Limitations and challenges of magnesium alloy stents.

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Abstract. Magnesium is a biomaterial that was already used in the past, but its usage as cardiovascular stents is very new in the market. As a result, there are still limitations on its usage. After extensive research, the main problems identified with these types of alloys were linked to the fact that there are still not enough studies on this novel stent. Its fast degradation is associated with biocompatibility issues, which is still discussed. The formation of hydrogen gas, magnesium ions and magnesium hydroxide as it degrades have been proven to be disadvantageous, since it has been linked to the formation of gas pocket and the alkalinization of the local tissue, which makes it difficult for new cells to adhere. The mechanical properties of magnesium are also known to be poor, and although there are a lot of modifications that can be made to tackle these issues, they are usually in detriment of another important characteristic and hinders the manufacturing and quality control process. Magnesium has low tensile strength and ductility, making it a brittle material for stent making. The poor scaffolding properties results in the need of a thicker wall strut, which can cause repeat revascularization and severe vessel lumen loss. The fast and heterogenic corrosion and mechanical profile also makes its long-term efficacy questionable. There is still no identification of the risk factors and lesion types it is able to treat.

Keywords: Magnesium alloy, stent, degradation, biocompatibility, mechanical properties, long-term

1. Introduction

The main purpose of a vascular stent is to be inserted through a delivery system into a person's narrowed lumen and expand, providing support for a better blood flow. It is a very efficient treatment for vascular diseases due to it being minimally invasive, effective, and safe [1]. Stents can be made of biodegradable materials or biostable materials, being either made of polymers or metals. Every material has different properties and limitations that define a stent's surface characteristics, mechanical properties and hemocompatibility and biocompatibility [2]. In order to make a stent as ideal as possible, its materials can be mixed either as alloys, to change the bulk properties, or as coatings, to change the surface properties [3].

The three main biodegradable metals used as stent materials are zinc, iron and magnesium, and the latter is the fourth more abundant element in the human body [4]. Magnesium is a third-generation biomaterial, meaning it has started being used only in this century [5]. During this time, it has had previous success in orthopedic implants [6], but the application in cardiovascular stents is even more recent. It is well known that the mechanical and corrosion properties of pure magnesium, specifically its low ductility, low strength, low elastic modulus and its degradation in vivo makes it a poor material on its own [2,7]. However, due to not being toxic and its biodegradable properties, it is a promising material in stent-making. Recent studies show an increase of magnesium alloys' applications in other biomedical implants with temporary functions, namely vascular stents, with increased approval in some markets[8,9]. In comparison to biostable bare metal stents, magnesium alloy stents have proven to be better in terms of reducing smooth muscle cell growth, thrombosis, in-stent restenosis, chronic inflammation reactions and other negative side-effects [10,11].

Even though a large number of experiments delivered promising results, it is well known that there needs to be more research into that, given that there still is discussions regarding certain topics, mainly biocompatibility. Research is also need in areas regarding long-term efficacy and patient selection. There's also the development of new methods to correct early corrosion and better the mechanical properties, and, even though they haven't been extensively tested, they show promising results.

2. Objective

To review research and analyze and compile information regarding the obstacles of employing magnesium alloy stents.

3. Research Methods

It was identified that the main limitations for magnesium were due to its degradation. From there, other problems were considered as consequences of this property: biocompatibility, mechanical properties and long-term safety and efficacy. Lastly, final parts considered as relevant were added to this discussion: manufacturing and patient selection.

Utilizing publication databases such as Science Direct [Elsevier], PubMed, Springer Link and EBSCO Host and citation and abstracts databases such as Scopus and Web of Science, the articles relevant to each topic were searched using the keywords in English.

4. Results and discussion

It is possible to note that the main difficulties in employing magnesium during the manufacturing of stents are:

4.1 Degradation and biocompatibility

Rapid degradation is still a limitation in magnesium-based cardiovascular alloys. Since it produces micro-debris and releases ions that may lead to adverse reactions such as inflammation and the prevention of the growth and adhesion of cells on the surface [11], its biocompatibility is still discussed. The fast corrosion could also lead to a premature loss of its mechanical properties.

It is known that the electrolytic physiological environment in which the magnesium stents are employed is not advantageous. When compared to other biodegradable materials such as iron and zinc, magnesium has the lowest electrode potential. This means that in vivo conditions, where there's an abundance of Cl-, this metal degrades quickly [12]. In addition, the pH value of human blood is a strong catalyst for the corrosion of Mg alloys.

