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Advantages of magnesium-based alloys in orthopedics and research progress in clinical applications

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ABSTRACT
In recent years, research on resorbable metal implants has gained a great deal of attention. Magnesium-based alloys have advantages in mechanical properties, biocompatibility, bioactivity, and antimicrobial potentials, but the excessive degradation rate limits their clinical applications. In order to tackle this problem, researchers have carried out various studies on surface modification techniques, and the magnesium-based screws have been certified by many countries and are now moving towards the field of clinical use. However, its clinical transformation into other orthopaedic materials still needs to solve the problem of mechanical strength as well as optimal matching of degradation behavior, where alloying and surface treatment are feasible solutions, and larger scale clinical testing and development of new types of magnesium-based implants with other functions are the directions for future research.

KEYWORDS
Magnesium-based alloys; Biological activity; Surface modification technology; Clinical application

1 Introduction

Research related to the new generation of biomedically degradable metallic materials such as magnesium, zinc and iron based alloys has become a hotspot for development and clinical research in recent years. The degradation rate of zinc-based alloys is between magnesium and iron, and their antimicrobial properties are more significant than magnesium, while they also have the disadvantage of poor mechanical properties. Iron-based alloys have the slowest degradation rate but better mechanical properties.

Neither zinc nor iron-based alloys produce gas during degradation in vivo. This paper provides an overview of the advantages of magnesium-based alloys in orthopedic applications, surface modification techniques, and current clinical applications. It also discusses and looks forward to the future development of magnesium-based alloys.

2 Advantages of magnesium-based alloys in orthopedic applications

2.1 Excellent mechanical performance

The density (1.74-2.00 g/cm3) and elastic modulus (41-45 GPa)[1] of magnesium-based alloys are closer to those of human cortical bone (1.80-2.00 g/cm3) and elastic modulus (3-20 GPa) [2], which are effective in avoiding the stress-masking effect in comparison with other materials.

2.2 Good biocompatibility

The main metabolites of magnesium-based alloys in the body are magnesium chloride and hydrogen, along with the production of hydroxide, which raises the pH of the surroundings. Mg2+ is the second most abundant divalent cation in the body after calcium ions, and acts as a cofactor in more than 600 enzymes, and as an activator in an additional 200 enzymes, most of which are present in bone and muscle, and an excess of magnesium ions can be metabolized and excreted via urine or feces.

2.3 Promoting osteogenic differentiation

In 2016, Zhang et al[3]. found that elevated extracellular Mg2+ entered the dorsal root ganglion (DRG) through two ion channels, (MAGT1) and (TRPM7), stimulated the secretion of calcitonin gene-related peptide (CGRP), and activated osteogenic differentiation of periosteal stem cells in a pure magnesium rod repair of femur fracture experiments in rats (see Fig. 1). Zheng et al[4]. developed a magnesium-containing hybrid intramedullary nail fixation system (Mg-IMN), and found that the intramedullary fixation system group rescued the delayed healing of osteoporotic fractures as well as the direct CGRP injection group in osteoporotic rat femur fracture experiments. These experiments revealed to researchers the mechanism by which magnesium-based alloys promote osteogenic differentiation. It should be noted, however, that too high a concentration of Mg2+ inhibits osteogenic differentiation of MSCs.

2.4 Promoting cartilage differentiation

Li et al[5]. demonstrated through in vitro experiments that Mg2+ enters bone marrow mesenchymal stem cells through the Trpm7 channel and activates HIF-1α, which promotes the secretion of Sox9 in the nucleus, which then enhances the expression of Acan and Col 2 proteins to promote chondrogenic differentiation, which was also confirmed in rat rotator cuff tear experiments. Wang et al[6]. found that secondary suturing of periosteum treated with pure Mg rods to tendon grafts significantly increased fibrocartilage production at the bone-tendon interface in rabbit anterior cruciate ligament reconstruction experiments.

