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Recent progress in the application of biodegradable metal implants

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Abstract

With the accumulation of data, magnesium-based degradable metal, iron-based degradable metal and zinc-based degradable metal implantable interventional devices have entered the clinic or carried out human experimental studies, and the future prospects are promising. In this paper, the definition, biodegradability and biocompatibility criteria and their classification are reviewed, and the research status and unsolved scientific problems of magnesium-based degradable metals, iron-based degradable metals and zinc-based degradable metals are introduced, and the future development opportunities and challenges of degradable metals are prospected. With a deeper understanding of scientific issues such as mechanical adaptation, degradation adaptation and tissue adaptation of degradable metal implants, more new materials, new technologies and new methods of degradable metals will be developed in the future, so as to effectively realize the precise adaptation of the two events of degradable metal material degradation and body tissue repair in time and geometric space.

Introduction

Biodegradable metal implants are the new future array towards the field of medicine and biotechnology[1,2]. Pointing out that the goal of the first generation of biomaterials is to obtain a suitable combination of material properties to replace tissues with a general combination, and to show the least toxicity in the host [3, 4]. Second-generation biomaterials are characterized by being absorbable by the human body or biologically active; The third generation of biomaterials has both absorbable properties and biological activity, and can help tissues heal themselves once implanted in the body [5]. Accordingly, conventional medical metal materials (stainless steel, cobalt-based alloys, titanium alloys) are classified as first-generation materials. In the 21st century, a new member of the family of medical metal materials has ushered in, that is, degradable metals that are considered to be the third generation of biomaterials [6, 7]. Compared with traditional medical metal materials, degradable metals avoid long-term retention in vivo due to their unique body fluid degradation characteristics, which is more in line with the needs of tissue regeneration. At the same time, degradable metals are naturally degraded [8, 9].

The absorbable process is completely inert to the biological inertia of traditional medical metals. The same biological activity, which brings beneficial biological effects such as in situ ion release, and is even considered to be a chemical and biological effect of continuous drug release during the entire total degradation[10, 11]. In the academic world, degradable metals have experienced the initial skepticism of the industry in 2001 to 2022 world biomaterials conference was set up as a sub-venue for the first time (marking the acceptance of the international biomaterials community, and then set up as a sub-venue for three consecutive sessions in 2016 and 2020), and then to the 2018 biomaterials definition consensus meeting organized by the International Union of Biomaterials Science and Engineering, the definition of degradable metals was voted on, and in 2020, the "degradable metals" It was included as a chapter in the 4th edition of the Biomaterials Science textbook in the United States. In the industry, it has been reduced in the last 20 years [12–14]. The R&D of metal related medical device products has also experienced device products (scaffolds, stents, dental and orthro-implants) [15].

Prototyping, in vitro and vivo biological evaluation, clinical research is ongoing until the product is approved for marketing. For example, the ISOTS 20721 standard gives the general evaluation criteria for degradable metal implants, the ASTMF3268 standard gives the test method for the degradation behavior of degradable metals in vitro, and the medical device technology evaluation center of the state food and drug administration of China officially promulgated the "Guidelines for the Registration and Review of Degradable Magnesium Metal Orthopedic Implants (No. 4 of 2022)" [16, 17], It will accelerate the product registration of degradable magnesium metal in the field of orthopedic implants. It also provides guiding principles for the use of other biodegradable metals in orthopedics [18,19].

It is worth mentioning that in the history of research and development of degradable metals and their devices, scientists and enterprises have made important contributions, including the development of patented magnesium alloys, iron-based alloys, zinc alloys and their surface degradation control methods with world own intellectual possessions rights in the field of basic research, as well as certified degradable pure magnesium bone nail products, iron-based absorbable vascular scaffolding products, and the first international implantation of degradable zinc alloy maxillofacial repair bone plates and bone nails into the human body [20–23].

This review article will share the literature review work on the basis of degradable metals. Some relevant research results obtained in the past and applied basic research, thoughtful on issues related to new biodegradable metallic products (in field of orthopedics and cardiovascular implants) explore and developments are presented, the dual criteria and classification of metals biodegradability and biocompatibility is presented, and then magnesium-based degradable metals and iron-based are introduced by category. Research status of degradable metals, zinc and iron based degradable metals solve scientific and technological problems and future product development opportunities with existing challenges (**Fig. 1**).

