REVIEW ARTICLE

A Mini Review on Biodegradable Magnesium Alloy Vascular Stent

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Biodegradable magnesium alloy stents are a new generation of vascular stents which can open up blocked blood vessels at an early stage, then degrade and be absorbed by the body at a suitable rate after the vascular has been repaired. Mg alloys are excellent materials for vascular stents benefit from their sufficient mechanical properties and good biocompatibility. At present, Mg alloy is also used as a green material in the research of vascular stents due to its biodegradable property. In this paper, based on the research situation of degradable Mg alloy stents in recent years, the research history, degradation mechanism, structural design and basic research experiments of Mg alloy stents are reviewed.

Introduction

The problem of population aging has become more and more serious in the worldwide, and cardiovascular disease concentrated on the elderly is particularly prominent. Cardiovascular disease is the leading cause of global loss of CVD health, followed by stroke [**1**]. In 2011, the United Nations officially recognized cardiovascular disease as a major concern for global health [**2**]. The picture below shows the incidence of middle-aged and elderly people in China. From **Fig. 1**, it can be seen that cardio-cerebrovascular diseases have become the most harmful factor of human health, and it is imminent to solve cardio-cerebrovascular diseases.

At present, the main medical methods for vascular diseases are the following: surgery, drug treatment and endovascular treatment. In order to alleviate the pain of patients, many science and technology were developed: for instance, balloon dilatation, bare metal stents, and drug implantation stents are used for the treatment of patients. However, when these devices are implanted into the human body, a series of long-term problems have been caused and have still not been resolved till now, such as thrombosis, hyperplasia, inflammation, increasing the patient's painful condition. So the researchers proposed to endow the vascular stent a biodegradable property, which can make the stent degrade and be absorbed by the human body at an appropriate rate after the vascular tissue be repaired. Biodegradable Mg alloy vascular material avoids foreign body effects on the human body during surgical and permanent implant removal [**3**]. The healing response of stent blood vessels can usually be divided into three overlapping stages: inflammation, granulation and remodelling. In the continuous research, the concept of "biological adaptation" between Mg alloy stent and local tissue microenvironment after implantation has been proposed [**4**]. The current research mainly focuses on the cultivation mechanism of biomaterials and cells, and advanced research has also explored the effect of polymer coatings on the corrosion behaviour of biodegradable stents [**5**].

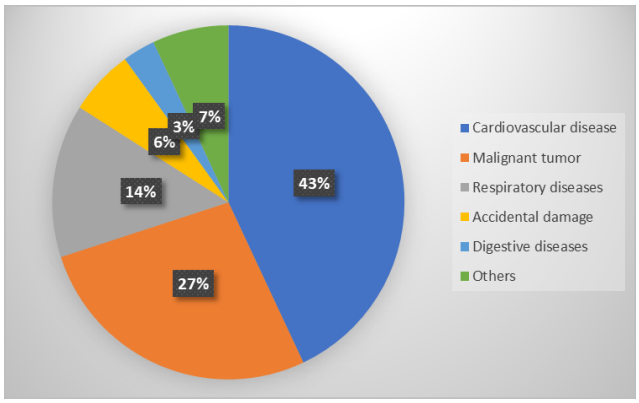

Fig. 1. Probability of disease in middle-aged and elderly people.

Development history of magnesium alloy stents

Since its birth, vascular stents have undergone three stages, namely bare metal stents, drug-eluting stents and biodegradable stents. Bare metal stents have good mechanical properties, but according to clinical experience, it has been found that metal stents as foreign bodies in the human body can cause local inflammatory reactions, intimal hyperplasia and restenosis, leading to in-stent restenosis of high ratio [**6**]. To solve this problem, researchers have been trying to produce second-generation drug-eluting stents, which successfully reduced in-stent restenosis by inhibiting neointimal hyperplasia of coronary artery disease [**7**]. But this stent has a certain degree of specificity that means patients with different complication need loading different drugs. It is more complicated in clinical use and cannot fundamentally solve a series of

complications. When the drug is completely released from the surface of the stent, it will still cause lesion restenosis and intimal hyperplasia. Therefore, researchers have proposed a biodegradable stent material. When the stent is implanted in the human body to complete vascular expansion, the stent can degrade in the human body, and the degradation products are not harmful to the human body. For the advantages of Mg alloy on the crucial biological functions and biocompatibility, it has attracted great attention [**8**].

