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REVIEW

Research Progress of Magnesium Alloys and Its Alloys in Medical Applications

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Abstract: As technology continues to progress, innovations in research and applications within the medical field are steadily emerging. Magnesium and its alloys, as emerging materials, exhibit characteristics such as low density, favorable biocompatibility, and biodegradable properties, rendering them highly promising for broad applications in the medical field.This article reviews the research and development of magnesium and its alloys in medical fields such as orthopedics, oncology, and neurology, as well as their use as biomedical materials. It summarizes how treatments including purification, alloying, and surface modification of magnesium can fully unlock the potential of magnesium and its alloys in targeted therapy, tissue repair, antibacterial applications, and fixation of medical implants. However, to achieve widespread clinical adoption of magnesium-based biomaterials, further breakthroughs remain necessary in areas such as biocompatibility, mechanical properties, and large-scale clinical validation.

Keywords: magnesium alloy, antitumor, vascular stents, intestinal scaffolding, staple

Introduction

Today, with the deepening of research on biomaterials, they are playing an increasingly important role in the field of clinical medicine.[1] Among them, metallic biomaterials have attracted significant attention from researchers due to their excellent biocompatibility and mechanical properties, such as stainless steel,[2] titanium and its alloys,[3] and cobalt-chromium alloys.[4] However, these non-degradable metallic materials, when used as implants, must be removed through surgery, which increases the financial burden and health risks for patients. Due to their poor antibacterial properties and the release of ions that may cause inflammatory reactions, patients often require antibiotics to control inflammation and prevent bacterial infections, leading to a growing problem of bacterial resistance.[5,6] To address these shortcomings, biodegradable metallic materials are gradually coming into focus.

Biodegradable metallic materials, such as magnesium, iron, and zinc, have gradually become a research hotspot due to their excellent mechanical properties and controllable degradation characteristics. These biodegradable metallic materials can be fully absorbed by the human body after implantation, avoiding the issues of long-term retention and secondary removal, significantly reducing the incidence of complications, additional costs, and the risk of new symptoms for patients, demonstrating broad application prospects. Magnesium is one of the essential nutrients for the human body, widely involved in various metabolic processes, and crucial for maintaining the normal physiological functions of tissues and organs such as the heart, brain, muscles, and bones.[7] It plays a key role in energy metabolism, protein synthesis, neural signal transmission, and muscle contraction, making it an indispensable element for human health. As a biodegradable implant material, magnesium undergoes gradual corrosion upon exposure to physiological fluids,

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Table 1 Magnesium Compared to Other metals[12–16]

Material	Density (g/cm^3)	Tensile Strength (MPa)	Elastic Modulus (GPa)	Surgical Removal Required?	Advantage	Limitations
Mg	1.74	65-100	41-45	No	Low density and elastic modulus; High specific strength; Degradability; Machinability.	Low mechanical properties; Hydrogen gas is released and accumulates in the surrounding soft tissue during the degradation of magnesium.
Stainless Steel	7.9–8.1	540-1000	190-205	Yes	Low cost; low ductility; high strength; good corrosion resistance.	High surface roughness and porosity.
Ti	4.4–4.5	758-1117	110-117	Yes	Excellent biocompatibility; high tensile strength; good corrosion resistance; low weight.	High cost; poor wear resistance and fatigue strength.
Zn	7.14	400-1540	90	No	Good processability; low melting point; low reactivity in the molten state.	Poor mechanical properties; excessively released zinc ions are cytotoxic to several mammalian cell lines.
Cobalt chromium alloy	8.3–9.2	450-1000	230	Yes	Indicated for multi-unit fixed dental and implant-supported prostheses.	Large pores; coarse grains; adversely affect the mechanical properties.
Fe	7.87	150	200	No	High strength; good formability.	Slow corrosion, The corrosion products are voluminous and prone to accumulation

ultimately dissolving completely in vivo. The resulting magnesium ions are efficiently eliminated via renal and fecal excretion pathways, minimizing risks of toxicity or immunological adverse effects.[8] Magnesium distinguishes itself among metallic biomaterials due to its exceptional biocompatibility (Table 1). The measured density value of magnesium is 1.74 g/cm^3, and static modulus of elasticity measurements show a range of values from 41–45 GPa. Magnesium exhibits mechanical properties closely matching those of natural bone tissue (10–23 GPa).[9] This favorable similarity in Young's modulus makes it a superior candidate for biomedical applications compared to alternative biomaterials.[10] Additionally, magnesium is easy to process and highly stable, making it suitable for manufacturing complex-shaped components.[11]

However, pure magnesium exhibits poor ductility and excessively rapid degradation and corrosion in physiological environments, while the excessive production of hydrogen gas may adversely affect surrounding tissues.[17] Furthermore, the pronounced crystallographic anisotropy of magnesium significantly constrains the activation of specific slip mechanisms. Consequently, unalloyed magnesium exhibits limited plastic deformability, a characteristic that has been experimentally validated.[18] To overcome the performance limitations of pure magnesium materials, researchers are working to develop new biodegradable bioalloys based on magnesium. By removing trace impurities, adding alloying elements, and modifying the alloy surface (Figure 1),[19,20] the advantages of magnesium can be more fully utilized. Recent research has demonstrated that biodegradable magnesium-based implants and their corrosion byproducts possess multifaceted biological activities. These include the stimulation of osteogenesis, suppression of inflammatory responses, and even exhibiting antitumor effects, as evidenced by in vitro and in vivo studies.[21,22]

The utilization of magnesium and its alloys as biomedical materials is not a recent development.Historical records indicate that as early as 1878, surgeon Edward Huse pioneered the use of magnesium wires for vascular ligation, followed by Dr. Albin Lambotte's implantation of magnesium plates for fracture fixation in 1906.[23] With advancing research on the physical properties and biocompatibility of magnesium, its potential in biomedical applications has significantly expanded. Magnesium-based materials demonstrate multifunctional clinical value. They can serve as targeted drug delivery carriers to precisely transport medications to tumor sites, thereby enhancing therapeutic efficacy

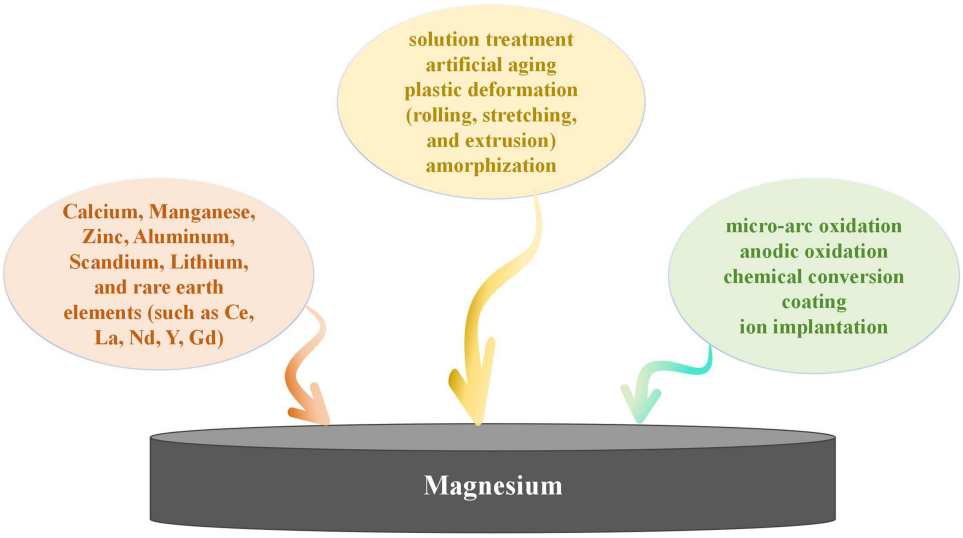

Figure 1 Treatment Methods for Magnesium.

while reducing side effects.[24] Furthermore, leveraging their excellent biocompatibility and controllable degradability, they promote the regeneration of neural and vascular tissues without requiring secondary removal surgeries.[25] In the field of orthopedics, magnesium alloys exhibit particularly prominent advantages. They function both as bone repair and replacement materials to guide bone tissue regeneration, and possess inherent antibacterial properties that can prevent secondary infections and accelerate healing. Notably, MAGNEZIX® screws have been utilized in over 25,000 cases worldwide, with clinical efficacy extensively validated.[26] Furthermore, magnesium-based implants and sutures provide biodegradable mechanical support in soft tissue repair, eliminating the need for additional extraction procedures.[27]

This article reviews the research progress of magnesium and its alloys in clinical applications, introduces their research and development in medical fields such as orthopedics, oncology, and neurology, as well as their use as medical materials. Finally, the challenges and development prospects faced by magnesium and its alloys are discussed.

Applications of Magnesium-Based Alloys in Oncology

Cancer represents a significant global public health challenge, with 2022 global cancer statistics indicating that it is the primary cause of mortality in 57 countries.[28] Global cancer statistics reveal that the number of new cancer cases worldwide was approximately 12. 7 million in 2008[29] and rose to about 20 million in 2022,[28] marking a 57. 4% increase over the decade. Cancer imposes a tremendous social burden and consumes substantial economic resources, with the cost of cancer treatment in China alone reaching 392. 462 billion yuan in 2018. It is projected that between 2020 and 2050, cancer will incur global economic costs amounting to $25.2 trillion, imposing a substantial burden on worldwide economic growth.[30] With the advancement of modern medicine, strategies for cancer prevention, screening, diagnosis, and management have been significantly optimized, and corresponding changes have occurred in cancer treatment methods. Current cancer treatment modalities encompass fundamental approaches such as radiotherapy, chemotherapy, and surgery, alongside emerging techniques including gene therapy, targeted therapy, and photodynamic therapy.[31,32] However, treatment efficacy remains constrained by pervasive drug resistance and inadequate control of tumor metastasis, resulting in persistently high overall mortality rates.[33] Consequently, there is an urgent need to accelerate the development of novel therapeutic technologies. Breakthroughs in biomedical materials have created new opportunities for cancer diagnosis and treatment. Magnesium-based alloys, with their biodegradability, mechanical suitability, and potential anti-tumor effects, are now a leading research focus in biomaterials.

