Fundamental Theory of Biodegradable Metals—Definition, Criteria, and Design

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Until now there has been no fundamental theory applicable for biodegradable metals (BMs). First, this paper optimizes the definition of BMs given in 2014. Second, the dual criteria of biodegradability and biocompatibility are proposed for BMs, and all metallic elements in the periodic table with accessible data are screened on the basis of these criteria. Regarding biodegradability, electrode potential, reactivity series, galvanic series, Pilling–Bedworth ratio, and Pourbaix diagrams are all adopted as parameters to classify the degradable and nondegradable nature of a material, especially in a physiological environment. Considering the biocompatibility at different levels, cellular biocompatibility, tissue biocompatibility, and human/clinical related biocompatibility parameters are put forward to comprehensively evaluate the biosafety of BMs. Third, for the material design of BMs, mechanical properties, chemical properties, physical properties and biological properties should be considered and balanced to guarantee that the degradation behavior of BMs match well with a tissue regeneration/repair procedure as the function of time and spatial location. Besides the selected metallic elements, some nonmetallic elements are selected as suitable alloying elements for BMs. Finally, five classification/research directions for future BMs are proposed: biodegradable pure metals, crystalline alloys, bulk metallic glasses, high entropy alloys, and metal matrix composites.

1. Introduction

Since the first biodegradable suture was approved in the 1960s,[1] various biodegradable polymer materials have been developed and used in medical devices for fracture fixation, interference screws, suture anchors, meniscus repair, and many other applications which have stepped into the market.[2] Meanwhile, the design of polymers for biomedical applications has formed relatively complete theoretical systems.[3] The definition of biodegradable polymers has been given as “Polymers that require enzymes of microorganisms for hydrolytic or oxidative degradation”[4] or “Polymers degrade both in vitro and in vivo into products that are either normal metabolites or into products that could be completely eliminated from the body with or without further metabolic transformations.”[5] Biodegradable polymers can be classified by source into natural biodegradable polymers and synthetic biodegradable polymers. They can also be classified into hydrolytic biodegradable polymers and enzymatic biodegradable polymers by the degradation
process. The biodegradation of biodegradable polymer has been well defined as “cleavage of hydrolytically or enzymatically sensitive bonds in the polymer leading to polymer erosion.” Furthermore, the criteria of selecting biodegradable polymers has been set, as well as the design strategy for developing customized biodegradable polymers in tissue engineering, nanoparticles and nanocarriers, and for gene delivery.

In the research field of inorganic biomaterials, take the concept of bioactive glasses as an example. The concept was originally proposed by Prof. Hench and since widely accepted. Bioactive glasses are in nature biodegradable. The definition of bioactive glasses has been given as follows: A bioactive material is one that elicits a specific biological response at the interface of the material which results in a formation of a bond between the tissues and the material. Bioactive glasses had been classified by composition into silicate bioactive glass, borate bioactive glass, and phosphate bioactive glass. The biodegradation of bioactive glasses had been depicted as “decomposition to small particles as well as dissolved ions, which participate in the enzyme/cell mediated reaction and new tissue forms.” The criteria for being regarded as bioactive glass include excellent osteoconductivity and bioactivity, the ability to deliver cells, and controllable biodegradability. The desired parameters/criteria for bioactive glasses/glass–ceramics to function as a suitable biomaterial have been set. Moreover, design strategies have been proposed in the following aspects: 1) different applications (including bone regenration, angiogenesis and soft tissue repair, chondrogenesis and osteochondral tissue engineering); 2) material design including functioning as bioactive ceramic phases in biodegradable composites and a bioactive glass coating; 3) functional design including controlled drug delivery and ion delivery; and 4) processing strategy.

Since 2001, there have been over 1000 publications on the research and development of biodegradable metals, with Mg-based alloys at the dominant position, as well as Fe-based alloys, Zn-based alloys, Ca-based alloys, and so on. Recently, the WE43-modified alloy stent and WE43-based alloy bone staple have reached clinical trials in Europe, South Korea, and China, respectively. In 2014, Prof. Yufeng Zheng from Peking University gave the first version of the definition of biodegradable metals and its classification. However, no fundamental theory that can guide the R&D of biodegradable metals has ever been set. More specifically, some important questions need to be clarified, including:

1) Is the definition given well enough to thoroughly understand biodegradable metals? 2) Which metallic elements in the periodic table can be categorized as biodegradable metals? Which kinds of metallic and nonmetallic elements can be incorporated into biodegradable metals as a matrix or alloying element/additive phase? 3) As biodegradable metals, what properties should be paid attention to when designing biodegradable metals? 4) After one decade of fundamental research, is there any field remaining unexplored and where is the material design of biodegradable metals headed?
The aim of this work is to construct the frame of the fundamental theory of biodegradable metals, with the definition and classification being modified, biodegradability, and biocompatibility criteria being given, and future material design directions for BMs being proposed.

2. Modified Definition of Biodegradable Metals

Once implanted into the body, the implant and the host cells/tissues participate in localized chemical reactions at the interface. A biodegradable bone screw (especially biodegradable Mg-based) being implanted after bone fracture is illustrated in Figure 1.[32] The biodegradation process of the Mg-based BM screw begins with the release of metallic ions, hydroxyl ions, hydrogen, and small metallic debris falling off. Some biodegradation products are beneficial to the healing process. They can be absorbed, metabolized, and assimilated by adjacent cells/tissues, improving bone remodeling and resulting in better recovery. Meanwhile, excess biodegradation products are excreted. After fulfilling its mission, the screw is completely biodegraded with no residues.

The first edition of the definition of biodegradable metals (BM) has been given in 2014 as “metals expected to corrode gradually in vivo, with an appropriate host response elicited by released corrosion products, then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues.”[31] Meanwhile, ASTM-F3160, which was launched in 2016 as the newly developed testing standard for such materials, defined Absorbable Metallic Materials as “an initially distinct foreign material or substance that either directly or through intended degradation can pass through or be metabolized or assimilated by cells and/or tissue.”[33]

Despite the first edition definition of BMs mentioning the host response and assistance with tissue healing, this specific part of the definition must be further elucidated. It is by being absorbed and utilized by cells/tissues that biodegradation products assist in the healing process. Therefore, the modified definition of BMs is “metals expected to corrode gradually in vivo, with an appropriate host response elicited by released corrosion products, which can pass through or be metabolized or assimilated by cells and/or tissue, and then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues.” In this way, the term “biodegradable metals” is identical to the term “absorbable metallic materials” in ASTM-F3160.

3. Criteria for Being Biodegradable Metals

Around 60% of elements in the periodic table are metallic elements. Therefore, a question arises: can all the pure metal elements or alloys made by these elements be regarded as biodegradable metals or not? In general, two major aspects, including biodegradability and biocompatibility, should be taken into consideration (Figure 2). Only metals or alloys with both 100% biodegradability and 100% biocompatibility can be appropriate candidates as potential biodegradable metals, according to the definition of BMs. Unlike traditional metals and alloys for biomedical applications, such as Ti alloys, Co-based alloys, and stainless steel, biodegradable metals are bioactive, and the degradation products sometimes are beneficial for improving the healing process (i.e., Mg2+ for bone healing) of local tissue. Furthermore, the corrosion process can be homogeneous at the material surface and deters penetration, satisfying the basic requirements for a drug carrier and making BMs promising as drugs/drug carriers as well as implants.[34] To our understanding, the degradation products of BMs are bioactive, and more likely to be a sustained-release “drug” itself, instead of an implantable “medical device.” Therefore, we selectively chose...
100% biodegradability and 100% biocompatibility as sufficient and necessary conditions, without considering mechanical support as a basic criterion. This is different from the general consideration for the nonbiodegradable metals and alloys for load-bearing biomedical applications.

