Chapter 3
Bioactive Ceramics and Metals for Regenerative Engineering

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CONTENTS
3.1 Bioactive Ceramics 32
  3.1.1 Bioactive Ceramics and Their Challenges 32
  3.1.2 Bioactive Ceramics with Osteoinductivity for Regenerative Engineering 33
  3.1.3 Bioactive Ceramics for Regenerative Engineering 35
    3.1.3.1 Calcium Phosphate Bioactive Ceramics 35
    3.1.3.2 Bioactive Silicate Ceramics 35
    3.1.3.3 Ceramic-Based Composite Scaffolds 36
  3.1.4 Processing and Fabrication of Bioactive Ceramics for Regenerative Engineering 36
3.2 Bioactive Metals 38
  3.2.1 Bioactive Metal with Osteoinductivity for Regenerative Engineering 39
  3.2.2 Biodegradable Metals for Regenerative Engineering 40
    3.2.2.1 Degradation Mechanism of Biodegradable Metals 40
    3.2.2.2 Types of Biodegradable Metals 41
  3.2.3 Biodegradable Metals with Clinical Application 42
  3.2.4 New Manufacturing and Processing Techniques of Biomedical Metals 45
3.3 Concluding Remarks and Perspectives 46
References 46

Regenerative engineering begins a new era for repairing damaged tissues or organs with the aim of creating living, functional tissue that has the ability to replace dysfunctional tissues or organs. While integrating the biological aspects of tissue regeneration via stem
cells, factors, and cytokines, regenerative engineering requires the materials not only to be bioactive but also to stimulate specific biofunctions and cellular responses at the molecular level [1] and, thus, initiate tissue regeneration.

Among the bioactive materials applied in the clinic, bioactive ceramics and metals, as well as their composites, have always played important roles. This chapter will review related up-to-date and ongoing work in this area.

3.1 BIOACTIVE CERAMICS

3.1.1 Bioactive Ceramics and Their Challenges

Bioceramics are ceramic materials that have been specially developed for repairing hurt or damaged hard tissues, such as bone and teeth [2]. Most of the existing bioceramics are biocompatible, and some of them are bioactive with good bone bonding capability and have been applied successfully in the clinic [3–5]. The challenges for bioceramics mainly lie in the following three areas:

First, the brittleness and low resistance to fatigue of bioactive ceramics limit their application to bone defect filling. Table 3.1 shows the comparison between natural bone and several typical bioactive ceramics. Many efforts have been made to enhance the mechanical properties of ceramics. One of the widely applied methods is to create a composite using a polymer, either natural or synthetic [6–9], which is more flexible but softer than bioceramics. Normally, these composites show improved mechanical properties with good biological performances still being maintained. Another promising method is to develop nano-ceramic scaffolds. Nano-materials have more strength and toughness than conventional materials, and considerable research has demonstrated the improved mechanical strength as well as bioactivity. For example, hydroxyapatite (HA) nano-ceramics prepared by selective laser sintering showed outstanding mechanical properties and bioactivity which can induce bone regeneration [10].

Second, an important challenge for bioceramics is to be biodegradable with their degradation kinetics matching the living tissue formation, which is usually slower [20]. The ideal implants for regenerative engineering need to work as primary scaffolds and then degrade gradually and finally be replaced by the new tissue. Generally, the degradation rate of a

<table>
<thead>
<tr>
<th>Materials</th>
<th>Compression (MPa)</th>
<th>Flexure (MPa)</th>
<th>Elastic Modulus (GPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural bone [11, 12]</td>
<td>Compact</td>
<td>131–224</td>
<td>78.8–151</td>
</tr>
<tr>
<td></td>
<td>Cancellous</td>
<td>3–20</td>
<td>3–20</td>
</tr>
<tr>
<td>Calcium-phosphate based ceramics [13, 14]</td>
<td>Dense</td>
<td>300–500</td>
<td>60–120</td>
</tr>
<tr>
<td></td>
<td>Porous (≥50%)</td>
<td>&lt;30</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Silicate-based ceramics [15–17]</td>
<td>Dense</td>
<td>200–400</td>
<td>50–100</td>
</tr>
<tr>
<td></td>
<td>Porous (≥50%)</td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Polymer-ceramic composites [18, 19]</td>
<td>–</td>
<td>5–100</td>
<td>10–200</td>
</tr>
</tbody>
</table>
ceramic could be adjusted partly by varying the phase composition [4, 21]. For example, a composite mixture consisting of poorly soluble HA and highly soluble beta-tricalcium phosphate (β-TCP) with different phase ratios is considered to be able to achieve an optimal degradability [3, 22, 23]. Another efficient approach for adjusting the degradation rate of bioceramics is to be combined with a degradable polymer [7, 24, 25].