Magnesium and its alloys are garnering increasing interest as a novel platform for oncologic applications. Magnesium and its alloys provide superior mechanical strength compared to polymers and enhanced biocompatibility over titanium, all while obviating the need for secondary removal surgery due to their biodegradable nature.[34,35] Beyond these structural

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advantages, magnesium ions exerts intrinsic antitumor activity. Its reaction with water in the tumor microenvironment generates hydrogen ions, which can propel drug-loaded particles and induce localized pH changes, both contributing to tumor suppression.[36] Furthermore, serum magnesium levels have been established as an independent prognostic factor in patients receiving immune checkpoint blockade, underscoring its systemic relevance in cancer outcomes.[37] These multifunctional properties position magnesium alloys as a promising therapeutic strategy, meriting further investigative pursuit.

Numerous researchers have contributed their perspectives on the treatment of osteosarcoma. Hakimi et al[21] employed a co-culture model of alloy materials and mouse osteosarcoma cells in vitro to assess the cytotoxicity of rapidly solidified EW62 (Mg-6%Nd-2%Y-0. 5%Zr) alloy. Compared with traditional cast alloys, its corrosion resistance and mechanical properties were significantly improved, while the cytotoxicity to mouse osteosarcoma cells was reduced. This alloy achieved a good balance between biodegradability and cytotoxicity. Li et al[38] developed a targeted treatment system for giant cell tumor of bone by constructing a CaP/zoledronic acid (ZA) composite coating on Mg-1.5wt%Sr alloy surfaces. The results demonstrated that the alkaline microenvironment generated by alloy degradation enhanced ZA bioactivity. This system exhibited multi-mechanistic antitumor effects through: inducing tumor cell apoptosis, increasing ROS levels, inhibiting osteoclast migration and osteolysis, while simultaneously activating the mitochondrial apoptosis pathway and suppressing NF-κB signaling. This study provides a novel material-based strategy for local bone tumor therapy. Kannan et al[39] coated AZ31 magnesium alloy with a samarium oxide (Sm) coating, significantly improving corrosion resistance and preventing chloride ion penetration into the substrate. The Sm coating not only promoted normal cell adhesion and proliferation but also induced osteosarcoma cell death through the release of Sm^3+ions, achieving an anticancer activity of up to 95%. This coating exhibited both anticancer and antibacterial properties, significantly inhibiting the growth of bone tumor tissue. Shao et al[40] successfully fabricated a bifunctional multilayer film on AZ31 magnesium alloy. First, a basic corrosion protection layer was formed through hydrothermal treatment, followed by the deposition of polydopamine (PDA) and loading of the antitumor drug doxorubicin (Dox). The modified magnesium alloy effectively killed bone tumor cells in vitro and suppressed tumor growth in nude mice through the synergistic effects of chemotherapy and photothermal therapy. Studies showed that this functional magnesium alloy possessed controllable tumor ablation capabilities, reducing the risk of recurrence and promoting bone reconstruction. Li et al[41] designed a biodegradable magnesium particle based on as-cast Mg-1. 5wt. %Sr alloy, which was modified with a micro-arc oxidation (MAO) coating and loaded with bisphosphonates (BP). The particles exhibited good biocompatibility in 2D and 3D cell cultures in vitro, inducing apoptosis and necrosis in OS cells, and inhibiting tumor invasion and cell cycle progression. BP-coated magnesium particles effectively inhibited tumor recurrence and growth and could be used to repair defects after tumor resection in OS treatment, offering a new option for malignant bone tumor therapy. Globig et.al[42] examined the impact of magnesium-based materials on a co-culture model of osteosarcoma cells and fibroblasts. Magnesium and Mg-6Ag significantly reduced the proliferation of cancer cells. Importantly, the pH increase caused by magnesium degradation was a major driver of cancer cell dormancy, suggesting that magnesium-based materials could be combined with other drugs to enhance chemotherapy efficacy and reduce drug resistance. Zhang et al[43] developed a biodegradable material based on AZ31 magnesium alloy, creating a black manganese-containing layered double hydroxide (LDHs) film-modified coating (PEO/LDH) through a combination of plasma electrolytic oxidation (PEO), immersion treatment, and hydrothermal treatment. This coating demonstrated significant effects in controlling implant biodegradation rates, inhibiting osteosarcoma (OS) growth, antibacterial activity, and promoting bone defect regeneration, offering a new strategy for complex OS treatment. Ge et al[44] developed an innovative therapeutic strategy integrating biodegradable magnesium-based implants with immunomodulatory treatment, demonstrating complete tumor eradication in OS cases. MgR's eddy thermal effect (ETE) exerted cytotoxic effects on tumor cells while activating antitumor immunity via dendritic cell maturation and immunogenic cell death induction in OS. MgR-mediated magnetic hyperthermia therapy (MHT) combined with immune checkpoint blockade treatment significantly enhances T cell infiltration capacity within the tumor microenvironment, induces macrophage polarization toward the M1 phenotype, and simultaneously promotes osteogenic differentiation. The heterogeneous ETE mediated by MgR comprehensively activated immunity within the OS tumor microenvironment, providing new insights for the application of MHT in OS treatment.

A significant number of clinical adverse events have shown that permanent staplers may lead to side effects like inflammation and allergic reactions, while also lacking localized anti-tumor capabilities.[45–47] Clinical data analysis reveals a significant inverse correlation between magnesium ion supplementation and the risk of colorectal tumor development.[48] Implantation of biodegradable magnesium needles after tumour removal may inhibit residual cancer cells.[49] Magnesium, being an essential element, is gradually absorbed by the body, exhibits excellent mechanical properties, and shows significant potential in intestinal applications. Zan et al[49] utilized high-purity magnesium to create staples for intestinal anastomosis. Research revealed that magnesium anastomotic implants could heal wounds resulting from colorectal cancer resection and suppress the recurrence of residual tumor cells in both in vitro and in vivo settings. They demonstrated excellent closure and tumor suppression in rabbits and tumor-bearing mice, respectively. Moreover, using in vitro co-culture methods, Magnesium staples suppressed the growth and migration of colorectal cancer cells and triggered their apoptosis. Magnesium ions exert antitumor effects through a dual mechanism: arresting the cell cycle at the G0/G1 phase while simultaneously activating the caspase-3 apoptotic pathway in a dose-dependent manner, thereby effectively inhibiting tumor cell proliferation. Li and colleagues[50] confirmed this by introducing a specific concentration of magnesium ions into the in vitro cell culture of the human colorectal adenocarcinoma cell line DLD-1.

In the treatment of other cancers, researchers have also demonstrated the anti-tumor properties of magnesium. Qiao et al[51] were the first to report that magnesium degradation can inhibit ovarian cancer. They implanted magnesium wires into tumor-bearing mice and observed a significant reduction in tumor volume while the mice maintained normal body weight. In vitro studies demonstrated that the degradation products of magnesium, Mg^{2+} and H_2, suppressed cancer growth. Both Mg^{2+} (>20 mM) and H_2 promoted apoptosis in SKOV3 cells. Qiao and colleagues demonstrated that magnesium degradation products, especially the released Mg2+ and H2, exert a potent inhibitory effect on the progression of epithelial ovarian cancer. Li et al[52] evaluated the anti-cancer effects of magnesium compared to traditional titanium (Ti) scaffold materials on hepatobiliary cancer. The results showed that biodegradable magnesium exhibited superior inhibitory effects on RBE cells and H22 tumors compared to traditional titanium alloys. Magnesium extracts suppressed the growth of the human cholangiocarcinoma cell line RBE, triggered apoptosis, and influenced cell adhesion and the cytoskeleton. In animal experiments, they obtained results similar to those of Qiao et al, with H22 tumor-bearing mice implanted with Magnesium wires showing significantly reduced tumor volume and weight, increased tumor cell apoptosis, and decreased expression of CAIX and HIF-1α. The findings suggested that biodegradable magnesium exhibits anti-tumor effects both in vitro and in vivo, highlighting its potential as a material for anti-cancer biliary stents. Bladder cancer, the second most prevalent malignant tumor in the urogenital system, continues to impose an increasing global disease burden., and Li and colleagues[53] revealed that $MgCl_2$/$MgSO_4$ suppresses bladder cancer cell proliferation and migration while inducing apoptosis through regulation of the Ras/ERK and Wnt pathways. Particularly noteworthy is the finding that the combination of $MgCl_2$ with valproic acid (VPA) synergistically downregulates Wnt signaling while activating the ERK pathway, thereby significantly enhancing antitumor efficacy. This combined therapeutic approach demonstrated promising treatment potential in both in vitro and animal models. These findings provide a novel strategy for combination therapy in bladder cancer management. Anisimova et al[54] conducted systematic experiments to evaluate the antitumor properties of two novel magnesium alloys (Mg-6%Ag and Mg-10%Gd). Both alloy materials demonstrated significant proliferation-inhibiting effects on the prostate cancer PC-3 cell line. In vivo studies, where needles of both alloys were implanted into B16 melanoma tumors in mice, revealed a significant reduction in cell numbers and destruction of tumor tissue, indicating anti-tumor effects. The significant anti-tumor effects observed in Mg-10%Gd ECAP specimens indicated that the performance of gadolinium-containing alloys far surpassed that of silver-containing alloys.

