Biodegradable Mg-Based Alloys for Orthopaedic Implants in Biomedical Applications

Yaqub Adediji and Ayub Adediji

Abstract: Orthopaedic implants, traditionally made from non-degradable materials like titanium and cobalt-chromium alloys, are used to replace lost bone or soft-tissue from various causes, including trauma and disease. These traditional implants often necessitate a second surgery for removal. Biodegradable implants, on the other hand, offer a significant advantage by eliminating the need for additional surgery, as they naturally degrade within the body over time. In this article, the properties, biodegradation, bone-regeneration, and the applications of biodegradable Mg-based alloys for orthopaedic implants in biomedical applications are explored. It also discusses the challenges and prospects of biodegradable Mg-based alloys as orthopaedic implants.

1. Introduction

Conditions such as bone deformities, nonunion or malunion fractures, massive bone loss, tumors, and far-reaching distressing injuries pose significant clinical challenges as traditional surgical procedures have limited efficiency in treating these disorders. Orthopedic implants are used to compensate for bone or soft tissue damages due to traumas, cancers, infections, amputations, and inflammations, either permanently or temporarily, until they recover [1]. Traditional orthopedic metal implants, such as titanium (Ti), cobalt-chromium (Co-Cr) alloys, and Ti alloys cannot be degraded in vivo. However, temporary implants are needed to be removed from the body after a certain period [2]. Hence, in such conditions, biodegradable implants are helpful as they eliminate the necessity of a second surgery to remove the planted implants.

In recent years, there has been an increasing emphasis on the investigation of biodegradable metals, including calcium, zinc, iron, and magnesium as orthopaedic implants due to their suitability as temporary implants. These metals have the capability to reduce the harmful implications related with long-lasting implant materials when used as temporary implant materials [3]. This can result in the prevention of secondary surgeries, thereby accelerating the process of tissue regeneration and minimizing further trauma. One notable example is the use of magnesium-based biomaterials, which have garnered significant interest due to their low cytotoxicity, low density, excellent biocompatibility, high bioresorbability, and proper mechanical properties [4].

This paper explores the properties, fabrication, biological functions, and surface modification of biodegradable Mg-based alloys for orthopaedic implants in biomedical Applications. It also discussed the challenges and prospects of biodegradable Mg-based alloys as orthopedic implants.

2. Properties of Magnesium & Its Alloys

Mg exhibits an elastic modulus between 40 to 45 GPa, which is close to that of the human bone (15-25 GPa). Similarly, Mg alloys are exceptionally lightweight with a density between 1.74 and 1.84 g/cm , which is close to that of bone (1.8–2.1 g/cm) leading to lighter implants and opposing the stress shielding effect [5]. Mg and its alloys have a natural ability to biodegrade due to their corrosion susceptibility in aqueous solutions especially if these contain chloride ions and its degradation products are non-toxic and osteogenic [6].

The most common nutritional alloying elements utilized in biodegradable Mg alloys for orthopaedic implants include calcium(Ca), zinc(Zn), manganese(Mn), strontium(Sr), tin(Sn), and silver(Ag) [7]. The alloying process increases yield strength, ultimate tensile strength, creep resistance, and strengthens the properties of Mg through grain refinement, precipitation hardening, and solid solution strengthening. Mg also exhibits excellent biocompatibility. Mg ions (Mg^{2+}) that are released during implantation and degradation are used in the regular metabolism and, to date, no critical toxic limits or side effects have been reported for Mg^{2+} ions[8].

3. Biodegradation of Magnesium in Vivo

Magnesium biodegradation in biological environments primarily involves electrochemical reactions. When magnesium (Mg) corrodes in aqueous solutions, such as body fluids, it follows an electrochemical degradation mechanism. This process can be summarized by the reaction in equation 1 [9]. This reaction produces magnesium hydroxide ($Mg(OH)_2$) and hydrogen gas. The magnesium hydroxide forms a slightly effective protective layer on the magnesium surface, which helps to prevent further corrosion to some extent.

$$Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2 \quad (1)$$

In the presence of chlorine ions, magnesium hydroxide reacts, leading to a local increase in pH value near the host tissue. Besides chlorine ions, body fluid also contains calcium and phosphate ions, which trigger the production of compounds such as calcium phosphate and/or calcium magnesium phosphate [10]. These compounds form a deposition layer on the magnesium surface, inhibiting further corrosion and pH increase. Additionally, body fluids contain organic components like proteins, cells, and even bacteria, which can adhere to the Mg surface, affecting its dissolution behaviour [11].

