Biodegradable Magnesium Alloys as Promising Materials for Medical Applications (Review)

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Non-degradable steel and titanium implants used to replace defects of the locomotor system or fabricate vascular stents provide maximum stability but have too many drawbacks. Currently, biodegradable magnesium alloys are considered as promising materials for creation of fixation devices in orthopedics and cardiovascular surgery. First attempts of using magnesium-based implants for bone fixation were made as early as at the beginning of the 20th century, however, due to a high corrosion rate and gas formation they turned out to be unsuccessful. Magnesium-based alloys developed recently demonstrate improved anti-corrosion and mechanical properties and are promising for manufacturing of biodegradable, biocompatible metal implants.

The microstructure of magnesium implants, their mechanical properties, electrochemical behavior, and kinetics of degradation are affected by alloying elements, methods of surface coating, and thermomechanical treatment of implants. All these factors determine the rate of alloy degradation in physiological environment and the level of gas formation. Although preclinical studies and even singular pilot clinical trials of the medical devices based on magnesium alloys have been carried out recently, there remain many unsolved issues preventing the introduction of biodegradable magnesium alloys in clinical practice.

This review discusses the most promising directions in the development of biomedical materials based on magnesium alloys, existing limitations, and challenges of their use. The possibility of employing biodegradable magnesium alloys in oncology is also shown.

Key words: biomaterials; biodegradation; biodegradable magnesium alloys; magnesium alloy-based implants.

Introduction

Biodegradable metals (titanium and its alloys and stainless steel) are widely used for orthopedic implants. The main limitations to their application are associated with their undesirable mechanical properties resulting in serious problems of bone remodeling [1, 2]. Since these materials do not degrade, repeat operations are required to remove the implant. The release of toxic ions owing to corrosion and microparticles due to material wear can cause inflammatory osteolysis [3–6]. If metallic implants and prostheses are used for a long time, a high concentration of prosthetic metal particles is found in the synovial fluid and the tissue surrounding the implant which is the result of continual release of metal particles from the implants under mechanical load [7, 8]. Though non-degradable metal implants are considered to be nontoxic, some of their components can promote the development of neoplasia [9]. Cases of osteogenic sarcomas developed after implantation of metallic

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endoprostheses have been recently described in the literature [10]. Thus, there is a need for development of biomaterials for the implants of a new generation which, while possessing the acceptable strength characteristics, would be biodegradable and would not require repeat surgical interventions to be extracted.

Recently, there has been a growing interest in biodegradable metallic materials. Among them, magnesium and its alloys, which are considered as promising candidates for medical applications, are being studied intensively [11–14]. Magnesium has some advantages over the materials used currently for metal structures and primarily for orthopedic implants. It attracted the attention of researchers owing to its good biocompatibility and mechanical properties that are similar to those of the native bone. Being characterized by biosafety and a good biocompatibility profile, magnesium is one of the most important microelements in the human body partaking as a cofactor in more than 300 different fermentative reactions and playing a significant role in the energy metabolism. The main product of degradation of a magnesium alloy is hydrogen which can also cause a favorable effect as it possesses anti-oxidative activity being a selective absorber of hydroxyl radicals and peroxynitrite. Ideal implants for bone fixation must have a slower resorption rate than the rate of bone remodeling. Biodegradable magnesium alloys can make it possible to achieve synchronization in the changes of their strength and the restoration of the bone tissue, whereas the mechanical properties of permanent implants from titanium and stainless steel remain unchangeable during the entire process of bone defect healing. This may cause a phenomenon of stress shielding manifesting itself as uneven remodeling of the bone tissue: a combination of resorption areas with hypertrophy of the bone tissue. Besides, bioresorbability of magnesium makes a repeat operation for implant removal unnecessary [15–17].