2.5 Promoting angiogenesis

Mg^{2+} can stimulate the secretion of vascular endothelial growth factor (VEGF) from human bone marrow MSCs through hypoxia-inducible factor 2α (HIF-2α) and peroxisome proliferator-activated receptor (PPAR)[7]. Vascular endothelial growth factor (VEGF) promotes H-type capillarization, which is required for bone formation[8]. Liu et al [9]reported that Mg^{2+} promotes the secretion of platelet-derived growth factor (PDGF) from mouse embryonic osteogenic precursor cells (MC3T3-E1), which improves angiogenesis.

2.6 Modulation of the immune response

Macrophages are the major cell type involved in acute and chronic inflammation, as well as in wound healing and fibrotic responses. M1 macrophages represent a "pro-inflammatory" phenotype, sustaining inflammation and producing cytotoxic products such as reactive nitrogen and oxygen species (RNS and ROS), whereas M2 macrophages exhibit " anti-inflammatory" phenotype, releasing cytokines to inhibit inflammation and promote wound healing. It has been reported [10] that $^{Mg2+}$ promotes macrophage polarization toward the M2 phenotype and reduces the

number of M1-type macrophages, thereby decreasing pro-inflammatory factors (TNF-α, IL-1β, IL-6).

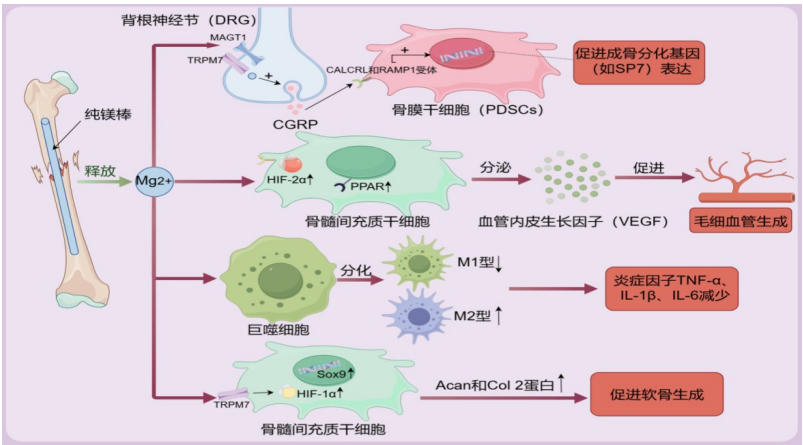

Figure 1 Schematic representation of the role of Mg^{2+} with surrounding cells after implantation of magnesium-based alloys

2.7 Antimicrobial potential

Magnesium-based alloys may also have bactericidal and bacteriostatic potential. Jesú et al[11]. cultured Staphylococcus epidermidis and Escherichia coli in media with different Mg2+ concentrations at constant pH and found that magnesium ions exhibited significant antimicrobial behaviors against Staphylococcus epidermidis and Escherichia coli. However, there is a lack of consensus on the reasons for this effect. On the one hand, it may be related to higher osmotic pressure, and it has also been proposed that the contact between the magnesium oxide particles and the bacterial cells is a key factor in the occurrence of their antimicrobial activity. The antimicrobial properties of magnesium-based alloys cannot be attributed to a single factor, but rather to a synergistic effect.

Therefore, Mg plays multiple roles in bone growth and regeneration. It plays direct and indirect roles in connecting bone, cartilage, blood vessels and the immune system. However, the higher chemical activity and degradation rate of Mg-based alloys limit the maintenance of their mechanical properties; while natural bone generally takes 8-12 weeks to heal completely, Mg-based alloys generally fail within 4-6 weeks. Hydrogen accumulation caused by its rapid degradation can delay the healing process, and in extreme cases can enter the blood vessels and cause gas embolism, while a continuous increase in local pH can lead to apoptosis and tissue necrosis. In order to reduce the degradation rate of magnesium-based alloys, in recent years, domestic and foreign researchers have conducted a large number of studies on the surface modification of magnesium-based alloys.