The chemical reaction that best describes its deterioration is [13]:

$$Mg+2H_2O \leftrightarrow Mg[OH]_2 + H_2 \qquad [1]$$

Which can be studied as the following partial reactions [14]:

$$Mg \rightarrow Mg^{+2}+2e \qquad [2]$$

$$2H_2O+2e \rightarrow 2OH^{-}+H_2 \qquad [3]$$

$$Mg^{+2}+2OH^{-} \rightarrow Mg[OH]_2 \qquad [4]$$

It is possible to see that one of the products of corrosion is hydrogen gas [H_2]. The impacts of a high concentration of this gas are still being discussed as a risk. The equation [1] shows that about 1 L of hydrogen gas can be produced by only 1g of pure magnesium. This high quantity of gas causes its accumulation in tissue cavities once the diffusion and solubility of hydrogen in the local tissue stops [15]. Its cells suffer a disturbance due to the fast rate at which the gas is produced, and a subcutaneous emphysema is formed, which can also cause discomfort [5]. Furthermore, these gas pockets cause separation of the tissue layers, which will delay the healing process and can lead to necrosis. The formation of the pockets decreased the survival rates of rats used for an in-vivo experiment and, if the gas bubbles are large, there is also a risk of it blocking the bloodstream and killing the patient [16].

On the other hand, it is defended that the hydrogen evolution is not a major problem [17]. The gas bubbles that were formed after implantation disappeared 2-3 weeks after surgery and the accumulation of gas could be sometimes punctured out with a syringe with no greater risks [14]. In addition, by knowing that the tolerated hydrogen evolution rate is 0.01 $ml/cm^2/day$, it is possible to choose an adequate alloy or provide treatments to reduce this rate in alloys that produce more hydrogen than that.

Moreover, in the equation [2], it is possible to see the formation of Mg^{+2}, which has been linked to negative stimuli for the cells when in high concentrations[18]. Part of the magnesium ions, which are soluble, also transforms into magnesium hydroxide ($Mg[OH]_2$), which is alkaline and is not water-soluble, as described in equation [4]. Even though the body can adapt to higher levels of pH up to a certain level, an increase in the pH levels in the environment, together with the high concentration of Mg ions, makes it more difficult for cells to adhere [11]. On one hand, this is positive since it hinders on-stent thrombosis, but it can also make it difficult for growth cells to adhere.

As said beforehand, the presence of Cl ions also contributes to de stent's corrosion, as can be seen in the following equations[6]:

$$Mg+2Cl^{-} \rightarrow MgCl_2 \qquad [5]$$

$$Mg[OH]_2+2Cl^{-} \rightarrow MgCl_2 \qquad [6]$$

The product, magnesium chloride, is highly soluble in water and poses no threats to the patient's health.

4.2 Mechanical properties

Compared to other materials, magnesium is not considered the best to be used in stents due to its mechanical properties. As shown in Table 1, it's Young's Modulus [19] is the lowest of them all, it is soft and has a low tensile strength. They also exhibit a lower compression resistance. These factors make it necessary for the stents to be thicker in order to provide the necessary support. This causes an increase in the area of metal-artery interaction, which is linked to higher chances of myocardial infarction and late thrombonic restenosis. Even though it can be mixed with rare earth metals to allow it to have thinner struts [20], there are complications that arise with these modifications. In addition, with a fracture toughness of 15-40 $MPa \cdot m^{1/2}$ and low ductility, it makes a very brittle material to be used as a stent.

A lot of adaptations can be made to better the mechanical properties of the stent. These modifications are usually related to shape optimization, alloying, coating and other treatments such as hot working, but they are generally very new and require more intensive research and testing.

Table 1 - The average of the mechanical properties of different metals used for stent-making. The Mg alloy used in this table is WE43 [2].

Metal	Elastic/ Young's modulus [GPa]	Yield strength [MPa]	Tensile strength [MPa]	Density [g/cm^3]
Mg alloy	44	162	250	1.84
316L SS	190	331	586	7.9
Pure Fe	211.4	135	195	7.87
Ta	185	138	207	16.6
Cp–Ti	110	485	760	4.5
Co–Cr	210	548	1085	9.2

4.3 Long-term safety and efficacy

Even though magnesium has been used as a biomaterial for years, its usage as a stent is still something new. It has been recorded that pure magnesium wires were used as ligature as far back as 1878 [5], and, as an implant, its most famous usage is for orthopedic implants [6]. However, the studies of magnesium alloys as cardiovascular stents are still few.

Due to early signs of vessel recoil and restenosis, it has been determined that its deterioration may be too rapid for the body to be able to complete the healing process. A pilot study conducted by Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents [PROGRESS AMS] showed that 12 months after the implantation of magnesium cardiovascular stents, there were no reports of death, acute myocardial infarction or thrombosis, and the vessel attained vasoreactivity within 4 months. However, together with the rapid degradation, the recoil and low radial strength caused an incidence of 45% of repeat revascularization [20] and severe vessel lumen loss [21].