However, magnesium alloys often suffer from pitting corrosion in chloride solutions, including body fluids. Pits formed are common initiation sites for crack formation and stress corrosion cracking (SCC). The hydrogen released from magnesium corroding in body fluids plays a significant role in corrosion-assisted cracking, as crack initiation and propagation are supported by hydrogen adsorption and diffusion into the material. Although the degradation product of pure Mg in the body is nontoxic, and the degradation product Mg2+ can also promote bone regeneration, too fast degradation of Mg implants in the body can easily lead to failure of fracture treatment [12]. Therefore, enhancing the corrosion resistance of Mg implants is vital for prolonging their fixation time in vivo.

4. Role of Magnesium in Bone Regeneration

Mg and Mg and its alloys are considered excellent materials for bone defect repair due to their superior biodegradation, biocompatibility, adequate elastic modulus as well as the osteoinductive activity of their degradation products [13]. Mg is a crucial element in the construction of soft tissue and bone, being involved in numerous biochemical reactions. It is essential for the human body, with a recommended intake of 310–420 mg of Mg ions daily for healthy adults [14]. Bone reconstruction is a complex process requiring the coordination of multiple stem cells within a suitable microenvironment. Research has shown that Mg and its alloys impact various kinds of osteogenic cells, promoting their differentiation and aiding in bone regeneration [15] [16]. The proper Mg ion content in bone tissue is critical for maintaining its mechanical properties. A decrease in Mg ion content can weaken the bone tissue, increasing fragility and the risk of fractures [17] [18].

Mg also plays a significant role in promoting angiogenesis during bone regeneration. Bone, being a dynamic, complex, heterogeneous, and highly vascularized tissue, requires the coordination of various processes for regeneration [19]. Mg aids in this process through its effect on bone tissue and vascular networks by increase the expression levels of angiogenic biomarkers [20], enhancing the migration and invasion capabilities of human umbilical vein endothelial cells [21]. It also promotes epithelialmesenchymal transition and cytoskeletal reorganization and stimulates proliferation and migration and sensitizes microvascular cell [22].

5. Applications

The integration of magnesium (Mg)-based alloys in the fabrication of Orthopaedic devices marks a notable advancement in biomedical applications. Mg-based alloys are used to manufacture a range of orthopaedic devices, including fixation plates, screws, and intramedullary hook pins each designed for specific types of bone fractures and surgical reconstructions [23]. These devices are designed to cater to a diverse set of fractures, such as those occurring in the femur, tibia, and osteoporotic bones, as well as for ultra fractures. Fixation plates and screws, essential for stabilizing fractures especially in load-bearing bones such as the femur and tibia, are crafted to align with bone contours, ensuring effective healing.

Mg-based implants are particularly beneficial for osteoporotic fractures, common in older adults, due to their biocompatibility and bone regeneration capabilities[24]. These properties help overcome challenges associated with reduced bone density, promoting effective healing, and minimizing the risk of recurrent fractures. They are also used to cruciate ligament reconstruction and fix tibia and femur cavities as well as femoral and ultra fractures. This is because it promotes new bone tissue formation, good osseointegration, and effectively inhibits graft degradation and improved biomechanical properties of tendon graft during the early phase of graft healing [25]. Overall, these alloys in orthopaedic devices represent a comprehensive approach to treating bone fractures and reconstructions, thus making them invaluable in modern orthopaedic surgery.

6. Challenges of Magnesium Alloy Based Implants

Despite the superior biodegradability, biocompatibility and the suitable mechanical compatibility of Mg& Mg based alloys for orthopaedic applications, . However, there are some challenges currently impeding its development and this is majorly due to its high corrosion rate in the complex physiological environment [26]. This rapid corrosion, especially at physiological pH values (7.4–7.6) and high chloride concentrations, leads to the quick conversion of Mg hydroxide to soluble Mg chloride which results in several problems. Firstly, the mechanical integrity of Mg alloy implants deteriorates too quickly, reaching inadequate mechanical properties before sufficient healing of the host tissue. The chloride environment and Mg ions from anodic dissolution species accelerate pitting corrosion, which can induce high localized stresses and lead to crack formation [27].

Moreover, rapid corrosion is associated with the release of hydrogen gas and these hydrogen bubbles can accumulate near the implant in gas pockets in the human body. This can delay healing and potentially lead to tissue necrosis due to the separation of tissues and tissue layers [28]. Also, dissolution of Mg significantly increases the pH near the implant surface. Though the body attempts to regulate pH balance, local alkalization around a rapidly corroding Mg implant is inevitable. This can negatively impact pH-dependent physiological reactions and potentially lead to alkaline poisoning if the regional in vivo pH exceeds 7.8 [29]. Thus, addressing these challenges is crucial for the successful clinical application of Mg biodegradable implants.