Finally, to date, there still remain several problems that bioactive ceramics must overcome, such as the toxicity of the degradation products, the complexity of the fabrication process, as well as the unsatisfied mechanical strength for load-bearing repair. The most effective way may be the fast and massive tissue formation within the scaffolds, which could lead to tissue regeneration and thus rebuild its biofunction. Therefore, to optimize and improve the bioactivity to induce tissue regeneration have always been the direction for research and development of bioactive ceramics [4, 26].

3.1.2 Bioactive Ceramics with Osteoinductivity for Regenerative Engineering

The first report of “osteoinduction” came from the work of Urist et al. who found the osteoinduction of BMP [27]. However, the discovery of osteoinduction of calcium phosphate (Ca-P) bio-ceramics highlighted the potential to explore a new generation of biomaterials. Ca-P osteoinductive bio-ceramics could induce tissue regeneration and, thus, is hopeful in achieving permanent restoration of damaged tissue.

In recent decades, much research has been conducted on the osteoinduction of Ca-P ceramics. One focus is on the important material factors which contribute to the osteoinductivity of the Ca-P biomaterials, as shown in Figure 3.1. Phase composition, referred to as chemical composition in some cases, was confirmed to affect the osteoinductivity. The most popular osteoinductive Ca-P ceramics include HA, β-TCP, and BCP (a mixture of HA phase and β-TCP phase with different ratios) [4, 28], and the reported osteoinductivity is in an order as BCP > β-TCP > HA >> α-TCP [29–31]. It seems that Ca-P ceramics with higher solubility could result in higher osteoinductivity, while the exception happens when the ceramic is too soluble to afford stable interface, such as β-TCP and α-TCP [32]. Macro- and micro-pore structures have been confirmed as necessary for Ca-P osteoinduction [33]. The porous structures accommodate the ingrowth of cells, and the interconnected porous channel functions to allow body fluid, blood vessels, and cells to develop toward the center of the scaffold, as well as the adequate exchange of oxygen and nutrition. Micro-pores (pore diameter <10μm) on the walls of macro-pores allow the body’s fluids to penetrate; they afford an inner rough surface for cell attachment, the adsorption of proteins [34], and the expression of osteogenic phenotype [4, 30, 35], as well as maintain the local concentration of dissolved Ca^{2+} and PO_4^{3−} and decrease the shear stresses exerted on the cells. Ca-P ceramics lacking a porous structure, such as Ca-P cements, do not show osteoinductivity [32]. Besides, other physiochemical characteristics of Ca-P bio-ceramics, such as bone-like apatite, nanoscale, and nanostructure [14, 36], the releasing of Ca^{2+} and PO_4^{3−}, the surface topography, as well as the surface mechanical properties, are found to be highly related to osteoinductivity. Optimizing these properties may endow the material with the function of inducing bone regeneration and, thus, enhance their bioactivity.
Another focus is on the mechanism of Ca-P osteoinduction. As for the biological process of bone regeneration, the microenvironment created by Ca-P bioactive ceramics benefits from the interactions between cells and matrix; subsequently, the biosignals initiate cell differentiation along the osteolineage and bone regeneration. Figure 3.2 shows the differentiation of mesenchymal stem cells (MSCs) along the osteolineage, induced by Ca-P bioactive ceramics, and the hypothesis for the osteoinductive mechanism of Ca-P, in which various interacted factors and processes have been involved. The existing theories mainly concern the adsorption of proteins and the interaction between Ca-P materials and different cells. Besides, as the osteoinduction of Ca-P involves not only the bone system but also the vascular and immune systems, a hybrid hypothesis was proposed and described as follows: first, the injury caused the invasion of the inflammatory factors and cells; second, the Ca-P ceramics work through soluble factors (such as Ca\(^{2+}\) and PO\(_4\)^{3−}\) ions), insoluble factors (such as their micro- or even nano-scale topographic features), and/or interact with inflammatory factors and cells, thus resulting in the adsorption and concentration of related proteins (osteogenic growth factors, cell adhesive proteins, and inflammatory factors), as well as the recruitment of various kinds of progenitor cells (monocytes, MSCs, endothelial cells, and pericytes); the process above may be accompanied with the dynamic dissolution/precipitation of Ca-P, and co-precipitation of proteins to form the bone apatite-like layer on Ca-P surface; third, there are two pathways that may lead to the osteoinduction: one is that Ca-P (as the changed form) directly stimulates the osteoblastic differentiation of MSCs;
the other one is that Ca-P interacts with the inflammatory cells (monocytes, macrophages, and osteoclast), which result in a more osteoinductive surface and higher concentrations of Ca\(^{2+}\) and PO\(_4\)^{3−}, as well as osteogenic cytokines, and finally, these factors trigger the MSCs differentiation. The last step may involve the angiogenesis, which could interact with both the Ca-P and inflammatory response, to contribute to osteoinduction by providing more osteogenic factors and MSCs.