Elements in the periodic table as a double criterion for degradable metals

As we all know, more than 60% of the elements on the periodic table are metallic properties, which elements are suitable for use as alternative elements for degradable metals, and how to control the amount used, all need to have a scientific criterion. In 2019, the authors of this paper [24, 25] proposed the dual

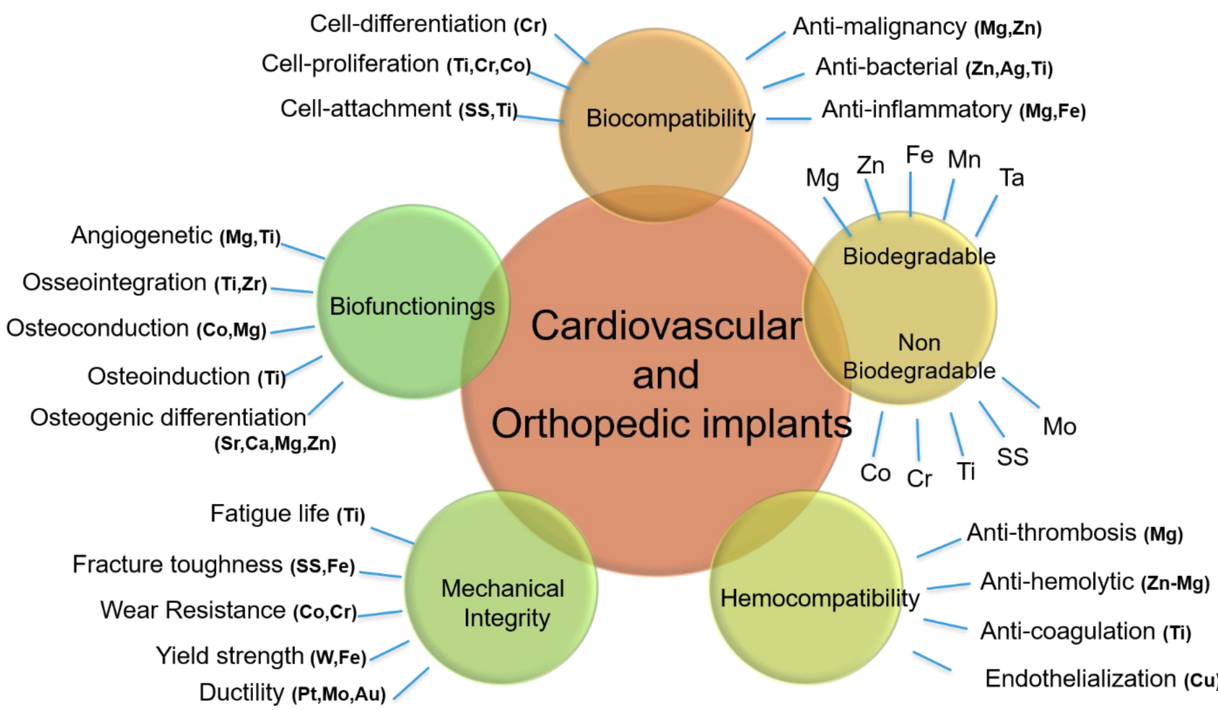

Fig. 1: Graphical representation of new biodegradable metallic products in the field of orthopedics and cardiovascular implants.

criterion of biodegradability and biocompatibility, arguing that only elements that meet 100% biodegradability and 100% biocompatibility can be selected [26].

Biodegradability criterion regarding the biodegradability criterion, the authors of this paper propose a number of parameters to reflect the chemistry of metallic elements with water. degrees, including chemical element reactivity, The activity of chemical elements refers to the ease with which elements react with other substances. The easier it is to react with other substances, the more active the elements are. The more difficult it is to react with other substances, the less active the element is, and the more stable it is [27]. The activity of the metal is a reflection of the tendency of the metal to form hydrated ions in the aqueous solution, that is, it reflects the difficulty of the oxidation reaction of the metal in the aqueous solution, which is based on the standard electrode potential of the metal. Lithium is the most active metallic element [28]. Normally, the standard electrode potential is based on the standard hydrogen atom as the reference electrode, that is, the standard electrode potential value of hydrogen is set at 0, compared with the hydrogen standard electrode, the higher potential is positive, and the lower potential is negative [29].

The P-B ratio is generated on the surface of the metal by combining the metal with oxygen. The volume of each metal ion in the oxide film is the same as that in the metal. The ratio of the volume of metal atoms [30,31]. The P-B ratio is in the range of 1~2 for metals, and a certain degree of compressive stress is produced in the oxide film on the surface, and the film is relatively dense and the metal has strong oxidation resistance. When the P-B ratio is less than 1 or greater than 2, tensile stress or excessive compressive stress occurs in the oxide film, which is easy to cause film rupture and low metal oxidation resistance [32,33]. The possibility of corrosion of metal materials under the condition of bit and pH.

Biocompatibility criteria regarding the biocompatibility criterion, the authors of this article will evaluate the biocompatibility and biosafety of the metal elements from three different levels: cytotoxicity, tissue safety, and human/clinical safety of the material [34]. A large number of studies have been conducted on the toxicity, severity, frequency and mechanism of toxic action of exogenous factors (chemical, physical, and biological) of chemical substances on organisms, including metal toxicological data at the whole, organ, cellular, and subcellular levels [35]At the cellular level, we use the parameter "Half Inhibition IC50", which is the concentration required for the extract of the material to inhibit cell growth by 50%, or the concentration of 50% cell viability. In the MTT method, the concentration of the drug required to reduce the absorbance OD value of the control group by half is as volume". [3,8]LD50 is usually expressed in the ratio of the mass of the toxic substance to the body weight of the test organism, such as "mg/kg body weight". Although toxicity is not necessarily proportional to body weight, this expression helps to compare the relative toxicity of different substances and the same substance in different sizes comparison of toxic doses between small animal’s measure [36,37].