3.1. Biodegradability Criteria

The biodegradation of biodegradable materials is a chemical reaction process. With regard to biodegradable polymers, hydrolysis or enzymatic reaction is accompanied by the change of Gibbs free energy. The biodegradation of BMs in nature is a corrosive corrosion process in a biological environment, and Gibbs free energy is also involved in the process. Therefore, the parameters “electrode potential,” “reactivity series,” “galvanic series,” “Pilling–Bedworth ratio” as well as “Pourbaix diagram,” which are generally used in the characterization of the corrosion of metals and alloys, are comprehensively adopted to reveal the biodegradability of biodegradable metals and predict the resulting degradation products.

3.1.1. Electrode Potential

Like any other reaction, the reaction of a metal with its environment can be measured by the Gibbs free energy change, $\Delta G$. The more negative the value of $\Delta G$, the greater the tendency of the metal to corrode. Corrosion is a mechanism in electrochemical reactions. The term electromotive force (emf) of the corrosion cell has been used to describe the relation between the Gibbs free-energy and electric energy$^{[13]}$. The emf of the two half-cell reactions of corrosion has a more well-known name, “electrode potential,” according to the International Union of Pure and Applied Chemistry (IUPAC) definition$^{[16]}$.

Metals express different corrosion potentials in different body fluids. However, no sufficient and generally accepted values for the corrosion potential value of metals in different body fluids have been established so far. Meanwhile, the standard electrode potential reveals the degradation tendency of metals in a neutral water environment. In theory, any metal with a standard electrode potential lower than that of hydrogen ($E^0 = 0 \, \text{V}$) shows the potential to be degraded (hydrogen evolution reaction) in an aqueous environment under standard conditions. The reaction of pure metal with water is spontaneous and irreversible. Therefore, numerous metals with reduction reactions having $E^0$ value more negative than that of the standard hydrogen electrode have been reviewed. Based on electrode potential data and publications, elements Mg, Fe, Zn, Ca, and Sr all exhibit a negative standard electrode potential. Meanwhile, over 40 metallic elements show a negative standard electrode potential. Furthermore, to some degree, when the standard electrode potential is negative enough, the corresponding degradation rate is positively related to the potential value. For example, Ca and Sr have more negative potential values and therefore their corresponding base metals exhibit extremely quick corrosion rates compared to Mg, Zn, and Fe. However, it is not absolute since many other properties, including surface properties (such as passivation) and environmental parameters, affect the corrosion rate as well.

Furthermore, according to standard electrode potential data, tungsten (W) displays a positive standard electrode potential value (0.1 V), implying tungsten will not undergo corrosion (hydrogen evolution reaction) in an aqueous environment at standard conditions. However, some metals still show a standard electrode potential lower than that of O, indicating corrosion from oxygen absorption in an aqueous environment$^{[15]}$. For example, previous research has shown tungsten biodegraded both in vitro and in vivo$^{[17,38]}$. A slow biodegradation process occurred when implanting tungsten into the subclavian artery of New Zealand white rabbits, with an increase of serum tungsten from 0.48 to 12.8 $\mu$g L$^{-1}$ at 4 months after surgery$^{[38]}$. The biodegradation of tungsten is considered oxygen-aided since the oxygen content is relatively high in the artery$^{[19]}$. The standard electrode potential of oxygen is 0.4 V, which is higher than that of W. Oxygen, along with other environmental parameters, such as blood flushing and vascular pulsation, leads to the biodegradation of tungsten. In fact, there are two standard electrode potentials for O: 0.40 V (O in a neutral aqueous environment) and 1.23 V (O in combination with H$^+$ in acids), making some metals degradable in strong oxidative acids.

Regarding oxygen absorption corrosion, some metals with standard electrode potentials slightly higher than zero may as well have the potential to corrode under some circumstances. Metals with accessible data displaying a standard electrode potential lower than zero and slightly higher than zero have also been shown in Figure 3$^{[40,41]}$. Some metals with extremely low standard electrode potentials may not be appropriate to act as biodegradable metal matrix elements, since most of them cannot even be stably stored in air. Meanwhile, previously illustrated metals with standard electrode potentials slightly higher than zero are much more stable. They may become biodegradable only in some specific environments. For example, in the digestive tract, the pH value of saliva, upper stomach, lower stomach, duodenum, small intestine and large intestine are 6.5–7.5, 4.0–6.5, 1.5–4.0, 7.0–8.5, 4.0–7.0, and 4.0–7.0 respectively, with variations dependent on the time of food intake.

The pH value of the environment is related to the electrode potential of the metal. Equation (1) shows the determination of electrode potential, where $E^0$ is the standard electrode potential, $R$ is the gas constant, $T$ [K] is the temperature, $F$ is Faraday’s...
constant, \([O]\) is the concentration of oxidized species, and \([R]\) is the concentration of reduced species. Therefore, \(E\) will change when the quantities of \(H^+\) or \(OH^-\) involved in the reaction change, due to the effect of \([R]\) or \([O]\). Such a shift of the value of \(E\) may affect the biodegradation behavior, depending on the pH value involved.

\[
E = E^0 + \frac{RT}{nF} \ln \left( \frac{[O]}{[R]} \right)
\]  

(1)

3.1.2. Reactivity of Metals

The reactivity series, which is similar but not identical to the electrochemical series (i.e., the position of Li, Na, and K is different), also reflects the reactivity of metals in an aqueous environment. The reactivity of metals from general chemistry textbooks is shown in Figure 4. Metals with extremely high reactivity can react with cold water. Mg shows slightly lower reactivity, reacting slowly with cold water but rapidly in boiling water and acids. Some other metals show lower reactivity than Mg and they can either react with acids or only react with strong oxidizing acids. It needs to be noted that Ti is found to react with concentrated mineral acids (HCl, H2SO4, HNO3, H3PO4, etc.).[42] Therefore, as previously discussed, Ti might be bio-degraded when used in medical devices in the human digestive system.

3.1.3. Galvanic Series (Corrosion Potential)

Corrosion potential is a mixed potential (also an open-circuit potential or rest potential) at which the rate of anodic dissolution of the electrode equals the rate of cathodic reactions and there is no net current flowing in or out of the electrode.[43] It is known that a metal in a corrosive environment has its own

Figure 3. Standard electrode potential of metallic elements in the periodic table reflecting the degradability. Note: O* indicates O standard electrode potential in an acidic environment.

Figure 4. Reactivity series of pure metals in various aqueous environments. All metallic elements with reactivity over five transverse lines (marked by red solid lines) can react with the corresponding aqueous environment, labeled above the transverse line.
corrosion potential. Corrosion potential is affected by aspects such as the alloying elements, environment composition, surface state, absorbed gas, and mechanical stress.\cite{35}

According to ASTM, galvanic series refers to a list of metals and alloys arranged according to their relative corrosion potentials in a given environment.\cite{44} Currently, there is no available data about the galvanic series of metals and alloys in body fluid. The galvanic series in seawater can be used as a reference since NaCl concentrations in seawater and body fluid are similar.\cite{45}

The ranking of pure metals from anodic (active) to cathodic (noble) in seawater is as follows: magnesium, zinc, cadmium, wrought iron, cast iron, lead, tin, active nickel, copper, passive nickel, titanium, silver, gold, platinum. Moreover, zirconium is reported to lie at the noble end of the galvanic series of metals in seawater.\cite{46} In reality, alloys rather than pure metals have been used in applications. Different alloying elements show different tendencies on the electrode potential as well as electrochemical kinetics.

Corrosion potential can be more significant than standard electrode potential for metal corrosion. The pure metals Mg and Zn occupy the active end of the spectrum and are well accepted as biodegradable pure metals. It is also applicable for the biodegradable alloys composed of multiple metal elements. For example, the immersion behavior of the intermetallic compounds in a Mg–Zn–Ca system is highly dependent on the basal element content.\cite{47} Experimental results have demonstrated that the compounds based on Ca showed the highest degradation rate (fully degraded in less than 1 h). Meanwhile, compounds based on Mg possessed better degradation resistance, whereas compounds based on Zn perform the best degradation resistance.

