating the corrosion process of this biodegradable metal. Different from other metals, Fe degradation is highly dependent upon oxygen availability. Often starts from grain boundary and as the corrosion proceeds, hydrogen and oxygen accumulate at these sites. As to pure iron with typical micron grain size, the degradation process in oxygen-free saline solution occurs according to the following reactions: first of all, iron as anode is oxidized (Eq. 3) and then hydrogen adsorption occurs on the surface of the metal ion in the cathode (Eq. 4). The metals atoms with hydrogen continue to react with H^+ in the solution and hydrogen is finally released (Eq. 5) diffusing into pure iron.

$$Fe \rightarrow Fe^{2+} + 2e^- \quad \text{(Eq. 3)}$$

$$H^+ + M + e^- \rightarrow MH_{ads} + H_2O \quad \text{(Eq. 4)}$$

$$MH_{ads} + H^+ + e^- \rightarrow M + H_2 \quad \text{(Eq. 5)}$$

When a physiological saline solution contains oxygen the corrosion process of pure iron occurs in a distinct form: the anodic iron is first oxidized into Fe^{2+}, as shown in Eq. 3, and then the electrons produced from the anode will be consumed in the cathode, as shown in Eq. 6.

$$O_2 + 2H_2O + 4e^- \rightarrow 4OH^- \quad \text{(Eq. 6)}$$

Doing to differences in potential these reactions occur preferentially in places, such as grain boundaries or interfaces between two phases. The formation of Fe^{2+} can give rise to two other reactions, either in the form of insoluble hydroxides (Eq.7 and 8).

$$2Fe^{2+} + 4OH^- \rightarrow 2Fe(OH)_2 \quad \text{(Eq. 7)}$$

$$2Fe(OH)_2 + O_2 + 2H_2O \rightarrow 4Fe(OH)_3 \quad \text{(Eq. 8)}$$

The corrosion layers formed on the surface of iron commonly consist of a bottom layer of Fe.$n$$H_2O$ (black), a middle layer of Fe_3O_4. $n$$H_2O$ (black), and an outmost layer of Fe_2O_3. $n$$H_2O$ (bronzing). The corrosion continues as the chlorides in solution penetrate into the hydroxide layer. The chlorides react with hydroxyl ions, forming hydroxide and acid, as shown in Eqs. 6-9.

$$Fe^{2+} + 2Cl^{-} \rightarrow FeCl_2 + H_2O \rightarrow Fe(OH)_2 + HCl \quad \text{(Eq. 9)}$$

During corrosion, the hydroxides, carbonates, and phosphate layers grown on Fe surface are considered the major inhibitors for a faster degradation [42, 44]. Simultaneously, the organic molecules, such as proteins, amino acids and lipids, adsorb on the surface, influencing the corrosion process and simultaneously the cells adhesion [44].

Besides the process itself, the degradation rate of the material is of great importance. The degradation has to be slow enough to guarantee mechanical integrity of the implant over the time of the healing process, and fast enough to assure that it would not cause any damage related to extended stay in the body. Taken that into account it is necessary to determine the degradation rate, the mechanical properties, the toxicity related to extended stay of the implant and, the toxicity caused by the corrosion products.

In vitro studies show that the corrosion rate of iron varies from 0.2 to 0.85 mm/year [9, 44-46] in Hank´s solution, PBS or 0.9% NaCl. When is used as electrolyte a simulated body fluid (Kokubo) the corrosion rate increase and varies from 7.17 to 25.10 mm /year [2, 47]. These values vary according to the production steps that the material has undertaken, composition of the alloys and fabrication methods. Therefore, several efforts have been made to improve the properties of Fe-based materials, based on new fabrication methods [2] and alloying [9], which were effective in improving the mechanical strength and corrosion rate of Fe-based materials, when compared with pure iron [2, 9, 42]. It was reported that by alloying iron with elements such as Mn, Pd, W, Sn, B, C, S, Si, Ga etc. an enhanced degradation rate was attained [2, 4, 9, 48, 49]. For instances, the addition of Mn within the solubility limit of Fe reduces the standard electrode potential of Fe making it more susceptible to degradation [2, 49]. Noble alloying elements, such as Pd, are frequently used in casting alloys for dental restorations and orthopaedic applications [2], as Pd induce microgalvanic corrosion by generating small and homogeneously dispersed Pd-rich precipitates that act as cathodic sites [49]. Recently, silicon has been added to the Fe–30Mn alloy [50]. An increased degradation rate and tensile strength was reported due to Si addition was attributed to a larger γ-austenite content, which corroded faster than ε-martensite in alloys containing silicon [49, 50]. Some Fe–Mn–Si alloys can have shape memory effects, which may be of special interest, for some applications, as an example, in stents [50]. However, to achieve an effective increase in the degradation rate, these alloying elements have to be added in very large weight percentages (e.g.> 15% Mn), which may raise some questions relating the toxicity and biocompatibility of these Fe-based alloys [4]. When considering the increase of the mechanical properties, alloying elements like Mn, Co, W, B, C and S were found to improve the yield and ultimate strength of iron [9]. In addition, the ferromagnetic nature of Fe and of its alloys cannot be used for specific applications, as in delicate cases where nuclear magnetic resonance (NMR) or magnetic resonance imaging (MRI) analysis is required to monitor patients recovery after surgery [3, 49]. For this particular issue, new Fe alloys compatible with high magnetic fields have been developed [51].

