

Review Article

Magnesium as a Biomaterial: Unlocking Innovations in Bone Regeneration and Healing: An Overview

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Abstract

Background: Dental implants may encounter failure at various stages, ranging from the osseointegration phase to the restorative phase within the oral cavity. The primary cause of dental implant failure is often attributed to the biological loss of bone integration with the implant surface. To address this issue, various strategies, such as dental implant surface coatings, modifications in implant biomaterials, etc. have been explored to mitigate the risk of implant failure. Emphasizing the significance of dental implant surface coatings, this review investigates the impact of Magnesium based coatings on cellular processes and their potential to enhance adhesion and osseointegration.

Objective: To review related literature covering different aspects of Magnesium based biomaterials and its applications in oral and maxillofacial rehabilitation.

Materials and methods: Electronic search was performed in PubMed, Scopus and Ovid to identify scientific studies and review articles that investigated Magnesium based implant biomaterial. The search included all articles published in English language in peer reviewed journals in the period from 2011 to 2024. The search followed a specific strategy which included combination of the following keywords: Magnesium, Implant Biomaterial, Titanium Magnesium composite, Corrosion and degradation, Magnesium-Hydroxyapatite, biocompatibility

Conclusion: Literature searches have shown that magnesium exhibits remarkable properties such as, biocompatibility, osteogenic potential, favourable soft tissue response and mechanical strength, suggesting that it is an excellent biomaterial for dental implants. Magnesium has various applications in clinical scenarios like maxillary sinus lifting surgery and alveolar socket preservation. Meanwhile, there are studies that highlight its drawbacks, such as

biodegradation and corrosion. It was also found that most of the studies on Magnesium dental implants are short-term studies and there is a need for more long-term clinical trials to prove that Magnesium is worth enough to replace titanium as a biomaterial in dental implantology.

Keywords: Implant Biomaterial; Bone Regeneration; Magnesium Titanium Composite

Introduction

For centuries, a diverse range of metals has served as implant biomaterial within the human body, leveraging exceptional properties such as strength, ductility and fracture toughness that surpass those of polymers and ceramics. Common choices like titanium and steel dominate, with titanium offering stability albeit at a higher cost, while steel, more affordable, presents increased reactivity. Despite previous use of cobalt-chromium alloys, researchers now avoid them due to adverse host reactions and toxicity [1]. Commercially pure titanium (Ti) and Ti alloys, renowned for their mechanical strength, biocompatibility,

corrosion resistance and low density, are widely embraced in dentistry. Despite these advantages, the persistent challenge lies in the potential for elasticity mismatch between the bone and implant material, which can lead to peri-implant bone atrophy during functional and parafunctional loading [2].

Attempts to address this included introducing low modulus β -type Ti alloys and residual porosity, each with trade-offs in mechanical properties [3]. Unlike Ti, Magnesium emerges as a novel biomaterial due to its natural occurrence in the human body, excellent biocompatibility and biodegradation potential. With properties akin to bone, including an elastic modulus of 45 GPa, Magnesium proves affordable and a low-density of 1.74g/cc [2]. However, its susceptibility to intense corrosion in chloride-rich environments poses challenges, necessitating studies on corrosion control.

This article comprehensively explores the potential of Magnesium as an implant biomaterial, highlighting its properties, surface modifications, advantages and the promising future of magnesium-based implants in oral rehabilitation.

Discussion

Properties

Magnesium, being abundantly available and the lightest metallic material, possess a density of 1.74 g/cc and an elastic modulus of 40-45 GPa, closely mirroring that of bone [4]. Magnesium alloys surpass biopolymers in strength, being 3-16 times stronger and exhibit superior ductility compared to bio-ceramics [4].

Functionally, Magnesium acts as a cofactor for enzymes in carbohydrate and lipid metabolism, playing a pivotal role in various metabolic processes. It stands as the fourth most abundant cation in the body, significantly contributing to the mineralization and development of hard tissue. Role of Magnesium as a stimulant in bone conduction and growth is intertwined with bone metabolism [5]. Magnesium deficiency impacts immune response, alters osteoblast and osteoclast activity and influences ion channel dynamics on cell membranes. Within the human body, Magnesium²⁺ ions are the second most abundant cation within cells. Magnesium plays critical roles in protein and nucleic acid synthesis, mitochondrial activity, ion channel modulation, DNA and RNA stabilization, plasma membrane stability, translational processes and support for osteogenic activity [5]. Approximately half of physiological Magnesium is concentrated in bone, amounting to 50-60% of human bone tissue, crucial for bone cell proliferation and new bone formation [5]. With mechanical properties like Elastic modulus (E) and density closely resembling human bone, Magnesium emerges as an ideal metal for orthopedic and bio-implants, minimizing the risk of stress shielding.