In clinical practice, local recurrences due to implantation of an orthopedic prosthesis after tumor resection in patients with primary or metastatic bone damage are an important unresolved problem. Therefore, the development of materials for implants with antitumor activity is also extremely vital. As demonstrated by the recent publications [18, 19], magnesium alloys can possess antitumor properties alongside a good biocompatibility, a suitable combination of mechanical properties, and biodegradability. The antitumor activity of magnesium is associated with its ability to evolve hydrogen during biodegradation which causes a cytopathogenic effect on tumor cells. Besides, different alloying elements have been shown to increase the cytotoxic properties of magnesium-based alloys [20, 21]. For example, for the Zn-doped Mg-Ca-Sr alloy, it has been established that Zn ions released into the cultivation medium during biocorrosion of the alloy inhibit proliferation of the tumor cells due to the alteration of the cell cycle and induction of cell apoptosis. Additionally, the ability of the tumor cells to migrate is reduced under these conditions. These data give grounds to suggest that Mg-Ca-Sr-Zn alloy may be considered as a prospective multifunctional material with antitumor activity. It can be proposed for application in orthopedic implants to compensate for bone defects after tumor resection and to prevent recurrences and metastases of malignant neoplasms. By *in vitro* tests, a cytotoxic activity against murine osteosarcoma cells exhibited by the products of biocorrosion of Mg-Nd-Y-Zr alloy produced by extrusion was established. They reduced the viability of the tumor cells during 24–48 h after the direct contact with the biocorrosion products on the alloy sample surfaces [22].

Problems with using magnesium alloys

At present, there are a number of unresolved questions connected with the perspectives of using magnesium-based alloys. First, pure magnesium and some of its alloys undergo extremely rapid corrosion under physiological conditions, which results in early implant loosening or disintegration before the formation of a new bone tissue. Rapid corrosion causes hydrogen to evolve excessively in the implantation area affecting negatively the adjacent tissues and preventing bone regeneration [23, 24]. Solving this problem is thus vitally important for the development of magnesium-based alloys with improved corrosion resistance in the principal physiological media.

Second, magnesium and its alloys are characterized by non-uniform degradation with the formation of local defects that contribute to the reduction of mechanical strength and may lead to implant fracture before the end of the expected service life. This makes it necessary to continue using conventional hard-alloyed devices with a low level of corrosion for the reconstruction of osteochondral defects as it has been done.

It should also be noted that hydrogen release makes the application of magnesium stents in the systems with circulating blood highly problematic, too [25–38].

Thus, despite a great potential of magnesium and its alloys as materials for biodegradable implants, rapid and uncontrolled degradation in a physiological medium accompanied by hydrogen release is the main limitation to the application of these materials [39]. In some cases, these limitations could be overcome by a proper selection of the chemical composition of the alloy and its thermomechanical treatment as it has been done, for example, for a new Mg-4Li-1Ca alloy [40–42], but to date there is no general methodology of searching for magnesium alloys with a desired profile of mechanical properties, biocompatibility, and corrosion resistance. However, it is evident that the development of novel and modification of the known magnesium alloys must be directed not only to the optimal combination of strength and plasticity but also to their programmable degradation under the conditions of the internal body media.

Modifying the biocorrosion rate of magnesium alloys

Doping and surface coatings are used to modify the corrosion rate of magnesium alloys and improve their biological properties. Calcium, manganese, zinc, and zirconium are the main candidates for doping since they are not toxic to the human body and can slow down the biodegradation rate. Metals such as aluminium, silver, yttrium, zirconium, and neodymium were also employed as doping elements to improve mechanical properties and corrosion behavior of alloys. Presence of these elements makes it possible to improve physical and mechanical characteristics of magnesium-based alloys by refining their microstructure and isolating intermetallic particles.

Calcium is necessary for normal functioning of a number of important body systems and, in particular, bone tissue, therefore it is considered as the major component for the introduction into magnesium-based alloys for biomedical implants. There are also data showing that calcium can display anticarcinogenic properties [17].

Manganese is added to many magnesium-based alloys to improve corrosion resistance and reduce the detrimental effect of impurities. Zirconium-containing magnesium alloys possess improved mechanical properties. Besides, zirconium decreases the rate of alloy degradation. Investigations showed that Mg-Ca, Mg-Zn, and Mg-Mn-Zn alloys have good biocompatibility *in vitro* and *in vivo* and possess an increased corrosion resistance, dissolving gradually in the bone tissue [43–46]. Mg-Al, AZ91, and AZ31 alloys are of great interest due to their commercial availability and good mechanical properties. However, their use appears to pose a danger of aluminium penetration into the organism promoting the development of dementia and Alzheimer's disease [47].