Biochemical perspectives

From a biochemical point of view, the human body is usually composed of more than 50 elements. According to the different content of elements in the human body, they can be divided into two categories: macro elements (elements with body content accounting for more than 0.01% of body weight) and trace elements (elements with body content between 0.01% ~ 0.005% body weight) [38,39]. Macro elements account for a large proportion of the body, and the organism needs a large amount, which is an essential element for the composition of the organism. The elemental composition of a standard healthy adult is 65% oxygen, 18% carbon, 10% hydrogen, 3% nitrogen, 1.5% calcium, 1% phosphorus, 0.35% potassium, 0.25% sulfur, 0.15% sodium, 0.15% chloride, 0.05% magnesium, etc., and these microelements account for about 99.9% of body weight [40,41]. Person essential trace elements are deficiencies that will cause the body to live trace elements with functional and structural abnormalities, various lesions and diseases. The criteria for essential trace elements include 5 aspects:

1) These elements are present in all tissues of a healthy body;

2) the concentration in the tissues is quite constant;

3) When this element is lacking, it can produce similar structural and physiological dysfunctions in different tissues;

4) supplementation of the element prevents such anomalous changes;

5) Supplementation of this element can restore the abnormal function and structure to normal. There are 8 kinds of trace elements necessary for the human body, including iodine, zinc, selenium, copper, molybdenum, chromium, cobalt and iron. According to biological activity, non-essential trace elements in the human body can be divided into inert trace elements and toxic trace elements [42–46].

The trace elements include aluminum, rubidium, germanium, etc., whether it has special physiological functions for the human body, it is not clear, and the toxic non-essential trace elements mainly refer to beryllium, cadmium, mercury, lead, arsenic, thallium, etc [47–49]. Blood element test refers to the use of professional instruments to detect various elements in human blood, common metal ions in the serum normal concentration value: serum magnesium: 0.8~1.2mmol/L, serum potassium: 3.5~5.5mmol/L, serum sodium: 135~145mmol/L; Serum calcium: 2.2~2.7mmol/L; Serum iron: 10.7~27mmol/L [50–52].

Nutrition concerned with daily intake of metals through food

The amount of the element the human body needs to consume food every day for the benefit of the body Trace elements, including zinc, iron, copper, manganese, strontium, iodine, cobalt, chromium, selenium, etc. [53,54]. Although the human body's demand for trace elements is very low, its effect is very large. For example, "manganese" can stimulate the multiplication of cells in immune organs and significantly improve the survival rate of macrophages[55]. Zinc is an important life-related element directly involved in immune function, and because zinc has immune function, the amount of zinc in white blood cells is 25 times higher than that of red blood cells. "Strontium" and "chromium" can prevent hypertension, diabetes and hyperlipidemia gallstones. Based on the nutritional survey data and the characteristics of China's diet, the Chinese Nutrition Society revised the current Dietary Nutrient Reference Intake Scale for Chinese Residents in 2000 based on China's recommended dietary nutrient supply (RDA) and with reference to foreign dietary reference intake documents, involving the following four nutrient level indicators: average requirement (EAR), recommended intake (RNI), appropriate intake (AI), and tolerable maximum intake (UL)[56–58].

The examples are as follows. 1) Appropriate intake of magnesium AI: 30mg (0~0.5 years old); 70mg (0.5~1 years old);100mg (1~4 years old);150mg (4~7 years old); 250mg (7~11 years old); 350mg (11~50+ years old); In pregnant women (early, middle, and late), the AI for magnesium is increased to 400 mg. 2) AI of iron: 0.3mg (0~0.5 years old); 10mg (0.5~1 years old);12mg (1~11 years old);Interestingly, after the age of 11 years, there are changes in the AI of iron in men and women: 16mg in men (11~14 years old); 20mg (14~18 years old); 15mg (18~50 years old); 18mg for women (11~14 years old); 25mg (14~18 years old); 20mg (18~50 years old), regardless of men and women, when the age is greater than 50 years old, the AI of iron becomes 15mg. In pregnant women, the AI for early, intermediate, and late iron was 15, 25, and 35 mg, respectively. The AI of lactating mother iron is 25 mg. 3) Recommended intake of zinc RNI: 1.5mg (0~0.5 years old); 8mg (0.5~1 years old);9mg (1~4 years old);12mg (4~7 years old); 13.5mg (7~11 years old), but the AI of zinc after more than 11 years of age changed in men and women: 18mg for men (11~14 years old); 19mg (14~18 years old); 15mg (18~50 years old); 15mg for females (11~14 years old); 15.5mg (14~18 years old); 11.5mg (18~50 years old), regardless of male or female, when the age is greater than 50 years old, the AI of zinc becomes 11.5mg [58,60–63]. If pregnant women, early, middle and About 1g, magnesium as the main element and add one of these elements Rb, Sr, Sn, Ba, Mn as an alloying element in the material used in it, if in the material used in the bone nail, the amount added is 0.1wt.%, which means that this type of element is introduced through the implant. The amount of the element entering the human body is close to the total content of the element in the human body 1/10, need to be vigilant; But if it is to be the elements Li, Cs, Mo, Y an element is added to the material used as an alloying element [64–67].