Biodegradable magnesium alloy stents were first developed by German bare Mg alloy stents. Traditional bare Mg alloy bare stents have good mechanical properties. The surface of the stent was not coated with any anti-proliferative drug. The earliest clinical trial was to implant bare Mg stents in knee lesions of 20 patients. A three-month clinical follow-up showed that the main clinical patency rate and limb salvage rate of the AMS stent were good, but the degradation rate in the body was too fast. It cannot support the repair of lesions and will be completely degraded, so it cannot be put to practical use. In order to change this shortcoming, BIOTRONIK improved the Mg alloy bracket [**9**], the stent is coated with a polylactic acid-glycolic acid copolymer drug coating and a paclitaxel drug coating. This is called the second Mg alloy stent. The revascularization rate of target lesions in the second-generation Mg alloy stent is significantly lower than that of bare Mg alloy stent, indicating that reasonable drug release is very important for the long-term application of Mg alloy stent. The Cypher stent is the first drug-eluting stent used clinically. A series of randomized controlled trials showed that Cypher stent was re-vascularized at 9 months after implantation compared to bare metal stent. Revascularization of target lesions was significantly reduced. After a long period of observation, the late official cavity was higher. Immediately after, the researchers improved the structure of the stent and adjusted the drug coating to add antibiotics [**10**], and installed two permanent X-ray markers on both ends of the stent. Third-generation Mg alloy stents are more difficult in clinical trials. After 6 months of clinical follow-up, the patient's late cavity loss was significantly reduced, and the stenosis rate was significantly reduced. The mechanical properties and degradation of the third generation Mg alloy stent were observed. Performance is superior to the previous two generations of alloy frames. **Table 1** shows the *in vivo* testing of biodegradable Mg -based stents.

Degradation mechanism of Mg alloy vascular stent

The Mg alloy reacts in water to form Mg hydroxide and hydrogen. When the water contains chloride ions, the Mg hydroxide reacts with it to form Mg chloride, which accelerates the reaction of the Mg alloy and accelerates the corrosion rate. The reaction equation is as follows:

$$Mg+2H_2O=Mg(OH)_2+H_2$$

$$Mg(OH)_2+2Cl^-=MgCl_2+2OH^-$$

Biodegradable Mg alloy vascular stents are becoming more and more important in the treatment of vascular diseases. Since the degradation process under physiological conditions is more complicated, only a few research groups are interested in the mechanism of obtaining potential processes [**16**]. Previous research on the degradation of Mg alloys was usually done in static in vitro immersion and in vivo experiments. However, these two tests only considered the substance's toxicity to cells. In fact, the degradation behaviour of Mg alloys is the result of multiple factors. Therefore, a special experimental device is used to simulate blood flow in blood vessels. The simulated body fluid flowing inside Hank's buffered saline solution will not only corrode the stent, but also apply periodic shear stress to it, which is closer to the micro-stress environment of human blood vessels. The shear stress induced by blood flow on the stent was simulated by computational fluid dynamics, and the degradation mechanism of Mg alloy in a dynamic environment was studied in combination with numerical simulation results [**17**]. At the same time, they systematically evaluated the application of biodegradable magnesium needles in bioreactors for cyclic loading and to simulate degradation of body fluid perfusion [**18**]. Compared with *in vivo* degradation of the same material in mouse subcutaneous and canine tibial implant models, this in vitro model has been shown to be useful for analysing the in vivo behaviour of complex degraded Mg-based alloys.