In recent years, quite a number of novel magnesium alloys have been developed and tested on orthopedic and cardiovascular models [48]. A certain progress has been achieved in doping magnesium with rare-earth (RE) elements to reduce the material corrosion in physiological medium [49]. New variants of magnesium alloys, e.g. Mg-Nd-Zn, have emerged, which are promoted as biomagnesium alloys. In this series of alloys, neodymium was chosen as a main alloying element in combination with zinc and zirconium. Neodymium is a RE element with low toxicity and its addition can significantly reduce electrochemical implant corrosion [50, 51]. But it should be noted that its long-term effects have not been studied sufficiently.

Investigations of RE elements *in vitro* showed that dysprosium (Dy) and gadolinium (Gd) possess high cytotoxic activity which, in the authors' opinion, requires close attention to the choice of RE for doping magnesium alloys [52, 53]. Therefore, to avoid problems related to potential toxicity in cases when high cytotoxicity is not intentional (see above) it is recommended to use the doping elements which have already demonstrated their good biocompatibility.

Good biocompatibility has been established for Mg-Ca-Zn (MCZ), Mg-Sr (MS), and Mg-Ca-Zn (MCZS) alloys. Introduction of these elements into alloy composition is suggested by their biological activity. Thus, zinc can promote a more rapid bone generation due to the production of alkaline phosphatase and collagen while calcium ions facilitate proliferation and differentiation of osteoblasts *in vitro*. Strontium is also recognized to be an osteogenic factor and can induce differentiation of mesenchymal stem cells into osteoblasts. In the ideal case, inclusion of calcium, zinc, and strontium can additionally reinforce a bone forming reaction to a magnesium alloy implant. Apart from the improvement of biological properties, the alloying elements can also contribute to the increase of the mechanical strength of the material. For example, magnesium alloyed with strontium and zinc, and also with calcium and zinc, showed better mechanical characteristics than pure magnesium. But it should be taken into consideration that adding alloying elements to improve osteogenic properties and mechanical strength can accelerate the corrosion rate of a magnesium-based material.

One of the results of alloying of magnesium is grain refinement, which can influence the rate of corrosion of the alloy. A more refined granular structure can also decelerate corrosion preventing its extension over the material surface [54]. At the same time, the secondary phases formed in magnesium alloys are usually electropositive in comparison with the magnesium matrix, thus promoting the reaction of cathodic reduction. The less corrosion-resistant magnesium matrix and more corrosion-resistant particles create multiple microgalvanic pairs enhancing microgalvanic corrosion [55]. Microgalvanic corrosion is likely to be an important factor for all alloys of interest as it is observed in the majority of magnesium alloys [56].

Recently, it has been shown that thermomechanical treatment in the form of severe plastic deformation (SPD) refines the grain structure efficiently, right down to nanoscale [57]. In the work [58], WE43 alloy of the Mg-Y-Nd-Zr system underwent SPD by equal channel angular pressing, multi-axial deformation, and rotary swaging with the resultant grain size below 1 μm. SPD resulted in an increase of the WE43 alloy strength by 40%. Grain refinement influenced positively the alloy's biocompatibility *in vitro*: induced hemolysis and cytotoxicity were reduced, the ability of the cells to proliferation increased, and the degradation rate slowed down [58].

Surface modification of magnesium alloys by the deposition of various coatings [59] (for example coatings from such materials as hydroxyapatite, chitosan, ceramics, and β-tricalcium phosphate) is effective in decelerating the degradation process of magnesium-based biomaterials and diminishing hydrogen evolution. Cellulose acetate coating was suggested to protect

Mg-Ca-Mn-Zr alloy against corrosion [57]. This coating is characterized by stability in physiological media and facilitates adhesion and proliferation of osteoblasts. Cellulose — a polymer comprising D-glucopyranose links — is the most common organic compound. Cellulose possesses good mechanical strength, biocompatibility, hydrophilic behavior, high sorption capacity, and relatively good thermal stability. Cellulose-coated implants reduce the intensity of fibrosis and facilitate bone regeneration [60].

