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Biodegradable Metal Stents: A Focused Review on Materials and Clinical Studies

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Coronary artery disease (CAD) is the most common type of heart disease caused by plaque building up along the inner walls of coronary arteries which narrows the lumen and reduces blood flow. Stenting is the current standard procedure to treat the disease by opening the narrowed arteries and restoring the blood flow. Stenting has been revolutionary evolved from the use of bare metal stents made of corrosion resistant alloys to the incorporation of anti-proliferative drugs in the drug eluting stents. Despite the advantages and limitation of the current stent technology, the permanent presence of stents in the arteries is questionable, especially for some applications, including pediatric, in presence of collateral arteries, and others. Biodegradable stents, designed to support the arterial wall and disappear after its remodelling, therefore constitute an interesting choice, possibly representing the next revolutionary treatment of CAD. Magnesium, iron, zinc and their alloys are among metals have been proposed as biodegradable stent materials. These metals are designed to degrade *in vivo* through corrosion process without posing toxicity problems to the body and called as biodegradable metals. Stents made of magnesium and its alloys have been the most studied, developed and reached clinical trials in humans, followed by those made of iron which reached in vivo studies in animals. Meanwhile, zinc is just recently proposed with only few studies have been reported. This papers presents a focused review on the development of biodegradable metals for stents.

Keywords: Coronary Artery Disease, Biodegradable Stent, Biodegradable Metals, Iron, Magnesium, Zinc.

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1. INTRODUCTION

Cardiovascular diseases (CVD) include coronary artery disease (CAD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism. In 2010, CVD was responsible for 31.9% death, which equals to one of every three deaths in the United States. At the same year, 34% of deaths due to CVD occurred before the age of 75 years, about 4 years earlier than the actual average life expectancy.[1] Among all CVD cases, CAD killed 379,559 Americans in 2010, about 50% of diseases mortality or 1 of every 6 deaths. Although the death rate related to CVD were declined up to 31% from 2000 to 2010, the burden of the diseases remains high.[1] In Canada, about 32% of deaths were caused by CVD, in which 54% related to CAD, 25% myocardial infarction and 20% stroke. In Europe, CVD caused over 4.3 million death each year with CAD as a main form accounting to almost 50% of CVD's mortality.[2] Treatment of CAD has been revolutionary evolved within the last decades from the old fashion of open heart surgery to the use of minimally invasive stenting procedures. This papers presents a focused review on the development of biodegradable metals for stents, discusses the rationale, present current progress and highlights concern on biocompatibility issues.

2. REVOLUTIONARY TREATMENT FOR CAD

Figure 1 summarizes the evolution of CAD treatment that are all performed to open blocked coronary arteries and to restore arterial blood flow to the heart tissue without open-heart surgery. Percutaneous transluminal coronary angioplasty (PTCA), known as balloon angioplasty, was considered as the first revolutionary technique. A guidewire, a special catheter is inserted into the coronary artery and past the blockage in the artery, the balloon mounted on the catheter tip is then inflated, compresses the fatty tissue and makes a larger opening inside the artery for improved blood flow.[3] However, its high

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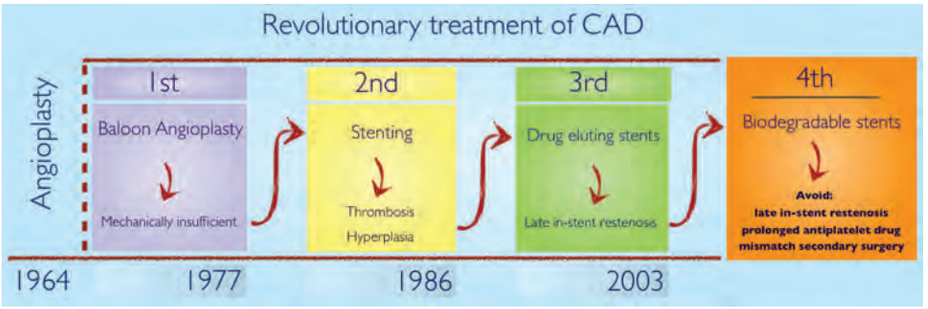

Fig. 1. Revolutionary treatment of CAD.

re-occlusion (restenosis) rate of the treated artery (30–40% within six months)[4] led to the second revolutionary treatment of percutaneous coronary intervention (PCI) or stenting.