To summarize the actual research on Fe-based biodegradable metals is focused in three main points: (i) accelerated degradation rate; (ii) enhanced mechanical properties and (iii) improved biocompatibility. To accelerate the degradation rate new alloys with different elements have been developed and/or new fabrication methods. To enhance mechanical properties researchers have been focus they work on the development of composites, adding alloying elements and/or new fabrication methods. Toward an improved biocompatibility the development of new surfaces or composites has been preferred [4, 49-51].

Pure Zinc and Zinc alloys

Bowen et al. [10, 52] made a breakthrough in the use of Zn as biomaterial when studying the corrosion rate of pure Zn in the aorta of an adult male Sprague–Dawley rats. Their results revealed a better corrosion rate for Zn than for Mg or Fe. Zinc, like Mg or Fe, has a preponderant metabolic activity in the human body. The physiological role of zinc (Zn^{2+}), an essential trace element, has been associated to panoply of metabolic pathways [16]. Zn ion concentration is tightly regulated via channels within the cell membrane. Once inside the cells, Zn^{2+} presents catalytic, structural and regulatory roles (Table 10.1). Among these roles the participation as a co-factor of enzymes responsible for DNA replication and signalling processes can be highlighted [16]. The distribution of Zn^{2+} through the body is of 85% in muscles and bones, 11% in skin and liver, with the remaining 6% being distributed throughout the rest of the tissues [16]. The importance of Zn^{2+} in muscles and bone remodelling suggests that a positive effect can arise by using Zn-base biomaterials in muscle-related and bone repair processes. Moreover, in delicate wound healing processes the high density of Zn (7.14 $g{\cdot}cm^{-3}$), when compared with that of soft tissues and bones, can be easily monitored by radiological techniques for the survey of such healing processes. As Zn degradation occurs a corrosion layer precipitates on the material surface. The formation of such layers is highly dependent on the available ions [53]. The initial dissolution of metallic Zn promotes Zn ions (Zn^{2+}) release (Eq. 10) into the surrounding tissues and blood stream (Eq. 10).

$$Zn \rightarrow Zn^{2+} + 2e^{-} \quad \text{(Eq. 10)}$$

This, as already refereed can have beneficial effects in the wound-healing processes, but when in excess, adverse effects can arise (Table 10.2). Studies performed on the corrosion rate of pure Zn revealed that when considered an implanted piece of *c.a.* 50 mg, the expected daily dose of Zn^{2+} released would be around 0.15 mg d^{-1} [10]. This is a value far below the recommended dietary allowance of 11 mg Zn per day [54]. In this interplay of Zn^{2+} release from the implanted pieces and organism homeostasis, there is still a missing piece - the precipitation of the resulting degradation products. This precipitation will not only consume the released Zn^{2+}, lowering the effective dose reaching the surrounding tissues, but will as well influence the interaction with adjacent cells. Several *in vitro* and *in vivo* studies performed with Zn biomaterials revealed that the presence of chlorides, carbonates and phosphates resulted in the precipitation of $Zn_5Cl_2(OH)_8$- simonkolleite, $Zn_5(CO_3)_2(OH)_6$- hydrozincite, $ZnCO_3$– smithsonite and $Zn_3(PO_4)_2$- hopeite [10, 53, 55-61]. The presence of hydroxyl ions also favours metals hydroxide precipitation (Eq. 11), whatsoever, this compound is readily dehydrated to form ZnO - zincite.

$$Zn^{2+} + 2OH^{-} \rightarrow Zn(OH)_2 \quad \text{(Eq. 11)}$$

This oxide, by being a semiconductor can itself catalyse oxygen reduction therefore favouring the degradation process of Zn-derived materials [62]. The relatively high content of calcium ions present in the body fluids can themselves contribute for the precipitation of $Ca_3Zn_2(PO_4)_2CO_3(OH)_2$- skorpionite and $Ca_5(PO_4)_3(OH)$ - hydroxyapatite [58, 60]. The precipitation of these CaP-derived compounds can bring physiological advantageous when envisaging the use of Zn for bone healing processes. These findings maybe somehow related with the favourable biocompatibility reported for Zn biomaterials [10, 58, 60, 61, 63-68]. The understanding of the mechanisms underlying this improved biocompatibility is still an important gap in the knowledge of Zn as a biomaterial. While so far Zn seems to be the perfect material in the field of degradable metallic devices, its softness,