Microstructure is known to be a key factor in corrosion behavior of magnesium and its alloys. It also determines the mechanical characteristics of materials. A correlation between strength and biocorrosion characteristics of magnesium alloys caused by microstructural effects has been demonstrated in a number of works [61–63]. Classical methods of alloy strengthening are based on the addition of alloying elements. The strength of magnesium-based alloys was demonstrated to increase significantly by the formation of second phase particles. Therefore, these high-strength magnesium alloys usually contain a certain number of intermetallic particles increasing their strength. This process can concurrently contribute to the improvement of strength and plasticity of the alloys and enhance the corrosion resistance as well [64].

The alloy microstructure can depend on the way it was produced and on alloying with other elements. For example, the microstructure and mechanical properties of an alloy are determined by the presence of calcium and the methods of material production. At a low calcium concentration (below 16.2%), a Mg-Ca alloy possesses a crystal structure similar to that of pure magnesium [65]. Addition of calcium increases the corrosion resistance and reduces the grain size. With an increase of this element content the grain size diminishes and, at the same time, more particles of the eutectic Mg_2Ca phase are observed at the grain boundaries [66–70].

The way of alloy fabrication is also of great importance for its mechanical properties and corrosion resistance. Thus, the authors of the works [71–73] have developed extruded Mg-Mn-Zn-Nd alloys. The experimental results showed that all of them had good ductility and significantly higher mechanical strength than those fabricated by casting. Tensile strength of the extruded alloys increased with the increase of the neodymium content. These alloys also exhibited good biocompatibility and much higher corrosion resistance than cast alloys.

One of the promising approaches to the control of magnesium alloy corrosion in biological media is their surface treatment [74]. An implant area is of great importance. It is believed that if the surface area of the magnesium implant is less than 9 cm^2, the dissolved Mg^{2+} ions will be easily consumed by the human body. However, quick formation of hydrogen/ hydroxide in the corrosion process may pose serious problems for patients.

The corrosion rate also depends on the geometry, composition, and location of the implant. Application of monocrystalline magnesium [75] and new technologies of surface coating with polymers may appear to be one of the perspective directions [76]. This will provide additional capabilities for adaptation to degradation and gradual replacement of the implanted device with a new tissue.

Intensive searching for various approaches including introduction of alloying elements into magnesium, coating with protective films and mechanical treatment, control of the alloy corrosion rate has been going on for a number of years. Despite these new strategies, an improvement of the corrosion rate control for magnesium alloys has been demonstrated only in the experiments *in vitro* [77–80]. At the same time, experiments on animals often provide data on insufficient reduction of the biodegradation process rate for these alloys. For example, biodegradable Mg-Ca-Zn alloy was tested on rabbits with a screw implanted into the bone for 24 weeks [81]. Histological and micro-CT analyses showed the formation of the bone tissue with a weak gas evolution and absence of foreign bodies around a slowly degrading specimen. On the basis of these rather limited data, the authors suggested that if the chemical composition of the magnesium alloy is selected correctly its microstructure may be designed in such a way as to make the mechanical properties of the alloy similar to the properties of the spongy bone. But even this optimistic assessment of the results did not allow the researchers to consider the tested alloy specimens as being suitable for devices with a load-bearing function. Farraro et al. [82] investigated the possibility of using magnesium-based alloys for functional tissue engineering. They used AZ31 alloy for fixation of tissue autografts during the reconstruction of the anterior cruciate ligament of the test animals. The experimental results showed that a fixation device based on the magnesium alloy promoted the restoration of the ligament function providing their mechanical integrity at the early stages and minimizing atrophy of the implanted fragments. Gradual resorption of the elements of a magnesium-based fixation device can make it possible to achieve reconfiguration and reinforcement of a ligament bioimplant.