If the amount of their addition in the material used in the bone nail is 0.1wt.%, it means that the amount of this type of element is introduced into the human body through the implant has been close to the total content value of the element in the human body, and it needs to be very vigilant; If an element of the elements Sc, Re and Mo is added to the material used as an alloying element, then their total amount in the human body is less than 1mg, and if the amount added in the material used in the bone nail is 0.1wt.%, it means that the amount is 0.1wt.%, which means that the implant is dissolved [68,69].

The amount of this type of element introduced into the human body is close to that of the element The biosecurity of the total content value in the human body is several times to dozens of times, and its biosecurity is worrying, and should not be used as much as possible [70]. In summary, for the dozens of elements listed in **Fig. 2**, the lower the content of the elements from left to right in the human body, the more careful the element selection should be, and the content that can be added to the degradable metal during use should be reduced [71]. However, we also see that the content of non-metallic elements present in the human body varies from high to low, including O, C, H, N, P, S, F, Si, Se, etc. Some elements can be directly added to Fe as alloying elements, such as C, N, P, Si, etc., and can also be added to degradable metals by surface treatment (ion implantation, infiltration, etc.), such as C, N, P, S and F can be introduced by carbonization, nitriding, phosphating, sulfidation and fluorination respectively [72,73].

The design

Biodegradable metal materials and devices needs to be considered including mechanical, physical, chemical and biological properties, and the performance requirements vary depending on the application context. For example, as a bone implant or cardiovascular stent, biodegradability, biocompatibility and mechanical properties can be considered as a three-in-one material [74]. When designing thin-film devices based on degradable metals for transient electronics [75], the design idea of biodegradability, biocompatibility, and electrical properties can be considered, and mechanical properties are not a necessary option. Therefore, in answer Which elements in the periodic table can be considered suitable as reducible When it comes to solving the scientific problem of alternative elements for metals, we propose only two criteria of biodegradability and biocompatibility, rather than three criteria that include mechanical properties[76].

The degradation process of degradable metals and the process of tissue repair

After vascular damage, the following three overlapping stages of repair are typically undergone. Inflammatory phase: blood and soluble serum fibronectin coagulate and form an extracellular matrix Cheng, marking the beginning of the inflammatory phase [77,78]. In the early stages of vascular repair, inflammatory cells, and some active factors are able to bind to specific sites on fibronectin. At the same time, platelets accumulate on the wound surface and are activated. Activated platelets release substances that promote local blood vessel contraction and thrombosis. At the same time, growth factors are released that can activate mesenchymal cells near damaged tissues [79]. Granulation stage: The beginning of the granulation stage is accompanied by the migration of local tissue cells to the wound site.