brittleness and low mechanical strength are limiting characteristics, especially when aiming the use in load-bearing implants (Table. 10.3). While zinc exhibits an outstanding elongation to failure of 60-80% it has a limited tensile strength of ~120 MPa (Table 10.1). Whatsoever an improved ductility and strength can be achieved by alloying Zn with minor alloying additions. The already proved increase in strength and superb elongation of commercial Zn-Al alloys is clearly surpassed by the detrimental effect of Al release to the organism [66, 69]. To overcome this toxicity issue, the addition of physiological relevant elements may bring an add-value in terms of biocompatibility [70, 71]. Magnesium, Ca and Sr, three important elements of bone matrix, were already used for alloying Zn. From those, Zn-Mg binary alloy are by far the most studied alloys aiming biomedical applications. Whereas several *in vitro* and *in vivo* assays are in agreement for these alloys biocompatibility [63-65, 68, 72-74], contradictory *in vitro* degradation rates have been reported when compared with pure Zn [63, 70, 74-76]. For Zn binary alloys composed by Ca or Sr, enhanced mechanical properties were attained with both the *in vitro* and *in vivo* data showing similar corrosion rates to those of pure zinc [74]. A common alloying element for Zn that can have beneficial health effects is Cu, as it can promote vascular endothelial cells proliferation while having antibacterial activity. Indeed these binary Zn-Cu alloys presented an excellent combination of strength and ductility, a low degradation rate and, as predicted, an antibacterial activity [77, 78]. Lithium, by being approved by the U.S. Food and Drug Administration (FDA) to treat manic depression [79], and Ag, a well-known antibacterial agent with low toxicity, were also tested as Zn alloying elements. In both cases, Zn-Li and Zn-Ag alloys presented improved mechanical properties [80, 81]. However the corrosion rate of Zn alloyed with Ag was slightly increased whereas with Li a similar degradation rate to that of pure Zn was attained [80, 81]. When using a third element for alloying Zn - Mg plus Ca, Sr or Mn, and Ca plus Sr - the mechanical properties are greatly improved [82-84], but the corrosion rates kept slightly higher than those of pure Zn [83, 84]. Despite these limited reports, there is an obvious trend in exploring Zn alloys for biomedical applications. In parallel with the development of these novel materials, there is an urgent need to standardize the *in vitro* corrosion tests for these Zn-based materials. These in turn have to be cross-compared with the attained *in vivo* results and validated. Only when following these standard procedures will be possible to define and guide the fabrication and design of efficient Zn-based biomaterials. As a matter of fact, when compared with Mg and Fe, Zn is the most unexplored metallic biomaterial as to the authors' best knowledge there are no reports of Zn use in human individuals [85] nor commercially available biomaterials.

In a general manner, these metallic biomaterials seem to have promising properties, which can be further improved. In this quest there are some general guidelines and other specific trends that can be highlighted. Generally, alloying can be a good strategy to improve the mechanical strength of Mg, Fe and Zn biomaterials. New fabrication methods and manipulation of the alloys microstructure can be other route. An increased biocompatibility is unquestionable a plus for any of these resorbable biomaterials that be typically achieved by surface functionalization. When considering the degradation rates, which have to be slow enough to guarantee the mechanical integrity of the implant over the healing process, and fast enough to ensure that it would not cause any damage related to extended stay in the body, similar strategies can be used. While for Mg the corrosion rate can be retarded by using, for instance, protective surface layers, for iron it can be accelerated by creating galvanic corrosion couples. In this sense, surface modifications and functionalization is undoubtedly an expedite strategy to adequate the corrosion rate of the alloys while improving their biocompatibility (Figure 10.2).

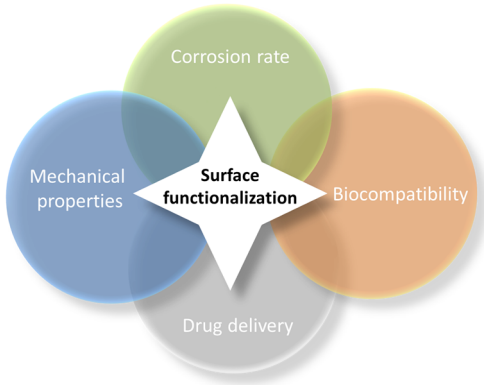

FIGURE 10.2
Schematic representation of the improved properties achieved by the surface functionalization of the metallic absorbable biomaterials

Overview of surface functionalization with nanoparticles and nanostructures

The main purpose of surface functionalization of pure Mg or Fe and alloys is to control their degradation rate. In the particular case of Mg, the degradation after surface functionalization can be highly mitigated but not stopped. Contrary, when considering Fe, the surface functionalization aims an increased corrosion rate. The underneath substrate degradation process will be constrained by the presence of cracks or defects on the coating. Therefore, the durability and integrity of the coating is crucial in biomedical applications. An improved surface biocompatibility and/or drug vehicle for controlled release can be regarded as a plus for pure Mg, Fe or Zn and alloys, although in the specific case of Zn, the surface functionalization of Zn should induce no more than slight changes in the corrosion rate of this metallic biomaterial. In a summarized form, the following sub-section will give an overview of different surface modifications that are reported in the literature. The various surface modifications/functionalization will be divided into three categories: inorganic, organic and composite.