3.1.3 Bioactive Ceramics for Regenerative Engineering

3.1.3.1 Calcium Phosphate Bioactive Ceramics

Among various bioactive ceramics, Ca-P ceramics are undoubtedly the most promising [3, 4, 23] and have been used widely in a variety of orthopedic treatments for diseased and damaged bones. Many products have been placed on the market. One product branded as Osteoinductive Calcium Phosphate Bioceramics (BAM®) by Engineering Research Center in Biomaterials, Sichuan University, has been cleared by the State Food and Drug Administration in 2003.

The products are mainly used in non-load-bearing orthopedic repair, and the research for the optimization of bioactivity to induce full bone regeneration is still ongoing. Currently, Ca-P coating with bioactivity on biomedical metals, such as titanium (Ti) metal and its alloys, stainless steel, and Co–Cr–Mo alloys, is widely used for the load-bearing purpose and has been successfully applied in artificial hip joint and dental implants.

3.1.3.2 Bioactive Silicate Ceramics

To date, more than 20 silicate ceramics with various compositions have been prepared [37–39]. The study of bioactive silicate ceramics for bone tissue regeneration has become a hot topic. The research has focused on the ceramic preparation methods,
mechanical strength, apatite mineralization, dissolution, bioactive properties and corresponding mechanism. The first and most famous silicate ceramics is Bioglass (BG), which has been approved by the Food and Drug Administration (FDA) and applied in the clinic for treating periodontal diseases and middle ear surgery. Another product branded as NovaBone® extended the application of BG to the orthopedic area [40–42]. Generally speaking, as silicate ceramics are in the form of powders, their clinical applications are still limited due to the relatively poor mechanical properties, in particular, low fracture toughness. A promising application is to deposit ceramic and glass onto the surface of Ti and its alloys to achieve excellent mechanical properties [43, 44].

3.1.3.3 Ceramic-Based Composite Scaffolds
A series of natural and synthetic polymers have been widely employed to prepare polymer–ceramic composite. The composites improve the mechanical properties more or less, while the disadvantage includes poor cell affinity and cell–matrix interaction resulting from the release of acidic degradation products.

Research also discussed adding inorganic materials in the composite scaffolds. Many types of composites such as Ca-P/Ca-Si composites and Ca-P/BG have been successfully prepared and showed higher bioactivity and more desirable degradability than those of single ceramics [45, 46].

3.1.4 Processing and Fabrication of Bioactive Ceramics for Regenerative Engineering
The bioactivity and clinical application potential of ceramics are highly dependent on the material compositions, the scaffold morphologies, and microstructure as well. The preparation of ceramics normally includes four steps, with the detailed process shown in Figure 3.3. Generally, the implants must have the shape or size matching the defects. More importantly, to endow the ceramics with bioactivity, the porous structure of the scaffold is key [6, 47–49]. Table 3.2 shows the different types of pores and their roles in biofunction restoration. Therefore, controlling pore structure is one of the most important procedures during ceramics scaffold preparation.

FIGURE 3.3 Normal process for the fabrication of bioactive ceramics.
Conventional fabrication methods of porous structure are listed in Table 3.3. Microsphere-sintering seems to be ideal because the pore size and porosity can be easily controlled, but it’s difficult to produce abundant micropores, and the ceramics using this approach don’t possess good bioactivity or osteoinductivity. Another feasible approach is H₂O₂ gas-foaming method, which is favorable to produce abundant micro pores besides interconnecting macro-pores. This method is low-cost, quick, and easy, but its disadvantage is that it is hard to control the porosity [3, 50].

Recently, three-dimensional (3D) printing has been employed to create complex porous ceramic matrices directly from powders [52–55], making it possible to produce bone grafts with complex shapes and internal channel networks mimicking bone structures. One of the limitations comes from the printing accuracy, including the printer controlling system and the “printing-ink.” At present, it’s difficult to control the microstructure on the micrometer scale. In addition, the present fabricating routines for ceramic scaffolds generally include the printing of the materials and the following sintering. Due to the shrinkage of ceramics in sintering, it’s difficult to get the designed scaffolds using direct 3D printing. Future research should develop novel prototyping methods to improve the precision controlled at the micrometer, the molding method to strengthen mechanical properties, and the structural design to optimize the bioactivity of the scaffolds.