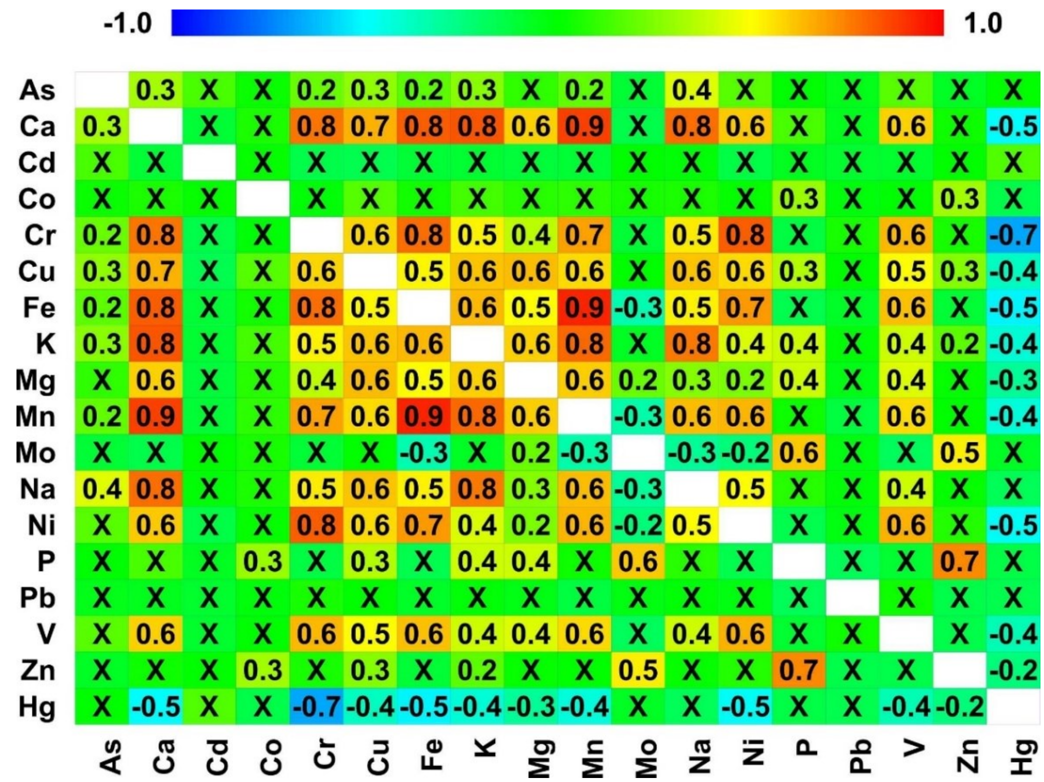

Fig. 2: Spearman's rank coefficients (r^2) for correlations of elements in cereal grains (n = 120). Adapted with permission [59].

Epithelial or endothelial cells migrate mainly from the wound margin, while fibroblasts or smooth muscle cells migrate from adjacent tissues [80]. Both types of cells proliferate at this stage, with epithelial or endothelial cells covering the wound surface and forming fibers Vitamin cells, or smooth muscle cells, synthesize and secrete extracellular matrix ingredients, especially hyaluronic acid and proteoglycans; 3) Vascular remodeling stage: Extracellular matrix deposition and remodeling will continue for several months [81].

Research status of degradable metals

Research status of magnesium-based degradable metals

Magnesium and its alloys are by far the most representative degradable metals. Materials are also the most deeply researched and applied material systems. Magnesium is an essential microelement for the human body, which is closely related to life maintenance and physical health, and is highly biocompatible. Magnesium is susceptible to corrosion in the body fluid environment, making it ideal as a temporary implant device. Looking back on the research and development history of degradable magnesium alloys, on the one hand, Mg-RE rare earth magnesium alloys have good strength, toughness and corrosion resistance and are considered as medical degradable metals [82].

Magnesium alloys, depending on the heat treatment and plastic deformation processes, have yield strength and tensile strength of more than 240 MPa and 350 MPa, respectively, and have good toughness (elongation > 10%).[24,83] At present, the two CE certified degradable magnesium alloy products in the European Union (MAGNEZIX® orthopedic screws and Magmaris vascular stents) are based on the patented alloy developed based on the composition of WE43 rare earth magnesium alloy.

Over the years, medical magnesium alloy systems containing essential elements have been obtained. Rapid development, including Mg-Ca, Mg-Zn, Mg-Li, Mg-Mn, Mg-Si, Mg-Sr and other binary alloys and Mg-Zn-Ca, Mg-Li-Ca, Mg-Sr-Zn, Mg-Ca-Sr, Mg-Ca-Si and other ternary alloys and Mg-Ca-Sr-ZN and other quaternary alloys. The tensile strength of these new medical magnesium alloys is basically below 300 MPa and the elongation is less than 20% [85]. In addition, the addition of some alloying elements can give magnesium alloy good plastic deformation ability, such as the elongation of as-cast Mg-6.8Li alloy can reach 42.58%, which is much higher than the elongation of as-cast pure magnesium (4.8%). For these alloy systems, the biocompatibility of the elements can be guaranteed to a certain extent, but alloys. In terms of comprehensive mechanical properties [86,87] and corrosion resistance, it is still inferior to containing Mg-RE alloy of rare earth elements (**Fig. 3**).

Research status of iron-based degradable metals

Iron in the human body can be divided into functional iron and non-reactive according to its function. There are two parts of energy to store iron. Functional iron accounts for 70% of the total amount of iron in the body, mainly in the form of heme in hemoglobin, muscle red egg white, heme enzymes, cofactors, etc [88]. Non-functional iron stores are mainly found in the liver, spleen and bone marrow in the form of ferritin and hemosiderin. Iron participates in the formation of atherosclerosis by catalyzing the generation of free radicals, promoting the peroxidation of lipid and protein parts of lipoproteins, and forming oxygenated LDL [89].
Compared with magnesium-based degradable metals and zinc-based degradable metals, iron-based degradable metal materials have much higher strength, and through cold working, heat treatment, alloying or other modification of the materials, they can even obtain excellent comprehensive mechanical properties comparable to cobalt-chromium alloys [91]. Iron-based degradable metals are similar to steel materials, and are easily modified through materials (alloying and surface treatment) and processes (hot and cold processing), combined with optimized scaffold design, to create absorbable stents with excellent comprehensive mechanical properties and ultra-thin wall thickness, which are the most promising to replace traditional permanent stents. The disadvantages of iron-based degradable metal materials are that the corrosion rate in vivo is very slow, and the solid corrosion products are extremely difficult to obtain from the implantation site be cleaned [92].