3 Surface modification techniques

3.1 Ion Implantation Technology

Ion implantation techniques include plasma ion implantation (PII), plasma immersion ion implantation (PIII), and plasma immersion ion implantation and deposition (PIII&D).PII is a process in which high-energy ions ejected from a target under a high-voltage static field in a high-vacuum state are accelerated and impacted onto the surface of the material, where their velocity slowly decreases and ultimately resides in the material (see Fig. 2).PIII processes are The device is immersed

in plasma and a high negative potential is applied to bias the substrate so that the substrate is surrounded by a plasma sheath. The plasma immersion ion implantation and deposition (PIII&D) process is a hybrid process combining plasma ion implantation and deposition. PIII&D involves the use of metallic plasma in the presence or absence of gaseous plasma. Efficient surface modification can be achieved by bombarding energetic ions generated from a cathodic arc plasma source, and the plasma process can be customized to obtain injection only or deposition only or a combination of injection and deposition.

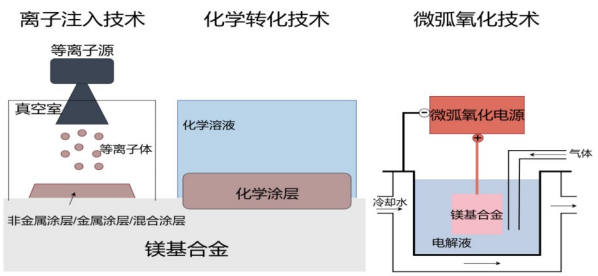

Figure 2 Schematic diagram of surface modification technology for magnesium-based alloys

According to the type of injected elements, the surface ion implantation of magnesium alloys can be categorized into non-metallic ion implantation, metallic ion implantation, and mixed ion implantation. Non-metallic ion implantation on the surface of magnesium alloys mainly includes carbon (C), nitrogen (N), oxygen (O), and silicon (Si).Li et al[12]. found that after N ions were injected into AZ31 magnesium alloy, the passivation layer formed on its surface showed good corrosion resistance in Hank's solution. Wan et al[13]. injected O on the surface of pure magnesium, the corrosion resistance of the material increased dramatically in chlorine-free PBS while the corrosion rate in chlorine-containing PBS was significantly increased. The corrosion resistance of the material in PBS without chloride ions was significantly enhanced, while the corrosion rate was accelerated in PBS containing chloride ions. Xu et al [14] generated an amorphous graphite layer on the surface of a magnesium alloy by C injection, and the material showed good corrosion resistance in both SBF and DMEM incubation fluids.

Among the types of metal ion implantation, neodymium (Nd), hafnium (Hf), tantalum (Ta) cerium (Ce), iron (Fe), aluminum (Al), and zinc (Zn) plasma implantations all showed different degrees of corrosion resistance. The corrosion resistance of the modified material was significantly improved and osteoblasts adhered and spread well on its surface. Liu et al[15]. formed a uniform ZnO layer on Mg-1Ca alloy by Zn ion implantation and deposition, and the modified Mg-1Ca alloy showed an elevated corrosion potential and a comparable corrosion current density in SBF solution, as well as a better cell adhesion and growth in short-term cell cultures. and growth in short-term cell culture.

The study of hybrid ion injection has given more possibilities to the material surface.Lin et al[16]. injected O/Ti ions on the surface of WE43 magnesium alloy by the PIII technique, and the TiO2 and Mg2TiO4 generated on the surface effectively improved the corrosion and antimicrobial resistance, as well as the corrosion and antibacterial properties. corrosion and antimicrobial properties, and can regulate the release of magnesium ions in vitro and in vivo through this specific Mg2TiO4, leading to osteoblast attachment, viability, proliferation and up-regulation of osteogenic markers such as ALP, type I Col I, Runx 2 and OPN on the surface of the material to promote in-situ bone regeneration. Liang et al[17] modified ZK60 magnesium alloy using Zr and O double plasma submerged ion implantation, which formed a hydrophobic, smooth, and ZrO2-containing surface gradient film on the surface, which not only strengthened the corrosion resistance of magnesium alloys, but The

antimicrobial effect can also be achieved by the synergistic effect of the high concentration of oxygen vacancies formed in the surface film of ZrO2, as well as the enhanced surface hydrophobicity and reduced surface roughness.