To achieve efficient cancer treatment, many researchers have used magnesium alloys as carriers for anti-cancer drugs, encapsulating chemotherapy drugs on the surface or inside the magnesium alloys to enhance therapeutic efficacy by controlling drug release rates. Zhao and colleagues[24] created doxorubicin (Dox) delivery nanoparticles for tumor-targeted chemotherapy utilizing rolling circle amplification (RCA) technology, enabling the efficient collection of substantial amounts of functional DNA. These DNA nanoparticles exhibit high biological stability. The 100 nm magnesium-based nanocarrier (Mg-RNC) developed by this team has four main features: excellent biostability, high doxorubicin loading, positive tumour targeting and pH-responsive release. More importantly, Mg-RNC@Dox not only exhibited the passive

retention effect (EPR) but also demonstrated active targeting effects. Another biodegradable molecularly imprinted polymer (MIPs) nanoparticle (Mg-SMSN/DOX-Ce6@MIPs) can target sialic acid (SA) overexpressed on the surface of tumor cells. The nanoparticle exhibited excellent targeting, pH-responsive drug release, and anti-tumor efficacy in breast cancer cells (MCF-7), offering a highly effective drug delivery platform for cancer therapy.[55] For economic and eco-friendly purposes, researchers created polysaccharide-based magnetic gel beads (CMCS-SA) incorporating $MgFe_2O_4$ nanoparticles, featuring high drug-loading capacity and pH- and magnetic field-controlled drug release.[56] It remained stable in simulated gastric fluid, released drugs continuously in simulated intestinal fluid, and accelerated release under an external magnetic field, showing biocompatibility with normal fibroblasts (3T3 cells) but significant inhibition of colon cancer HCT116 cells. Pacheco et al[57] developed pH-sensitive solid magnetoliposomes (SML) for the controlled release of doxorubicin (DOX). SML exhibited a DOX encapsulation efficiency of up to 98% and demonstrated more efficient drug release in acidic conditions (pH=5). Co-culture experiments with HepG2 cells confirmed that SML reduced cancer cell viability to 26. 8%, demonstrating its more efficient drug delivery capability. Physical approaches can also accurately regulate drug release rates. Peng and colleagues[58] investigated the response of a new nanocarrier, MgFe2O4@CuS functionalized with aminopropyltriethoxysilane (APTES), to magnetic fields, near-infrared light, and electromagnetic wave radiation. They found that the release of ibuprofen (IBU) from MgFe2O4@CuS-APTES-IBU could be adjusted by the duration and number of cycles of electromagnetic wave and near-infrared light treatment. Compared to near-infrared light, electromagnetic wave irradiation resulted in higher drug release rates and stronger tissue penetration capabilities. For applications needing fast and deep payload delivery, Lopez-Ramirez and colleagues[59] developed an active microneedle delivery system utilizing magnesium microparticles. Magnesium interacts with interstitial fluid to generate hydrogen gas (H_2), overcoming the dermal barrier and improving drug delivery. This system enables rapid burst release and sustained delivery without external stimulation, significantly enhancing immunotherapy efficacy and extending survival. This system enables rapid burst release and sustained delivery without external stimulation, significantly enhancing immunotherapy efficacy and extending survival. Zhou et al[60] prepared Mg@PLGA particles using microfluidic emulsion technology for tumor photothermal therapy. The research revealed that the photothermal performance and cytotoxicity of the microparticles were mainly influenced by magnesium content, not their size or structural characteristics, suggesting that magnesium content is crucial for their anti-tumor effects.

Magnesium can also serve as a vaccine adjuvant, enhancing anti-tumor immune responses by improving immune reactions. Chen and colleagues[61] created a dual-adjuvant nanovaccine using human serum albumin (HSA), incorporating imiquimod (R837) and magnesium, to strengthen anti-tumor immunity. The vaccine transports dual adjuvants and neoantigens to lymph nodes through HSA, stimulating dendritic cells and T cells, and facilitating the gradual release of antigens and adjuvants. In melanoma models, the vaccine markedly suppressed tumor growth and extended the survival duration of mice. In melanoma models, the vaccine markedly suppressed tumor growth and extended the survival duration of mice. Dai et al[62] constructed a novel antigenic nanoparticle vaccine named HemoMap, consisting of the antigenic peptide Tyrp1 and magnesium nanoparticle adjuvant. The vaccine targets lymph nodes, increases Tyrp1 expression in dendritic cells, and activates CD11c and CD8 lymphocytes. In melanoma models, HemoMap markedly suppressed tumor growth and boosted the anti-tumor activity of splenic lymphocytes. These findings indicate that magnesium-based nanovaccines have clinical translation potential.

Magnetic hyperthermia therapy (MHT) employs alternating magnetic fields (AMF) to heat magnetic thermogenic agents, such as magnetic nanoparticles, in tumors for the purpose of tumor ablation. Compared to conventional hyperthermia techniques, MHT offers the distinct advantage of superior tissue penetration depth.[63,64] Yang et al[65] were the first to discover that non-magnetic biodegradable magnesium alloy MgA (Mg:Zn:Ca = 97. 7:2. 0:0. 3%) can achieve tumor magnetic hyperthermia ablation under low-field-strength alternating magnetic fields (AMF). MgA rods quickly heat surrounding tissues in AMF, with the heating efficiency largely determined by the rod's diameter and length. This mechanism demonstrated effective tumor cell killing in vitro and precise ablation of large tumors in a rabbit solid tumor model. Manohar et al[66] improved hyperthermia by adjusting the size and morphology of Cu-doped Zn-Mg ferrite nanoparticles using a solvothermal reflux method, successfully inhibiting the growth of human breast cancer cells. They also proposed that adding targeting molecules to these nanoparticles could improve treatment precision and reduce damage to healthy tissues. As previously mentioned, MHT combination therapy was employed by Ge and colleagues,[44]

who used the vortex heat effect of MgR to enhance T-cell infiltration in the tumour microenvironment and to induce macrophage polarisation towards the M1 phenotype, yielding positive outcomes in OS treatment. This further confirms the feasibility of MHT in cancer therapy.Han et al[67] recently developed a layered double hydroxide-modified nano-magnesium implant (Zn-LDH@Mg) that induces tumor cell pyroptosis under AMF stimulation. Experimental results demonstrate that this distinctive form of immunogenic cell death not only directly eliminates tumor tissue but also significantly enhances systemic antitumor immune responses by activating dendritic cell antigen presentation. Notably, this pioneering study represents the first successful integration of biodegradable magnesium-based materials with magnetothermal therapy, providing a novel technical approach for hepatocellular carcinoma (HCC) treatment.

Numerous studies have demonstrated that magnesium can exert anti-tumor effects through multiple pathways. Through targeted processing techniques, the mechanical properties, biocompatibility, and degradation rates of magnesium-based materials can be systematically regulated. Furthermore, combined application strategies with various anti-cancer therapies have expanded their clinical translation prospects. However, current research in this field primarily focuses on theoretical exploration and preclinical validation, requiring further evaluation of safety and efficacy through standardized clinical trials. Meanwhile, achieving precise positioning of implants, ensuring controllability of the treatment process, and maintaining stability of therapeutic outcomes remain critical challenges to be addressed in the future.

Applications of Magnesium-Based Alloys in Neurology

Research indicates that magnesium is a key element in maintaining neuronal function. Magnesium is involved in the formation of membrane phospholipids and synapses, signal transduction, and regulation of neurotransmitter delivery.[68–70] Additionally, magnesium facilitates axonal growth and neural stem cell proliferation, modulates inflammatory responses, and consequently suppresses apoptosis.[70,71] Moreover, studies have confirmed that magnesium deficiency is not only significantly associated with the development and progression of diabetic peripheral neuropathy (DPN), but also closely linked to the pathological processes of neurodegenerative diseases,[72–75] such as Parkinson's disease and Alzheimer's disease.[76,77] Consequently, magnesium plays an irreplaceable and critical role in preventing related disorders and maintaining neurological health.[78]

Mg^{2+} exerts beneficial effects on nerve cells and the nervous system in both in vitro and in vivo settings.[79,80] Mg^{2+} is capable of repairing peripheral nerve and spinal cord injuries. For instance, magnesium supplementation enhances sciatic nerve regeneration in rats and reduces inflammatory responses following nerve crush injury.[81] Additionally, $MgSO_4$ exhibits vascular and neuroprotective properties after spinal cord contusion in rats,[82] and an appropriate concentration of Mg^{2+} can promote the proliferation of neural stem cells.[83] Supplementing with magnesium salt solutions can enhance the cell density and axonal generation of primary mouse neuronal stem cells.[71] Calcium overload-induced apoptosis is recognized as a pivotal mechanism underlying secondary spinal cord injury (SCI), with excessive activation of N-methyl-D-aspartate receptors (NMDARs) by excitatory amino acids released from dying cells serving as the critical mediator of this pathological process.[84] Research demonstrates that Mg^2+ exert neuroprotective effects through dual mechanisms: competitively blocking NMDARs while simultaneously inhibiting the opening of voltage-gated calcium channels (VGCCs). This coordinated action effectively reduces calcium ion influx and prevents neuronal apoptosis induced by calcium overload.[85] Pioneering studies bySe-baa et al[86] and Hopkins et al[87] have proposed the implementation of Mg-containing substrates for neural prosthetic devices, including electrode arrays and regenerative nerve conduits. Contemporary research has increasingly focused on elucidating the neuroprotective mechanisms of magnesium ions through comprehensive in vitro investigations.[71,88] The scientific consensus indicates that Mg^2+ exhibits multiple beneficial effects on neural tissues providing cytoprotection against oxidative stress in mature neurons, enhancing the proliferation capacity of hippocampal neural progenitor cells and preferentially directing their differentiation toward neuronal rather than glial lineages in living organisms. These properties may contribute to the attenuation of neurodegenerative pathology observed in Alzheimer's disease models.[89,90] RClinical investigations have established a significant association between post-traumatic hypomagnesemia and the progression of secondary neurological damage.[91] Experimental data demonstrate that magnesium administration confers neuroprotection in traumatic brain injury through several distinct pathways: suppression of excitatory neurotransmitter release at synaptic terminals, antagonism of NMDA receptor-mediated calcium influx, and potentiation of adenosine-mediated presynaptic modulation.[92,93] Both preclinical

and clinical studies consistently report that the magnitude of serum magnesium depletion following cerebral trauma positively correlates with the severity of resulting neurological deficits.[91,94] Magnesium is also crucial in neuronal maturation and neuropathology, with proper magnesium supplementation providing neurotrophic effects that support neuronal development.[77] Vennemeyer and colleagues[95] documented the biocompatibility of pure magnesium wires for repairing sciatic nerve gap injuries. Magnesium wires facilitate the regeneration of neuronal axons, demonstrated by an increase in the number of regenerated axons and the cross-sectional area of regenerated myelinated nerve fibers.[96] Additionally, the use of magnesium wires can enhance nerve regeneration, offering potential for the treatment of nerve injuries.[87,95]