Antibacterial and Antioxidant Effects of Magnesium Alloy

Magnesium alloys exhibit promising properties in promoting periodontal tissue repair by maintaining Human Gingival Fibroblast (HGF) activity [6]. They induce HGFs to differentiate into osteocytes, aiding alveolar bone repair and implant stability. Additionally, Magnesium alloys inhibit *S. sanguinis* proliferation, reducing inflammatory reactions and preserving HGFs' biological activity. With antioxidative stress effects, Magnesium alloy implants could enhance Gram-positive bacteria inhibition in oral cavities, improving implant osseointegration stability for future dental implant restoration [6].

Osteogenic Potential of Magnesium

Porous structure of magnesium enhances biocompatibility and avoids stress shielding. Magnesium ions promote bone cell proliferation, accelerating osseointegration. As bone cells grow into porous dental implants, equivalent alveolar bone stress decreases, indirectly increasing implant load-bearing capacity. Magnesium-based alloys, used in Guided Bone Regeneration (GBR) membranes and meshes, offer mechanical strength for large bone defects, making them promising for bone regeneration [7].

Magnesium for Bone Augmentation

Magnesium-based alloys serve as bone filling materials, contributing to bone regeneration. Various studies highlight the potential of Magnesium Hydroxyapatite (MgHA), Magnesium-doped hydroxyapatite and Magnesium-doped wollastonite in enhancing bone induction, reducing alveolar bone resorption and promoting bone formation. Clinical trials support effectiveness

of MgHA in alveolar preservation, making Magnesium-alloys promising candidates for bone substitutes [7].

Corrosion and Biodegradation of Magnesium

While magnesium alloys possess advantageous properties, their high corrosion rate poses challenges. Corrosion can lead to premature implant failure and interfere with tissue healing. The corrosion mechanism involves hydrogen evolution, affecting the healing process [8]. Magnesium-containing bone substitutes, like MgHA, demonstrate enhanced solubility and osteogenic properties, but controlling corrosion rates remains a challenge, requiring further *in-vivo* investigations. The human body fluid is composed of water, electrolytic ions and proteins like albumins, globulins and fibrinogen, along with dissolved oxygen. Magnesium, as the most electronegative engineering metal with an electrochemical potential of -2.3 V compared to a standard hydrogen electrode, is prone to corrosion in various aqueous environments, including human body fluids. The corrosion of magnesium results in the formation of an oxide/hydroxide layer on the surface, which, unfortunately, does not provide effective protection in most aqueous environments.

The following reactions represent the corrosion of magnesium alloys in most aqueous environments, including the physiological environment [8].

Anodic reaction: $\text{Mg(s)} \rightarrow \text{Mg}^{2+} + 2\text{e}^{-}$ (1) (aq)

Cathodic reaction: $2\text{H}_2\text{O(aq)} + 2\text{e}^{-} \rightarrow 2\text{OH}^{-} + \text{H}_2$ (g) (2) (aq)

Overall reaction: $\text{Mg(s)} + 2\text{H}_2\text{O(aq)} \rightarrow \text{Mg(OH)}_2\text{(s)} + \text{H}_2$ (g) (3)

The hydroxide layer that formed on the surface of magnesium is not stable in the presence of chloride ions in human body fluid. The presence of chloride ions quickly converts the hydroxide layer into highly soluble magnesium chloride.

$\text{Mg(OH)}_2 + 2\text{Cl}^{-} \rightarrow \text{MgCl}_2 + 2\text{OH}^{-}$ (4) 2 (s) (aq) (aq)

The disappearance of the hydroxide layer in the presence of chloride ions fastens the corrosion of magnesium alloys. Additionally, hydrogen gas (H_2) evolution during magnesium corrosion can create subcutaneous gas bubbles (2) and gas bubbles adjacent to the implants, which can cause the separation of tissues and/or tissue layers. *In-vitro* studies report the critical tolerance level of hydrogen to be $<0.01 \text{ mL/cm}^2/\text{day}$ and this has been widely used to screen magnesium alloys for temporary implant applications [8].