Although ion implantation techniques can enhance the corrosion resistance of magnesium-based alloys, they do not provide effective long-term protection due to problems such as limited coating thickness and non-uniformity. The material is also prone to problems such as coating flaking during implantation into biological organisms. Therefore, researchers need to conduct more experimental studies on ion implantation technology and ion implantation post-treatment to solve the above problems.

3.2 Chemical conversion technology

Metal surface layer atoms and media anions react with each other, in the metal surface to generate good adhesion isolation layer, this layer of compounds isolation layer is called chemical conversion film. Medical magnesium-based alloy surface more effective chemical conversion coating including hydrothermal treatment coating, calcium and phosphorus conversion coating, fluoride conversion coating and rare earth conversion film.

3.2.1 Hydroxide coatings

Zhu et al [18] prepared a Mg(OH) 2 layer on the surface of AZ31 magnesium alloy using NaOH solution, this treatment process is simple, the resulting coating is firmly bonded to the substrate and shows good corrosion resistance, but the resulting coating is easily damaged by Cl- . Researchers have also proposed a bimetallic hydroxide (LDH) structure. Peng et al[19] introduced a magnesium-aluminum layered double hydroxide coating (Mg-Al LDH) on the surface of a JDBM magnesium alloy using a hydrothermal method, and the experimental results showed a reduced rate of degradation of the coating, and a significant increase in the level of cell adhesion, migration, and proliferation on the coating surface, with a reduced rate of hemolysis and an improved biocompatibility.

3.2.2 Calcium-phosphorus conversion coating

The composition of Ca-P coating is similar to the inorganic composition of human bone tissue and has excellent properties of inducing osteogenesis and osseointegration and excellent biocompatibility, which makes it one of the most valuable biomodified coating materials for research. Ca-P coatings generally contain hydroxyapatite (HA), β -tricalcium phosphate (β -TCP), dicalcium hydrogen phosphate (DCPD), and calcium phosphate (OCP), etc. Ma Fei et al[20] prepared Ca-P coatings on the surface of AZ31 magnesium alloy scaffolds by chemical deposition, and static immersion experiments showed that the scaffolds had significantly improved corrosion resistance and also promoted cell adhesion and proliferation.

Wang Qing et al[21] prepared DCPD coatings on the surface of JDBM magnesium alloy scaffolds, and the scaffold extract promoted the migration of endothelial cells to form tubes, the adhesion and growth of bone marrow MSCs, as well as the enhancement of osteogenic differentiation, and in vivo experiments showed that the JDBM-DCPD scaffolds promoted the regeneration of blood vessels and new bone.

The next step to focus on is the angiogenic ability of Ca-P coating and further study the intrinsic mechanism of Ca-P coating in promoting osteogenic-angiogenic cross-linking. Since the static immersion experiments cannot fully simulate the dynamic humoral environment of the human body, further in vivo experiments are needed to verify the results of the in vitro experiments.

3.2.3 Fluoride conversion coatings

Magnesium-based alloys in contact with hydrofluoric acid (HF) react violently to form a dense MgF2 protective film on the alloy surface. This protective film can effectively avoid the contact of corrosive medium with the substrate, thus improving the corrosion resistance of the alloy.Li et al[22] treated ZK30 magnesium alloy screws with HF to prepare nanoscale MgF2 coatings on their surfaces. The screws were immersed in SBF for 30 days and were found to maintain their original shape and mechanical properties.Riaz et al[23].prepared a composite coating of Mg(OH) 2 and MgF2 on the surface of ZK60 magnesium alloy using a combination of water bath and HF treatments, and found that the surface corrosion potential of the alloy was increased, and the rate of hydrogen precipitation was significantly reduced. These results indicate that the MgF2 coating can significantly improve the corrosion resistance of magnesium alloys, but this method requires the use of highly corrosive hydrofluoric acid, which is dangerous to operate.