In a preclinical study, nails from magnesium alloys containing different calcium concentrations were tested after intraosseous implantation in rabbits. Three-month observations enabled the authors to establish that implanted nails, judging from their reduced diameters, were gradually degrading. Besides, it was found that a new bone was forming around the Mg-Ca alloy whereas there was no visible bone growth around the nails from thallium. This demonstrates preferential integration of Mg-Ca nails with the bone and osteogenesis in the peri-implant zone.

Thomann et al. [83] investigated the effect of magnesium doping with the elements such as calcium, aluminium, and RE elements on the corrosion process.

It was found that after the implantation of the alloy into the cavity of the white rabbit's tibia marrow for a period of 12 months, this alloy provided a strong integration of the implant and bone followed by a gradual implant degradation by 11, 31, and 51% after 3, 6, and 12 months, respectively. Magnesium alloys containing zinc and manganese showed satisfactory mechanical properties. However, these alloys degraded relatively quickly: during 9-week implantation bioresorption was 10–17% and 18 weeks later it grew to 54%. In 2001–2005, Witte et al. [84] investigated *in vivo* decomposition of magnesium alloys with aluminium and zinc and RE elements (neodymium, cerium, lanthanum, and others). The study showed the alloy degradation 18 weeks after the operation with significant increase of bone formation in comparison with the control group (a polylactide nail). RE elements were detected in the corrosion layer of the amorphous $Ca_3(PO_2)_4$, but not in the surrounding bone tissue.

In recent years, various magnesium alloys developed to optimize degradation, mechanical properties, and biological reaction were studied. Trincă et al. [85] proposed to use a magnesium-based alloy with the addition of 0.4% of calcium and 0.5% of silicium. Histological examinations showed intensive and active bone formation 2 weeks after the implantation. X-ray and computer tomography detected the presence of experimentally created defect in the tibia and revealed the main stages of bone tissue regeneration concurrent with the process of implant specimen biodegradation. Wang et al. [86] implanted cylinders from Mg-Zn-Zr alloy into the tibiae of white rabbits. 23 weeks later, the implants were found to undergo partial biodegradation and the density of the surrounding spongy bone was increased. Micro-CT confirmed that a newly generated bone tissue on the surface of the remaining implant was formed after 12 to 24 weeks with the formation of multiple cavities filled with gas. The gas generated during Mg-Zn-Zr alloy degradation caused cavitation of the spongy bone but did not affect osteogenesis around the magnesium alloy. Exploration of Mg-Sr alloy showed that due to intercrystalline distribution of the second phase and microgalvanic corrosion Mg-Sr alloy, obtained by casting, decomposed more rapidly than the extruded alloy. Other authors [87] verified the fact that this alloy facilitated bone restoration during *in vivo* implantation.

Clinical investigations of magnesium bioimplants

Lambotte [88] was the first to apply a magnesium alloy in orthopedics in 1906 when he used magnesium fixation elements for osteosynthesis. After the operation, extensive subcutaneous gas cavities were formed and on day 8 fragments of the destroyed magnesium plate were removed. The effect of biodegradation was most likely intensified by electrochemical mechanisms caused by the application of the steel screws for magnesium plate fixation. Though his first attempt was unsuccessful, Lambotte proceeded to do experiments on animals and found that complete magnesium resorption could occur over 7–10 months after the implantation. Later, in the 1930s, clinical investigations of pure magnesium without steel screws in children with bone fractures turned out to be more successful [89].

In recent time, only singular clinical pilot tests of magnesium alloys have been described. They demonstrate regeneration of the bone that occurs concurrently with continual implant degradation and the emergence of a biomimetic matrix for calcification at the degradation front which initiates the process of bone formation. Bone formation on the surface of the magnesium alloy gives rise to deceleration of degradation of the implant, which is completely replaced by new bone after 1 year [85]. Thus, degradability of a biodegradable magnesium alloy may contribute to the process of neo-bone formation and replacement of the decomposing fixation device with bone tissue. Biodegradability of the magnesium-based devices was established by the clinicians who conducted this study as an important factor which makes it possible to avoid repeated surgical procedures and changes the existing technology of fabricating fixation elements for bones [90].