Magnesium surface functionalization

To overcome some of the problems related to excessive degradation rate of magnesium and simultaneously to increases the biocompatibility, the osteointegration and cell adhesion, some strategies for the functionalization of Mg surface can be pursue. In this section the state-of-the-art of biodegradable inorganic coatings applied on magnesium and its alloys will be summarized. Calcium phosphate based coatings are the most commonly used and investigated biodegradable inorganic coatings. Most of the calcium phosphate coatings are designed by assembling calcium phosphate particles with nanometric sizes in a thicker layer. However some of these Hap nanocoating have weak adhesion and can suffer delamination, break and release of molecular debris and/or de-agglomeration when are implanted in the body.

Song et al. [86] reported that the degradation rate of a Mg alloy was decreased by the surface functionalization with different calcium phosphate coatings such as: brushite ($CaHPO_4 2H_2O$), hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) and fluoridated hydroxyapatite ($Ca_5(PO_4)_3(OH)_{1x}F_x$), with these two last coatings further promoting the nucleation of osteoconductive minerals. Among these coatings, the fluoridated hydroxyapatite layer stood out as the more stable one. Another study developed by Li et al. showed that bone-like fluoridated hydroxyapatite is also able to increase the cellular proliferation and differentiation of hBMSCs cells, when compared with the uncoated Mg alloy [87]. Wang et al. [88] not only reported an improved corrosion resistance achieved by a soluble Ca-deficient hydroxyapatite coating, but also an increase in the ultimate tensile strength and time of fracture of the coated Mg-Zn-Ca alloy. This promising coating promoted the formation of new bone tissue, proving its valuable use for *in vivo* applications [88]. A chemical treatment method has also been used to directly produce Ca–P-based coatings on magnesium and its alloys [89]. One interesting study developed by Xu et al. [89] revealed the effect of porous and netlike Ca-P layer formed on the surface of a Mg alloy. The *in vitro* cell tests showing an induce proliferation and adequate adhesion of L929 cells, were effectively translated by the *in vivo* data presenting a promising surface bioactivity with an early bone growth at the implant/bone interface [89]. Again, Tomozawa et al. [90] using a hydrothermal method produced hydroxyapatite coatings that reduced the corrosion rate of pure Mg and enhanced cells attachment, proliferation and differentiation, with the *in vivo* data corroborating this retarded corrosion rate for an implanted Mg piece [91]. Recently, C. Santos et. al. [92] using a parallel nano assembling process fabricated a phosphate coating loaded with hydroxyapatite nanoparticles and graphene oxide (GO) (Figure 10.3) and show that the presence of hydroxyapatite nanoparticles as well as the mixture of GO with hydroxyapatite nanoparticles decreased the current density, when compared to a single phosphate coating or uncoated Mg. An induced apatite formation in a simulated body fluid solution suggested a potential cytocompatibility of this HapNP/GO/phosphate coating [92].

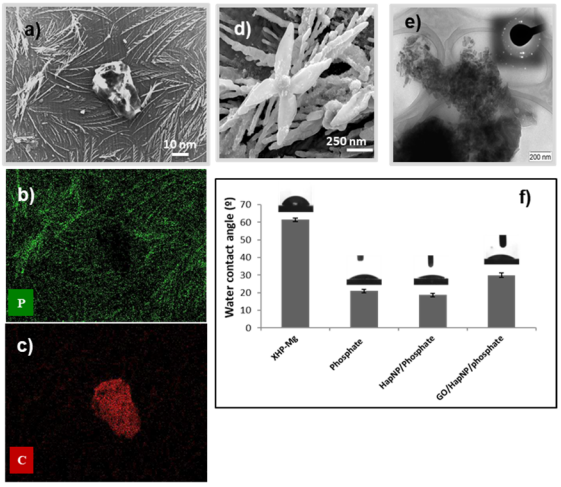

FIGURE 10.3
(a) XHP-Mg coated with Phosphate/Hap/GO obtained by electrodeposition; (b, c) corresponding energy dispersive X-ray spectroscopy (EDS) maps; (d) detail SEM image of phosphate coating with hydroxyapatite nanoparticles (e) TEM image of Phosphate/Hap/GO coating and (f) water contact angle of bare and coated XHP-Mg