Nowadays, coronary stents are almost universally used in PCI procedures.[5] A stent is a tiny, expandable metal coil that is inserted into the newly-opened area of the artery to help keep the artery from narrowing or closing again. The third revolution emerged in response to high incident of thrombosis and hyperplasia with metal stents where the rate of in-stent intimal hyperplasia was reported to reach 20–30%.[6] Anti-proliferative drugs were coated onto the stents leading to the development of drug eluting stents (DES). The first generation of DES constitutes either sirolimus or paclitaxel as antiproliferative drugs and biodegradable polymers as coating on metal stents. Apart of their astonishing first impression, first generation of DES was associated with complications due to very late stent thrombosis that occurs between 0.36–0.6% per year to at least 2 years after DES implantation,[7] impaired endothelialisation leading to blood clotting onto stent struts,[8] and polymers-induced hypersensitivity inducing localized vascular inflammation and apoptosis of smooth muscle cells.[9] Second generation of DES used limus drugs and more biocompatible polymers such as phosporylcholine (a natural component of cell membrane). Nonetheless, DES was found to trigger late stent thrombosis due to denudation once the coating washed away.[10,11] Lately, with the forth revolution was on its way with the introduction of biodegradable stents. It is expected to be disappeared once the arterial remodelling has been completed, thus avoiding chronic disadvantages.[12,13] Degradation could constitute an advantage for stent material while it was considered to be a disadvantage in permanent metal stents. It will lead to the elimination of the implant, which could relate to the temporary need of coronary artery stent. When a stented artery remodeling is completed, there are little reasons for the stent to permanently remain. This new paradigm has led the idea of biodegradable stents. The use of biodegradable stents could solve some problems associated with DES mostly the late stent-thrombosis since the stent would completely disappear from the artery.

3. EMERGING BIODEGRADABLE METALS FOR CORONARY STENTS

Biodegradable stents can be fabricated from biodegradable polymers or biodegradable metals. In this article, we focus on biodegradable metals that are defined as metals expected to degrade (corrode) gradually *in vivo*, with an appropriate host response elicited by released corrosion products, then dissolve completely upon fulfilling the mission to assist with tissue healing with no implant residues.[14] Up to date, magnesium, iron and zinc are the three class of metals proposed as biodegradable metals for biomedical applications.

3.1. Magnesium (Mg)

High allowable daily intake for Mg (about 400 mg/day; US FDA) makes the systemic cytotoxicity of Mg unlikely.[15] However, pure Mg is considered to be chemically reactive and to have poor mechanical properties for stent application. Hence, it is often alloyed with elements such as calcium (Ca), Zinc (Zn), strontium (Sr), zirconium (Zr), rare earth elements, and aluminum (Al) to decelerate its corrosion rate and to improve its mechanical properties.[16] Despite the wide variability of elements that have been alloyed with Mg, few are considered to have potentials pursuing all the way to the clinical stage. Among the most recent applications of Mg for stents is the use of Mg-6Zn alloy for common bile duct biodegradable stents and tested in rabbit model up to 3 weeks implantation period.[17] The *in vivo* experiments showed that Mg-6Zn stents did not affect several important biochemical parameters or harm the function or morphology of the bile duct, kidney, pancreas and liver, and therefore suggested that the alloy is a safe biocompatible for common bile duct. There were at least two latest reports on clinical studies of Mg stents. First, the Absorbable Metal Stent Implantation for Treatment of Below-the-Knee CLI (AMS-INSIGHT) clinical study involving 117 patients with 149 CLI lesions that revealed a comparable results between those treated with PTCA and PTCA + stenting and concluded that the stent's efficacy in long-term patency over standard PTCA in the infra-popliteal vessels was not evident.[18] Second, the Clinical Performance and angiographic Results of Coronary Stenting with Absorbable

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Metal Stents (PROGRESS-AMS) where 71 Mg stents were implanted in 63 patients and revealed that the stents can achieve an immediate angiographic response similar to that of other metallic stents and be safely degraded after 4 months.[19] However, all *in vivo* and clinical studies on Mg stents suggested the necessity to prolong degradation time.

3.2. Iron (Fe)

High blood Fe content (400–500 mg/L) and high allowable daily intake (up to 40 mg), which about the weight of the whole stent, make the toxicity of iron stent arguable.[4] Among the most recent application of iron for stents is the assessment of the safety and efficacy of Fe stents was conducted by a short-term implantation of Fe and Co–Cr (control) stents in the coronary arteries of juvenile domestic pigs.[20] The results showed that the intimal thickness, intimal area, and percentage of occlusion were better for the Fe stents which lead to a conclusion that Fe stents were relatively safe. Long-term implantation of Fe stents in the descending aorta of mini-pigs that showed no difference in the amount of neo-intimal proliferation between SS316L (control) and Fe stents, no sign of Fe overload or Fe-related organ toxicity as well as any evidence for local toxicity due to corrosion products.[21] Although iron has a comparable strength and ductility to those of stainless steel, its degradation rate is considered too slow for stent applications.[22,23] Slower degradation rate of Fe-based alloys within *in vivo* system is mainly caused by the appearance of passive layers (oxides or phosphates) that blocks further oxidation process.[24]