Research status of zinc-based degradable metals

Compared with magnesium and iron-based metals, the standard corrosion voltage of Zn (-0.762VSCE) is between Fe (-0.440VSCE) and Mg (-2.372VSCE), which means that it has a more suitable degradation rate [93,94]. As an essential element, zinc is one of the most important elements in protein synthesis and energy metabolism, and is involved in a variety of enzymatic reactions in the body. 90% of the body's zinc is stored in bone tissue, and zinc plays an important role in bone formation and mineralization. Studies have shown that zinc plays a biphasic role by inhibiting osteoclast bone resorption and promoting osteoblast bone formation, thereby increasing bone mass. In addition, zinc has been shown to promote collagen synthesis by promoting osteoblast proliferation, upregulating alkaline phosphatase activity [95]. A decrease in bone Zn content is often observed in postmenopausal women with osteoporosis and is directly proportional to bone loss. In addition, compared with magnesium-based degradable metals, zinc-based degradable metals have significantly higher mechanical strength, and there is no gas generation during the degradation process in vivo, and no local alkaline environment is generated, which is more suitable for orthopedic clinical applications [96].
In addition to the good osteogenic potential, the antimicrobial properties of zinc-based metals have also received the attention of scientists. Zn2+ can interact with the surface of bacteria and change the charge balance of bacterial cell membranes, resulting in bacterial deformation and rupture. Therefore, theoretically, all zinc-based metal species have antibacterial potential [98,99] (**Fig. 4**).

Future prospective

In 2021, the authors of this paper and Academician published an opinion article in the journal Matter [100], proposing the concept of precision bio adaptation and expounding the principle of precision bio adaptation, emphasizing that the mechanics and degradation behavior of materials should be precisely adapted to the physiological process of tissue repair in the dimensions of time and space. This will provide guiding principles for the design of materials for degradable metals [101].
A higher level of biomaterials on the basis of physical safety and biocompatibility and a more comprehensive theoretical interpretation. Degradable metals designed based on the theory of precise bio adaptation should actively adapt and create a biological microenvironment in the process of tissue repair, so as to realize the overall adaptation of materials and living organisms. The theory of precise bio adaptation points out that the main characteristics