Several biodegradable polymeric coatings, such as polycaprolactone (PCL)[93-95] poly(L-lactic acid) (PLLA) [93, 95], poly(DL-lactide-co-glycolide) (PLGA) [95, 96], poly(3,4-ethylenedioxythiophene) (PEDOT) [97], collagen and chitosan were applied to Mg and Mg alloys. Among those polymers, PLLA and PCL are the most studied ones. Usually these are applied to slow down Mg degradation,but can be used as well to improve surface biocompatibility and/or for drug release. For instance, Xu and Yamamoto [93] improved the early corrosion resistance of magnesium and cytocompatibility by applying porous films of PLLA and PCL. From those a better adhesion strength was reported for the PLLA film than for the PCL film, and the low molecular weight films exhibited a better adhesion strength than the high molecular weight ones [93]. Additionally the corrosion results have shown that these polymer films improved the corrosion resistance of Mg substrate and the polymer surfaces were suitable for SaOS-2 cells attachment and growth [93]. Wong et al. [94] also fabricated a PCL and dichloromethane membrane that reduce the degradation rate and maintained the bulk mechanical properties of a magnesium alloy during the degradation process. Again, *in vitro* studies showed a good cytocompatibility of PCL coatings for osteoblast eGFP and SaOS-2 cells. This was successfully translated for *in vivo* applications, as after implantation the PCL coatings could retarded degradation while promoting new bone formation [94]. Poly(DL-lactide-co-glycolide) is another polymer often used due to its good biocompatibility and ability to control degradation rates of magnesium. Ostrowski et al. [96] developed PLGA coatings with different thickness on magnesium alloy. It was observed that in the first 3 days the coatings provide protection for the Mg substrate and reduce the degradation rate, but after this period of time, PLGA coating did not maintain a reduction in corrosion rate. Despite the formation of gas pocket during the degradation processes, which could have contributed for PLGA detachment, an improvement biocompatibility was achieved in the earlier stage of implantation [96]. Recently, the comparison made by Jiang et al. [95] revealed that PLGA (50:50) coating promotes better HUVECs cells adhesion and spreading, when compared with PLGA (90:10), PLLA and PCL. This increased biocompatibility was suggested to be related with three possible factors that promoted HUVECs directly attached on the surface of PLGA (50:50)-coated Mg: (1) the higher concentration of Mg^{2+} ions released into culture media with a concentration range of 9–15 mM during the degradation; (2) the lower Ca^{2+} ion concentration detected in culture media at 1.3–1.6 mM; and (3) the favourable surface conditions of PLGA (50:50), when compared with the other sample groups [95]. Sebaa et al. [97] used an electrodeposition method coated Mg reported that PEDOT was another polymer that could control the degradation rate of magnesium and improve the cytocompatibility. Due to the specific conductive properties of the PEDOT, it was additionally possible to control an anti-inflammatory drug (dexamethasone) delivery using an electrical stimulation [97]

While the development of polymeric coatings in opening new strategies for matching Mg degradation with that of wound-healing, the research for the perfect polymeric formulation is still an on going feature.

The composite coatings usually possess combined properties that can be an advantageous in terms of multi-functionality purposes.

Cordoba et. al. [98] reported that coated AZ31 and ZE41 with a silane-based coating modified with titanium IV iso-propoxide on AZ31 and ZE41 was able to slow down Magnesium alloys corrosion rate, and this composite coating favoured the formation of a non-stoichiometric hydroxyapatite-rich layer. In another perspective, Zomorodian et al. [99] applied on AZ31 magnesium alloys pre-treated with hydrofluoric acid by dip coating, a composite coating with polyetherimide (PEI)and several diethylene triamine containing different hydroxyapatite contents. This coating was able to slow down the corrosion rate of AZ31 magnesium alloys in Hank's solution, and enhance the adhesion and proliferation of MG63 osteoblastic cells, especially in presence of hydroxyapatite

nanoparticles. More recently, the same author developed a biocompatible polycaprolactone (PCL coating functionalized with nano hydroxyapatite particles for enhanced biocompatibility and with an antibiotic, cephalexin, for anti-bacterial purposes and applied on AZ31 alloy. They showed that it is possible to tailoring new multifunctional composite coatings that can store antibiotics and nano hydroxyapatite particles, while controlling the *invitro* degradation of Mg alloys [100]. Dong et al. [101] developed a surface drug delivery system composed by Epoxy resin-ZnO/PCL-Ibuprofen, which was able to sustained release profiles of ibuprofen for 22 days. Not only was this new coating able to improved corrosion resistance of a Mg alloys, but it could as well potentially decrease local cellular inflammation processes during the early stage of implantation [101].
While the polymeric coatings have already proven their effectiveness in the corrosion protection of Mg and alloys, the addition of inorganic coatings is undoubtedly the far most promising strategy in terms of improved biocompatibility properties. When combining these two approaches, the composite coatings stand out as the more versatile coatings for Mg implants.