Table 1. *In vivo* tests of biodegradable Mg based stents.

Stent system	Experiment model	Biocompatibility	Degradation time	Ref.
AE21	pigs, coronary artery	There were no thromboembolic events, 40% of lumen loss correspond to neointimal formation	89 d	[11]
WE43	Minipigs, coronary artery	Rapid endothelialization after 6 days, inflammation and intimal hyperplasia caused by degradation	98 d	[12]
AMS	Preterm baby, pulmonary artery	No associated inflammatory response, increased arterial diameter after stent implantation	5 months	[13]
Biosove-I DREAMS, PLGA+ paclitaxel	46 patients	The target lesion failure rate was 7% at 12 months. The lumen area was significantly reduced at 6 months and 12 months of follow-up.		[14]
Biosolve-II DREAMS 2G, PLLA+ sirolimus	123 patients	The target lesion failure rate was 4%. The QCA parameters remained stable from 6 months to 12 months. Target lesion failure rate was	12 months	[15]

So far, many strategies for reducing the rate of corrosion of vascular stents have been explored, and the degradation of vascular stents in the body can be controlled. Mg-Y-Gd-Nd alloy is an absorbable Mg alloy stent, which has poor corrosion resistance and difficult to control the corrosion rate in its as-cast condition. Therefore, a new Mg-Zn-Y-Nd alloy (Zn / Y atomic ratio of 6) was designed to improve the corrosion due to the existence of quasicrystals. The above two alloys were prepared by a sub-rapid solidification process and studied in dynamic simulated body fluid.Its corrosion behaviour (body fluid velocity 16m/180m1 min^{-1}), the results show that Mg-Zn-Y-Nd alloy has better corrosion resistance in dynamic SBF due to grain refinement [**19**]. The two-step alkali metal fluoride treatment can effectively prevent pitting corrosion caused by galvanic corrosion by effectively removing the second phase on the surface of the substrate and forming a dense and defect-free Mg fluoride coating. Tests in a rat subcutaneous implantation model showed that the Mg-Zn-Y-Nd alloy treated with two-step fluoride was uniformly corroded and the corrosion rate was low [**20**]. The smooth TiO_2 film has excellent thrombus resistance and can improve the corrosion resistance of Mg alloy stents. An improved solvothermal method was used to prepare flower-like nanostructured TiO_2 films on Mg-Zn-Y-Nd alloy substrates. Its corrosion resistance in simulated body fluids can be improved by the protection of TiO_2 film [**21**]. Preparation of nano-scale MgF_2 film on Mg-Nd-Zn-Zr alloy finally reduces the corrosion rate and improves biocompatibility. MgF_2 membranes have enhanced viability compared to naked matrices. In addition, animal experiments of implanting MgF_2-coated JDBM stent into rabbit abdominal aorta confirmed that the stent has excellent histocompatibility and showed no signs of thrombosis and restenosis in stent blood vessels [**22**]. Micro- and nano-scale structures were constructed on the surface of AZ31 Mg alloy by wet chemical method. The superhydrophobic surface was treated and the blood compatibility of the superhydrophobic surface was studied by hemolysis and platelet adhesion tests. As a result, the corrosion resistance of Mg alloy in PBS was improved, and the adhesion of platelets on the surface was suppressed. This conclusion provides a basis for further controllable degradation [**23**]. Wang et al. studied the effect of degradation products of Mg alloy on nitric oxide (NO) released from vascular endothelial cells [**24**]. The results showed that the concentration and reaction time of degradation products were positively correlated with the release of NO, and the degradation time was negatively correlated with the release of NO. It can be speculated that there is a certain relationship between the release of NO in vascular endothelial cells and the degradable Mg alloy vascular stent, and the influence of this factor can be considered when preparing the vascular stent.