3.3. Zinc (Zn)

Zinc was firstly use as an alloying element for Mg. Its presence within the alloy was tolerable as such 50 wt% Zn in the alloy was still appropriate as a biodegradable implant. However, the use of Zn within the context of biodegradable implants is relatively new.[25,26] Zn-based alloys could preferable over Mg-based alloys since they can be fabricated by classical routes such as die casting and hot rolling. Moreover, they have lower melting point, lower reactivity, and superior machinability compared to those of Mg-based alloys. Zinc alloys with up to 3 wt% Mg was recently investigated for bone fixation applications.[26] More works have to be done on Zn-based alloys to confirm their suitability as biodegradable metals.

4. *IN VIVO* AND CLINICAL STUDY UPDATE ON BIODEGRADABLE METAL STENTS

In vivo models give superior understanding of biological responses towards implant materials compared to *in vitro* models. They consist of complex systems of cellular interactions, hormones, dynamic blood circulation, excretions, etc., which are absent within *in vitro* models leading false negative results. It was reported that a variety of polymers in powdered form were mildly toxic to mouse fibroblast cells which their proliferation rate was decreased. On the other hand, *in vivo* study showed moderate toxicity when the same materials were implanted intramuscularly in rat model.[27] Similarly, it has been reported that *in vitro* model of fibroblast and epithelial cells showed a higher number of materials which give growth inhibition compared to *in vivo* intramuscular rabbit model. It was then proposed that within *in vitro* model, the cells were not as dense as within an *in vivo* model. Thus the cells within *in vitro* model were particularly more vulnerable as the extent of cell–cell cooperation is at a minimum.[27]

Experimental cost and ethical issues of animal testing often hold down the development of *in vivo* models. Animal of choice often adds a particular consideration, as relevance to that of human system is important. Small animal models such as rodents and rabbits have the advantages being convenient and cost effective. However, despite the essential structural similarity of the vascular walls, their cardiovascular system is not considered to represent the same system in human. Thus, their biological responses within cardiovascular system will be different. Porcine appears to be a popular animal model to study the biocompatibility of cardiovascular stent materials due to its size and its capacity to implant in coronaries and atherosclerosis. Pure iron stents have been implanted in the coronary arteries,[20] descending aorta,[21] and iliac artery of the porcine model.[28] It was shown that iron-based material did not induce any significant neointimal proliferation, thrombosis, local tissue necrosis, or pronounced inflammatory responses up to 12-month implantation period although a compelling degradation of the stent strut was observed. Similar results were found in New Zealand White Rabbit model up to 18-month implantation period, confirming the potentials of iron as cardiovascular stent material.[29]

As seen in Figure 2, Fe was the first metal being implanted in animal model. Iron stents were implanted descending aorta of New Zealand white rabbit for 18 months. Despite comparable mechanical properties of Fe-based alloy to that of stainless steel, no human implantation has been reported up to now. Porcine is popular animal model since its cardiovascular system resembles to that of human.[16,21,29–37] Moreover, coronary artery and descending aorta are the most popular implantation sites in the porcine model. In contrast, Mg-based alloy stent has been implanted in human lower limb artery, pulmonary artery, aorta, and coronary artery. Similar to iron stent, porcine model is a popular model for Mg implantation.[21]

5. BIOCOMPATIBILITY ISSUES OF BIODEGRADABLE METALS

Biocompatibility assessment is mandatory in order to make sure that the materials for coronary stent fabrication will not promote an inflammatory response or systemic toxicity. The assessments include non-functional tests, in which

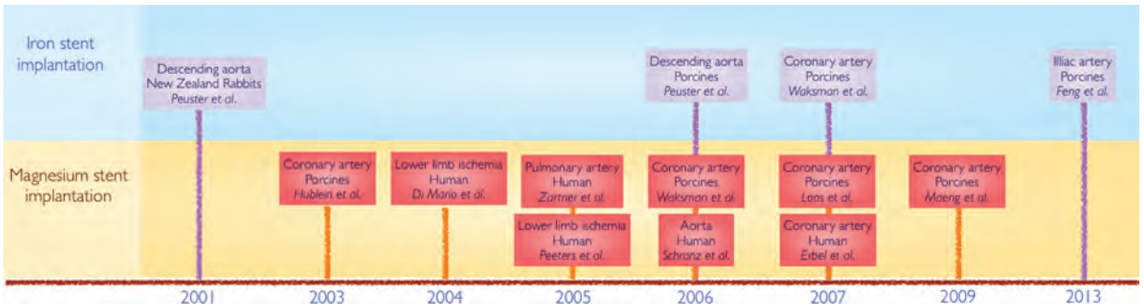

Fig. 2. Implantation of Fe and Mg stents in animal models and humans.

the materials have not fabricated into the stent yet; and functional tests, in which the materials are in the form of real stents and tested in the artery. In fact, non-functional and functional tests are compulsory since the beginning of the material development. This delicate work is required in order to provide proofs of safety to the regulatory agency such as FDA (Food and Drugs Administration of USA) and to the patients prior to release to the market.