Iron surface functionalization

While an increased biocompatible surface is a plus for any kind of bioabsorbable metal, the requirements for controlling the degradation rate can be antagonist. While for Mg and alloys the surface functionalization could decrease the corrosion rate, for iron an increased corrosion rate can be preferentially achieved by the development of new iron based alloys. In this sense, there are few studies reported in literature relating the surface functionalization of iron. Most of the work is related with an improved biocompatibility and hemocompatibility of pure iron, with the corrosion resistance being enhanced in some cases or decreased in others. It is already known that when using iron as a biodegradable implant a rapid and localized corrosion would compromise the mechanical stability in the early stage of implantation. Additionally, the rapidly formed and accumulated corrosion products might exceed tissue tolerance and bring biological risks. To this end, several surface modifications have been proposed. Up to now, there are limited studies investigating the functionalization of iron surface with an organic coating. Lin et al. [102] developed an ultra-thin iron-based drug-eluting coronary scaffold. The polished nitriding iron scaffolds were first electroplated with a thin zinc layer, then coated with a layer of poly (D,L-lactide) (PDLLA) carrying sirolimus. These scaffolds for up to 13 months were implanted into the abdominal aortas of rabbit had significantly shortened period of corrosion without inducing any negative biological reactions. During the whole implantation period of iron scaffold was no found infiltration of inflammatory cells such as neutrophils, lymphocytes [102]. In another study, Li et al. [41] fabricated on iron substrates using an anodic oxidation approach, oriented and arranged α-Fe_2O_3 (hematite) nanotubes. The nanotubes were designed as deposits which were loaded with antiproliferation drug rapamycin to accelerate the re-endothelialization process. These nanotubes were then coated with PLGA for the control of drug release. A faster corrosion rate was attained for the 50 nm Fe_2O_3 nanotube arrays than for pristine Fe. Additionally, the initial burst release of the loaded drug was reduced by the presence of the PLGA coating and extended the rapamycin release time to 30 days. The endothelial cells (ECs) results obtained on the coated samples showed higher cell viability than the vascular smooth muscle cells (VSMCs) viability suggesting a favoured re-endothelialization and decrease VSMC proliferation [41].
Again, there are not many studies dedicated to the functionalization of iron surface with inorganic coatings. Orinakova et al. [103] using an electrochemical deposition method reported that a coated iron with hydroxyapatite and manganese-doped hydroxyapatite layer. Both corrosion results and static immersion test in a Hank´s solution after 13 weeks showed the sequence of the corrosion

rate to be Fe coated with hydroxyapatite < Fe coated with manganese-doped hydroxyapatite< Fe. The *in vitro* cytotoxicity results showed a moderate negative effect on osteoblasts viability [103].

Within the inorganic surface functionalization, ionic implantation into pure iron is the most surface treatment reported in literature. Having this in mind and using plasma immersion ion implantation and deposition (PIII&D) Zhu et al. prepared Fe-O film on the surface of pure iron to improve its corrosion resistance and biocompatibility. The Fe-O film fabricated under the condition of low oxygen flow effectively enhanced the corrosion resistance of pure iron when compared with high oxygen flow. Besides, hemocompatibility studies indicated that the number of platelet adhesion, platelet activation was remarkably decreased when compared with pure iron. Additionally the adhesion and proliferation of HUVECs cells was also favoured by the presence of the Fe-O film [104]. Another work developed by Zhu et al. [105] was carried out to implant lanthanum ion into pure iron through metal vapour vacuum arc (MEVVA) source injection technology. The obtain results confirmed that La ion implantation could improve the corrosion resistance of pure iron in a simulated body fluid (SBF). Additionally, comparing to pure iron and 316L SS, the presence of lanthanum on iron surface decreases the prothrombin time, thrombin time, and platelet adhesion, thereby improving blood compatibility [105].

Pure Fe was surface-modified by Ta ion implantation with different incident ion doses by Wang et al. The obtained results confirmed the formation of Ta/Fe oxide mixtures at the outmost surface (60–80 nm in thickness) of the implanted layer. The pure Fe modified by the Ta ion implantation exhibited a higher corrosion rate in simulated body fluids when compared with pure iron, due to the formation of severe pitting corrosion. Additionally the cytocompatibility of osteoblasts has been significantly improved by applying the Ta ion implantation on pure Fe [106].

Using a vacuum sputtering technique, micro-patterned Au disc arrays were deposited on the surface of pure iron. According to Cheng et al. the surface treatment with Au produce a more uniform corrosion in Hank´s solution with an almost four times higher degradation rate than the uncoated ones. Additionally, was insignificantly the influence of micro-patterned Au discs with different diameters on the corrosion rate of pure iron [40].

Huang et al. coated pure iron with platinum discs with different sizes (Φ20 μm × S5 μm and Φ4 μm × S4 μm). The pure iron modified with platinum formed plenty of galvanic cells with the iron matrix which significantly accelerated the degradation of pure iron. Furthermore, it was revealed that a uniform degradation could be controlled by the designability of the coating such as the shape, size as well as distribution of Pt discs. Additionally, no toxicity to human umbilical vein endothelial cells was observed for pure iron coated with Pt discs, but a significant inhibition on proliferation of vascular smooth muscle cells was observed. Moreover, it was demonstrated that Pt discs effectively reduced the number of adhered platelets [107].