A small-scale short-term pilot clinical study [91] showed that a biodegradable magnesium-based screw was roentgenographically and clinically equivalent to the common titanium screws. The authors did not observe any reaction to a foreign body, osteolysis, or systemic inflammatory reaction. But a limited period of observation (6 months) necessitates further prospective randomized investigations with a longer period of observation to validate these findings.

Thus, the data of the described investigations give reasons to make a conclusion that in aggregate they confirm the good potential of magnesium-based alloys for biocompatible, bioactive, and biodegradable scaffolds in bone tissue engineering. Further optimization of the technology for magnesium alloy fabrication may become a promising direction for creation of bioengineered constructs [92].

Biodegradable magnesium stents

As has been previously reported, magnesium-based alloys are considered to be prospective materials for biodegradable coronary arterial stents. Despite a wide and successful application of metal and polymer stents problems still arise: inflammation in case of a long-term usage and the necessity of repeated surgical intervention. Polymer stents are unable to provide sufficient mechanical strength for a period required for the restoration of initial elasticity of a native blood vessel [93]. The state of the art in the field of metal and polymer stents calls for the development of new approaches to improve the quality of treating stenotic and damaged coronary arteries. An ideal solution to this problem would be creation of a biodegradable stent which after having

fulfilled its function and provided the necessary support for the restoration of the injured artery would undergo bioresorption.

There are two main candidates for biodegradable metal stents: alloys based on iron and magnesium. A biodegradable iron-based stent (Fe>99.8%) was tested on rabbits. The results showed that implantation of this device into the aorta did not cause any signs of inflammatory response, neointimal proliferation, or toxicity. However, these stents do not degrade during a long period of observation [94]. Therefore, a more rapid degradation rate is required for iron stents demanding further investigations directed towards the correction of the stent composition and its geometric design.

Biodegradable magnesium-based alloys were used as an alternative to the iron-based stents. The problems of toxicity of the doping elements, which can be significant in the abovementioned bone implants based on magnesium alloys, seem not so serious when used in coronary and vascular stents due to their small dimensions. But a clinical study of magnesium stents [95] showed their extremely rapid degradation (less than a month after implantation) followed by vessel restenosis and loss of mechanical properties.

A successful application of coronary stents based on a biodegradable magnesium alloy was demonstrated in another clinical study [96]. Further improvements of magnesium stents were presented in the works of the same group of investigators [97, 98]. Projects aimed at the assessment of long-term clinical trials of biodegradable magnesium alloy-based stents were described in the works [99–101].

Undoubtedly, in near future the efforts of a great number of researchers from many countries engaged in the problems of bioresorbable magnesium stents will result in a serious progress in this field.

Conclusion

The analysis of the literature data showed that despite a great potential of using biodegradable magnesium alloys there exist a number of problems preventing their clinical application. First, pure magnesium and some of its alloys are subject to excessively rapid corrosion under physiological conditions which leads to early implant loosening or disintegration before bone tissue remodeling and fast evolution of gaseous hydrogen may have a harmful effect on the adjacent tissues. Second, magnesium and its alloys are characterized by local and non-uniform degradation resulting in the reduction of the mechanical strength of an implant.

It follows that the development of new magnesium alloys with controllable biodegradation is of great importance for various branches of clinical medicine. In addition to orthopedics and cardiovascular surgery where applicability of bioresorbable magnesium alloy has been actively investigated, the employment of these alloys in oncology is also believed to be promising. It is in oncology that cytotoxicity of the alloying elements, commonly regarded as a negative factor restricting the application of the alloy in biomedical implants, may become its advantage through imparting improved mechanical strength and therapeutic antitumor properties to the implant. Implants from porous magnesium materials impregnated with antitumor preparations can elute drugs during biodegradation with a controllable rate preventing tumor recurrence in patients with osteogenic sarcoma after malignant neoplasm resection.

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Conflicts of interest. The authors have no conflicts of interest to declare.

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