In Figure 3, Zn showed higher standard electrode potential than Ti, but it will act as an anode and corrode if it is connected with Ti in seawater. The fact that Ti and Zr are much nobler in NaCl solution makes it inappropriate to regard them as BMs. Ti and Zr have high polarization resistance.\cite{48} Polarization resistance ($R_p$), as the slope of the polarization curve at the corrosion potential $E_{corr}$, is defined by the following equation:\cite{49}

$$R_p = (dE/dI)_{E_{corr}} \quad (2)$$

Polarization resistance has been widely utilized in the electrochemical determination of traditional bio-inert materials.\cite{48} Zr and Ti alloys are well known as permanent implant materials in medicine, since a dense surface oxide film can be formed on the surface.

With regard to the surface state, the surface oxide film is critical for the corrosive behavior of the metals. Pilling–Bedworth ratio ($R_{PB}$, as calculated by Equation 3) is used to define the integrity of the surface oxide film, where $M$ is the atomic or molecular mass, $n$ is the number of atoms of metal per molecule of the oxide, $\rho$ is density, and $V$ is the volume. Based on their $R_{PB}$ value, metals can be classified into three groups. $R_{PB} < 1$ indicates a loose oxide film on the surface. Lower values of $R_{PB}$ are usually found in high activity alkali metals and alkaline-earth metals. However, a higher $R_{PB}$ value is not necessarily better. $R_{PB} > 2$ suggests the leakage or cracking of the film, which cannot provide good protection. The oxide film is compression-strengthened, compact and sometimes considered passivated (such as Ti and Al) when $1 < R_{PB} < 2$, which will provide good protection from further corrosion. Details for the $R_{PB}$ of metals can be found elsewhere.\cite{35,50} Figure 5 summarizes the correlation between standard electrode potential and $R_{PB}$ of metals with accessible data.

$$R_{PB} = \frac{V_{oxide}}{V_{metal}} = \frac{M_{oxide} \cdot \rho_{metal}}{n \cdot M_{metal} \cdot \rho_{oxide}} \quad (3)$$

3.1.4. Pourbaix Diagram

To better predict corrosion, the Pourbaix diagram has been developed. It indicates regions of potential and pH in which metal undergoes corrosion and other regions of potential and pH in which metal is protected from severe corrosion.\cite{50} For example, zinc has shown higher corrosion rates at both low...

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Figure 5. $R_{PB}$ and standard electrode potential values of metallic elements.
and high pH values (dissolved as Zn$^{2+}$ in acidic solutions and ZnO$^{2-}$ in basic solutions), and a lower corrosion rate in a neutral environment.\cite{51}

The Pourbaix diagram provides not only the evidence of corrosion, but also the prediction of corrosion products. Figure 6 shows the calculated Pourbaix diagram of pure Mg, Fe, and Zn in physiological concentrations. The concentration of Mg is set to be $1 \times 10^{-3}$ m. The concentrations for HPO$_4^{2-}$ and HCO$_3^-$ (CO$_2$aq)) in the diagram are set to be identical to the concentrations in human blood plasma ($0.001$ mol L$^{-1}$ for HPO$_4^{2-}$, and $0.027$ mol L$^{-1}$ for CO$_2$(aq)).\cite{52}

The potential of tissue fluid is reported to be around 0.78 V. Therefore, Mg will react in the fluid and become Mg$^{2+}$ in physiological conditions (pH $\approx 7.4$, $E \approx 0.78$ V) according to the diagram. As the reaction proceeds, local pH increases. Ideally, MgCO$_3$ and Mg(OH)$_2$ form successively. However, due to the nonuniform corrosion of Mg, a pitting-induced very high pH value would introduce Mg(OH)$_2$ instead of MgCO$_3$ on the surface. The remaining HPO$_4^{2-}$, PO$_4^{3-}$, and CO$_3^{2-}$ can further react with Ca either in the solution or in the alloys as alloying elements. As for Fe, since the pH change is limited, Fe$_2$O$_3$ will form eventually. However, in the defined region there is no sign of CO$_3^{2-}$ or HCO$_3^-$, but HPO$_4^{2-}$ exists. As for Zn in a physiological environment, ZnO remains the only solid product. No Zn$_3$(PO$_4$)$_2$ would be formed, reflected from Figure 6c, which is in accordance with previous studies.\cite{52}

3.1.5. Brief Summary on Biodegradability Criteria

Based on standard electrode potential, reactivity, and galvanic series (corrosion potential), all the metallic elements with standard electrode potential lower than zero exhibit the potential to initiate corrosion in a neutral aqueous environment. Furthermore, metals with an electrode potential slightly
higher than zero may be degraded under certain microenvironments inside the human body. In general, electrode potential and galvanic series show the tendency for corrosion, but the degree of the corrosion kinetics or degradation process is dependent on some specific aspects, such as the surface film condition and environmental parameters such as pH and flow. These can be reflected by Pilling–Bedworth ratio and Pourbaix diagram.

### 3.2. Biocompatibility Criteria

Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application.\(^{[53]}\) The toxicity of metals is the toxic effects of certain metals in certain forms and doses on life.\(^{[54]}\) Biocompatibility is a complex concept, which can be affected by many factors. As it is known, ISO 10993 defines a way to evaluate the toxicity of biomaterials. It is applicable for traditional nondegradable metallic biomaterials, such as Ti alloys, Co-based alloys, and stainless steels, but it is not 100% applicable for BMs. The biocompatibility of materials can be considered on several levels including cellular biocompatibility, tissue biocompatibility, and most importantly human/clinical related biocompatibility. Hereafter, technical parameters regarding the biocompatibility evaluation at these three levels are summarized and comprehensively discussed for BMs. One thing which must be mentioned is that the data about human cells (such as Human Umbilical Vein Cells) and tissues (such as blood) are listed in the human/clinical biocompatibility section instead of cellular biocompatibility or tissue biocompatibility sections.

#### 3.2.1. Cellular Biocompatibility

IC\(_{50}\) (50% inhibitory concentration) is an index widely utilized to indicate cytotoxicity. The value of IC\(_{50}\) indicates half inhibitory concentration, which provides evidence for the element toxicity at the cellular level. Current data for the toxicity of metallic ions are scattered and incomplete. The data from different labs, at different times, with different cell lines, might exhibit a similar variation trend but the numerical value would be different. Hereby we adopted the IC\(_{50}\) data reported by A. Yamamoto et al. with several species of metallic ions being evaluated at the same time under the same condition (Figure 7).\(^{[55]}\) Different cells show different responses to different kinds of metallic ions. However, in general, most metallic ions show less toxicity to L929 cells than to MC3T3-E1 cells. Among them, Li showed the highest IC\(_{50}\) value for both MC3T3-E1 and L929 cells, while elements V and Ag revealed IC\(_{50}\) values lower than 10\(^{-5}\) mol L\(^{-1}\) for both kinds of cells. Also, the results showed a tendency that most of the low toxicity metal salts (IC\(_{50}\) > 10\(^{-3}\) mol L\(^{-1}\)) are hard (Lewis) acid metallic elements (Li\(^+\), Rb\(^+\), Cs\(^+\), Sr\(^{2+}\), Ba\(^{2+}\), Cr\(^{3+}\), Fe\(^{3+}\), Zn\(^{2+}\), and W\(^{6+}\)), while soft (Lewis) acid metallic elements showed relatively higher toxicity, such as Ag\(^+\), Hg\(^+\), and Au\(^+\) (data not shown). Other metallic salts with metallic ions between hard and soft have relatively moderate toxicity around 10\(^{-4}\) mol L\(^{-1}\). Such a correlation indicates that the toxicity of metallic ions is to some degree dependent on the ability to bind to proteins. It deserves to be mentioned that the IC\(_{50}\) value of the salts of metallic major elements Na, K, Mg, and Ca are seldom investigated, but the salts MgSO\(_4\), CaCl\(_2\), NaCl, and KCl have been adopted to provide the essential electrolyte for cells in DMEM. This implies the IC\(_{50}\) of these four major elements can be much higher than other metallic ions illustrated above.