Magnesium is clinically used for neuroprotection, including in eclampsia, preeclampsia, traumatic central nervous system injuries, cerebral ischemia, stroke, and Parkinson's disease.[92,97,98] From a neuroprotective standpoint, Wolf and colleagues[99] demonstrated that when administered during the vulnerable 24–32 week gestational period, magnesium sulfate significantly decreases the occurrence of moderate and severe cerebral palsy in premature infants, confirming its protective effects on the developing brain. In the field of ocular medicine, experimental investigations have revealed that magnesium acetyltaurate (MgAT), when introduced directly into the eye, provides effective protection to retinal ganglion cells and optic nerve fibers. This protective mechanism appears particularly effective against the harmful effects caused by excessive NMDA receptor stimulation, as observed in experimental glaucoma studies. [100]

Studies have explored the role of magnesium ions in promoting peripheral nerve repair through inflammation suppression, although the mechanisms underlying magnesium deficiency-induced inflammatory responses remain incompletely elucidated. Pan et al[101] were shown to elevate Mg^{2}+ levels in plasma and neural tissue, enhance neurobehavioral and electrophysiological performance, and attenuate neuroinflammation by reducing macrophage infiltration and pro-inflammatory cytokine expression. Experimental findings by Arfuzir et al[102] demonstrated that MgAT pretreatment effectively suppressed the elevated expression of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) induced by endothelin-1. Furthermore, this intervention prevented the activation of both NF-κB and c-Jun signaling pathways in response to endothelin-1 stimulation, consequently mitigating macrophage-mediated inflammatory responses in the studied animal model.

In peripheral nerve regeneration, nerve guidance conduits (NGCs) have emerged as a clinically viable alternative.[103] Magnesium-based biodegradable alloys demonstrate particular promise as NGC scaffold materials due to their optimal combination of biocompatibility, suitable mechanical strength, and pro-regenerative properties that facilitate axonal regrowth. Li et al[96] implanted magnesium wire bridges to reconnect severed nerve stumps. Four-week postoperative assessments showed significant improvements in the magnesium-treated group, including higher sciatic functional index (SFI) scores, upregulated expression of nerve growth factor (NGF) and increased levels of neurotrophin receptors. These results indicate that magnesium scaffolds provide both structural guidance and biochemical stimulation, effectively promoting axonal regeneration through the lesion site. Hopkins et al[87] systematically evaluated magnesium wire implants for peripheral nerve repair across varying defect lengths. Histological analysis demonstrated successful regeneration of neural cells and axonal regrowth at the resection sites in short-gap injuries; in long-gap repairs, while no functional improvement was noted in the empty conduit plus magnesium wire group compared to the graft group, regenerated tissue linked to the nerve stumps was still detected, demonstrating that magnesium wires can improve the regeneration of injured nerves. The filling material in the conduit also affects the degradation rate of magnesium wires. Vennemeyer et al[95] placed magnesium wires in polycaprolactone nerve conduits for 6 weeks to repair a 6 mm gap in the sciatic nerve of adult rats. The experimental findings demonstrated that the implanted magnesium wires became effectively integrated with newly formed neural tissue, while only eliciting minimal inflammatory responses at the implantation site.

Some researchers have improved the properties of biomaterials by incorporating Mg^{2+} to enhance their ability to promote peripheral nerve regeneration. Sun et al[104] hybridized Mg^{2+} with poly(glycerol sebacate) (PGSM) to create PGSM-Mg and investigated its improved properties. PGSM-Mg demonstrates superior biodegradability and controlled release of Mg^{2+}. Compared to several other scaffolds, it better promotes the adhesion and proliferation of Schwann cells (SCs) and enhances the expression of more nerve-specific genes, showing great potential for promoting peripheral nerve regeneration. Ramburrun et al[105] added magnesium oleate (MgOl) and N-acetyl-L-cysteine (NAC) in varying proportions to poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) as different experimental groups. They observed linear-

oriented fiber deposition in the morphology of PC12 cells, along with improved cell proliferation. The enhanced PHBV displayed excellent physical properties, facilitating its use in the processing and fabrication of nerve conduits.

The heterogeneity of neural tissue injury presents a major challenge for regeneration and repair. To address this, developing diversified biomaterial systems that work synergistically with magnesium ions (Mg^2+) for different injury types could significantly advance neural regeneration research. Key priorities include precisely controlling Mg^2+ release kinetics through material engineering to maintain therapeutic concentrations while preventing local toxicity, systematically evaluating and optimizing the degradation profiles and mechanical properties of Mg^2+-incorporated biomaterials and establishing material-microenvironment interactions to enable targeted Mg^2+ modulation during nerve repair. Progress in these areas may yield novel therapeutic strategies for neural regeneration medicine.

Applications of Magnesium-Based Alloys in Vascular Surgery

Magnesium was first identified as a distinct element by Joseph Black in 1755. Remarkably, within just a few years of its discovery, scientists began investigating its potential as a biodegradable material for medical implants. Due to its unique combination of physicochemical properties, magnesium quickly emerged as a promising candidate for two major clinical applications: orthopedic bone substitutes and cardiovascular implants.[106] A fundamental requirement for cardiovascular implants is possessing excellent cytocompatibility and hemocompatibility.In the physiological environment, magnesium primarily undergoes hydrolysis, generating magnesium hydroxide and hydrogen gas as the main degradation products. Hemolysis rate does not predominantly depend on Mg^2+ concentration (remaining below 5% even at 1000 μg/mL), but is fundamentally determined by environmental pH. When pH exceeds 11, the hemolysis rate increases drastically from 5% to 53.8%, indicating that strongly alkaline conditions serve as the primary trigger for hemolysis.[26] However, the clinical application of magnesium-based implants faced several challenges, including excessively rapid and heterogeneous degradation in physiological environments, abrupt release of degradation byproducts and premature loss of mechanical integrity due to concurrent hydrogen evolution during corrosion. To address these limitations, researchers have developed two principal modification strategies: alloying with trace elements and surface coating technologies. Among various coating materials, titanium dioxide (TiO_2) nanoparticles have shown particular promise due to their established chemical stability and biocompatibility. Notably, TiO_2's safety profile is well-documented in pharmaceutical applications, with official recognition as a non-toxic excipient in standard pharmacopeia references.[107] TiO2 thin films are widely used to modify vascular stents due to their excellent properties, such as anti-thrombogenicity, rapid endothelialization, and good blood compatibility.[108] Hou et al[109] prepared anatase TiO_2 nanosheet films (50 nm thick) on biodegradable Mg-Zn alloy stents using a simple solvothermal method, reducing the degradation rate of the magnesium alloy. Yang et al[108] deposited TiO_2 films on Mg-Zn alloy using the ALD method, and the TiO_2-150°C nanoscale films protected the magnesium alloy from corrosion and promoted the adhesion and proliferation of endothelial cells (ECs). The degradation products of magnesium-based materials mainly consist of loosely structured $Mg(OH)_2$. Therefore, researchers have attempted to form uniform and dense magnesium-based hydroxide layers on the surface of magnesium alloys to improve their corrosion resistance.[110] Peng et al[111] developed an innovative surface modification approach for JDBM magnesium alloy by incorporating Mg-Al layered double hydroxide (LDH) through a hydrothermal pretreatment process with Mg(OH)2 as precursor. Electrochemical characterization including Tafel polarization analysis and hydrogen evolution measurements demonstrated that the LDH coating not only enhanced the substrate's corrosion resistance but also remarkably improved endothelial cell (EC) functions in terms of adhesion, migration and proliferative capacity under in vitro conditions. Other researchers have modified magnesium alloys through different methods. For example, Lin et al[112] developed a novel surface modification strategy for JDBM magnesium alloy stents through hydrofluoric acid (HF) treatment to create a uniform magnesium fluoride (MgF_2) conversion coating. This approach demonstrated multiple clinical benefits: significantly enhanced re-endothelialization capacity in arterial implantation models, maintained adequate mechanical integrity throughout the critical healing period and exhibited exceptional histocompatibility as a biodegradable vascular scaffold. Gao et al[113] proposed a chitosan (CS)/heparinized graphene oxide (HGO) coating using a layer-by-layer (LbL) assembly strategy on alkali-treated magnesium alloy. Electrochemical measurements, pH changes, and Mg^{2+} release results indicated that the multilayer coating significantly altered the corrosion resistance of the magnesium alloy. Additionally, the CS/HGO multilayer coating significantly reduced platelet adhesion and accelerated