### TABLE 3.2 Porous Structures in Natural Cancellous Bone and Their Functions [22, 50, 51]

<table>
<thead>
<tr>
<th>Pore</th>
<th>Size (μm)</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro-pore</td>
<td>100–800</td>
<td>Facilitating the rapid bone ingrowth and vascularization</td>
</tr>
<tr>
<td>Minor-pore</td>
<td>10–100</td>
<td>Favorable to exchange of nutrient substances and growth of cells</td>
</tr>
<tr>
<td>Micro-pore</td>
<td>&lt;10</td>
<td>Beneficial to the penetration of body’s fluids and favorable to protein adsorption</td>
</tr>
</tbody>
</table>

### TABLE 3.3 Fabrication Methods for Three-Dimensional Porous Ceramic Scaffolds

<table>
<thead>
<tr>
<th>Methods</th>
<th>Pore Diameter (μm)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsphere-sintering</td>
<td>10–1000</td>
<td>High mechanical properties; controlled pore size and porosity</td>
<td>Lack of micropores; use of template</td>
</tr>
<tr>
<td>Gas-foaming [3, 58–60]</td>
<td>100–800, &lt;100</td>
<td>Abundant micropores; interconnecting pores, low cost</td>
<td>Difficultly in controlling pore structure</td>
</tr>
<tr>
<td>Freeze drying [61–63]</td>
<td>10–600</td>
<td>Biomimetic 3D porous structure</td>
<td>Time-consuming</td>
</tr>
<tr>
<td>Organic foam impregnation [64–67]</td>
<td>100–5000</td>
<td>Easily controlling, high porosity</td>
<td>Lack of micropores; low mechanical properties; use of template</td>
</tr>
<tr>
<td>Electrospinning [68–70]</td>
<td>0.1–50</td>
<td>High porosity; abundant micropores</td>
<td>Lack of macropores; low mechanical properties</td>
</tr>
<tr>
<td>3D printing [52–55]</td>
<td>50–1000</td>
<td>Controlled pore size and porosity; highly reproducible</td>
<td>Need special equipments</td>
</tr>
</tbody>
</table>
The sintering process is necessary for the fabrication of bioceramics with certain mechanical properties and structures. In the meantime, some microstructures could be produced by sintering such as nano-sized crystals and micro-porous structure. Traditional sintering processes include muffle sintering, hot pressure sintering, and vacuum sintering (Table 3.4). High temperature sintering would increase the mechanical strength of ceramics while, in turn, result in larger-sized crystals and denser microstructures, which are regarded as adverse to its bioactivity. Therefore, some new sintering processes such as spark plasma sintering, two-step sintering, and microwave sintering to produce ceramics with nano-crystals and increased micro pores show potential in improving the bioactivity of the ceramics.

### 3.2 BIOACTIVE METALS

The introduction of metal as biomaterials has been known in medical applications for a long time. In their early development, mechanical strength and corrosion were two main problems faced by metal implants. With the development of new generation bio-materials, the separate concepts of bioactive materials and biodegradable materials have converged.

With the recent development in biomaterials, a new concept of biodegradable metals (BM) has been dramatically developed. The BMs are defined as materials used for medical implants that allow the implants to degrade in human body environment [83]. In materials science, BMs can be classified as pure metals, alloys, and metal matrix composites. Given the concerns for the biosafety of the corrosion products, the alloying elements and their quantities should be controlled without causing adverse pathophysiological and toxicological effects.

#### TABLE 3.4 Advantages and Disadvantages of Different Ceramic Sintering Routes

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muffle sintering [3, 71]</td>
<td>Inexpensive device; high yield; suitable for conventional and large size of ceramic fabrication</td>
<td>Time and energy consuming; unsuitable for nanoceramic fabrication</td>
</tr>
<tr>
<td>Hot pressure sintering [72, 73]</td>
<td>Suitable for conventional and dense ceramic fabrication; high mechanical strength</td>
<td>Low yield; time and energy consuming; unsuitable for nanoceramic fabrication</td>
</tr>
<tr>
<td>Vacuum sintering [74, 75]</td>
<td>High yield; suitable for conventional and large size of ceramic fabrication</td>
<td>Special equipment, time and energy consuming; unsuitable for nanoceramic fabrication</td>
</tr>
<tr>
<td>Spark plasma sintering [76–78]</td>
<td>Rapid process; low energy cost; suitable for nanoceramic fabrication</td>
<td>Expensive devices; low yield; difficult for large size of ceramic fabrication</td>
</tr>
<tr>
<td>Two-step sintering [79, 80]</td>
<td>Inexpensive device</td>
<td>Time and energy consuming; difficult for nanoceramic fabrication</td>
</tr>
<tr>
<td>Microwave sintering [3, 14, 81, 82]</td>
<td>Rapid process; low energy cost; suitable for nanoceramic fabrication</td>
<td>Expensive devices; difficult for large size of ceramic fabrication</td>
</tr>
</tbody>
</table>
3.2.1 Bioactive Metal with Osteoinductivity for Regenerative Engineering