7. Conclusion and Future Prospects

In conclusion, magnesium and magnesium-based alloys are promising for bone replacement due to their similar Young's modulus to human bone, sufficient strength, and excellent biocompatibility and biodegradability. These properties make Mg ideal for bone regeneration. However, using Mg in physiological environments is challenging, necessitating the research and development of Mg scaffolds that are mechanically stable and corrode at a controlled rate.

Despite magnesium (Mg) and its alloys showing promise in clinical applications, there's still a shortage of extensive clinical studies. Further long-term biosafety assessments are needed to determine the most suitable candidates for Mg-based implant use. Additionally, developing Mg-infused polymer or ceramic scaffolds could enhance healing in significant bone defects by stimulating new bone growth with bioactive Mg ions. Investigating Mg hybrid systems could broaden their clinical applications. Combining Mg-based implants with inert metals could also widen their usage. Finally, integrating various implant processing technologies, like additive manufacturing, represents a future research avenue for Mg and Mg alloy medical implants.

References

1. Antoniac I, Miculescu M, Mănescu Păltânea V, et al. Magnesium-Based Alloys Used in Orthopedic Surgery. *Materials (Basel)*. 2022;15(3):1148. doi:10.3390/ma15031148

2. Xu L, Pan F, Yu G, Yang L, Zhang E, Yang K. In vitro and in vivo evaluation of the surface bioactivity of a calcium phosphate coated magnesium alloy. *Biomaterials*. 2009;30(8):1512-1523. doi:10.1016/j.biomaterials.2008.12.001

3. Han HS, Loffredo S, Jun I, et al. Current status and outlook on the clinical translation of biodegradable metals. *Materials Today*. 2019;23:57-71. doi:10.1016/j.mattod.2018.05.018

4. Tsakiris V, Tardei C, Clicinschi FM. Biodegradable Mg alloys for orthopedic implants – A review. *Journal of Magnesium and Alloys*. 2021;9(6):1884-1905. doi:10.1016/j.jma.2021.06.024

5. Gu XN, Zhou WR, Zheng YF, et al. Corrosion fatigue behaviors of two biomedical Mg alloys – AZ91D and WE43 – In simulated body fluid. *Acta Biomaterialia*. 2010;6(12):4605-4613. doi:10.1016/j.actbio.2010.07.026

6. Kraus T, Fischerauer SF, Hänzi AC, Uggowitzer PJ, Löffler JF, Weinberg AM. Magnesium alloys for temporary implants in osteosynthesis: In vivo studies of their degradation and interaction with bone. *Acta Biomaterialia*. 2012;8(3):1230-1238. doi:10.1016/j.actbio.2011.11.008

7. Witte F, Hort N, Vogt C, et al. Degradable biomaterials based on magnesium corrosion. *Current Opinion in Solid State and Materials Science*. 2008;12(5):63-72. doi:10.1016/j.cossms.2009.04.001

8. Li L, Gao J, Wang Y. Evaluation of cyto-toxicity and corrosion behavior of alkali-heat-treated magnesium in simulated body fluid. *Surface and Coatings Technology*. 2004;185(1):92-98. doi:10.1016/j.surfcoat.2004.01.004

9. Walker J, Shadanbaz S, Woodfield TBF, Staiger MP, Dias GJ. Magnesium biomaterials for orthopedic application: A review from a biological perspective. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 2014;102(6):1316-1331. doi:10.1002/jbm.b.33113

10. Staiger MP, Pietak AM, Huadmai J, Dias G. Magnesium and its alloys as orthopedic biomaterials: A review. *Biomaterials*. 2006;27(9):1728-1734. doi:10.1016/j.biomaterials.2005.10.003

11. Jang Y, Collins B, Sankar J, Yun Y. Effect of biologically relevant ions on the corrosion products formed on alloy AZ31B: an improved understanding of magnesium corrosion. *Acta Biomater*. 2013;9(10):8761-8770. doi:10.1016/j.actbio.2013.03.026

12. Zhang J, Hiromoto S, Yamazaki T, et al. Macrophage phagocytosis of biomedical Mg alloy degradation products prepared by electrochemical method. *Materials Science and Engineering: C*. 2017;75:1178-1183. doi:10.1016/j.msec.2017.02.126

13. Zheng LZ, Wang JL, Xu JK, et al. Magnesium and vitamin C supplementation attenuates steroid-associated osteonecrosis in a rat model. *Biomaterials*. 2020;238:119828. doi:10.1016/j.biomaterials.2020.119828