Protective Coatings to Enhance the Corrosion Resistance of Magnesium Implants

To improve the corrosion resistance of magnesium alloys various strategies, like surface modification using energetic radiation, conversion coatings and alloying have been employed. The most widely used strategy is the Application of conversion coatings [8]. Essential characteristics that a material should possess to be used as a coating material are biocompatibility and good barrier properties.

Biodegradable Polymeric Coatings

To improve the corrosion resistance of magnesium implants different biodegradable Polymers Like Polycaprolactone (PCL), Poly-Lactic Acid (PLA) and poly(lactic-co-glycolic acid) have been used [9]. Surface pre-treatments, like micro-arc oxidation and plasma electrolytic oxidation, along with the incorporation of metal particles such as ZnO and TiO₂, appear to enhance the consistency and adhesion of polymeric coatings and diminishing the porosity of coatings [9]. This leads to a significant enhancement in the corrosion resistance of magnesium implant.

Biodegradable Silane Coatings

To improve the corrosion resistance of magnesium alloys various Silane coatings have been widely used in different corrosive environments. A few of the silane coatings are biocompatible and various literatures related to silane coatings on magnesium implants concluded that the corrosion resistance of magnesium implants with silane coating significantly improved due to the hydrophobic nature of silane, which restrained the inflow of corrosive ions to the metal substrate's surface.

Graphene-Derivative-Based Coatings

Graphene and graphene derivatives have gained significant recognition as coatings for implants. These coatings have been documented to enhance adhesion and promote the growth of human osteoblast-like cells, suggesting potential for facilitating the differentiation of mesenchymal stromal cells into the osteoblast lineage.

Prosthetic Applications of Magnesium

Applications of Magnesium as Bone Substitutes in Osteogenesis

Magnesium incorporation into Hydroxyapatite (HA) emerges as a strategy to enhance biological and physicochemical properties of HA. When implanted in human alveolar sockets for four months, MgHA exhibits extensive newly formed bone, characterized by lamellar and braided tissues, with no inflammatory infiltration. Magnesium effectively hinders the detrimental crystallization of HA by adsorbing onto its surface, blocking crystallization sites [5]. Compared to pure HA, MgHA demonstrates improved solubility at the physiological pH value of 7.4. This enhancement raises the local concentrations of Magnesium ions and phosphate, fostering nucleation site formation and apatite growth. Both *in-vitro* and *in-vivo* experiments showcase that Magnesium addition enhances the bone induction of porous HA in a dose-dependent manner [10]. Recent applications of MgHA have demonstrated its efficacy in producing bone substitutes with remarkable biocompatibility and osteogenic activity [11].

Clinical trials, including studies by Crespi, et al., reveal that MgHA effectively reduces alveolar bone resorption and promotes bone formation, surpassing the outcomes of Calcium Sulfate (CS) and rivaling allograft porcine bone grafts [11]. This aligns with systematic reviews, such as Barallat's, concluding that MgHA stands out as one of the most effective bone substitutes for alveolar preservation, exhibiting osteogenic effects similar to CS and porcine-derived bone grafts [12].

Magnesium as Bone Substitute in Maxillary Sinus Lift Surgery

MgHA finds application in human maxillary sinus lifting surgery. Histomorphological findings revealed that MgHA granules exhibit favorable osseointegration properties, albeit less robust than autogenous bone. Given the acknowledged status of autologous bone as the gold standard in bone regeneration materials, the osteogenic impact of MgHA in maxillary sinus augmentation is deemed acceptable [13]. A prospective clinical study over two years showcased the viability of nanostructured MgHA as a reinforced filler for vertical ridge augmentation. The nanostructured MgHA successfully elevated alveolar ridge height, even in instances of early implant loading. Furthermore, when compared to pure HA scaffolds, MgHA scaffolds displayed heightened osteogenesis and angiogenesis activities *in-vitro*, offering a substantial enhancement to the restoration of goat calvarial defects [14].