the adhesion and proliferation of ECs. Gu et al[114] synthesized poly(triethoxy(octyl)silane (PTHOS) coatings on AZ31B magnesium alloy through electrodeposition at different cathode potentials (−1. 8, −2. 0, and −2. 2 V). The experimental results demonstrated that the silane coating prepared at −2.0 V exhibited superior corrosion resistance, with a significantly slower degradation rate compared to coatings formed at −1.8 V and −2.0 V. Furthermore, the modified coating displayed excellent biocompatibility characteristics: significantly enhanced viability of ECs, effectively reduced hemolysis rate and markedly decreased platelet adhesion. Since single-layer coatings struggle to meet the practical application requirements of magnesium-based stents, some researchers have studied magnesium alloys with strong bonding strength and excellent functional properties. Peng et al[115] proposed a method of coating MgF_2 with PLLA on AZ31-based stents. The results showed that the MgF_2/PLLA coating maintained high corrosion resistance after expansion, and the MgF_2 coated with PLLA exhibited better cell adhesion. Superficially, this suggests that the MgF_2/PLLA hybrid coating is preferable for Human umbilical vein endothelial cells (HUVECs) adhesion. Wang et al[116] developed a silk fibroin composite coating containing heparin (Hep) molecules and Gly-Arg-Glu-Asp-Val-Tyr (GREDVY) peptides on hydrofluoric acid-treated MgZnYNd alloy surfaces. Electrochemical and immersion tests demonstrated that compared to bare MgZnYNd alloy, this coating exhibited superior corrosion resistance while reducing platelet adhesion and hemolysis rates, as well as prolonging coagulation time, demonstrating excellent hemocompatibility.

In the cardiovascular field, there have been reports of related clinical trials. The research team led by Zartner[117] first reported the successful application of a magnesium alloy bioresorbable scaffold (BRS) in treating accidental ligation of the left pulmonary artery, demonstrating the stent's complete degradation after fulfilling its vascular support function. Histological evaluation at 5 months post-implantation revealed complete re-endothelialization of the stented segment, with no significant calcification, necrosis, or structural damage observed in the arterial wall. The degraded region was naturally replaced by crystalline calcium phosphate deposits. Immunohistochemical analysis further confirmed that the neointima consisted of smooth muscle cells, with no detectable inflammatory cells (CD68+, CD3+, CD79+, or MAC+ cells) at the implant-tissue interface. These findings indicate that the magnesium alloy scaffold maintains vascular patency while inducing only minimal vascular wall alterations, showcasing excellent biocompatibility and functional reliability. This study provides critical clinical evidence supporting the use of bioresorbable scaffolds in pulmonary artery disease management. Clinical studies have demonstrated differential therapeutic outcomes of magnesium alloy stents in vascular disease treatment. Schranz et al[25] successfully applied a magnesium alloy stent to treat aortic coarctation in a neonate. Although the stent lost mechanical integrity due to corrosion after 15 days requiring secondary implantation, serum magnesium levels remained within physiological range after complete degradation. In contrast, McMahon et al[118] reported that while a magnesium alloy stent immediately restored vascular patency without adverse effects when treating main pulmonary artery collateral stenosis in a 2-month-old infant, significant restenosis was observed during 4-month follow-up. These clinical observations suggest that the matching between degradation kinetics of magnesium alloy stents and vascular remodeling still requires further optimization.

The "DREAMS 2G" stent received CE certification and became the first biodegradable magnesium alloy stent to be marketed in Europe in June 2016, under the trade name Magmaris.[119] Biotronik implanted 123 "DREAMS 2G" stents into 123 patients with coronary artery disease to evaluate the efficacy and safety of the stent. Clinical results showed that the "DREAMS 2G" stent completely degraded within 9 months after implantation. The 12-month follow-up results indicated that the "DREAMS 2G" stent had good safety, with late lumen loss (LLL) of approximately 0. 39±0. 27 mm, demonstrating the stent's numerous advantages, such as better radial support, higher vascular compliance, lower acute recoil rate, and no cases of cardiac death or stent thrombosis post-implantation.[120] Additionally, Biotronik conducted a clinical trial (coded "BIOSOLVE-III") to further assess the efficacy of Magmaris. Subsequent clinical evaluations have validated both the safety profile and therapeutic efficacy of the Magmaris bioresorbable scaffold.[121] Extensive studies confirm magnesium stent safety, but key challenges remain: overly rapid degradation and inadequate endothelialization. To address these, next-generation stents must balance controlled degradation with timely endothelial healing.

Applications of Magnesium-Based Alloys in Orthopedics

Bone implants play a crucial role in the treatment of orthopedic-related diseases. Today, with the rapid development of bone tissue repair and regeneration technologies, bone implants have become one of the highly demanded products in the

market. The rapid growth of the biomaterials market has driven significant advancements in bone implants. Modern manufacturing methods, advanced biomaterial designs, and the architecture of medical devices have greatly evolved over the past 20 years.[122,123] Traditional orthopedic implant biomaterials include bioinert metals and plastics, such as titanium alloys, stainless steel, cobalt-chromium alloys, and polyether ether ketone (PEEK), among others.[124] To date, metal implants represented by titanium alloys and stainless steel have been widely used in clinical practice. Although these implants exhibit good biocompatibility, excellent corrosion resistance, and superior mechanical strength, maintaining long-term structural stability in the body and meeting clinical needs such as load-bearing, they still have certain limitations, such as causing physical discomfort, chronic inflammatory reactions, and the release of potentially harmful toxic elements.[125–127] So far, the infection rate caused by implants in orthopedic surgeries ranges from 2% to 5%.[128] Over the past 20 years, magnesium and its alloys have been extensively studied due to their advantages, such as density and elastic modulus similar to bone, reduced stress shielding effects, excellent biocompatibility, safe degradability, and absorbability.

When evaluating the application of magnesium-based alloys in orthopedic implants, understanding the effect of magnesium ion concentration on stem cells is crucial. Stem cells proliferate and differentiate into osteoblasts, which are the building blocks of new bone formation. Abed et al[123] studied how magnesium ions affect gap junctional intercellular communication (GJIC) in human osteoblasts. They found that a concentration of 3 mM Mg^{2+} significantly enhanced cell viability, while magnesium ions also increased alkaline phosphatase activity and osteocalcin levels. Zhang et al[129] noted that after implanting pure magnesium pins into the distal femur marrow of rats, new bone formation occurred around the cortical bone. Additionally, magnesium promotes bone formation through various mechanisms. Magnesium increases the number of osteoclast precursors,[130,131] facilitating the formation of H-type blood vessels.[132,133] It also has osteoimmunomodulatory effects, promoting the polarization of macrophages to the M2 phase and inhibiting their conversion to the M1 phase.[134,135] The magnesium ions released from the degradation of magnesium implants in the body are captured by nerve axons on the bone surface, prompting the axons to release more calcitonin gene-related peptide, which acts on periosteal stem cells to promote bone repair.[129]

Due to its high corrosion rate, hydrogen evolution, and localized tissue pH elevation in the human body, magnesium and its alloys may cause harm to surrounding tissues, significantly hindering further applications. Therefore, improving the biological performance of magnesium and its alloys is key to overcoming these drawbacks for orthopedic use. Researchers have enhanced the hardness, strength, and castability of alloys by adding different elements to magnesium. For example, adding an appropriate amount of Ca to Mg can refine grains, inhibit grain boundary compounds, reduce the potential difference between the second phase and the matrix, and increase the density of the oxide film, thereby hindering corrosion and improving the corrosion resistance of magnesium alloys.[136,137] Ragamouni et al[138] noted that Mg-Zr alloys with added Sr showed better integration with new bone tissue in rabbit bone. Other scholars have demonstrated that the gradient change in Li content in Mg-xLi-Zn alloys (x=3, 6, 9 wt%) has a concentration-dependent killing effect on osteosarcoma cells (MG-63) and promotes bone growth.[139] Various surface modification techniques have also enhanced the potential of magnesium and its alloys in orthopedic applications. Barajas and Fintová[140,141] both demonstrated that fluorinated magnesium alloys improved corrosion resistance, biocompatibility, antibacterial properties, and osseointegration.[142] Bisphosphonates (BPs) are well-established drugs for treating metabolic bone diseases such as osteoporosis, Paget's disease, tumor-induced hyperkalemia, and inflammation-related bone loss.[142,143] Studies have also shown that BPs have advantages in modifying magnesium alloys.[144] Li et al[145] prepared a bilayer coating of zoledronic acid (ZA) and CaP on an Mg-Sr substrate to promote the osteogenic performance of the implant material. They reported that the bilayer-coated Mg-Sr substrate could control osteoclast formation and the osteogenic NF-κB and estrogen receptor α (ERα) signaling pathways, while increasing the ratio of receptor activator of nuclear factor kappa-B ligand (RANKL) to osteoprotegerin (OPG).

The introduction of magnesium materials in the field of orthopedics can be traced back to the early 20th century. Tammann et al[146] were among the first to report the use of magnesium in bone nails and plates for fixing traumatic bones. According to Lambott (1900), a 17-year-old patient's fracture was repaired using magnesium plates and steel nails, but galvanic corrosion between the magnesium plates and steel nails was observed the day after surgery, with rapid hydrogen evolution accelerating the degradation of the magnesium plates. McBride[147] conducted another significant study. They

focused on the application of Mg-Al-Mn alloy in screws, bolts, and plates, and experienced 20 fracture treatments. In these cases, the implants were completely absorbed, with no adverse reactions observed. Lee[148] used Mg-Ca-Zn screws to repair 53 cases of radial fractures, all patients demonstrated normal bone healing. Although hydrogen gas evolution was observed around the screws during the early implantation phase, this phenomenon did not adversely affect the healing process, and the generated gas bubbles were completely absorbed by the surrounding tissues within 2–4 weeks. Research conducted by Amerstorfer et al[149] has also confirmed that neither the hydrogen gas generated nor the metal ions released during the degradation of magnesium alloy implants adversely affect the process of bone tissue regeneration. Zhao et al[150] published a study in which magnesium screws were used to fix vascularized bone grafts in patients' femoral heads. Compared to traditional methods, this approach demonstrated better therapeutic outcomes.