Moreover, chlorides of some rare earth elements (REEs), including Y, La, Ce, Pr, Nd, Eu, Gd, and Dy, have been evaluated for their toxicity to three kinds of cells including RAW264.7, human osteosarcoma cell line MG63, and human umbilical cord perivascular cells (HUCPV).\(^{[56]}\) RAW264.7 cells showed more sensitivity to all of the chlorides, with initial inhibitory concentration (ICC) ranging from 30 × 10\(^{-6}\) M (Ce) to 2000 × 10\(^{-6}\) M (Gd and Dy). MG63 showed higher tolerance limits since the lowest ICC was 60 × 10\(^{-6}\) M found in cerium chloride, while other REE chlorides except La showed a much higher ICC at 2000 × 10\(^{-6}\) M. Among the three kinds of cells, HUCPV showed the highest tolerance when exposed to the chlorides. For HUCPV, europium chloride showed no ICC in its investigated range. High ICC at 2000 × 10\(^{-6}\) M was found in all other chlorides except La and Ce. The results not only presented the performance of ionic REEs, but also showed different responses from cells. The preliminary results of the REEs showed promising candidate elements for BMs from a cellular level.
The LD50 (Lethal Dose, 50%) values of the chlorides of the nutrition elements via oral intake are shown in Figure 8. No data were available for the chloride of elements K or Mo. It is apparent that the tolerance limit of different metal salts varies. MgCl2 shows the highest LD50 value of 5000 mg kg\(^{-1}\), and the lowest is found in NiCl2, with an LD50 of 186 mg kg\(^{-1}\). Overall, all the chlorides of the nutrition elements show relatively high tolerance over 100 mg kg\(^{-1}\).

The mouse intraperitoneal LD50 summary for all REEs except promethium (Pm) have been given, as shown in Figure 9. Sc shows the highest LD50 value while Y presents the lowest LD50 value. The chloride of lanthanide displays a moderate LD50 value from 300–600 mg kg\(^{-1}\).

**Inflammatory and Aggregation in Tissues and Organs**: One aspect that warrants attention is the potential element aggregation in serum and organs. The potential for inflammatory aggregation in serum and organs necessitates the concern for long-term biocompatibility, although no side effects have been found during the research period. The accumulation in serum and organs is often accompanied with local ion release to the circulation system. It is unknown whether this could lead to harm within the host’s lifespan.

So far, only limited results report such a concern since the aggregation in organs can be a long and chronic process. Recent work on biodegradable Zn alloys has found that macrophages were able to penetrate the corrosion layer and cause a long-term inflammatory response, where Al addition increased macrophage activity. As for ion aggregation, the serum Mg\(^{2+}\) level has been reported in some in vivo applications of biodegradable Mg alloys. The results commonly demonstrated no difference or a slight increase (but still in normal range) followed by a decrease. Moreover, a previous study reported that the accumulation of Mg\(^{2+}\) was found especially around the walls of the blood vessels within the bone, and then decreased via metabolic regulation. Other reports have shown no accumulation of Mg\(^{2+}\) in both serum and organs in rats over a long research period. In addition to Mg, Al in the AZ31 implant has been reported with significant and time-relevant accumulation in the spleen, kidney, liver, and lungs after 13 months of implantation. Moreover, recently researchers have paid close attention to the accumulation of REEs in organs. The implantation of Mg–Gd alloy in rats has confirmed accumulation of Gd ions in the spleen, lung, liver, and kidney with the 36 week implantation. Similar trends of severe accumulation of 10–20 fold increases of lanthanum, cerium, neodymium, and praseodymium in the organs have been reported after 3.5 years of implantation, despite the fact that the total amount of the misch metal occupied only 2 wt% in the alloy. So far, publications on the trace element accumulation in organs are scarce. The current reported accumulations of metallic ions after implantation of Mg-based BMs have been summarized in Figure 10. To some degree, the accumulation may show increased risk for long-term chronic toxicity of some elements.

**3.2.3. Human/Clinical Related Biocompatibility**

**Elements Existing in Human Body**: So far C, H, O, N, K, Cl, Na, Ca, P, S, and Mg are recognized as major elements in biochemistry, while As, F, Si, V, Fe, Zn, Mn, Ni, Cu, I, Cr, Mo, Se, Co, and Pb are generally accepted as trace elements for humans. Moreover, in recent years, element Li has been considered as trace element. It is worth noting that many other metallic elements have been selected as trace elements in different books. Dr. Jensen classified the trace elements into four categories. Essential trace elements include Fe, Zn, Cu, I, Se, Mn, Mo, Cr, and Co. Nonessential but
useful elements include Si, V, Sn, Ni, As, B, Sr, Li, and Ge. Elements toxic at trace levels include Sb, Be, Cd, Pb, Hg, and Tl, while nontoxic trace elements with unknown function in the body include Al, Ba, Bi, Br, Cs, Au, Rb, Ag, Zr, and W. Based on the above information, we plotted the classification of nontoxic metallic elements in the human body in Figure 11.

The content of major elements and minor elements in the human body had been illustrated, including O (43,000 g), C (16,000 g), H (7,000 g), N (1,800 g), Ca (1,200 g), P (780 g), S (140 g), K (140 g), Na (100 g), Cl (95 g), Mg (25 g), F (6 g), Fe (4 g), Zn (3 g), Si (1 g), Pb (0.12 g), I (0.02 g), Ni (0.015 g), Se (0.014 g), Cr (0.012 g), Mn (0.012 g), Cu (0.007 g), Li (0.007 g), As (0.007 g), Mo (0.005 g), Co (0.002 g), and V (0.002 g). Meanwhile, many elements have been found in the human body, which do not act as essential elements, including Ti (700 mg), Br (260 mg), Al (60 mg), Th (40 mg), Ce (40 mg), Be (35 mg), Ba (22 mg), Cd (20 mg at age 50), Hg (6 mg), Cs (6 mg), Sb (2 mg), Ag (2 mg), Nb (1.5 mg), Zr (1 mg), La (no more than 1 mg), Te (0.7 mg), Ga (0.7 mg), Y (0.5 mg), Tl (0.5 mg), Bi (less than 0.5 mg), In (0.4 mg), Sc (0.2 mg),

Figure 10. Summary of element accumulation in serum and organs reported in animal studies of biodegradable Mg alloys. [60-62, 64-67]

Figure 11. Classification of metallic elements in the human body.
Ta (0.2 mg), Au (less than 0.2 mg), U (0.1 mg), Sm (0.05 mg), W (0.02 mg), and Ra (3×10⁻⁸ mg).

Nevertheless, it was unclear if some elements, including Sb, Ba, B, Br, Cs, Ge, Hg, Sr, Tl, Be, Bi, Ga, Au, In, Nb, Sc, Te, Sr, Ti, Zr, and W, should be classified as essential nutrition elements or toxic elements. Some elements’ role in human metabolism has not been clarified yet. For example, the biological effects of tungsten (W) are still not clear. On the one hand, rats were found to have slightly enhancement in growth when supplemented with tungsten at 5 μg mL⁻¹ in water. On the other hand, tungsten slightly shortened the longevity of mice and rats. For human diet, tungsten is rarely involved. A previous report has demonstrated an elimination of trace-level (NH₄)₂¹⁸⁵WO₄ after oral intake. Meanwhile, early research has reported 97% of oral tracer dose K₂¹⁸⁵WO₄ and K₂¹⁸⁷WO₄ were excreted via urine and feces. Furthermore, rare earth elements have been proved to be somehow tolerable by the host for now. They have been widely used in Mg-based BMs as alloying elements, which show no side effects to the host, meanwhile enhancing the mechanical properties.

Regarding the toxicity of a certain element, it is dosage, time and form dependent. Both high dosage within a short time and continuous intake at a low dosage for a long time may result in risk and even death. In most literature, the trace elements As, Cr (excluding Cr³⁺), Cd, Pb, and Ni in humans have been reported with multiple negative health effects, either by exposure, inhalation, and/or other kinds of contact. More specifically, only Cr³⁺ plays a role in the biological process, but other ionic states of Cr, ranging from Cr²⁺ to Cr⁶⁺, are all toxic. Considering the potential neurotoxicity of Al and the reported accumulation in organs, it is not recommended for use in the material design of biodegradable metals.