14. Saris NEL, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium: An update on physiological, clinical and analytical aspects. *Clinica Chimica Acta*. 2000;294(1):1-26. doi:10.1016/S0009-8981(99)00258-2

15. Díaz-Tocados JM, Herencia C, Martínez-Moreno JM, et al. Magnesium Chloride promotes Osteogenesis through Notch signaling activation and expansion of Mesenchymal Stem Cells. *Sci Rep*. 2017;7(1):7839. doi:10.1038/s41598-017-08379-y

16. Hung CC, Chaya A, Liu K, Verdelis K, Sfeir C. The role of magnesium ions in bone regeneration involves the canonical Wnt signaling pathway. *Acta Biomaterialia*. 2019;98:246-255. doi:10.1016/j.actbio.2019.06.001

17. Liu W, Guo S, Tang Z, et al. Magnesium promotes bone formation and angiogenesis by enhancing MC3T3-E1 secretion of PDGF-BB. *Biochemical and Biophysical Research Communications*. 2020;528(4):664-670. doi:10.1016/j.bbrc.2020.05.113

18. Wang Z, Liu Q, Liu C, et al. Mg2+ in β-TCP/Mg–Zn composite enhances the differentiation of human bone marrow stromal cells into osteoblasts through MAPK-regulated Runx2/Osx. *Journal of Cellular Physiology*. 2020;235(6):5182-5191. doi:10.1002/jcp.29395

19. Xing F, Xiang Z, Rommens PM, Ritz U. 3D Bioprinting for Vascularized Tissue-Engineered Bone Fabrication. *Materials (Basel)*. 2020;13(10):2278. doi:10.3390/ma13102278

20. Gu Y, Zhang J, Zhang X, Liang G, Xu T, Niu W. Three-dimensional Printed Mg-Doped β-TCP Bone Tissue Engineering Scaffolds: Effects of Magnesium Ion Concentration on Osteogenesis and Angiogenesis In Vitro. *Tissue Eng Regen Med*. 2019;16(4):415-429. doi:10.1007/s13770-019-00192-0

21. Pan S, An L, Meng X, Li L, Ren F, Guan Y. MgCl2 and ZnCl2 promote human umbilical vein endothelial cell migration and invasion and stimulate epithelial-mesenchymal transition via the Wnt/β-catenin pathway. *Experimental and Therapeutic Medicine*. 2017;14(5):4663-4670. doi:10.3892/etm.2017.5144

22. Bernardini D, Nasulewic A, Mazur A, Maier JAM. Magnesium and microvascular endothelial cells: a role in inflammation and angiogenesis. *FBL*. 2005;10(2):1177-1182. doi:10.2741/1610

23. Chaya A, Yoshizawa S, Verdelis K, Noorani S, Costello BJ, Sfeir C. Fracture Healing Using Degradable Magnesium Fixation Plates and Screws. *Journal of Oral and*

Maxillofacial Surgery. 2015;73(2):295-305. doi:10.1016/j.joms.2014.09.007

24. Han P, Cheng P, Zhang S, et al. In vitro and in vivo studies on the degradation of high-purity Mg (99.99wt.%) screw with femoral intracondylar fractured rabbit model. *Biomaterials*. 2015;64:57-69. doi:10.1016/j.biomaterials.2015.06.031

25. Klíma K, Ulmann D, Bartoš M, et al. A Complex Evaluation of the In-Vivo Biocompatibility and Degradation of an Extruded ZnMgSr Absorbable Alloy Implanted into Rabbit Bones for 360 Days. *Int J Mol Sci*. 2021;22(24):13444. doi:10.3390/ijms222413444

26. Alvarez-Lopez M, Pereda MD, del Valle JA, et al. Corrosion behaviour of AZ31 magnesium alloy with different grain sizes in simulated biological fluids. *Acta Biomater*. 2010;6(5):1763-1771. doi:10.1016/j.actbio.2009.04.041

27. González S, Pellicer E, Suriñach S, et al. Biodegradation and Mechanical Integrity of Magnesium and Magnesium Alloys Suitable for Implants. In: *Biodegradation - Engineering and Technology*. IntechOpen; 2013. doi:10.5772/55584

28. Seal CK, Vince K, Hodgson MA. Biodegradable surgical implants based on magnesium alloys – A review of current research. *IOP Conf Ser: Mater Sci Eng*. 2009;4(1):012011. doi:10.1088/1757-899X/4/1/012011

29. Ng WF, Chiu KY, Cheng FT. Effect of pH on the in vitro corrosion rate of magnesium degradable implant material. *Materials Science and Engineering: C*. 2010;30(6):898-903. doi:10.1016/j.msec.2010.04.003