In 2013, the compression screw MAGNEZIX® CS became the first magnesium implant approved for human use, with its chemical composition being Mg-Y-RE-Zr alloy. Windhagen[151] used this screw in hallux valgus surgery and evaluated the outcomes using the American Orthopaedic Foot & Ankle Society's clinical rating system for the hallux and a visual analog scale at 6 months post-surgery. The results showed that the biodegradable magnesium-based MAGNEZIX® CS screws and the titanium alloy group had similar outcomes in terms of pain assessment and range of motion in the first metatarsophalangeal joint. Additionally, MAGNEZIX® CS was clinically equivalent to traditional titanium screws, with no cases of foreign body reactions, osteolysis, or systemic inflammatory reactions observed. Plaass et al[152] used MAGNEZIX® CS screws for distal metatarsal osteotomy, demonstrating favorable clinical outcomes. Biber et al[153] were the first to report the use of MAGNEZIX® CS screws in trauma, using the implants to fix lateral malleolus fractures in ankle fractures. The K-MET cortical bone screws and headless screws from the Korean company U&i, composed of Mg-Ca-Zn alloy, received marketing approval from the Korean Ministry of Food and Drug Safety for the repair of distal radius fractures, with complete healing observed 6 months after fixation.[154] On July 1, 2019 the National Medical Products Administration (NMPA) of China officially approved pure magnesium screws for multicenter clinical trials in the treatment of steroid-induced osteonecrosis. Considering the potential health risks of alloying elements to patients, 99. 99% high-purity magnesium orthopedic internal fixation implants were manufactured. These pure magnesium screws have been used to fix autologous vascularized bone flaps for the treatment of ischemic necrosis of the femoral head, showing long-term (12 months) efficacy.[150] These screws have also been successfully used in the fixation of vascularized iliac bone grafts for displaced femoral neck fractures in young patients, with better outcomes compared to conventional internal fixation and a lower incidence of complications such as ischemic necrosis.[155] The clinical translation of magnesium-based implants has achieved remarkable progress. Notably, over 25,000 MAGNEZIX surgical procedures have been performed, with 36-month follow-up data demonstrating successful osseointegration. K-MET screws achieved complete healing and absorption within 6–12 months in 53 patients.[26] From a regulatory perspective, the RemeOs™ screw (developed by Bioretec Ltd., Tampere, Finland) has become the first magnesium-based orthopedic implant to simultaneously receive both FDA Breakthrough Device Designation and De Novo marketing clearance (2023). In the same year, OSTEOREVIVE magnesium-based bone void filler also obtained FDA 510(k) clearance.[156] Nevertheless, this field continues to face challenges, urgently requiring more extensive preclinical and clinical data along with long-term in vivo studies for further validation.

Applications of Magnesium-Based Alloys in Dentistry

In recent years, titanium, whether used as an implant for dental crown restoration or as screws to fix the mandible, has revealed many drawbacks, such as a lack of antibacterial activity, the inability to be absorbed by the human body requiring secondary surgery, and the tendency to induce apoptosis in periosteal cells.[157,158] To address these shortcomings, Zhao et al[159] investigated the degradation and antibacterial properties of Mg-Cu alloy as a periodontal bone substitute material in vitro. The results showed that Mg-Cu alloy could significantly eliminate pathogenic bacteria in periodontal tissues, such as Porphyromonas gingivalis and Actinomyces gingivalis, making it a promising graft to reduce infections in periodontal surgeries. Wang et al[160] summarized the preparation of magnesium alloy coatings on the surface of titanium implants. The results showed that magnesium-coated titanium implants exhibit excellent antibacterial and antioxidant properties, promoting the proliferation and osteogenic differentiation of gingival fibroblasts while inhibiting inflammatory responses and oxidative stress, thereby improving the stability and success rate of the implants. Both Shan

and Rider et al[161,162] explored the potential of magnesium as a barrier membrane in guided bone regeneration therapy. They concluded that magnesium barrier membranes have an appropriate degradation rate, good biocompatibility, and excellent bone regeneration capabilities, and are replaced by healthy tissue after complete absorption. This addresses the shortcomings of collagen membranes in oral surgery, such as insufficient mechanical protection, and the need for secondary surgery to remove titanium-reinforced membranes and non-absorbable membranes.

Regarding the corrosion rate of magnesium alloys after oral wound closure, Modabber et al[163] were the first to immerse Mg-Ca-Zn alloy in artificial saliva for 5 days and then transfer it to Hank's salt solution to simulate the environmental changes after oral wound closure. The results showed that the alloy pre-exposed to saliva slowed the corrosion rate after wound closure, preventing early implant failure due to excessive corrosion and reducing the occurrence of side effects. Mg-Zn-Ca alloy shows great promise as a craniofacial and maxillofacial fixation device. S. Dargusch et al[164] produced an alloy using the Twin Roll Casting (TRC) process, which not only meets the requirements for craniofacial and maxillofacial fixation devices but also promotes tissue proliferation and remodeling. Kăcarević et al[165] developed WZM211 magnesium fixation screws with an MgF_2 coating for guided bone regeneration (GBR) surgery. The results showed that the magnesium screws outperformed polymer devices in mechanical properties, maintaining high strength even after 4 weeks of degradation and avoiding the need for secondary surgery, with no adverse effects of degradation products on surrounding tissues. Whether as a coating or an alloying element, magnesium demonstrates excellent potential for application in oral surgery.

Some clinical data also demonstrate that magnesium alloys are more suitable for oral surgery. Kozakiewicz et al[166] compared the clinical outcomes of magnesium alloy screws and titanium alloy screws in open reduction and internal fixation (ORIF) of mandibular head fractures, as well as the quality of bone healing. They first compared the recovery of 10 patients using magnesium alloy screws and 11 patients using titanium alloy screws, finding that magnesium alloy screws gradually absorbed after bone healing, and their mechanical properties were close to those of bone tissue. However, the fixation strength of magnesium alloy screws weakened over time, so a multi-screw fixation strategy helped improve fixation stability. Further observation of computed tomography (CT) and texture analysis in 60 patients with mandibular head fractures revealed that the quality of bone healing with magnesium alloy screws was comparable to that with titanium alloy screws, but the bone structure at the fracture site showed higher density. The results fully indicate that magnesium alloy screws provide good stability during bone healing, avoiding the need for secondary surgery to remove fixation materials, making them more suitable for the fixation of mandibular head fractures. However, this study lacks long-term follow-up data for the 60 patients, making it impossible to determine the prolonged effects of magnesium alloy screws on the human body. Additionally, there exists a significant gap in clinical validation regarding the application of magnesium alloys in periodontal bone regeneration. These areas represent critical directions for improvement in future clinical translation efforts.

Applications of Magnesium-Based Alloys in Medical Devices

Magnesium and its alloys, with their favorable physical properties such as low density and Young's modulus, as well as excellent biocompatibility, have become a focal point as metal implant materials. By removing trace impurities, adding certain alloying elements, and modifying the alloy surface,[167] magnesium alloys can fully leverage their biodegradable characteristics, having been successfully applied in the manufacturing of surgical instruments including surgical clips, biliary stents, intestinal stents, and urethral stents (Figure 2). Compared with conventional non-degradable titanium alloys, magnesium alloys demonstrate significant advantages. While titanium alloys persist long-term in the human body, potentially compromising imaging quality in computed tomography (CT) and magnetic resonance imaging (MRI) examinations and possibly triggering metal allergies, magnesium alloys effectively circumvent these drawbacks.[168] This section will elaborate on the application of magnesium-based materials in surgical clips, as well as tracheal and urethral stents, while other applications are summarized in Table 2.

Surgical Clip

Surgical clips are one of the most commonly used tools for duct ligation in abdominal surgeries, especially in laparoscopic procedures, where the operating area is highly limited, and clips are often used as an alternative to sutures.

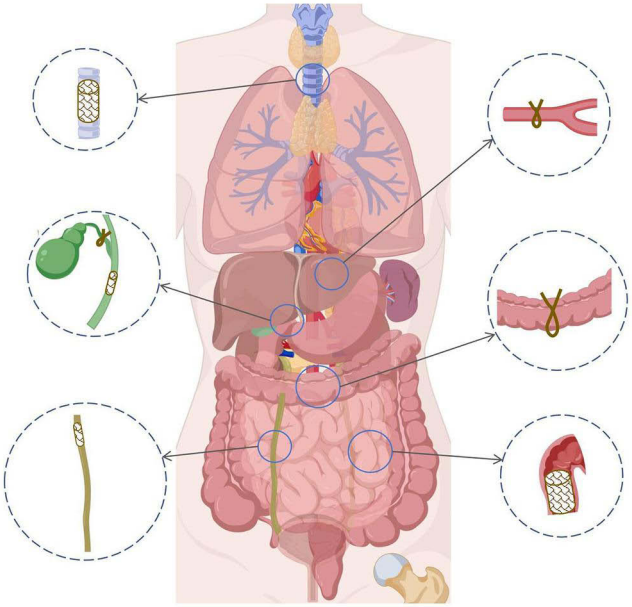

Figure 2 Schematic diagram of clinical applications for biodegradable magnesium alloy implants.