Serum Concentration of Elements: The available data about the serum concentration of nutrition elements are summarized in Figure 12. Different kinds of metallic elements show significantly different concentration ranges. Element Na shows the highest concentration range in serum of over 100 mmol L⁻¹ and element V shows the lowest concentration range in serum of less than 10⁻⁴ mmol L⁻¹. The concentrations of elements Na, K, Ca, Mg, Fe, Zn, and Cu in serum are higher than 0.1 mmol L⁻¹, while the concentrations of elements Mn, Mo, and Cr are relatively lower.

Despite the difference in serum concentration range for different elements being large, the individual concentration of each element in serum should be within a certain range, due to the fact that serum concentration can be a predicting index of some diseases. For instance, if the concentrations of Na, K, and Mg ions are higher than the normal ranges it will induce hypernatremia, hyperkalemia, and hypermagnesemia, respectively, indicating a specific toxicity. Meanwhile, lower concentration of Ca and Fe ions imply hypoparathyroidism and iron-deficiency anemia, respectively. Additionally, all the elements have their own specific concentration range not only in serum, but also in bones and other tissues and organs where they play a part in metabolic function. The serum concentration may provide insight into the concentration range in tissues.

Dietary Average Daily Intake and Recommended Daily Intake: Regarding the intake of an element, the dietary average daily intake (ADI) and recommended daily intake (RDI) provide information on the current availability of food supplies and recommended intake of nutritional elements. The ADI and RDI of the major elements and trace elements (with the data of elements Ni and Co not available) are shown in Figure 13. It is worth noting that the difference in RDI for different people and countries varies, but the species of minerals are consistent. In addition, some elements have higher ADI than RDI, indicating overdosage in daily intake, while other elements show lower ADI than RDI. According to literature, insufficient nutrition intake occurs in K, Ca, Mg, Fe, Zn, Mn, Cu, Mo, and Cr, implying extra supplement is needed. Therefore, the addition of these elements in biodegradable metal implants may help as a supplement for the human body. These two indexes are frequently considered when choosing metallic elements for biodegradable metals and when discussing the biosafety of a certain metal ion on the local tissue. It is important to stress that ADI and RDI are based on food supply, which means that the elements entering the human body after the digestion and absorption taking place in the stomach and intestinal tract will be only several percentages of the original dosage. This would be different from the local release at a certain tissue or organ. When BMs are implanted at a certain position in the human body, the
elements stay and accumulate there unless they diffuse into dilution with the surrounding tissue liquid. It is the local concentration of a certain element going beyond the tolerance limit of the human body that causes toxicity, and it is inappropriate to conclude it as "biosafe" simply because the total weight of the implanted BMs is lower than the multiplication of ADI or RDI with the implanted days for a certain element.

Trace elements with recommended daily intake are considered the second favorable element group for BMs, including Zn, Fe, Mn, Cu, Cr, and Li. Group III is composed of both trace elements without recommended daily intakes and nonessential but useful elements, including Mo, Co, Ni, Sr, and Sn. The last group includes those nontoxic elements with unknown function or elements with insufficient data. These elements include Al, Ba, Bi, Cs, Rb, Ge, Zr, W, and REEs. More specifically, since MC3T3-E1 IC₅₀ is used, such a preference of element choice for BMs may be more appropriate in bone implants.

However, it is known that the existence of an element in the human body does not necessarily make said element a good choice for biomedical metallic materials, let alone biodegradable metals. For example, as illustrated above, only Cr³⁺ plays a role in a biological process while other ionic states of Cr ranging from Cr²⁺ to Cr⁶⁺ are all toxic. Aluminum is reported to have an uncertain potential neurotoxicity. Thus, currently Cr is not a good option for biodegradable metals. Ideal biodegradable metals will be 100% biodegradable and 100% biocompatible, absorbed or excreted by the body. The guide for elemental impurities in brand name and generic drug products from the U.S. Food & Drug Administration has been referenced. Basically, 3 classes (class 1, 2, and 3) have been defined according to their permitted daily exposure (PDE): Class 1 indicates human toxicants that have limited or no use, and includes As, Cd, Hg, and Pb; Class 2 refers to elements that are generally considered as route-dependent human toxicants, and includes Co, Ni, V, Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se, and Tl; Class 3 has relatively low toxicity via oral administration but poses a potential risk when administered via inhalation and parenteral routes, including Ba, Cr, Cu, Li, Mo, Sb, and Sn. Other elements may have either low inherent toxicity and/or differences in regional regulations, which are not addressed, including Al, B, Ca, Fe, K, Mg, Mn, Na, W, and Zn. Details can be found in Table 1. Judging from the guide for elements in drugs, elements in Class 1 and class 2 are considered inappropriate for usage in the composition of biodegradable metals. Elements in class 3 and unclassified elements need to be evaluated one by one.

Clinical Data: Presently, there have been several biodegradable metal medical devices approved into market in Europe and South Korea and under clinical trials in China, including Mg, MgCaZn, and MgRE based commercial screws, and FeN and Mg-RE based coronary stents. The limited follow-up information from after implantation into the human body revealed no side-effects to patients, and long-term and large patient-into-group data are expected to let us draw a conclusion about the biosafety of the elements Mg, Ca, Zn, RE, Fe, and N being used in these medical devices.

Hemocompatibility: Hemocompatibility of biomaterials indicates the categories of thrombosis, coagulation, blood platelets, hematology, and immunology. With regard to BMs, previous in vitro evaluations of hemocompatibility focused on hemolysis and platelet adhesion, as well as coagulation evaluations. A relatively higher hemolysis rate is found for bare biodegradable Mg alloys, which has not been reported in either biodegradable Fe alloys or biodegradable Zn alloys. Metallic ions and increased pH values were found to be the primary reasons for high hemolysis. Considering the dynamic and relatively stable pH value of body fluids, a specific standard method is needed to simulate the real in vivo hemolysis of BMs instead of the current ISO 10993. In addition, the in vivo reports on other aspects, such as thrombosis, hematology and immunology are still limited and encouraged to better understand the hemocompatibility of BMs.

Table 1. Permitted concentrations of elemental impurities in brand and generic drug products.

<table>
<thead>
<tr>
<th>Element</th>
<th>Class</th>
<th>Oral PDE [µg d⁻¹]</th>
<th>Parenteral PDE [µg d⁻¹]</th>
<th>Inhalation PDE [µg d⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cd</td>
<td>1</td>
<td>5(0.5)</td>
<td>2(0.2)</td>
<td>2(0.2)</td>
</tr>
<tr>
<td>Pb</td>
<td>1</td>
<td>5(0.5)</td>
<td>5(0.5)</td>
<td>5(0.5)</td>
</tr>
<tr>
<td>As</td>
<td>1</td>
<td>15(1.5)</td>
<td>15(1.5)</td>
<td>2(0.2)</td>
</tr>
<tr>
<td>Hg</td>
<td>1</td>
<td>30(3)</td>
<td>3(0.3)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Co</td>
<td>2</td>
<td>50(5)</td>
<td>5(0.5)</td>
<td>3(0.3)</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>100(10)</td>
<td>10(1)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Ni</td>
<td>2</td>
<td>200(20)</td>
<td>20(2)</td>
<td>5(0.5)</td>
</tr>
<tr>
<td>Ti</td>
<td>2</td>
<td>8(0.8)</td>
<td>8(0.8)</td>
<td>8(0.8)</td>
</tr>
<tr>
<td>Au</td>
<td>2</td>
<td>100(10)</td>
<td>100(10)</td>
<td>10(1)</td>
</tr>
<tr>
<td>Pt</td>
<td>2</td>
<td>100(10)</td>
<td>10(1)</td>
<td>10(1)</td>
</tr>
<tr>
<td>Ir</td>
<td>2</td>
<td>100(10)</td>
<td>10(1)</td>
<td>10(1)</td>
</tr>
<tr>
<td>Os</td>
<td>2</td>
<td>100(10)</td>
<td>10(1)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Rh</td>
<td>2</td>
<td>100(10)</td>
<td>10(1)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Ru</td>
<td>2</td>
<td>100(10)</td>
<td>10(1)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Se</td>
<td>2</td>
<td>150(15)</td>
<td>80(8)</td>
<td>130(13)</td>
</tr>
<tr>
<td>Ag</td>
<td>2</td>
<td>150(15)</td>
<td>10(1)</td>
<td>7(0.7)</td>
</tr>
<tr>
<td>Pt</td>
<td>2</td>
<td>100(10)</td>
<td>10(1)</td>
<td>1(0.1)</td>
</tr>
<tr>
<td>Li</td>
<td>3</td>
<td>550(55)</td>
<td>250(25)</td>
<td>25(2.5)</td>
</tr>
<tr>
<td>Sn</td>
<td>3</td>
<td>6000(600)</td>
<td>600(60)</td>
<td>60(6)</td>
</tr>
<tr>
<td>Cr</td>
<td>3</td>
<td>11 000(1100)</td>
<td>1100(110)</td>
<td>3(0.3)</td>
</tr>
</tbody>
</table>