Structural design of biodegradable vascular stent

For the structure of vascular stents, the stent design directly affects its mechanical properties [**25**]. Cardiovascular stents require high mechanical properties, both to ensure good expansion capacity and to have good flexibility. The main factor is that the elongation of the stent material is low, which causes a large stress and strain after the stent is expanded, which causes cracks or fractures. Therefore, the stress and strain inserted into the stent is one of the effective means to improve the damage. According to the characteristics of Mg alloy materials and the requirements of the stent, a variety of stent structures have been designed [**26**]. These stent structures will affect the initial diameter, support length and number of circumferential supports of the Mg alloy stent structure on the expansion. First, find the structure suitable for the Mg alloy stent [**27**], and then use ANSYS software to analyse the effects of materials, geometry, etc. on the stent expansion and compliance.

Gang *et al.*, uses a multi-pass cold drawing process to convert seamless hollow billets into micro−tubes with an outer diameter of 2.9 mm and a wall thickness of 0.217 mm [**28**]. Finally, the radial direction of the cardiovascular stent prepared by laser cutting of the vascular stent. The expansion force is more than four times the maximum vascular compression pressure of normal adults, which meets the requirements of the mechanical properties of cardiovascular stents. After the second extrusion, the grain size is greatly reduced and the strength of the basic texture is also enhanced. The elongation increased from about 23% of the JDBM alloy rods just extruded to about 48.8% of the micro-tubes just extruded, and increased by 112% through double extrusion. The high elongation is attributable to the enhanced activation of non-substrate slip caused by significant grain refinement [**29**].

Micro−tubes with high-precision scaffolding materials are limited due to poor processability at room temperature. Mg-Zn-Y-Nd alloy tube blanks are first produced by hot extrusion. Wang et al. prepared a high-precision micro-tube with an outer diameter of about 2.0 mm and a wall thickness of about 0.15 mm through the combination of multiple cold drawing and inter-pass annealing [**30**]. After annealing, the micro-tubules showed improved mechanical properties and had a tendency to uniformly corrode in simulated body fluid solutions. Mao et al. used a cyclic extrusion compression method to process the Mg-Zn-Y-Nd alloy, and its size was greatly refined to 1 μm [**31**]. The second phase particles were separated by grain boundaries to be distributed in size and shape and uniformly in the crystal grains. In the end, the alloy showed uniform corrosion and mechanical properties were also improved.

The combined method of cyclic expansion extrusion, direct extrusion and microtubule extrusion was used to make WE43 Mg microtubules [**32**]. The ultimate micro-tube length and elongation were increased, and the microhardness increased. With good hardness uniformity, this method provides a method for manufacturing ultrafine-grained Mg microtubes. The Mg alloy ZM21 was selected and a forming process was used. Micro-tubes with an outer diameter of 2.9 mm and a wall thickness of 0.2 mm were successfully produced in the fourth pass of cold drawing

without intermediate annealing. This work confirms that the forming process of Mg alloy vascular stent is feasible [**33**].

Basic research on Mg alloy vascular stent

Coronary stent implantation in humans should be consistent with the recovery time of the vascular endothelium. From the perspective of materials science, adding rare earth elements such as tin, manganese, zirconium and other alloys to Mg can effectively improve its mechanical properties and reduce the corrosion rate. Song et al. studied the degradation of pure Mg in simulated body fluids (SBF) [**34**]. The results show that pure Mg in SBF is similar to pure magnesium in normal saline and does not have a good effect in protecting the human body. Zhao *et al.*, compared the corrosion of three materials in SBF, namely pure Mg (99.9%), magnesium zinc zirconium (ZK60), and magnesium zinc zirconium (Mg-5. 6Zn-0. 55Zr-0. 9Y.) [**35**]. The results show that the addition of bismuth and other elements is feasible for Mg alloy materials, and at the same time, it can improve its corrosion resistance. In 2003, Heubelin *et al.*, first studied Mg alloy cardiovascular stents [**11**]. They chose AE21 Mg alloy as a bioabsorbable metal stent. A bioabsorbable metal stent was placed in the coronary arteries of domestic pigs. No blood clot formation, myocardial infarction and allergy were found during follow-up. The AE21 stent started to degrade within 1-2 months. Subsequently, Biotronik developed an absorbable metal stent using a Mg alloy (WE43). In piglets' coronary arteries, 12 AMS were implanted, and 6 common metal stents were implanted as controls. At the fourth week, coronary angiography showed that the minimum diameter of the coronary artery of AMS was higher than that of the control group. In the eighth group, the degree of intimal hyperplasia of AMS was lower than that of the control group. Compared with the control group. AMS has anti-intimal hyperplasia, no thrombosis and other severe inflammation. Mario et al. implanted Mg alloy stents in the coronary arteries of 33 miniature pigs [**36**]. Coronary angiography performed 1 month later showed that the minimum diameter of the Mg alloy stent group was larger than that of the control group. After 2 months, the minimum diameter of the Mg alloy stent group increased, while the minimum diameter of the control group remained basically unchanged. This indicates that Mg alloy scaffolds have an inhibitory effect on smooth muscle cells.

