Cellular response of biodegradable AZ31 magnesium alloy stent in artery

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Abstract. Because of the increasing incidence of coronary artery disease, the use of cardiovascular stents is gradually increasing. In percutaneous coronary intervention, advantage of bioresorbable stent is that the stent does not remain in the human body after completing the necessary mechanical support to ensure the blood vessel open, and finally degrades into harmless molecules. Compared with bare stents, which require long-term retention in the body, the incidence of restenosis in stent or late stent thrombosis was lower. Current biodegradable stent mainly include polymers, biodegradable stents and metal alloy stent. Magnesium-based stent degradation and its copolymers are used in the application of biological absorbable stents and attract the attention of researchers.

1. Introduction
Cardiovascular diseases are the leading cause of death, accounting for nearly one third of all deaths worldwide. In cardiovascular disease, endovascular stenosis caused by endovascular atherosclerosis is the main manifestation of cardiovascular disease [1]. Endovascular stenosis will lead to reduced blood flow to the heart, oxygen and nutrients cannot be timely added to the heart, and atherosclerotic blood vessels are more prone to rupture, causing myocardial infarction and other problems [2]. Using stent for interventional surgery is one of the most effective methods for the treatment of intravascular stenosis [3]. With the rapid development of science and technology and the unremitting pursuit of human health, vascular stent technology has been constantly updated, from the initial drug balloon to metal bare stent, and now to the widely used drug-eluting stent and focus on the degradation of stent.

2. AZ31 magnesium alloy stent and cellular response

2.1. Studies on vascular endothelium and endothelial cells
The degradable magnesium-based stent has become a hotspot in the field of degradable stent because of its good biocompatibility and biodegradability. At present, a large number of animal experiments and clinical trials related to magnesium-based stent have been carried out at home and abroad [4]. However, the evolution of the degradation products of magnesium based vascular scaffolds in the whole degradation process, as well as the effects of soluble ions and solid degradation products generated by degradation on surrounding cells are still unclear, and the interaction between magnesium based scaffolds and surrounding vascular tissues in the pathological model of narrow vessels is also unclear and has not been reported in relevant literature [5].
2.2. Endothelial injury and reendothelialization after stent implantation

Endothelial cells can synthesize and secrete more than 10 kinds of bioactive substances, which typically have a nitric oxide, Endothelin, VEGF, prostaglandin I2, Recombinant Tissue-type Plasminogen Activator, Transforming Growth Factor, heparin, von Willebrand Factor and so on [6]. Under normal physiological conditions, the synthesis and secretion of various biological active substances can maintain a dynamic balance to ensure the normal vasculature contraction and stable and orderly repair of damaged endothelial cells [7]. The main process of the formation of new blood vessels is the migration and proliferation of endothelial cells to form tubular structures. At present, endothelial cells are mostly selected for in vivo and in vitro studies on vascular formation and vascular repair mechanism at home and abroad, among which HUVEC, the human umbilical vein endothelial cell, is the most widely used in current studies because of its rich sources, simple separation and good simulation of physiological conditions [8].

3. Factors affecting vascular endothelialization

After stent implantation after PCI, excessive proliferation and migration of vascular endothelial damaged smooth muscle cells, as well as excessive expression and deposition of extracellular matrix are likely to result in delayed endothelialization. The main mechanisms follow: the endothelial structure and function are damaged, and the friction and mechanical stimulation caused by stent implantation and balloon expansion can compress the vascular intima, and even tear or peel off the vascular intima, thus destroying the integrity of the monolayer [9]. At this time, the proliferation and migration of vascular smooth muscle cells, as well as the proliferation of extracellular matrix and intima are the main causes of in-stent restenosis. In addition, the thickness of the bracket, wire and bracket joint after the formation of the blood vessel walls bulge affect the lining of the surface morphology, blood flows through stent parts will be near the stent wire forming eddy current or turbulence, such as low shear zones, and stent wire thickness, spacing, and to local turbulence flow and vortex to influence by vascular endothelial cells regulate the expression of genes and, in turn, affects the structure and function of endothelial cells, which lead to endothelial dysfunction, inhibition of stent endothelial change again after injury [10].