From a clinical point of view, the ideal biomaterial acting as a bone substitute should possess osteoconductive and osteoinductive ability, as well as suitable mechanical properties [31, 84]. As osteoinductive biomaterials, the important factors for osteoinduction are thought to be (i) the chemical composition of the biomaterial surface and (ii) the surface morphology of the biomaterial. The formation of calcium phosphate bone-like apatite surface of the material is considered to be an important factor in osteoinductive materials. At the same time, the porous structure is considered to be an essential factor to induce bone formation. That is, all biomaterials that induce apatite layer in the body may have the potential to be osteoinductive materials when they possess a specific porous structure.

Since the 1980s, it has been reported that bioactive metals could be converted into an osteoinductive material through specific chemical and thermal treatments. It is well established that metal implants bond to living bone through an apatite layer that forms on their surfaces in the living body. The metals with bone-like apatite formation ability on its surface, when given a proper porous structure, demonstrated their osteoinductive ability [85].

Generally, Ti was reported to show that it has a superior in vitro apatite-forming ability and that it can directly bond to living bone in vivo. However, in most cases, appropriate surface treatments are necessary to modify and activate the metal surface, thus endowing a porous metal with osteoinductive bioactivity. Surface treatments may change the surface microstructure and chemical composition of porous Ti. Porous Ti with different surface treatments showed excellent ability to induce bone-like apatite formation, thus possessing in vitro bioactivity. For example, surface treatments including acid-alkali treatment, hydrogen peroxide treatment, hydrogen peroxide solution containing tantalum chloride treatment, and chemical and thermal treatments performed on porous Ti, showed varied in vitro bone-like apatite forming ability and in vivo osteoinductivity. In dorsal implantations for 3 and 5 months, ectopic bone formation was found histologically in most porous Ti metals after implantation in the thigh bone of adult dogs for 2 months (Figure 3.4). These results demonstrated that surface treatments could endow porous Ti with apatite-forming ability in vitro and induce ectopic bone formation.

![SEM of porous Ti metals at magnifications of (a) 35×, (d) 100×, and osteoinduction phenomenon of the porous Ti metals after implantation in the thigh bone of dogs for 2 months.](image-url)
3.2.2 Biodegradable Metals for Regenerative Engineering

The concept of commercialized BM medical devices design opens an extreme new horizon and provides additional insight. Metallic biomaterials are no longer required to be inert but they should be able to assist in and promote the healing process. In practical clinical applications, several specific clinical problems (such as bone fracture and vessel blockages) need BMs for tissue healing process. The temporary support of BMs can only be provided by an implant made of degradable metals, which allow the implant to progressively degrade after fulfilling its function. Undoubtedly, with more successes emerging, BMs are becoming rising stars in the next generation of metallic biomaterials [86, 87].

3.2.2.1 Degradation Mechanism of Biodegradable Metals

As a key issue for BMs, biodegradation mechanism should be carefully investigated. In the last decade, including the corrosion mechanisms and their influencing factors, degradation rate control and ion release behavior of BMs have been widely studied [88]. The typical mode of degradation in BMs is through a corrosion process [89]. The corrosion generally proceeds by an electrochemical reaction with electrolyte to produce oxides, hydroxides, hydrogen gas, or other compounds. In the nearly neutral physiological environment, the corrosion reactions involve the following anodic dissolution of the metal and the reduction reaction (cathodic reaction); the corresponding degradation reactions are given in Equations (3.1)–(3.4):

\[
\begin{align*}
\text{Oxidation reaction:} & \quad M \rightarrow M^{n+} + n e^- \\
\text{Reduction reaction:} & \quad 2\text{H}_2\text{O} + 2e^- \rightarrow \text{H}_2(\text{g}) + 2\text{OH}^- \\
\text{Reduction reaction:} & \quad 2\text{H}_2\text{O} + \text{O}_2 + 4e^- \rightarrow 4\text{OH}^- \\
\text{Product formation reaction:} & \quad M^{n+} + n\text{OH}^- \rightarrow M(\text{OH})_n
\end{align*}
\]

When metals react with body fluid, they release electrons and form positive ions. In electrochemistry, the values of standard electrode potential provide a way to compare the relative ease of different metal elements to lose electrons and form ions in solutions. For biodegradable metals, they have a greater tendency to form their ions compared to hydrogen. The degradation mechanism of BMs is mainly electrochemical corrosion, and electrochemical measurements are conducted to predict the corrosion rate of BMs in vitro.