Biocompatibility is a compulsory requirement for today's implants. It refers to the ability of a material to perform a particular function within living tissues and is followed by appropriate host responses, minimum inflammatory and toxicity reactions both locally and systematically. Nowadays, stainless steel or Chrome–Cobalt or Nickel–Titanium are known as golden standard for metallic materials for cardiac stents. Therefore, available standards to assess the biocompatibility are all attributed to corrosion resistant materials. As biodegradable metals are now considered as a potential future for cardiovascular stent application, assessment standards need to adopt these metals. Guidelines for biocompatibility assessment of new candidate implant materials are provided by the ISO (International Standard Organization) as guided by ISO-10993 part 1–20 and ASTM 1983.[38] The tests consist of *in vitro* and *in vivo* assays with respect to cytotoxicity, hemocompatibility, mutagenicity, hypersensistivity, genotoxicity, carcinogenicity, sensitivity and systemic effects as depicted in Figure 3.

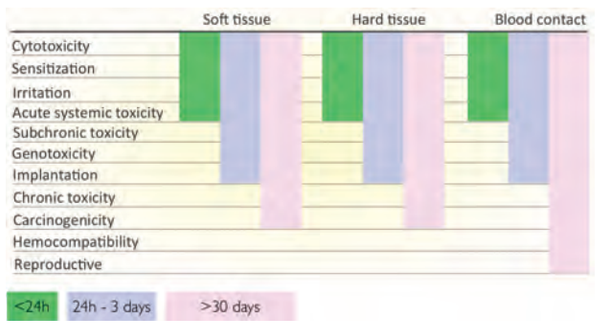

Fig. 3. Common testing requirements for corrosion resistant materials based on ISO 10993 and ASTM 1983 standards. Adapted from.[39]

Those assays are devoted for corrosion resistant materials and are not specifically addressed to assess biodegradable metals. Moreover, the year that the guidelines were made, 1983, is considered to be no longer suitable with materials development nowadays. However, they have potentials to be used to assess biodegradable metals. Biocompatibility tests of biodegradable metals have to take into account the release of metallic ions as degradation products. The release of metal ions creates imbalance charges or oxidative stress and could form complexes with metal chaelators prior to the formation of reactive oxygen species.[40] Its presence is closely related to DNA damage which can lead to cell death or cellular over proliferation. These toxicity events can be attributed to the alteration of genetic regulation inside the cells due to the released metal ions. Therefore, genetic regulation might play an important role in dealing with the degradation products.

Detrimental effect of degradation products could be strong enough to damage cells and may be easily observed morphologically. This is what the conventional methods are most likely able to do. In a particular case, detrimental effect of the degradation products could be invisible morphologically even though the cells are internally disturbed. The disturbance may stay inside the cells during a certain time and eventually will lead to severe chronic damage. For this, the conventional methods to assess the biocompatibility of biodegradable metals need to be adjusted in a way that continuous release of degradation products is taken into account. Assessing the biocompatibility of biodegradable metals can be performed through the basic mechanisms of cellular response towards degradation products as foreign materials. Altered cellular behaviour driven by the genetic regulation can be used as a new approach to investigate the biocompatibility of biodegradable metals. Therefore, it enriches the conventional methods with more sensitive detection limit towards the cellular state in the presence of the degradation products. Hence, chronic damages can be predicted.[41]

5.1. CONCLUSION

The application of biodegradable metals for coronary stents constitutes a great potential to revolutionize the

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next treatment for coronary artery disease. As the diseased artery is fully recovered, there is no logical reason for the stent remains in the artery. And as the biodegradable metal stents disappear after fulfilling its mission, late stent thrombosis, impaired endothelialisation, and prolonged antiplatelet therapy are mostly unlikely. However, although the excitement of this field is high, especially in industry, one should recognise that the fact that the lack of correlation between *in vitro* and *in vivo* studies, as well as the limited number of *in vivo* and clinical studies reported in literature represent major limitations for the development of the field. And suggest major challenges to be fulfilled by scientists at both academic and industrial level, including designing alloys with predictable degradation time as a function of the application, developing imaging techniques for the *in vivo* and eventually clinical monitoring of material degradation *in situ*, and assessing unequivocally the destiny of the degradation products and its effect on the physiology and more generally body functions.

Disclaimers

The authors confirm that the present article contains our original views and not related to an official position of the institution.

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