Mostavan et al. produce in an electrolytic bath a bilayer alloy composed of electroformed iron (E-Fe) and iron-phosphorus (Fe-P) on top of iron. The obtained results showed that an increase in amount of $NaH_2PO_4 \cdot H_2O$ in the electrolyte increase the amount of P deposited on iron. Additionally the electrochemical corrosion tests showed that corrosion rate was strongly influenced by deposition conditions and a P amount of ~2 wt.%, the corrosion rate was 1.46 mm/year closed to corrosion rate for biomedical applications [108].

Huang et al. adopted metal vapour vacuum arc technology to implant Zn ions [109] and Ag ions onto the surface of pure iron. Although the corrosion rate in Hank´s solution is higher than pure iron, the corrosion mechanisms in presence of Zn and Ag ions were totally different.

For Zn ion-implanted pure iron, occurs the formation of a Fe-Zn solid solution due to a certain solubility of zinc in iron. The formed Fe-Zn solid solution corrodes faster than pure iron. The authors

believe that due to lower corrosion potential, zinc atoms were first oxidized, then the structure of iron lattice collapsed, and the released iron atoms were oxidized subsequently.
In the case of Ag, there is no solubility of silver ions in iron. The silver ions tended to form Ag nanoparticles. These Ag nanoparticles acted as cathodes and formed galvanic cells with iron matrix, which acted as anodes due to the high standard electrode potential of Ag (+0.7996V), which is much higher than that of pure iron (-0.44V). In the specific case, occurred a galvanic corrosion mechanism which significantly increased the corrosion rate of pure iron and made the corrosion more uniform [109].
The surface of pure iron has been also functionalized with a nitride layer using plasma nitriding by Chen et al. [110]. The obtained layer was mainly composed of $Fe_{2-3}N$ and Fe_4N. The authors showed that nitriding layer decrease the degradation rate of pure iron. Due to the importance of nitriding iron as biodegradable metal, Lin et al. tested the cytotoxicity of this layer. They showed that high concentration of iron ions (up to 124 μgml^{-1}) exhibited no *in vitro* cytotoxicity to fibroblasts cells (L-929). Additionally the authors observed that the corrosion products of nitriding iron also exhibited no toxicity to the same cells [110].

Zinc surface functionalization

As clearly demonstrated so far, surface functionalization can have an important impact in the corrosion rate of bioabsorbable metallic materials. When considering Zn-based biomaterials the corrosion rate meets that of wound-healing repair. While for Mg and Fe, coatings should be used to modulate the corrosion rate, for Zn only slight alterations in the degradation rates are acceptable. For Zn alloys, whatsoever, the increased corrosion rate depicted for some of them [13] can be improved by using adequate coatings. This can be another path to peruse the perfect Zn-based biomaterial. Coming back to pure Zn, its functionalization can be directed towards inducing cell adhesion while avoiding microbial spreading. There are only few reports of altered Zn surface envisaging such biomedical purposes, being those strictly based in inorganic coatings [59, 60]. When aiming to immobilize ZnO on Zn surface, a well-known antimicrobial agent that can aid overcoming the growing trend of microbial resistance, the corrosion rate of Zn changed. When coated with ZnO, Zn has a slightly higher corrosion rate due to the galvanic coupled formed between Zn and ZnO coating. Nevertheless, this less desirable effect was clearly surpassed by the antimicrobial and antibiofilm activities depicted, and also by the precipitation of bone analogue compounds that can favour the biocompatibility of such materials [59, 60]. Figure 10.4 shows an example of a ZnO coating on Zn, where homogenous distributed ZnO clusters (Fig. 10.4 a-c), composed by lamina-like structures (Fig. 10.4 d) of ZnO (Fig. 10.4 e-g) are visible on Zn surface. Contrarily to other reported ZnO coatings [111], this coating did not alter the water contact angle of the material surface (Fig. 10.4h). The presence of ZnO coatings with distinct superficial characteristics can be used as another strategy to further functionalize Zn/ZnO surface. An example of a composite coating based on ZnO is the combined addition of hydroxyapatite nanoparticles (Fig. 10.5). The electrodeposition procedure used yielded a homogeneous coating (Fig. 10.5a) composed by ZnO flowered structures (b) containing hydroxyapatite nanoparticles (Fig. 10.5c-g). This so far unexplored coating may render additional physiological advantageous when envisaging bone-healing applications.