The biological environment has a considerable influence on the corrosion reactions of BMs. The corrosion mechanism and apatite formation process of BMs in the human biological environment are shown in Figure 3.5. From a chemical point of view, the chemical environment of blood plasma is highly soluble for BMs, especially because of the presence of a high concentration of chloride ions. Other ions present may also strongly contribute to the corrosion process. Besides, the body temperature of 37°C typically accelerates
Another significant factor determining the corrosion behavior of metals is the pH value. However, it is still a challenge for researchers to figure out the real corrosion mechanism of BMs in the human biological environment.

### 3.2.2.2 Types of Biodegradable Metals

The developed BMs include three main body systems: (i) Mg-based BMs, (ii) Fe-based BMs, and (iii) Zn-based BMs and other BMs (Ca-based and Sr-based BMGs, etc.). Table 3.5 shows some research progress for the three BM systems since 2010. It is clear that among these BMs, Mg-based BMs are the hottest topic and have been extensively published. Fe-based BMs are reported recently on alloy design and some animal testing as potential vascular stent. Zn-based BMs are studied by fewer researchers but seem to be a promising candidate in the family of BMs. Most research focuses on degradation rate controlling, in vitro cytotoxicity, and animal testing. Several Mg-based alloys have been reported and their degradation rate has been proven to be too fast and rarely homogeneous. Fe-based alloys show appropriate mechanical properties but very low degradation rate. Zn-based

**FIGURE 3.5** Corrosion mechanism and apatite formation process of BMs in human biological environment.
BMAs have corrosion rates faster than Fe, but slower than Mg. Considering Mg-based BMAs need decreased degradation rates while Fe-based BMAs need enhanced degradation rates, Zn-based BMAs are believed to be the next rising star in the BM family. However, there has been a paucity of reports in the literature regarding clinical trials.

3.2.3 Biodegradable Metals with Clinical Application

Figure 3.6 shows two main application products of BMAs, i.e., stents and orthopedic implants [113]. Stenting has become a proven procedure for the treatment of coronary artery occlusions. During this procedure, a stent is delivered and placed into a narrowed coronary artery by using a catheter system that is inserted into the artery through a small incision in the arm or groin. Since its first application in 1987 [114], stents have progressed from the conventional bare metal to the drug eluting and the most recent biodegradable stents.

Presently, biodegradable stents have been successfully applied in clinical trials. In 2005, Peeters et al. [115] reported that absorbable metal stents (AMS) (BIOTRONIK, Berlin, Germany) were implanted in 20 patients for the treatment of below-knee lesions. No patients showed any symptoms of allergic or toxic reaction to the stent material. The stents were nearly completely degraded 6 weeks after implantation. The first successful implantation of an Mg-based stent into the pulmonary artery of a preterm baby was reported by Zartner et al. in 2005 [116]. In the clinical trial, a Lekton Magic AMS by Lekton Inc. was implanted into the left pulmonary artery of a preterm baby. The degradation process

FIGURE 3.6 Two main clinical application products of BMAs: (a) stents; (b) and (c) orthopedic implants.
### TABLE 3.5 Some Research Progress of the Three BM Systems