3.2.4 Rare earth conversion membranes

Rare-earth transformation is the process of subjecting a magnesium-based alloy to a solution containing rare-earth elements and generating a coating containing the rare-earth elements on the surface of the magnesium-based alloy. In recent years, researchers have favored studies related to rare earth conversion coatings containing cerium, yttrium, praseodymium, and lanthanum. Kannan et al[24] prepared samarium oxide (Sm2O3) coating on AZ31 magnesium alloy, which improved the corrosion resistance several times than the bare alloy.It is worth the researchers' attention that the coating possesses anti-tumor and anti-bacterial properties, which gives a chance to solve the problems of bone tumors postoperative bone defects and recurrence, which provides a new direction to solve the problems of bone tumor after surgery.

3.3 Micro-arc oxidation technology

Micro-arc oxidation (MAO) technology is the alloy material as anode, graphite or stainless steel as the cathode into the electrolyte solution to apply the appropriate voltage, in the alloy surface to form a layer of oxide ceramic film. Yang et al[25]. in the ZK60 magnesium alloy surface preparation of MAO coatings, found that the internal structure of the coatings are more dense, the surface is rough and porous, the composition of the coatings analyzed and found that the coating is composed of MgO and Mg2SiO4, due to the chemical stability of Mg2SiO4 not easy to be corroded, can play a good protective effect on magnesium alloys. MgO and Mg2SiO4, due to the chemical stability of Mg2SiO4, it is not easy to be corroded, and it can play a good protective role for magnesium alloy. Liu et al[26]. coated a type of MAO coating for the first time on the surface of the ZK60 magnesium alloy with the MAO technology on the AZ91 magnesium alloy, which is the first time in the world to be coated with a type of MAO coating on the surface of the ZK60 magnesium alloy. A lithium-containing nanoporous coating was firstly applied on AZ91 magnesium alloy by MAO technology, and the in vitro study showed good corrosion resistance, biocompatibility, angiogenesis and osteogenic differentiation, and the in vivo study confirmed the ability of osseointegration and repair of bone defects.

3.4 Composite treatment technology

Zhu et al[27] successfully prepared corrosion-resistant and biocompatible AZ31 by ultrasonic cold forging (UCFT) and subsequent MAO technology magnesium alloy surface, and the results showed that the surface grains of AZ31 magnesium alloy were refined within a depth of 400 μm due to the

ultrasonic cold forging pretreatment, which provided more discharge channels for the subsequent micro-arc oxidation. The corrosion resistance of MAO/UCFT/AZ31 was significantly improved by immersion experiments in simulated body fluids and electrochemical tests. Also, the MAO/UCFT/AZ31 samples showed good cytocompatibility. These results may be beneficial for the development of biodegradable medical materials in the future. Guo et al[28] coated the MAO-treated AZ31 magnesium alloy surface with a Ce4+-containing polyacrylamide (PAM) gel, and prepared and obtained a Ce-PAM/MAO coating avoiding pitting corrosion and realizing auto-repairing, which was analyzed by XPS and SEM-EDS, and the self The self-repairing performance may be related to the role of Ce4+ and the bridging effect of PAM gel, and this study presents for the first time the surface modification of magnesium alloys capable of self-healing.

4 Conclusion and Prospects

In general, the advantages of magnesium-based alloys have been emphasized by more and more researchers, and the mechanism of magnesium ion action has been gradually revealed. Since the human physiological environment is a complex system, we cannot just focus on the in vitro degradation, the study of corrosion mechanism in the in vivo bone tissue environment and dynamic blood microenvironment, and the reaction between corrosion products and immune cells such as dendritic cells, neutrophils and macrophages are more worth exploring. Surface coatings of magnesium-based alloys have a variety of possibilities in terms of corrosion resistance, biocompatibility, osteoinduction, anti-tumor, and antimicrobial properties, etc.

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