Fu *et al.*, compared three kinds of cardiovascular stents composed of 316L stainless steel, Mg alloy and Zn alloy: The Mg alloy stent showed its advantages of biodegradability and bioactive properties, but also with the lack of too rapid degradation rate and late restenosis [**37**]. Liu *et al.*, added 16 kinds of rare earth elements (REEs, including Sc, Y, La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Du, Ho, Er, Tm, Yb and Lu) into Mg as alloying elements, and found that binary Mg-RE model alloys presented good mechanical properties with wide range and also no cytotoxic effect, wherein the Mg-light REE alloys showed generally better corrosion resistance compared to Mg-heavy REE alloys [**38**]. In addition, lots of scientists have reported that series of functional coatings are crucial factors for enhancing the corrosion resistance and improving surface endothelialisation of the Mg alloy vascular stents [**39-49**].

We explored the application of polydopamine (PDA) / hyaluronic acid (HA) coatings with different HA molecular weights in cardiovascular materials [**50**]. The Mg-Zn-Y-Nd alloy coated with PDA/HA-2- and PDA/HA-4 has better biocompatibility. It was implanted into the abdominal artery of SD rats. The results showed that PDA /HA-2 had good corrosion resistance and biocompatibility. This method provides a new idea for cardiovascular material equipment. Another work of our research group immobilized specific junction peptides (REDV) of endothelial cells on the surface of Mg-Zn-Y-Nd alloy with PDA deposition [**51**]. The PDA/ REDV coating promoted endothelial cell attachment, and also had the ability to enhance endothelial cell viability. In some disadvantages in vascular stent materials, the layer-by-layer self-assembly method was also used to modify the surface of Mg-Zn-Y-Nd alloy with citric acid (CA) and dopamine [**52**]. The CA/PDA layer exhibited the characteristics of promoting the growth and diffusion of vascular endothelial cells and promoting better biocompatibility.

Conclusion & future prospective

Through continuous research on biodegradable Mg alloy stents, its performance in various aspects and clinical trial results are getting closer to the requirements of an ideal stent, and the prospect is very good. However, the current clinical trials of biodegradable Mg alloy stents are randomized trials of simple lesions. The clinical data obtained are not enough to prove that Mg alloy stents can be used by the entire population, so we need to do a lot of experiments to prove this. At present, the problem that needs to be solved is that the degradation rate of Mg alloy in the body is too fast, and it cannot play a role in revascularization. If degradation is too slow, it will stimulate vascular smooth muscle proliferation for a long time and increase the possibility of stenting restenosis. At the same time, the blood vessel diameter and blood flow at different locations are not exactly the same, it is necessary to classify the requirements of the mechanical properties and degradation rate of the stent.

It is believed that with further systematic research on the biocompatibility, degradation rate and pharmacological mechanical support properties of Mg alloys, biodegradable Mg alloy stents will become more and more perfect.

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Keywords

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