<table>
<thead>
<tr>
<th>Types of BMs</th>
<th>Materials</th>
<th>Published Time</th>
<th>Progress and Findings</th>
<th>Potential Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg-based BMs</td>
<td>ZEK100 alloys [90]</td>
<td>2016</td>
<td>Evaluate the bioabsorbable metallic biomaterial/cell interfaces that may lead to toxicity</td>
<td>No declaration</td>
</tr>
<tr>
<td>Mg–Zn–Ca–Sr BMGs [91]</td>
<td>2016</td>
<td>In vitro responses of bone-forming MC3T3-E1 pre-osteoblasts to Mg–Zn–Ca–Sr BMGs were studied</td>
<td>No declaration</td>
<td></td>
</tr>
<tr>
<td>Mg–3 wt% Zn alloy (MZ3) [92]</td>
<td>2016</td>
<td>Hot rolled Mg-3 wt% Zn alloy (MZ3) has been investigated for its potential in orthopedic implants</td>
<td>Orthopedic implantations</td>
<td></td>
</tr>
<tr>
<td>Mg–8Er–1Zn [93]</td>
<td>2015</td>
<td>A novel Mg–8Er–1Zn alloy with the ultimate tensile strength (318 MPa), tensile yield strength (207 MPa) and elongation (21%) were reported</td>
<td>No declaration</td>
<td></td>
</tr>
<tr>
<td>Mg60Zn35Ca5 and Mg72Zn23Ca5 [94]</td>
<td>2015</td>
<td>Used first-principles molecular dynamics simulations to elucidate the structure of Mg60Zn35Ca5 and Mg72Zn23Ca5 bulk metallic glasses</td>
<td>No declaration</td>
<td></td>
</tr>
<tr>
<td>Nano-HA reinforced AZ31 [95]</td>
<td>2014</td>
<td>Embedded nHA particles enhance the biomineralization and control the degradation</td>
<td>Skeletal implants</td>
<td></td>
</tr>
<tr>
<td>Mg and Mg10Gd1Nd [96]</td>
<td>2014</td>
<td>Pre-incubation of material under cell culture conditions formed a natural protective layer, improved the biocompatibility of BMs</td>
<td>Orthopedic implantations</td>
<td></td>
</tr>
<tr>
<td>AZ31/(P1, 4, 4, 4 dpp) surface coating [97]</td>
<td>2014</td>
<td>Reported a new surface coating for Mg alloy AZ31 based on a low-toxicity ionic liquid, tributyl(methyl) phosphonium diphenyl phosphate, to control its corrosion rate</td>
<td>Stents</td>
<td></td>
</tr>
<tr>
<td>RS66 [98]</td>
<td>2013</td>
<td>In vitro and in vivo experiments were conducted to analyze the biodegradation behavior and the biocompatibility</td>
<td>Prosthesis implantation</td>
<td></td>
</tr>
<tr>
<td>Mg–Zn [99]</td>
<td>2011</td>
<td>Conducted biocompatibility test in vitro and biodgradation in vivo</td>
<td>Orthopedic implantations</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### TABLE 3.5 (Continued) Some Research Progress of the Three BM Systems

<table>
<thead>
<tr>
<th>Types of BMs</th>
<th>Materials</th>
<th>Published Time</th>
<th>Progress and Findings</th>
<th>Potential Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe-based BMs</td>
<td>Fe0.75B0.15Si0.1100-xNbx (x = 0, 1 and 3 at%) metallic glasses [100]</td>
<td>2016</td>
<td>Alloys exhibit excellent apatite-forming ability in simulated body fluids, which is expected to be applied in stents and orthopedic implants</td>
<td>No declaration</td>
</tr>
<tr>
<td>Fe-based BMs</td>
<td>Fe-based glassy alloys [101]</td>
<td>2016</td>
<td>Studied the multiple corrosion potentials alkaline solution</td>
<td>No declaration</td>
</tr>
<tr>
<td>Fe-based BMs</td>
<td>Fe-based metallic materials [102]</td>
<td>2015</td>
<td>Cytotoxicity of corrosion products of Fe-based stents relative to pH and insoluble products were studied</td>
<td>Stents</td>
</tr>
<tr>
<td>Fe-based BMs</td>
<td>Fe80-x-yCr0.5MoyP13C7 bulk metallic glasses [103]</td>
<td>2015</td>
<td>Alloys exhibit no cytotoxicity to NIH3T3 cells, and exhibit high corrosion resistance and excellent biocompatibility</td>
<td>No declaration</td>
</tr>
<tr>
<td>Fe-based BMs</td>
<td>Pure Fe and two alloys (Fe-10 Mn-1Pd, Fe-21 Mn-0.7C-1Pd) [104]</td>
<td>2014</td>
<td>The study investigated the degradation performance of three Fe-based materials in a growing rat skeleton over a period of 1 year</td>
<td>No declaration</td>
</tr>
<tr>
<td>Fe-based BMs</td>
<td>Fe–Mn–C–Pd alloys [105]</td>
<td>2013</td>
<td>The research studied the alloying elements’ influence on metabolic processes</td>
<td>No declaration</td>
</tr>
<tr>
<td>Fe-based BMs</td>
<td>Fe–Mn–Pd alloys [106]</td>
<td>2010</td>
<td>Proposed design strategy for the development of Fe-based alloys offering both an enhanced degradation rate and suitable strength and ductility</td>
<td>Medical applications</td>
</tr>
<tr>
<td>Fe-based BMs</td>
<td>Fe(73.5)Si(13.5)B9Nb3Cu1 alloy [107]</td>
<td>2010</td>
<td>Studied the corrosion behaviors of amorphous and nanocrystalline Fe-based alloys in NaCl solution</td>
<td>No declaration</td>
</tr>
<tr>
<td>Zn-based BMs</td>
<td>Zn–Mg and two Zn–Al binary alloys [108]</td>
<td>2016</td>
<td>Alloys were developed by casting process and homogenized followed by hot extrusion. Tube extrusion was performed to produce tubes for biodegradable stents. Corrosion tests were performed using Hanks modified solution</td>
<td>Stents</td>
</tr>
</tbody>
</table>