The concentration limits in parentheses are selected to assess the elemental impurity content in drug products with daily doses of no more than 10 g per day. Adapted with permission. Copyright 2014, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).
and reducing apoptosis.\textsuperscript{[96,97]} In addition, residual debris may also affect the biocompatibility. Regarding this, a previous investigation has confirmed that macrophages can stretch filopodia to engulf two corrosion product particles with diameters of 5 \(\mu\)m and 3 \(\mu\)m within 10 min, providing preliminary safety results for biodegradable Mg alloys.\textsuperscript{[98]}

3.2.4. Summary on Biocompatibility Criteria

Biocompatibility can be evaluated at different levels: cellular biocompatibility, tissue biocompatibility, and human/clinical related biocompatibility. Each level provides different insight to better understand a host's response to materials. Clearly, the human/clinical related biocompatibility data are the most important. The composition of various elements existing in the human body, and the threshold value for a healthy concentration of each element, both in hard tissue and in soft tissues, provide a valuable reference for the introduction of BMs into the human body by the implantation of a medical device. More strictly, BMs should be considered as a "drug." If we evaluate the biosafety of a new kind of BM as a new "drug," without question, its biocompatibility can be guaranteed.

3.3. Necessary and Sufficient Conditions for Being Biodegradable Metals

The dual criteria of "Biodegradability" and "biocompatibility" work as two necessary and sufficient conditions to screen potential alloying elements for BMs. As illustrated in Figure 14, all the nonradioactive metallic elements in the periodic table have been screened. By biodegradability criteria, elements including Ti, Zr, Tc, Re, Ru, Os, Rh, Ir, Pt, Pd, Cu, Ag, Au, Ge, Sb, and Bi, are excluded. The remaining metallic elements are further evaluated by biocompatibility criteria, and thus elements Be, Al, Hf, V, Nb, Ta, Cr, Co, Ni, Ga, Cd, In, Tl, and Pb, have been excluded. Finally, only elements Ca, K, Na, Mg, Fe, Zn, Rb, Sr, Sn, Ba, Mn, Li, Cs, Mo, Y, Sc, RE, and W could be regarded as candidate elements for BMs, ordered from highest to lowest composition of the human body (data given in Section 3.2.3). Ca shows the highest content in the human body. Despite Ca-based intermetallic compounds Ca\textsubscript{2}Si and CaMgSi have shown high biodegradation rates, Zn-added CaZn intermetallic compounds showed much improved corrosion resistance.\textsuperscript{[47,99]} Also, K and Na have high reactivity and cannot even be stably stored in air, let alone be within the metal matrix of biodegradable metals. However, since these elements have high concentrations and tolerances, the additional content of them can be high within intermetallic compounds with other elements. Mg, Fe, and Zn are generally accepted elements as BMs. In addition, Rb and Sr both exhibit a presence higher than 100 mg in humans, while Sn, Ba, Mn, Li, Cs, and Mo are all higher than 1 mg in humans. The fact that these elements exist in humans, albeit at low concentrations, makes them potential alloying elements for BMs, instead of being matrix elements. Furthermore, Sc, Y, RE, and W all show very limited existence in the human body. For all potential alloying elements in general, the lower the natural content within the human body, the more care which must be taken in evaluating the need for its usage as an alloying element, and the less content which can be added into BMs when used.

4. Guidance on Material Design of BMs

4.1. Key Material Properties of BMs

The dual criteria of biodegradability and biocompatibility define the metallic elements in the periodic table qualified to be regarded as BMs. In general, these pure metal elements can be considered raw materials, and not used directly. Further material design is needed based on these candidate elements in Figure 14, together with other nonmetallic elements, to achieve optimized material properties which can then be used to manufacture medical devices for specific medical treatments. For a finalized BM medical device working in vivo, key aspects such as mechanical properties, chemical properties, physical properties, and biological properties should be comprehensively considered during material design, as illustrated in Figure 15.

4.1.1. Chemical Properties

Regarding the targeted chemical properties of BMs, the main concern is the chemical reactions between a BM and body fluid in the microenvironment surrounding an implant. So, by regulating the composition of the BMs and their processing techniques, people try to control the chemical reaction of the BMs for optimization of both the degradation mode and rate. For different medical devices, there should be different degradation mode designs. Pitting corrosion is common for most of the pure metals, and secondary phases can be introduced into the matrix by alloying with other elements. Correspondingly, galvanic corrosion between the matrix and the secondary phase can occur. It competes/coexists with the localized pitting corrosion of the BMs and macroscopically uniform corrosion is expected from the surface towards the inside. The situation will become more complex when the BMs processed in a certain medical device are exposed to different corrosion microenvironments at different implantation sites due to the difference in contacting tissues. Moreover, the local stress state at different positions in the same medical device can vary, and the stress will influence the degradation behavior despite the medical device being made of the same BM. Therefore, the ultimate goal is to realize the controllable inhomogeneous degradation of BMs as a function of time and spatial location, to closely match the local tissue regeneration/repair process.

4.1.2. Biological Properties

The biological properties of BMs are derived from the biological effects of degradation products of BMs to the surrounding host, therefore the standard for good biological properties should aim for "100% biocompatibility" plus "additional biofunctions." Thus far, promotion of osteogenesis, anti-inflammatory effects, antibacterial functionality, antitumor
function, and inhibition of restenosis have been implemented in the material design of BMs.

4.1.3. Mechanical Properties

The mechanical properties of BMs involve the static and dynamic mechanical data, such as the stress–strain relationship during tension, compression, torsion and bending, and fatigue under in vivo chemical and thermal conditions. Moreover, the degeneration of mechanical properties over time should be studied.

The tensile properties of Mg-based, Zn-based, and Fe-based BMs reported in literature, along with pure Ti have been summarized in Figure 16. Biodegradable Fe and its alloys show superior mechanical properties, which are approaching those of 316L stainless steel. The most investigated biodegradable Mg alloys show a wide range of ductility, but the ultimate tensile strengths are generally lower than 400 MPa. Currently, the limited data of newly developed biodegradable Zn alloys have shown that the mechanical properties are similar between Zn-4 at%Li alloy and T4A annealed Ti, whose tensile strength should be higher than 550 MPa and elongation higher than 15%, according to ISO 5832-2. Moreover, new reports on
biodegradable Zn alloys show great potential for adjustable mechanical properties. High strength Zn alloys microalloyed with Mg (Zn–0.08Mg) presented a tensile strength higher than 600 MPa,\textsuperscript{[126]} while another Zn–0.2Mn alloy showed a good ductility of more than 70%,\textsuperscript{[125]} With regard to a load-bearing bone implant application, the mechanical properties of BMs should at least try to be comparable with pure Ti.\textsuperscript{[119]} Furthermore, the mechanical support should be maintained higher than 80% at 6 months postsurgery. Until now information about the degeneration over implantation time of the mechanical properties is

Figure 15. Key properties for material design when choosing BMs.