Magnesium in Alveolar Socket Preservation

MgHA was employed in conjunction with collagen scaffolds for alveolar socket preservation. A recent double-blinded prospective clinical trial disclosed that the impact of combining MgHA and collagen scaffolds for alveolar socket preservation aligned with that of the deproteinized bovine bone matrix [15]. The composite scaffold of MgHA was nearly entirely substituted by newly formed bone tissue six months post-implantation. The MgHA composite scaffold, featuring high porosity, exhibits excellent operability when wetted with liquid, positioning it as a promising bone substitute with enhanced effectiveness.

Magnesium as Scaffold Material

The Magnesium-doped wollastonite (CaSiO_3 ; CSi) ceramic enhances the mechanical strength and osteogenic properties of the initial scaffolds, indicating significant potential for mending thin-walled bone defects [16]. Elevating the Magnesium content fosters the expression of osteogenic genes and increases the production of skeletons and osteoids. The greater the Magnesium doping ratio, the higher the densification, leading to a lower degradation rate of the wollastonite bioceramic [17]. Additionally, the incorporation of SrO and MgO into TCP scaffolds enhances both the mechanical and *in-vivo* biological performance of the resulting TCP scaffolds.

Magnesium-Based Alloys for Bone Regeneration

Novel GBR membranes have been fabricated using Magnesium-based alloys. Meshes made from Magnesium and its alloys have sufficient mechanical properties to maintain the space of the osteogenic site and can be used in large bone defects.

Magnesium for Surface Modification of Dental Implants

The incorporation of magnesium into titanium composite materials has been the focus of numerous studies, revealing its potential to enhance the osseointegration and stability of Ti implants. In comparison to Calcium (Ca) modification, surface Magnesium modification has demonstrated greater effectiveness in stimulating the osteogenic differentiation of Bone Marrow Mesenchymal Stem Cells (BMSCs). This effect is likely achieved by improving cell adhesion and inhibiting the phosphorylation of β -catenin [17]. An innovative Magnesium-SLA-Ti implant was developed by Song, et al., using a vacuum arc source ion implantation method, incorporating Magnesium into the sand-blasted and acid-etched (SLA) Ti implant [18]. Implanting these Magnesium-SLA-Ti implants into the mandibles of dogs for a bone healing response study revealed, through histomorphological and resonance frequency analysis, that Magnesium augmentation increased both bone-implant contact and implant stability. Furthermore, Galli, et al., created Ti implants with a mesoporous surface loaded with Magnesium, suggesting that Magnesium release from the implant surfaces facilitated osseointegration during the early stages of healing (0-3 weeks) which is highly desirable for implant early loading [18].

Titanium Magnesium Composite as a Dental Implant Biomaterial

In a study by Martin Balog, et al., a novel Ti-12vol.%Magnesium bimetallic composite material was introduced, utilizing a cost-effective approach through powder metallurgical warm extrusion of elemental Ti and Magnesium powders. The microstructure of the composite featured Magnesium filaments arranged along the extrusion direction and uniformly distributed within the Ti matrix. The as-extruded composite exhibited a reduced Young's elastic modulus of 92.1 GPa and a low density of 4.12 g/cm³. Importantly, the mechanical strength and fatigue performance were maintained, comparable to Ti Grade 4, the reference material commonly used for dental implants. In immersion tests within Hank's solution, the biodegradable Magnesium component gradually diluted and selectively formed pores at predetermined locations within the Ti matrix, which remained intact. Corrosion of Magnesium contributed to a further decrease in Young's modulus and enhanced macro and micro surface roughness. The results from mechanical and corrosion testing suggest that this bioactive composite holds promise for manufacturing biomedical implants with improved mechanical compatibility and enhanced potential for osseointegration, especially in applications involving intense load-bearing scenarios.

According to Sul's group and Cho's group, the optimal Magnesium ion concentration promoting osseointegration for Magnesium-doped Ti implants, manufactured through plasma ion implantation and microarc oxidation, was determined to be 9% [19,20]. Beyond surface composition, various factors like microscopic morphology, roughness, hydrophilicity, pore configurations, oxide thickness, crystal structure and other surface characteristics can influence cell behavior and implant osseointegration [20]. The effects and roles of many of these factors remain unclear, necessitating further research for the widespread use of Magnesium-rich Ti implants.