The endodermis at the stent implantation site after PCI was damaged, and the endodermal matrix was exposed in the blood. The endodermal collagen fibers combined with vWF factor in plasma, vWF allosteration and binding with platelet GPI, and platelets and fibrinogen accumulated in large amounts in the damaged endodermis [11]. Meanwhile, large amounts of Thromboxane A2 and ADP, vWF, 5-HT, Ca^{2+}, fibrinogen and Thromboxane are released [12]. Then GP IIb/III Fg receptor exposure combination of Fg, prompting more platelet aggregation form clots. With the continuous enlargement and organization of thrombus, the intima is thickened and restenosis is formed [13].

4. Implantation of AZ31 magnesium alloy stent

4.1. Pure magnesium and magnesium alloy supports

The degradation products of magnesium and magnesium alloy in human body exist in the form of ions. Some of the degradation products of magnesium are absorbed by human body, and the surplus is discharged from the body through liver and kidney. It has been reported that magnesium was used as a surgical implant material in 1907. Previous clinical studies on magnesium have also confirmed that magnesium has good biocompatibility, so it can be used in biomedical materials [14]. However, the rapid corrosion rate of magnesium-based materials limits its application as a biological implant. Although there have been some researches on magnesium, the emergence of inert materials such as stainless steel, titanium alloy and cobalt alloy has neglected the researches on magnesium. The techniques of controlling corrosion resistance and improving mechanical properties of magnesium alloys have been greatly improved. Since the beginning of the 21st century, many researches on biodegradable biomaterials have been carried out by researchers at home and abroad. (Table 1)
Table 1. Elemental composition of different magnesium-based stents.

| Numble  | Mg   | Zn | Ca | Mn | Zr |
|---------|------|----|----|----|----|
| AZ31B   | Bal  | 0.74 | -  | 0.35 | -  |
| WE43    | Bal  | 0.2 | -  | 0.13 | 0.36 |
| AZ31    | Bal  | 0.8 | -  | 0.37 | -  |
| ZW21    | Bal  | 2   | 0.25 | 0.15 | -  |
| AZ91D   | Bal  | 0.6 | -  | 0.25 | -  |
| Mg-Sr   | Bal  | -  | -  | 0.003 | -  |

4.2. AZ31 magnesium alloy stent

Biodegradable magnesium based scaffolds have been studied in many animal studies and clinical trials. AZ21 magnesium alloy stents were successfully implanted for the first time in the carotid artery of beagle 56 days [13, 14], the experimental results show that AZ21 magnesium alloy stent has good biocompatibility. Previous study points out that the proper alloy element is added in the magnesium alloy can improve the corrosion resistance of magnesium and magnesium alloying of compared with the pure magnesium, its surface cuts the number of platelet adhesion and hemolysis also weakened [15]. Compared with biodegradable polymers such as PLA, magnesium alloys are more easily processed, have better stiffness and mechanical properties. Biodegradable magnesium alloys are regarded as a kind of revolutionary metal biomaterials in Europe and America. Current research is more magnesium alloy WE43, AZ21, AZ31 Mg - zinc - Mn, et c, because of poor corrosion resistance of pure magnesium, degradation soon after implantation in the human body, therefore, in order to improve the corrosion resistance of magnesium, researchers would be some alloy elements added to pure magnesium alloying, or through drawing, such as channel extrusion of magnesium grain refinement, in order to increase the corrosion resistance of magnesium.

5. Conclusion

Vascular endothelial damage after stent implantation is the main cause of many risks. Subsequent thrombosis and proliferation of vascular smooth muscle cells are easy to lead to in-stent restenosis. Several studies have also found that accelerating endothelial coverage on the scaffold surface can effectively reduce the formation of ISR and LST. Therefore, vascular endothelial integrity should be restored as soon as possible after stent placement. Previous studies have shown that the proliferation and migration of adjacent mature endothelial cells to the injury site contribute to the reendothelialization due to the control of autonomic and external signals. In addition, subsequent studies have confirmed that the mobilization, homing, migration and differentiation of stem cells are also important ways to repair endothelial injury.

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