It is not a doubt that magnesium stents are far more efficient than permanent stents in terms of reducing thrombosis, restenosis and hypersensitivity reactions [22–24], but the alkaline environment created by its degradation has proven to hinder surface endothelization after the implantation, which can cause long-term complications [11].

In addition, it was recorded a loss in its long-term efficacy due to its poor scaffolding abilities [26]. The irregular expansion and crimping cause an uneven stress concentration [27] and residual stress distribution [28], and it is aggravated by its fast degradation process [21].

4.4 Manufacturing and quality control

There are several ways to enhance a property of magnesium alloys in order to make them more efficient. It is possible to purify the stent, alloy it or coat its surface [16] or put them through other treatments. However, these modifications usually include a downside, usually being the acceleration of the corrosion process. For example, the addition of heavy rare earth elements allows a better resistance, and methods that better its strength also contribute to a faster degradation [12].

Similarly, to elevate the corrosion resistance of magnesium, it is possible to add beneficial alloy elements such as Ca, Mn, Y, Zn, Sn, Sr, Zr, etc. and reduce the amount of harmful elements [Co, Ni, BA, Cd, Al, etc.], creating binary, ternary and quaternary magnesium alloys that maintains the mechanical properties. Nonetheless, these elements are not able to improve magnesium biocompatibility and can even lead to a toxic product of degradation [13] and won't be able to resolve the fast degradation process in vivo. In addition, the process needed to form these alloys is complicated and special equipment is needed. The quantity of each alloy element must be restricted to a certain range, although it is very difficult to control it with precision [11].

Additional problems require a controlled environment for the fabrication of these stents. An example is the fact that molten magnesium oxidates very quickly, and Mg powders are very pyrophoric, which restricts and complicates its fabrication.

Another challenge is to study how to best preserve the stents' structure while it degrades. The main corrosion patterns in magnesium alloys are uniform corrosion, stress corrosion and pitting corrosion. With that in mind, the design and scaffolding pattern of the stent must be made in order to withstand these non-uniform changes [26]. There were a few successful shape optimizations that proved to be efficient throughout the corrosion process [28].

In sum, to control its corrosion or mechanical properties, a lot of processes can be done. This means every stent can and must be highly customizable to ensure the best results.

Unfortunately, it is very difficult to ensure consistent quality when the factors of its manufacturing can and must change constantly.

On the other hand, magnesium is a metal considered to be very versatile and easy to machine by high-speed milling and turning [29] and has a high castability when compared to other metals. When compared to polymers, its superior mechanical properties due to their metallic nature, higher thermal conductivity and the fact that it is recyclable puts it at preference [12]. It is also a relatively cheap option compared to the other materials, such as aluminum [30].

4.5 Patient selection

Lastly, there needs to be more research to determine which patients would benefit more from magnesium stents when compared to permanent stents.

The fact that magnesium is a biodegradable metal is very positive for children and adolescents since their blood vessels continue to grow as they mature [31]. There is also no need for redilation and later surgical removal. These factors were decisive to the success of the implantation of a magnesium stent as a treatment for a baby with congenital heart disease [32,33]. However, there was also a case in which the implantation wasn't successful for another baby with the same profile [2].

There were studies on the use of magnesium alloys to treat heart disease in adults as well. Although the results seemed promising, the number of patients were very small, and don't allow a definitive conclusion to the efficacy of this intervention[34]. Another study with patients with acute coronary syndrome showed that magnesium alloys presented much more late lumen loss than permanent metal stent [35], as well as an early scaffold dismantling, which caused late-stent thrombosis and a heterogenous neointimal tissue and an increased death risk [36].

In adults, magnesium alloys have proven to be very effective in treating patients with critical limb ischemia [37].

It is possible to conclude that there is still no extensive research capable of identifying the best patients for this intervention. There is minimal identification of risk factors. Although certain types of lesions showed promising results, other diseases, such as acute coronary syndrome, proved to have inconsistent results after treatment. Pediatric patients are also thought to be the ones that are the most appropriate for these stents, but the few researches made on this area were inconclusive.

5. Conclusions

In conclusion, the main impediments in the usage of magnesium alloy stents are due to how new they are in the market. Its main problems are rapid degradation and consequent discussions on its biocompatibility, which is still considered by some as being poor. This, in combination with the poor mechanical properties of the material brings non-consistent results regarding long term efficiency.

Moreover, the stent may undergo several treatments to tackle certain problem areas, but these modifications often bring negative consequences. This hinders its manufacturing, that is already difficult due to the alloy elements control, controlled environment and other numerous mandatory customizations the stent must undergo.

Numerous other factors need to be determined through extensive research, such as preferred patient profile, risk factors and how effective the treatment is with certain age and lesion type.

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