Infections leading to soft tissue inflammation and subsequent bone loss are significant contributors to implant failure. Bacterial biofilms pose a challenge for external antibiotics, as they are often resistant to antimicrobials [21]. Addressing this, Magnesium is employed to modify Ti implant surfaces, simultaneously promoting osteogenesis and providing anti-infection benefits [5]. For instance, Shen, et al., developed a metal-organic framework coating rich in Magnesium and Zn ions on an alkali-heat treated Ti surface. This coating, releasing substantial Magnesium in the early postoperative period, exhibited strong antibacterial and anti-inflammatory properties, significantly enhancing new bone formation around the implant [20]. Additionally, Yu, et al., introduced Zn/Magnesium ion co-implantation Ti dental implants (Zn/Magnesium-PIII) through Plasma Immersion Ion implantation (PIII). The released Zn and Magnesium ions not only improved osteogenesis and osseointegration at the bone-implant interface but also inhibited the adhesion and growth of common oral bacteria, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Streptococcus mutans*. The broad-spectrum antimicrobial activity of Magnesium equips dental implants to combat bacterial infections in the challenging, bacteria-laden oral environment [22].

Magnesium-Based Fracture Fixation Systems

Magnesium-based BMs are considered as promising candidates for biodegradable bone fixation screws and plates due to the excellent mechanical strength and good biocompatibility. Magnesium-based alloys screws are the only BM bone fixation device that has achieved clinical translation [23]. The elastic modulus of Magnesium-based alloys is very close to those of natural bone, especially natural cortical bone, which greatly weakens the "stress shielding" effect, thus, decreasing bone resorption.

Researchers have found that Magnesium-based alloy fixation provides sufficient mechanical strength for maxillofacial bone healing [24].

Leonhardt, et al., made a case report in 2017 where absorbable magnesium-based headless screws were utilized in the treatment of condylar head fractures in five patients. The study revealed positive outcomes, including successful fracture reduction, optimal screw placement, unrestricted mandibular movement within three months post-surgery and satisfactory occlusion. Importantly, there were no indications of edema associated with hydrogen gas or other complications arising from screw degradation. These findings suggest that the use of absorbable magnesium-based screws is a promising option for stabilizing condylar head fractures with favourable postoperative results and minimal complications. It's crucial to consider individual patient factors and fracture characteristics for successful outcomes. Randomized controlled trials or cohort studies using Magnesium-based plates and screws in maxillofacial surgery is not available currently. However, with additional *in-vivo* studies to probe the biocompatibility this will be possible in the future.

Challenges

Nonetheless, the swift degradation of magnesium results in an elevation of local pH levels, although the body's blood and tissue fluids can mitigate such pH changes. The highly alkaline extracellular environment stemming from Magnesium's rapid corrosion proves unfavourable for the survival and osteogenic differentiation of human Bone Marrow-Derived Stem Cells (hBMSCs) [2]. This alkaline condition may even lead to alkalosis. Substantial amounts of hydrogen are generated in the initial stages following Magnesium implantation, potentially resulting in the formation of localized gas cavities, particularly if soft tissue sealing is effective. The accumulation of hydrogen gas, to some extent, compresses surrounding tissues, adversely affecting cell adhesion, proliferation and differentiation. The interference caused by hydrogen gas accumulation can impede implant osseointegration and the formation of bone around the Magnesium implant [8]. Hence, it becomes imperative to mitigate the degradation rate of Magnesium-based biomaterials (BMs). Comprehensive *in-vitro* and *in-vivo* testing is crucial, considering stress-induced corrosion and uncertainties regarding the effects of larger implants on local pH and magnesium ion concentrations. Additionally, the use of larger implants in animals or humans introduces unknowns regarding the tolerability of the surrounding tissues to the local rise in pH and increase in magnesium ion concentrations. Further research is warranted in this area to address these critical aspects.

Conclusion

In conclusion, magnesium demonstrates promising potential as an implant biomaterial, particularly in the context of bone regeneration and augmentation. Its integration with hydroxyapatite (MgHA) and other ceramics enhances mechanical strength, osteogenic properties and overall biocompatibility. MgHA, when applied in various clinical scenarios such as maxillary sinus lifting surgery and alveolar socket preservation, has shown positive outcomes in terms of osseointegration, even if not surpassing the gold standard of autologous bone. However, challenges in controlling degradation rates warrant further research, emphasizing the need for clinical trials to establish long-term success in dental implants. Continued research and refinement of magnesium-based materials hold promise for advancing the field of orthopedics and implantology, offering innovative solutions for enhanced bone healing and implant performance.

Conflict of Interests

The authors have no conflict of interest to declare.

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