Naoko et al[186] developed a ductile magnesium alloy containing Ca and Zn and investigated the in vivo degradation behavior and vascular occlusion applicability of the prepared magnesium alloy when implanted in the extraperitoneal tissue of mice. They confirmed that the Mg-0. 2at% Zn-0. 1at%Ca (Mg-0. 55mass%Zn-0. 16mass%Ca) alloy clips were non-cytotoxic, and the addition of Ca and Zn improved the ductility of the magnesium alloy. The alloy showed no significant gas cavities or inflammatory reactions four weeks after implantation in mice. Yoshida et al[34] performed cholecystectomies on nine female beagle dogs, using either magnesium alloy clips or titanium clips to ligate the cystic duct. The results indicated that the magnesium alloy clips produced significantly fewer artifacts than titanium clips and were almost completely absorbed within six months post-surgery. The magnesium alloy clips outperformed titanium in terms of anti-adhesion, degradation extent, and tissue fibrosis. This study demonstrated the safety, biocompatibility, and sufficient mechanical strength of the novel magnesium alloy clips in canine cholecystectomies. Bai et al[187] prepared biodegradable Mg-Zn-Ca alloy clips using a combination of hot extrusion and blanking. The extruded Mg-Zn-Ca alloy exhibited a fibrous structure, with increased substrate strength after blanking, and annealing improved its ductility. In vitro experiments showed that the alloy clips maintained closure performance for two weeks even under 300 mmHg pressure. In vivo experiments confirmed that the Mg-3Zn-0. 2Ca alloy clips stably occluded blood vessels within two weeks, meeting clinical requirements and making them ideal candidates for soft tissue fixation devices, such as surgical clips. Urade et al[188] ligated blood vessels in 30 Wistar rats using titanium clips (Group A) and magnesium alloy clips (Group B), followed by resection of the left lateral liver lobe to test the performance of the magnesium alloy clips. The study revealed that the shape of the magnesium alloy clips was maintained for 12 weeks, demonstrating the feasibility of using magnesium alloy clips for vascular closure during hepatectomy. However, further research is needed on the hemostatic performance and degradation behavior of the clips after vascular sealing, as well as the impact of blood flow on the clips. Zheng et al[27] prepared MAO/PA composite coatings on Mg-Zn-Y-Nd alloy and evaluated the corrosion resistance and biocompatibility of the MAO/PA/Mg-Zn-Y-Nd alloy through in vitro and in vivo experiments, exploring the feasibility of dual-coated magnesium alloy clips in rabbit model cholecystectomies. In vitro experiments demonstrated that the MAO/PA coating significantly enhanced the corrosion resistance of the magnesium alloy and exhibited excellent biocompatibility and cell adhesion. Additionally, MAO/PA-coated alloy clips were used in rabbit model cholecystectomies without signs of significant tissue damage or severe foreign body inflammation, and blood biochemical tests and HE staining showed no notable abnormalities. Although various methods such as high purification, alloying, and surface modification have been employed to improve corrosion resistance, the issue of rapid corrosion in

Table 2 Applications of Magnesium Alloys in Other Fields

Application		Material Type	Key Findings	Cite
Wound healing	Diabetic wound	MN-MOF-GO-Ag	Microneedles can deliver Mg^2+ to promote cell migration and angiogenesis, thereby accelerating wound healing.	[169]
		Hydrogel containing β-glucan/Mg^2+/Zn^2+(BGMZ)	Hydrogels can remodel the inflammatory microenvironment, promote neovascularization and re-epithelialization, thereby achieving high-performance healing of diabetic wounds.	[170]
		CSP@Cu-Mg	Sponges demonstrate multifunctional capabilities including hemostasis, exudate absorption, and sustained release of Mg^2+ and Cu^2+, which collectively exert anti-inflammatory and pro-angiogenic effects to significantly enhance diabetic wound healing.	[171]
		Magnesium ion-chelated nanofiber membranes	The material enables sustained release of Mg^2+, possesses favorable mechanical properties and biocompatibility, effectively reduces early inflammation, and significantly accelerates wound healing in diabetic rats.	[172]
	Infected wound	GEL/BG@Cu + Mg	Hydrogel has the ability to synergize sterilization, promote angiogenesis and promote nerve regeneration, and comprehensively accelerate the healing of infected wounds.	[173]
		MgO@polydopamine+Chitosan Gel	This integrated system effectively suppresses scab formation and enhances drug delivery to wound sites, offering an innovative approach for treating infected wounds.	[174]
		WO3/MgO@CS	The composite material demonstrates enhanced antibacterial activity and excellent cell viability (121%), effectively promoting the healing of bacteria-infected wounds.	[175]
		PLGA (poly(lactic acid-glycolic acid) copolymer), polycaprolactone (PCL), and magnesium	The fabricated sutures are biodegradable and generate electrical stimulation through mechanical stretching, accelerating wound healing by 50% while reducing infection risks.	[176]
		RSF/Mg (II)	Compared to pure silk fibroin membranes, the composite membrane exhibits superior adhesion, mechanical flexibility, and anti-inflammatory/antioxidant capabilities, significantly accelerating wound healing in mice.	[177]
Ophthalmology	Contact lens	N-vinyl-2-pyrrolidone and magnesium oxide nanoparticles	It significantly enhances the oxygen permeability and mechanical strength of hydrogel contact lenses, meeting the requirements for high-performance lenses.	[178]
	Glaucoma Treatment	HA-Mg	The biodegradable HA-Mg drainage plate effectively controlled intraocular pressure in rabbit eyes, completely degraded within approximately 4 months, and demonstrated good safety profile without significant inflammatory reactions.	[179]
Gynaecology	Intrauterine device	HP-Mg, Mg-1Ca, Mg-2Zn	The material demonstrates controlled degradation in simulated uterine fluid, exhibits no cytotoxicity toward uterine cells, and induces only mild transient inflammation in vivo, confirming its potential for gynecological applications.	[180]
Otorhinolaryngology	Sinus stent	Mg-2 wt%Nd	The material exhibits controlled degradation rate and favorable in vivo biocompatibility in the sinus mucosal environment, making it suitable for manufacturing biodegradable nasal stents.	[181]

(*Continued*)

Table 2 (Continued).

Application		Material Type	Key Findings	Cite
Biosensors and detection tools	Blood test	Magnesium-based micromotor	The laccase-coated magnesium-based micromotors enhance interaction frequency with dopamine molecules in blood through autonomous motion, enabling highly sensitive and selective electrochemical detection.	[182]
	Biosensing	MgO	The miniaturized flexible sensor demonstrates high sensitivity and excellent linearity for simultaneous detection of glucose and pH levels.	[183]
	Organize welding electrodes	Mg-Nd-Zn-Zr	This study demonstrates reduced thermal damage during tissue welding procedures while simultaneously enhancing tissue anastomosis strength.	[184]
	Implantable Energy	Magnesium-oxygen biobattery	The mitochondria-inspired magnesium-oxygen biobattery achieves exceptionally high in vivo energy density with excellent biocompatibility, enabling power supply for implantable medical devices.	[185]

magnesium alloy implant materials remains unresolved. However, for surgical hemostatic clips, magnesium alloy materials only need to maintain mechanical strength for 24 weeks,[188] making poor corrosion resistance less of a critical issue for their use as surgical clips.

Biliary obstruction caused by biliary stricture is a common bile duct disease, typically resulting from tumors and biliary surgery. Currently, the first-line treatment for benign biliary strictures (BBS) is endoscopy, as it is less invasive and more convenient than surgery,[189] particularly endoscopic retrograde cholangiopancreatography (ERCP) combined with stent placement, which has become the preferred method.[190] Due to the high incidence of adverse events associated with T-tube placement, various CBD stents have been designed to replace T-tubes, usually made of degradable polymers or metals. Chen et al[191] studied Mg-6Zn alloy as a biodegradable metal implant, conducting electrochemical tests, immersion tests, and hydrogen evolution experiments in bile and Hanks' solution to evaluate the in vitro and in vivo degradation behavior of Mg-6Zn alloy. The results showed that the degradation rate and hydrogen evolution rate of Mg-6Zn alloy immersed in bile were higher than in Hanks' solution. The degradation rate of Mg-6Zn alloy stents in animals closely matched the clinical requirements for CBD support materials. This study demonstrated the broad application prospects of Mg-6Zn alloy as a CBD stent. Chen et al[192] examined the biocompatibility and degradation behavior of Zn-3Cu alloy, Zn-3Cu coated alloy, Mg-Nd-Zn-Zr (referred to as JDBM) alloy, and JDBM coated alloy to select the best alloy for common bile duct surgery. The study results showed that JDBM alloy and JDBM coated alloy exhibited excellent in vitro and in vivo biocompatibility, making them safe biodegradable materials for CBD surgery. Ni et al[193] established a numerical model of laser-engraved magnesium alloy biliary stents to predict the impact of stent degradation on the biomechanical behavior of the stent-bile duct coupling system. The results showed that after the stent was placed in the narrowed bile duct, degradation began from the middle to the ends and from the edges to the interior after 234 hours. The stent remained in close contact with the bile duct wall from the start of degradation until 690 hours, with a low likelihood of causing bile duct wall tissue damage. Zhang et al[194] used finite element analysis to study the mechanical properties of WE43 magnesium alloy biliary stents in bile ducts with different ellipticities, aiming to better understand the influence of bile duct ellipticity on the interaction of the stent-bile duct coupling system. The results indicated that increased bile duct ellipticity made stent expansion more difficult. They employed a zero-order optimization algorithm to effectively reduce the maximum equivalent stress of the stent, making the stress distribution of the stent and bile duct more uniform and improving the expansion effect of the diseased bile duct. In summary, although magnesium alloys have the drawback of rapid degradation in other applications, they are more suitable as CBD stents considering the required support time for the biliary tract. In terms of chronic inflammation, mechanical obstruction,

intimal hyperplasia, and extracellular matrix deposition, magnesium-based alloys also outperform nickel-titanium alloys and stainless steel stents.