(Continued)
had been completed 5 months after implantation. In 2007, the PROGRESS-AMS clinical trial, sponsored by BIOTRONIK GMBH & Co. (Berlin, Germany), was conducted to assess the efficacy and safety of AMSs in eight centers. A total of 71 stents, 10–15 mm in length and 3–3.5 mm in diameter, were successfully implanted after pre-dilation in 63 patients. No myocardial infarction, subacute or late thrombosis, or death occurred. In 2016, Haude et al. [117] reported the first-in-man trial (BIO-SOLVE-1), which was conducted with 46 patients at five European centers. The 12-month results showed no cardiac death or scaffold thrombosis. As the above literature had reported, the biodegradable stents had been optimized to provide better degradation resistance than their predecessors, which demonstrated full degradation in 9–12 months.

Patients with bone disease or bone fractures are commonly admitted to the clinic. Thus, fractured bone fixtures, such as plates, screws, pins, nails, wires, and needles, consisting of BMs, have become a large potential market. So far, ZEK 100, LAE 442, MgCa 0.8, and MgYREZr Mg-based alloys have been fabricated in different orthopedic applications for experimental models and clinical trials.

### 3.2.4 New Manufacturing and Processing Techniques of Biomedical Metals

Usually, normal manufacturing and processing methods can be applied to obtain the BMs devices. However, rather than make alloys using a traditional melting process, some nonconventional processing techniques could improve their properties.

<table>
<thead>
<tr>
<th>Types of BMs</th>
<th>Materials</th>
<th>Published Time</th>
<th>Progress and Findings</th>
<th>Potential Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn–Mg alloy [109]</td>
<td>2015</td>
<td>Zn–Mg alloys with different Mg contents were prepared by melting-casting method. The nano-structure of Zn-3 wt% Mg alloy contributes to a general corrosion</td>
<td>No declaration</td>
<td></td>
</tr>
<tr>
<td>Zn alloys [110]</td>
<td>2013</td>
<td>Zinc exhibits ideal physiological corrosion behavior for bioabsorbable stents</td>
<td>Stents</td>
<td></td>
</tr>
<tr>
<td>CaZn-based bulk glassy alloy [111]</td>
<td>2011</td>
<td>Develop CaZn-based glassy alloys with low Young’s modulus, high fracture strength, good corrosion resistance and cytocompatibility</td>
<td>Orthopaedic implantations</td>
<td></td>
</tr>
<tr>
<td>Zn–Mg alloys containing up to 3 wt% Mg [112]</td>
<td>2011</td>
<td>The corrosion rates of the Zn–Mg alloys were determined to be significantly lower than those of Mg and AZ91HP alloys</td>
<td>No declaration</td>
<td></td>
</tr>
</tbody>
</table>
In recent years, some advanced manufacturing technologies have been proposed in BMs fields. For instance, by using 3D printing technology, the BMs can be directly processed into scaffolds or implants. To fabricate bone scaffolds, 3D porous structures have been pursued to allow for bony ingrowth to mimic the natural porous structure of bone. It has been possible to create a controllable porous, interconnected architecture via 3D printing technology. By using 3D printing, complex, customizable parts from metal powders can be directly manufactured into scaffolds with precise porosity. Researchers believe that 3D printing will be a promising technology for manufacturing BMs products.

3.3 CONCLUDING REMARKS AND PERSPECTIVES

The development of regenerative engineering provides an effective approach for tissue repair and regeneration. The selection of scaffold material and structure optimization is important to fully mimic the 3D network structure of natural tissue. Bioactive ceramics and metals are drawing more attention due to their excellent biocompatibility and osteogenesis. Thanks to the founding of bioactive ceramics with osteoinductivity, more focus is on the design of material bioactivity to induce tissue regeneration, to realize the replacement of damaged tissue by the regenerated new tissue. To achieve the objective, on the one hand, it is necessary to explore the responding mechanism between biomaterials and cells on a molecular and genetic level to supply principles for improving material bioactivity; on the other hand, it is necessary to probe new material designs and fabrication techniques to obtain tunable and optimized mechanical and degradation properties. For metals with superior mechanical properties, a future revolution might come from biodegradable metal implants. By optimizing the bioactivity of metals to achieve specific biological function such as osteoinduction and regulation of metal degradation, biometals are also expected to be able to achieve bone tissue regeneration in the future.

REFERENCES


113. Ding, W., Opportunities and challenges for the biodegradable magnesium alloys as next-generation biomaterials. Regenerative Biomaterials, 2016. 3: pp. 79–86.