Figure 16. Illustration of mechanical properties of Mg-based, Fe-based, and Zn-based biodegradable metals during tension in air at room temperature.
still limited due to the complexity of the animal testing required and the nonuniformity of the material degradation; this is influenced by factors such as the multiple stress modes which exist at implantation position.

4.1.4. Physical Properties

For medical devices serviced inside the human body, some physical properties should be considered. For instance, MRI compatibility is one important physical property of implantable biomaterials. Biodegradable metals should be MRI compatible, otherwise before 100% degradation such metals would be problematic in MRI scans of the patient. Also, good wettability can improve the biocompatibility by making it easier for cells to attach and proliferate. Well-defined radiopacity of the BMs is quite important for the visibility of a medical device under X-ray fluoroscopy at low irradiation dosage. Electrical conductivity is not a necessary property for biodegradable materials. However, biodegradable metals naturally have this property. It is known that electrical stimulation has been confirmed in its role in promoting healing. The electrical conductivity of biodegradable metals provides a potential when external stimulation is needed, and provides the potential for monitoring the healing process by gathering electrical signals.

4.2. Future Material Design Directions

Candidate elements for the synthesis of biodegradable metals in the periodic table have been summarized on the left side of Figure 17. Elements Mg, Fe, and Zn are generally accepted in biodegradable metal matrices. As illustrated above, other metallic elements with high content in the human body are Ca, K, and Na. Until now, only amorphous Ca-based BMs and none of pure metals Ca, K, and Na have been reported to be stable in air. There are no reports on Na- or K-based BMs as of yet. There are other elements, both metallic and nonmetallic, which are considered potential elements for alloying with BMs. However, it should be noted that less of an element should be introduced into the body if less of that element exists within the body naturally. At the same time, it may not be wise to sequence the safety of these elements in this way since each element has a unique metabolic pathway within the body and the body displays a different ability to adjust and excrete each element.

For the direction of future material design of BMs, five groups of BMs are proposed: i) biodegradable pure metals; ii) biodegradable crystalline alloys, including alloying with metallic elements or nonmetallic elements; iii) biodegradable bulk metallic glasses; iv) biodegradable high entropy alloys, and v) biodegradable metal matrix composites, as illustrated on the right side of Figure 17. These five items can also serve as new classification of BMs, updating the old version about the classification of BMs proposed in 2014.[31]

4.2.1. Biodegradable Pure Metals

Elements Mg, Fe, and Zn at high purity have been generally accepted as biodegradable pure metals. Despite several years of development, new progress is still being made on pure Mg and Fe, let alone the relatively newer pure Zn. High purity Mg screws have been reported to treat osteonecrosis in 48 patients.[30] At 12 months, the diameter reduction is 25.2 ± 1.8%, with significantly promoted bone formation around the screw and flap fusion region. Recently, biodegradable porous pure Mg[127] and pure Fe[128] were fabricated by selective laser melting and direct metal printing, respectively. The electrochemical tests showed that the degradation rates of porous iron are nearly 12 times higher than those of cold-rolled bulk iron. Pure Zn was introduced as a candidate biodegradable metal.[129] It exhibited steady corrosion without local toxicity for up to at least 20 months postimplantation into the murine artery.[34] A pure Zn stent could maintain mechanical integrity for 6 months and degraded 41.75 ± 29.72% of its volume after 12 months postimplantation in the abdominal aorta of a rabbit.[130]

Besides, Mg, Fe, and Zn, some elements illustrated in the left side of Figure 17 have high reactivity and cannot even stably exist in air. Such elements include Na, K, Ca, Li, Sr, Sn, Ba, Cs, and Rb. Meanwhile, some other metals show slow corrosion rates in an aqueous environment, such as Mo and W. Pure Mn showed similar corrosion behavior to Fe and Zn in Hank's...
solution, yet it is brittle and the tolerance limit of Mn for either ECV304 or L929 cells is significantly lower than either Fe or Zn.[131] These facts imply that only Mg, Fe, and Zn can be used as biodegradable pure metals.

Impurities in pure metals have significant effects on the properties of pure metals. For instance, Fe, Cu, Co, and Ni are considered common impurities detrimental to the corrosion resistance of Mg alloys.[132,133] As for pure Zn, typical impurities include Cu, Sb, Fe, Sn, and Cd, which significantly increase the corrosion rate of Zn and cause problems similar to what impurities in Mg alloys do.[134] Besides increased corrosion rate, some impurity elements have poor biocompatibility, such as Ni in Mg and Cd in Zn. For example, Ni, which is a common impurity in Mg, has been reported to strictly maintain a limit under 5 ppm in pure Mg. However, in some Mg or Mg alloys the content of Ni can be as much as 50 or 100 ppm.[135] For a bone screw weighing 1 g a Ni mass of 5 µg (5 ppm) is considered tolerable by the FDA's guidance for PDE, while a content of around 50 or 100 ppm would be considered dangerous.

Therefore, from the viewpoint of biodegradation and biocompatibility, impurities should be strictly controlled. Thus, for the future design of biodegradable pure metals, the purity used for biodegradable Mg, Fe, and Zn is recommended to be higher than 99.99, 99.99, and 99.999 wt%, respectively, to guarantee the biosafety for both total amount and daily released amount.

4.2.2. Biodegradable Crystalline Alloys

Alloying provides opportunities to tailor the mechanical, chemical, physical, and biological properties of biodegradable pure metals. Overall, the selection of alloying elements for BMs is matrix dependent. The selection should consider basic aspects such as solid solubility, as well as the role and quantity of alloying elements regarding mechanical properties, corrosion resistance, and biocompatibility. More detailed progress of biodegradable crystalline Mg-based alloys,[131,136–139] Fe-based alloys,[113,140,141] and Zn-based alloys[142,143] can be found. To date, multiple alloy systems have been developed with some of them either entering the market already or under clinical trial. From checking the phase diagram of previously screened elements, no phase diagram has been found for either Cs or Rb with biodegradable Mg, Fe, and Zn. Therefore, they have been temporarily excluded as alloying elements for biodegradable crystalline alloys.

As for future development, several directions have been summarized as follow:

1) The addition of macroelements such as K, Na, and Ca into biodegradable crystalline alloys. Except for Ca, macroelements Na and K, which have a significant role in metabolism, have never been investigated as the alloying elements for biodegradable alloy till now. In fact, despite their high reactivity and low melting point, it is still possible to add these elements in biodegradable crystalline alloys. For example, Na has been successfully added into Mg alloys with a Sn–Na master alloy.[144]

2) The addition of nonmetallic elements (O, C, H, N, P, S, F, Si, and Se) into biodegradable crystalline alloys. As illustrated in the left bottom part of Figure 17, most of the nonmetallic elements exist in the body at a large quantity. It needs to be noted that I and Cl also have a content higher than 10 mg in the human body, but they have been excluded since they can neither form a second phase nor have solid solubility in Mg, Fe, or Zn. A Fe–N alloy stent has been reported to show good long-term biocompatibility in both rabbit and porcine models.[89] The clinical trial for it started in China in July 2018.

3) Develop new kinds of biodegradable zinc crystalline alloys. Zinc and its alloys are newly developed BMs and show an ideal corrosion rate as well as good potential in mechanical properties.[129,145] Research on the addition of nutrition elements to Zn has not been thoroughly explored. The influence of alloying elements on the properties of Zn-based BMs is still not as clear as that of Mg-based BMs and Fe-based BMs. Moreover, the long-term animal and clinical trial should also be performed with the appropriate Zn alloys to better understand Zn alloys as biodegradable metals.