Over the years, many new intestinal anastomosis techniques and devices have been proposed and widely used. Among them, due to their biodegradable nature, excellent biocompatibility, and significantly higher mechanical stability and ductility compared to polymers,[35] magnesium and its alloys are considered candidate materials for surgical staples. Yan et al[195] implanted small rod-shaped alloy samples into the cecum of rats and compared the effects of Mg-6Zn and titanium implants on the rat intestine through biochemical, radiological, pathological, and immunohistochemical methods. They quantified the host response at the cecal incision interface to evaluate the intestinal tissue biocompatibility of Mg-6Zn alloy, thereby assessing the ability of Mg-6Zn to replace titanium staples in general surgical intestinal reconstruction and determining whether Mg-6Zn could serve as a staple needle for intestinal reconstruction. The study showed that Mg-6Zn alloy has good in vivo biocompatibility, outperforming titanium in promoting healing and reducing inflammation, making it a promising candidate for intestinal reconstruction staplers. They also compared the effects of Mg-6Zn and Ti-3Al-2. 5V alloys on TGFβ/TNF-α/VEGF/b-FGF during intestinal healing in SD rats through in vivo serum magnesium levels, radiology, pathology, and immunohistochemistry, thereby evaluating the different roles of the two alloy implants in intestinal healing. The results indicated that Mg-6Zn enhanced the expression of TGF-β1 in healing tissues, promoted the expression of vascular endothelial growth factor and basic fibroblast growth factor, and facilitated angiogenesis and healing. Mg-6Zn alloy reduced the expression of tumor necrosis factor (TNF-α) at different stages and decreased inflammatory responses, performing better than Ti-3Al-2. 5V. Wu et al[196] designed and developed a new biodegradable magnesium surgical staple for gastric anastomosis to reduce the impact of residual stress on magnesium corrosion. They modified the original 90° angle of the U-shaped staple to 100° and found that the modified magnesium staple exhibited good biocompatibility, with no fractures or severe corrosion cracks during degradation, and the anastomosis site was well closed without leakage or bleeding. Amano et al[197] redesigned the shape of the surgical staple to be more rounded, without acute bending points, to reduce stress concentration caused by the staple and anastomosis, thereby preventing breakage or degradation at the bending points. The new magnesium alloy (Mg-2. 5wt%Nd-1wt%Y, FAsorbMg™) has sufficient ductility, with mechanical properties and biodegradability similar to magnesium alloys such as Mg-Y-RE-Zr and WE43, demonstrating satisfactory biocompatibility and clinical feasibility. Huang et al[198] developed a magnesium-zinc-strontium (Mg-Zn-Sr) alloy intestinal anastomosis ring and implanted it into pig intestines, systematically evaluating the biological performance of the anastomosis ring. Postoperative monitoring of blood routine, liver and kidney function, electrolytes, and other biochemical indicators showed normal results, and pathological examinations revealed no significant abnormalities. Wang et al[199] compared the effects of Mg-6Zn and titanium alloys on collagen metabolism during intestinal healing and assessed whether Mg-6Zn alloy could become a promising candidate for modern general surgical intestinal reconstruction staplers. The study showed that Mg-6Zn alloy outperformed titanium alloy, enhancing the expression of type I/III collagen in healing tissues and relatively inhibiting the expression of MMP-1/-13, leading to more mature collagen formation at the anastomosis site. Magnesium alloy stents also show great potential in alleviating intestinal obstruction and stenosis symptoms. Wang et al[200] used a rabbit model to evaluate the performance of paclitaxel-eluting poly-L-lactic acid-coated Mg-Zn-Y-Nd alloy stents and compared the tissue responses at different retention times after insertion into the intestine with bare stents. The results showed that the PLLA/paclitaxel group had significantly lower cell viability compared to the bare Mg-Zn-Y-Nd alloy and PLLA-coated Mg-Zn-Y-Nd alloy, effectively avoiding cell proliferation-induced intestinal stenosis. They also used a single-filament integrated weaving method to weave Mg-Zn-Y-Nd alloy filaments into mesh stents and implanted magnesium alloy stents with different treatments (PLLA treatment, MAO/PLLA/paclitaxel treatment, and bare alloy) into the intestines of New Zealand white rabbits to study the degradation and support performance of paclitaxel-coated stents. Macroscopic and SEM analyses showed that the MAO/PLLA/paclitaxel/Mg-Zn-Y-Nd stent had better corrosion resistance than the PLLA/Mg-Zn-Y-Nd stent. The MAO/PLLA/paclitaxel/Mg-Zn-Y-Nd stent degraded significantly in the body within 8–12 days, leading to structural collapse and expulsion from the body, and the stent could not be located after 12 days.

Tracheal Stent

Airway stenting is the primary therapeutic approach for patients with airway stenosis. Currently, silicone and metallic stents are widely used in clinical practice, providing significant therapeutic benefits.[201] However, these permanent stents

require secondary surgical removal, increasing patient discomfort and risks. Consequently, there is a growing demand for biodegradable airway stents. Presently, biodegradable airway stent materials are primarily categorized into two types: biodegradable polymers and biodegradable alloys. Common polymers include poly(L-lactic acid), poly(D, L-lactide-co-glycolide), polycaprolactone, and polydioxanone, whose final metabolic products are carbon dioxide and water. Magnesium alloys are currently the most commonly used biodegradable metallic materials. Jang et al[202] simulated the tracheal epithelial mucus surface and investigated the effects of bicarbonate ions (HCO3-) and mucin in Gamble's solution on the corrosion behavior of AZ31 magnesium alloy. The results showed that bicarbonate ions in Gamble's solution facilitated the formation of robust corrosion products on the magnesium alloy surface, while mucin adsorbed onto the surface, slowing the corrosion rate. Luffy et al[203] preliminarily assessed the potential of magnesium alloys in tracheal applications. By simulating airway conditions and corrosion environments in a bioreactor, the researchers tested pure magnesium, AZ31, and Mg-3Y alloys. Among these, the Mg-Y alloy exhibited the slowest corrosion rate, with only a 15. 1% volume loss after 24 weeks of immersion. The study also demonstrated that magnesium alloys showed excellent tracheal tolerance and acceptability after six months, with minimal foreign body reactions and no negative impact on airway function. Li et al[204] compared the degradation and biocompatibility of magnesium, zinc, and iron as tracheobronchial stent materials. The results indicated that magnesium and zinc exhibited favorable cell adhesion and proliferation capabilities along with appropriate corrosion rates. However, none of these studies conducted animal experiments to further validate material compatibility. Wu et al[205] were the first to verify the feasibility of the ultra-high ductility magnesium alloy biodegradable airway stent LZ61-KBMS. This stent demonstrated outstanding corrosion resistance in vitro under flow conditions while safely degrading in rabbits without affecting airway growth. The airway tissue showed good tolerance to the metal matrix and its degradation products, with no significant local or systemic toxic reactions observed. However, this alloy has a potential risk of fracture between 4–8 weeks, and the study did not establish a tracheal stenosis model. Therefore, magnesium alloys still holds significant potential for development as an airway stent material.

Urethral Stents

Ureteral stent placement is a routine practice and fundamental indwelling procedure in modern urology. From the initial use of polyethylene and silicone as stent materials to the current traditional materials (such as silicone) and the latest polymers (such as polyurethane), as well as metal stents made of nickel-titanium alloy or nickel-cobalt-chromium-molybdenum alloy.[206] However, with the increasing number of adverse events associated with ureteral stents, attention has shifted to biodegradable materials. Tie et al[207] were the first to conduct in vivo studies using magnesium alloy as a urethral stent in large animal models. The results showed that compared to traditional alloy processing techniques, the rheo-solidification process significantly refined the microstructure of the magnesium alloy, improved tensile strength, and made the corrosion rate more uniform. The degradation time of this stent perfectly matches the expected indwelling time of clinical ureteral stents and does not cause postoperative inflammation or pathological changes in the urinary system. Compared to commonly used ureteral stent materials such as stainless steel, magnesium alloy stents exhibit superior biocompatibility and antibacterial properties. They also demonstrated that Mg-Sr-Ag alloy has better mechanical properties, corrosion resistance, and antibacterial activity than pure magnesium, and can reduce the incidence of other complications. Lu et al[208] developed a ureteral stent made of degradable polyurethane and magnesium alloy, which can completely degrade within 4 weeks and has better drainage capacity, reducing the need for secondary surgeries. Pacheco et al[209] studied the corrosion rates of AZ31, Mg-1Zn, Mg-1Y, pure Mg, and Mg-4Ag in artificial urine to gain a more detailed understanding of their corrosion patterns and tendency to form encrustations. They concluded that Mg-1Y might be a more suitable material for urethral stents, but further investigation is needed to determine whether its degradation products could lead to urinary stone formation.

Conclusions and Future Aspect

Magnesium and its alloys, as revolutionary biomedical materials, represent a paradigm of interdisciplinary integration between medical science and materials engineering. From initial exploratory research to current clinical applications, magnesium-based materials have consistently demonstrated unique biological value. Their exceptional biocompatibility

ensures harmonious coexistence with human tissues. Currently, magnesium alloys have achieved remarkable progress in orthopedics, cardiovascular surgery, oncology, and other medical fields.

Nevertheless, the research and application of magnesium and its alloys in healthcare face several challenges. For instance, the biodegradation rate and mechanical properties of magnesium require further optimization. Additionally, more comprehensive investigations are needed regarding the biocompatibility and potential toxicity of magnesium-based materials.

With the advancing development of precision medicine, the application prospects of magnesium alloys in future medical practice appear increasingly promising. Future research should focus on precise regulation of degradation processes, optimization of biomechanical properties, and promotion of large-scale clinical validation to fully realize the immense potential of this biomaterial.

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Disclosure

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