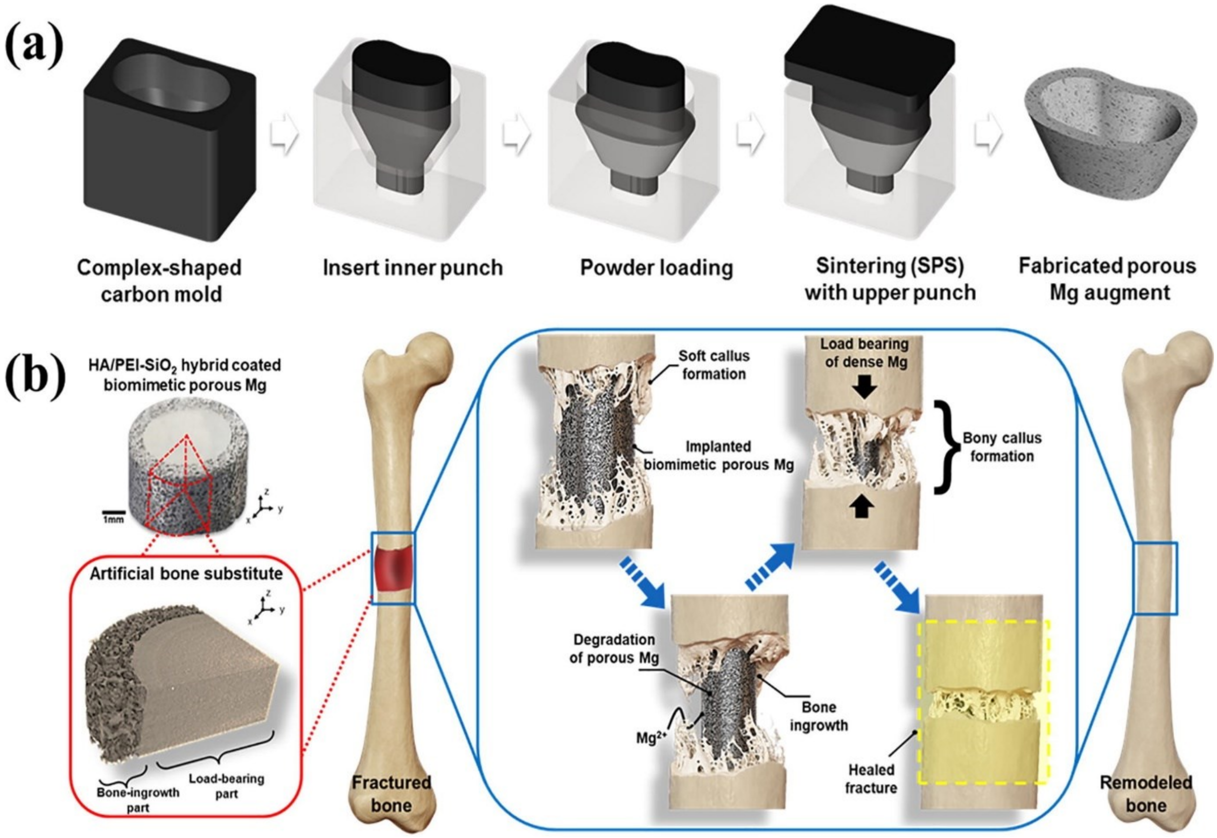

Fig. 3: (a) 3D Schematics procedure of fabricating biomimetic porous Mg augment by SPS for orthopedic application and (b) additional design of biomimetic porous Mg in which the porous Mg possesses a dense internal core surrounded by a porous outer layer as artificial bone substitute and schematic diagram of bone fracture healing process in tandem with the degradation of biomimetic porous Mg scaffold, adapted with permission [84].

of the development of new degradable metal materials include intelligence, precision, life and multi-function. The future direction of degradable metals includes a number of trends. Degradable metals with shape memory effect, such as Fe-Mn-Si alloy and Mg-Sc body.

Regarding degradation regulation, for degradable metal bulk materials, there is already a large one. The amount of composition formula and hot and cold processing process to preliminarily control the material. The degradation mode of the material (uniform corrosion or pitting, whether it includes galvanic corrosion between the second phase and the matrix, etc.) to obtain a suitable degradation. Speed, the current surface coating construction can also further regulate the degradation rate, including both accelerated degradation coatings and slowed degradation coatings, usually the latter is the main one. However, at present, these main coatings do not have the function of external field control, and the future development direction will be the new functional coating, that is, the degradation of the coating can be intervened by means such as the external light field, electric field, and magnetic field, and then the degradation cycle and degradation rate of the degradable metal can be regulated. This allows for an initial mitigation. The mechanics of the degradable metal matrix that degrades while maintaining the overall structure. Performance integrity, and then the ability to use external fields to actively accelerate the degradation of the coating itself by body fluids at a point in time when it is not required to be protected. In addition, from the perspective of degradation regulation, the highest level that researchers will pursue in the future must not be uniform degradation, but controllable inhomogeneous degradation.

The development of degradable metal films for active implantable electronic components and devices is a cross-border interdisciplinary research. The community engaged in bioelectronics research is cleverly using degradable polymers and degradable metal films to construct various electronic components (**Fig. 5**).