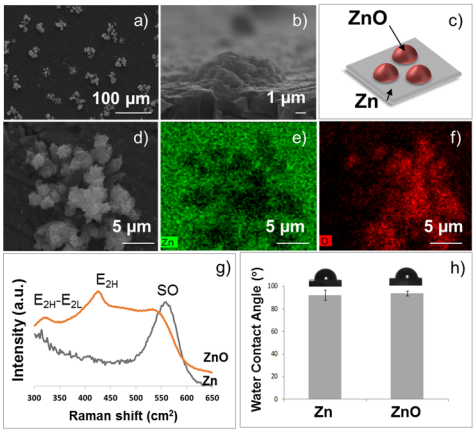

FIGURE 10.4
Zn plate coated with ZnO clusters obtained by electrodeposition with a square-wave potential of -0.6 V vs. SCE and -1.9 V vs. SCE of 1s each for 20 times; (a) top scanning electron microscopy (SEM) image, (b) cross-section SEM image view and (c) schematic representation of the coating; (d) top SEM image of a ZnO cluster and (e, f) corresponding energy dispersive X-ray spectroscopy (EDS) maps; (g) Raman spectra and water contact angle of bare and coated Zn

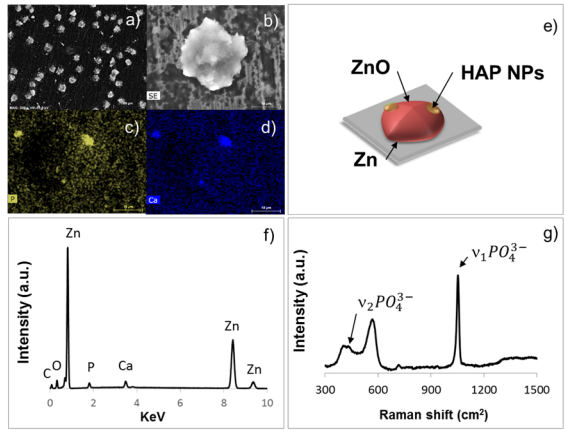

FIGURE 10.5
Zn plate coated with ZnO flowers and hydroxyapatite nanoparticles (HAP NPs) obtained by electrodeposition with a constant cathodic potential of -1.9 V vs. SCE for 20 s followed by a constant anodic potential of 0.5 V vs. SCE for 60 s; (a) top scanning electron microscopy (SEM) image of the coating; (b) top SEM image of a ZnO-HAP cluster and (c, d) corresponding energy dispersive X-ray spectroscopy (EDS) maps; (e) schematic representation of the cluster; (f) EDS and (g) Raman spectra of the coated Zn sample

Conclusion and future trends

Today the development of innovative biodegradable metals is one of the most interesting research topics at the vanguard of biomaterials. Undoubtedly, biodegradable metals represent the next generation of metallic biomaterials, which have as main purpose support transient healing process. It is expected them to have *in vivo* controlled biodegradation, with a positive host response until complete tissue healing and implant absorption. Until now, the newly-developed biodegradable metals that have been explored include three classes of metals: Magnesium (Mg), Iron (Fe) and Zinc (Zn) as well as respective based alloys. They have been investigated as alternatives for the currently-used permanent orthopaedic, cardiovascular and paediatric implants. Magnesium and Mg-based alloys are the most studied biodegradable materials with three levels of investigations conducted so far: *in vitro*, *in vivo* and human clinical trials, with both iron and zinc reaching to *in vivo* animal testing. Although biodegradable metals are very promising materials there is still a long way to go to characterize and optimize their performance, namely (i) the interaction between their degradation products and the surrounding tissues and consequent physiological effects, and (ii) the correlation between the *in vitro* and *in vivo* studies including degradation mechanisms and loss of mechanical integrity.

Although far from being widely studied, these metallic biomaterials have already proven to require an improvement in their characteristics. To answer these questions the scientific community has been functionalizing the surface of biodegradable metals. Magnesium, the most studied bioabsorbable material, has a rapid degradation *in vivo* that needs to be controlled. Organic,

inorganic and composite coatings have been applied to overcome its fast degradation and earlier lose in mechanical integrity.
Iron due to its mechanical properties has recently attracted a renewed interest of researchers. The studies published so far are mainly related with the functionalization of iron surface by ionic implantation. Few studies were focused on the functionalization of iron with organic or inorganic coatings, clearly indicating a gap in this field, namely towards the development of strategies to accelerate the *in vivo* degradation of iron-based materials.
Zinc, unlike the other two metals is at an early stage of development. Most of the studies are still focused on modifying the mechanical properties of pure zinc to meet clinical requirements. While there is no question relating zinc degradation, new strategies to overcome the emerging antimicrobial resistance have been recently published towards the functionalization of zinc with zinc oxide. Apparently these are very promising results to cope with the growing trend of implant-associated infections. Much remains to be explored, particularly when envisaging improved zinc properties so that it can be used as an alternative to the current non-biodegradable metals.
Overall, the multidisciplinary research on biodegradable metals is an exciting field, believed to be in a near future the key factor toward unquestionable substitution of permanent implants for transient healing processes.

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