4) Another part of crystalline alloy research is development of biodegradable intermetallics. Different from biodegradable crystalline alloys, biodegradable intermetallics themselves are hard to prepare and require special equipment for research even if they automatically form in biodegradable crystalline alloys.[146] Ca2Si and CaMgSi intermetallic compounds were reported to spontaneously disintegrate to powder within a few days.[99] Also, so far the reported ultimate compression strength of Mg2Si and Mg2Ca intermetallic compounds were ~80 and ~120 MPa, respectively, without showing plastic strain.[99] The corrosion resistances of biodegradable intermetallic compounds are very dependent on the element composition. Mg17Al12 showed quick corrosion and broke into small pieces after several hours of immersion, while Mg2Si and Mg17Al12 were reported to present much improved corrosion resistance, with the corrosion rate 0.21 ± 0.01 mm y–1 for Mg2Si and 0.53 mm y–1 for Mg17Al12.[99,147,148] The biodegradation tendency of intermetallic compounds in a Mg–Ca–Zn system is very much dependent on the quantities of each element: Ca-based intermetallic compounds (i.e., Ca2Zn3) disintegrated within 1 h, Mg-based intermetallic compounds (i.e., Mg2Ca) disintegrated within 6 h, while Zn-based intermetallic compounds presented a weight change less than 1% after 250 h immersion.[47] Considering their relationship with biodegradable crystalline alloys, the research of biodegradable intermetallics would be helpful to understand the in vivo biodegradation sequence as well as absorption and excretion of biodegradable crystalline alloys. The problem that needs to be solved is the preparation technique for customized intermetallics. As reported previously, it may require a different method to prepare different intermetallics.[149] More detailed experiments for biodegradability and biocompatibility should be done on the common intermetallics such as Mg2Ca, MgZn2 and others already existed in approved clinical devices.

4.2.3. Biodegradable Bulk Metallic Glasses

Bulk metallic glasses, with their amorphous/glassy structure, avoid grain defects that traditional crystalline metals have and provide a means of obtaining high strength and elasticity at the same time. So far, Ca-based, Mg-based, Zn-based and Sr-based bulk metallic
glasses have been reported.[150] With its amorphous structure, Mg-based bulk metallic glasses can have a compressive strength higher than 900 MPa.[151] However, the critical diameter of biodegradable bulk metallic glasses are around several millimeters, which is far from satisfactory for most medical device fabrications.

The direction of development for most biodegradable bulk metallic glasses have been summarized: 1) increase the critical fabrication size; 2) design new bulk metallic glass systems without toxic elements commonly existing in bulk metallic glasses; 3) increase ductility and decrease embrittlement, which are detrimental during processing.[150]

4.2.4. Biodegradable High Entropy Alloys

High entropy alloys are defined as alloys with five or more principal elements, each of which has a concentration between 5 and 35 at%.[152] Such design leads to significantly higher mixing entropies when the alloys are in their liquid or random solid state, and introduces unique properties such as high strength/hardness and high corrosion resistance.[153] For example, no obvious sign of biodegradation was observed after 4 weeks of implantation in a mouse femur from a Ca20Mg20Zn20Sn20Yb20 high-entropy bulk metallic glass, while significant osteogenesis was found after 2 weeks implantation.[154]

So far, the studies on biodegradable high entropy alloys are limited. With the good mechanical properties and corrosion resistance showed, the direction of future developments should concentrate on the following aspects: 1) avoid toxic metallic elements as principle elements when designing the alloys; 2) introduce nonmetallic macroelements into biodegradable high entropy alloys since it has already been proven that C and N can work as principle elements in high entropy alloys;[155,156] 3) combine experiment and computational work to know the phase diagram and mechanism involved.

4.2.5. Biodegradable Metal Matrix Composites

The composites of biodegradable metals with other biodegradable metals, inorganic biomaterials or biopolymers can integrate the advantages of different biomaterials. Various BM-based composites have been evaluated including Mg–HA,[157,158] Mg–FA,[159,160] Mg–PLGA–TCP,[161,162] Mg–(MgO, MgZn intermetallics),[163] Fe–Fe2O3,[164] Zn–ZnO,[165] and Zn–HA.[166] BM–matrix composites are unlikely to be fabricated by adding the biopolymer into the molten BM directly, but it is feasible to fabricate composites by pouring liquid BM into porous inorganic biomaterials. An implantable transient device made from Mg, MgO, and Si acting as a programmable nonantibiotic bacteriocide provides good antibacterial properties in vivo.[167] Also, a biodegradable stent designed with temperature sensors and encapsulation has been reported to enable flow sensing, temperature monitoring, data storage, wireless power/data transmission, inflammation suppression, localized drug delivery, and hyperthermia therapy.[168]

The future material design strategy for biodegradable metal matrix composites should either combine the advantages from each component or incorporate new functionality to make it a “smart device.”

5. Concluding Remarks

Biodegradable metals are a rising star in the field of metallic biomaterials, and undeniably more and more medical devices made of BMs will be approved into markets all over the world. The fundamental theory of BMs was teased out in the present work, and the basic skeleton of facts about BMs including the definition, the dual criteria of biodegradability and biocompatibility and its effect on material design is constructed for the first time. This foundation makes for a better understanding of the rationale behind element selection for BMs, establishes the material design as the highest priority and ensures the resulting BMs are upgraded from 100% biodegradable to 100% bioabsorbable. Several key conclusions have been drawn as follows:

1) With respect to the definition of “Biodegradable Metals” in our previous work,[134] it has been updated to “metals expected to corrode gradually in vivo, with an appropriate host response elicited by released corrosion products, which can pass through or be metabolized or assimilated by cells and/or tissue, and then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues.” In this way, it is identical to “Absorbable Metallic Materials,” termed in ASTM F3160.

2) The dual criteria of biodegradability and biocompatibility regarding whether a metallic biomaterial is a biodegradable metal has been proposed. For the biodegradability criteria, electrode potential, reactivity, galvanic series (corrosion potential), Pilling–Bedworth ratio, and Pourbaix diagram could be used as parameters to classify the nature of the material as biodegradable and nonbiodegradable; for the biocompatibility criteria, three levels of biocompatibility parameters including cellular biocompatibility (IC50), tissue biocompatibility (LD50, inflammatory and aggregation in tissues and organs), and most importantly, human/clinical biocompatibility (ADI, RDI, and FDA’s guide on element impurities for drugs) were used for screening metallic elements in the periodic table as suitable candidates for biodegradable metals. After screening, elements Ca, K, Na, Mg, Fe, Zn, Rb, Sr, Sn, Ba, Mn, Li, Cs, Mo, Y, Sc, RE, and W are believed to be qualified metallic candidates for biodegradable metals. In general, Ca, Mg, Fe, and Zn are potential candidates for matrix elements, metallic elements Ca, K, Na, Mg, Fe, Zn, Rb, Sr, Sn, Ba, Mn, Li, Cs, Mo, Y, Sc, RE, and W, and nonmetallic elements O, C, H, N, P, S, F, Si, and Se, are potential candidates for alloying elements.

3) With regard to the material design of biodegradable metals, four main properties, “mechanical property,” “chemical property,” “physical property,” and “biological property” should be considered to reach the best combination of properties.

4) Five classifications or future development directions of biodegradable metal families have been proposed: biodegradable pure metals, biodegradable crystalline alloys, biodegradable bulk metallic glasses, biodegradable high entropy alloys, and biodegradable metal matrix composites.

There are still other important issues, which need to be established for the fundamental theory of biodegradable
metals, such as the degradation model and control, mechanical property degeneration with time, bioactivity of biodegradable metals and their bioactivity degree, surface biofunctionalization of biodegradable metals, thin films of biodegradable metals and their application in transient electronic devices, 3D printing of biodegradable metals and coupling with nondegradable metals, biodegradable inorganic materials, biomolecules and cells, and so on. These specific theory elements would help people better understand the nature of biodegradable metals, and guide the novel designs of future medical devices, and even give rise to the controllable release of various degradation products (various metal ions, hydrogen) as a complex “drug” after implantation into a certain tissue or organ.

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Conflict of Interest
The authors declare no conflict of interest.

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