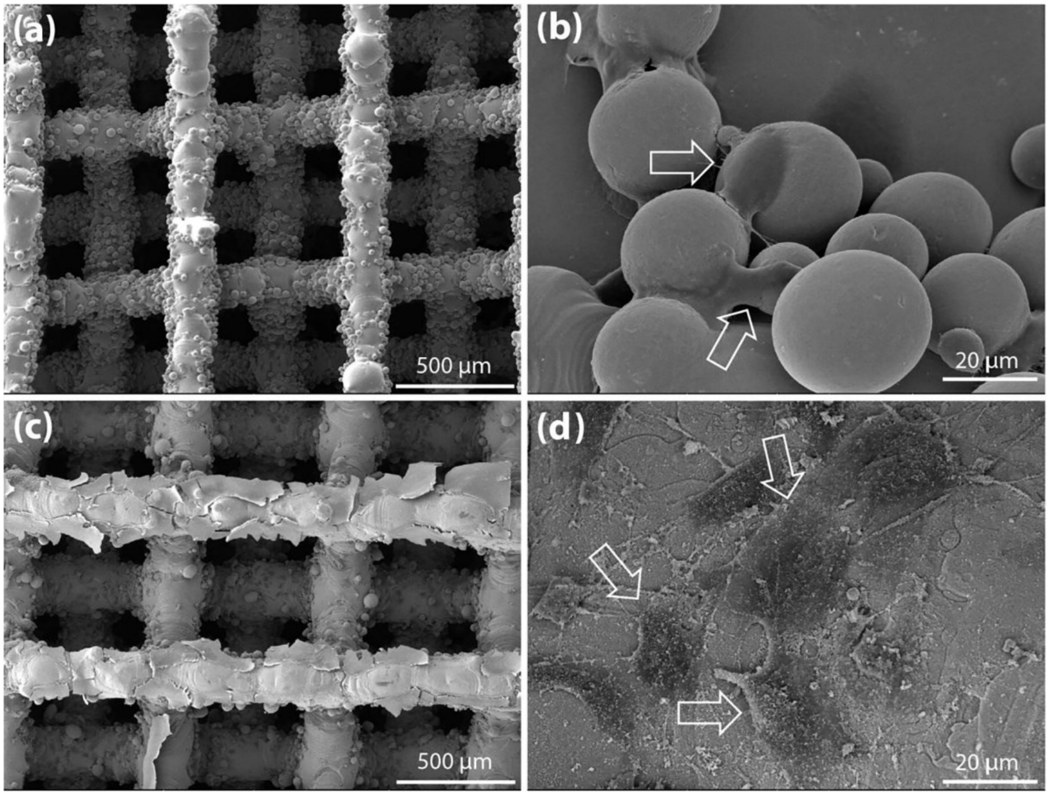

Fig. 4: Ultrastructural analyses of cell attachment *in vitro*. MG-63 cells on Ti-6Al-4V (a, b) and iron (c, d), respectively. Lower magnification scanning electron micrographs (SEM) of scaffold lattice structures (a, c) and higher magnifications (b, d) after seeding. Arrows indicate individual cells. Magnification indicated by scale bar, adapted with permission [90].

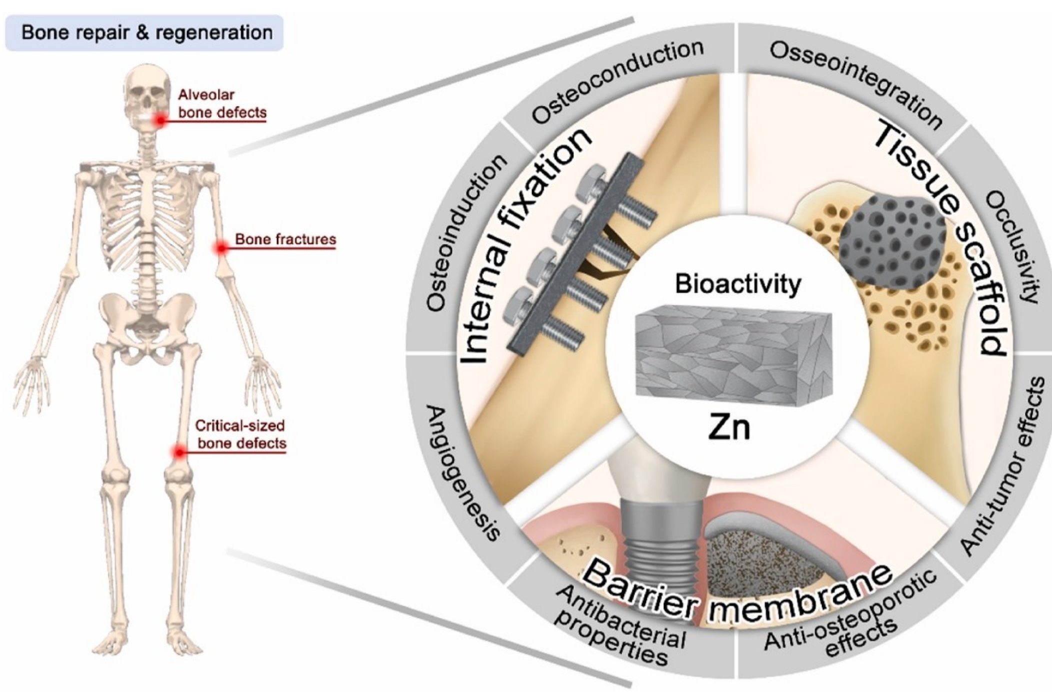

Fig. 5: Schematic illustration of possible clinical applications of Zn-based biodegradable metals, adapted with permission [97].

Conclusion

In the future, new methods for the design and preparation of new degradable metal materials, new technologies and equipment, and high-throughput characterization methods will be developed in view of the characteristics of diverse compositions, microstructures, mesoscopic pore structures, complex preparation processes, and diverse structures and properties, so as to significantly improve the R&D efficiency of degradable metal materials from demand, optimization, preparation, detection, and application. For example, machine learning is used to quickly predict the properties of degradable metal materials, accelerate the design and development of new degradable metal materials and high-throughput theoretical calculations, provide guidance for material design, and shorten the material research and development cycle. Use artificial intelligence technology to explore the relationship between the composition, process, organization, performance, and service environment of related materials; Calculate the pharmacology and pharmacokinetics of degradation products of degradable metal implant materials.

At present, degradable metals have been evaluated and studied in the fields of bone restoration, oral restoration, neurotherapy, vascular tissue repair, orifice repair, surgery, reproductive pregnancy avoidance, and bioelectronic devices. In the future, although degradable metals cannot completely replace titanium alloys, cobalt-based alloys and other substitutes for large bone defects, or joint prosthesis manufacturing, such materials are expected to be such as nitinol with its unique shape memory and hyperplastic properties are used in the manufacture of implantable interventional devices. Choosing to use the same implant will be used in some clinical applications because of its unique body fluid degradation with certain biological functions.

Conflict of interest

The authors declare no conflict of interest.

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