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Review

Current status on clinical applications of magnesium-based orthopaedic implants: A review from clinical translational perspective

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ABSTRACT

As a new generation of medical metallic material, magnesium (Mg) and its alloys with or without surface coating have attracted a great deal of attention due to its biodegradability and potential for avoiding a removal operation after the implant has fulfilled its function for surgical fixation of injured musculoskeletal tissues. Although a few clinical cases on Mg-based orthopaedic implants were reported more than a century ago, it was not until recently that clinical trials using these implants with improved physicochemical properties were carried out in Germany, China and Korea for bone fracture fixation. The promising results so far suggest a bright future for biodegradable Mg-based orthopaedic implants and would warrant large scale phase II/III studies. Given the increasing interest on this emerging biomaterials and intense effort to improve its properties for various clinical applications, this review covers the evolution, current strategies, and future perspectives in the development of Mg-based orthopaedic implants. We also highlight a few clinical cases performed in China that may be unfamiliar to the general orthopaedic community.

1. Introduction

1.1. The drawbacks of current commercialized medical devices in orthopaedic field

Musculoskeletal disorders are the most prevalent health problems in human that seriously affect the quality life of the patients. Due to demographic changes, the number of elderly suffered from musculoskeletal disorders is growing rapidly, and this phenomenon will persist [1]. Biomaterials are commonly used in orthopaedic surgeries as bone substitutes, fixatives and stabilization devices for fractured bones, ligament and tendon repair and total hip arthroplasty (THA) [2]. Currently, permanent metals with good mechanical strengths and biocompatibility, including stainless steel (SS), titanium (Ti) alloys and cobalt-chromium (CoCr) alloys, have been widely used in orthopaedic field [3,4]. However, their limitations include stress shielding which induces re-fracture and may compromise the bio-efficacy of these inert metallic devices, especially in patients with osteoporotic fractures [5–7]. More importantly, a second surgery will be often required to remove the implanted hardware to avoid potential adverse effects after fracture healing [8]. To seek for novel biomaterials for orthopaedic devices, biodegradable polymers, e.g. polylactide (PLA), polyglycolide (PGA) and co-polymers, have gained increasing attention. These polymers have suitable mechanical properties close to cancellous bone, degradable behavior in the human body, and compatible diagnostic imaging for healing assessments [9], so they have great potential in replacing the current permanent devices in low-load bearing fracture sites. The current list of the US Food and Drug Administration (USFDA) approved polymer products with biodegradation properties for orthopaedic applications include poly(L-lactic acid) (PLLA), poly(glycolic acid)(PGA) and their copolymers poly(lactic-

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co-glycolic acid)(PLGA) [10,11]. However, surgery failure may occur when using these polymer based devices as a result of their insufficient mechanical strength or brittleness. More seriously, the by-products of these polymers can induce long-term inflammatory responses in peri-implant tissue [12]. Furthermore, the complete degradation of polymer devices may not encourage osseous ingrowth from long-term clinical observations [13]. Therefore, it is crucial to develop a new generation of medical metallic materials that are biodegradable, biocompatible, and does not affect bone ingrowth after surgical implantation.

1.2. The advantages of Mg based implants over standard counterparts

One of the main advantages of magnesium (Mg) based implants over standard permanent metal implants is its biodegradability. Mg can degrade via corrosion, which originates from its standard electrode potential of −2.372 V versus normal hydrogen electrode (NHE). A metal with such a low standard electrode potential can corrode in aqueous solutions via the formation of magnesium hydroxide ($Mg(OH)_2$), and equivalent mole of hydrogen gas (H_2) [14]. The intermediate corrosion products can either be absorbed or metabolized in the form of Mg^{2+} by reacting with Cl^- ions in the body fluid or digested by macrophages [15,16]. In addition to its biochemical features and functions, Mg possesses appropriate mechanical strength that is close to cortical bone, which may address concerns on re-fracture or unsatisfactory healing outcome at the fracture site by reducing stress shielding [17]. More importantly, Mg implants have been widely reported to positively stimulate new bone formation, which is beneficial to bone fracture healing [17]. In conclusion, Mg based orthopaedic devices seem possible from the mechanical and biological points of view, given the corrosion of the device can be controlled *in vivo* [6,18].

1.3. The research history of Mg as orthopaedic implant biomaterials in translational medicine

This part is intended to review the history of biodegradable metal Mg developed for orthopaedic applications [19]. The first clinical study using Mg materials as orthopaedic implants can be dated back to more than 100 years ago (Fig. 1). In 1900, Payr introduced the idea of using Mg plates and sheets in joint arthroplasties to regain or preserve joint motion for the very first time [20], even though Lambotte might have performed studies on Mg implants in dogs yet without reporting in the academic community due to unsatisfactory treatment outcomes. In 1906, Lambotte conducted a trial to repair bone fracture in human using Mg plate and iron screws [21,22]. Unfortunately, this combination of metals led to rapid corrosion of Mg plate due to the electrochemical reaction, so a revision surgery had to be performed in the patient as a result of insufficient stabilization. Lambotte also performed studies using Mg nail alone to fix supracondylar fractures in 4 children and observed a total restoration of joint function without any complications. Although the high initial corrosion led to formation of gas cavities, these cavities slowly disappeared after several weeks. The formation of gas cavities with fast corroding Mg implants has been negatively commented by physicians, but these cavities had no detrimental influence on the final clinical outcome. Verbrugge treated a diaphyseal humeral fracture in a child using Mg plate and screws. Three weeks later, the Mg plate almost completely degraded and the bone fracture line was no longer visible [23]. Around 1938, McBride conducted a series of trials on exploring the potential clinical applications of Mg products [24]. According to the corrosion characteristic of Mg, he designed several operation techniques which were adapted to the use of Mg implants. In addition, he believed that Mg implants were more appropriate to be used as fixation devices for autogenous bone graft. In 1940, Maier used pins made of spindle-shaped Mg sheets to fix two humeral fractures in humans [25]. The healing process was uneventful in the first patient; however, the implant had to be removed at 12 days after surgery in the other patient due to a continuous formation of gas cavities. In both cases, Maier observed good functional results after 14 years. In 1948, Troitskii et al. reported successful treatments of 34 cases of pseudarthrosis with a plate and screw combination made of an Mg–Cd alloy [26]. The complete degradation of Mg implants was successfully replaced by newly formed bone tissue. As the degradation of Mg metals can produce OH^- ions and subsequently lead to an increase in pH in the microenvironment, Troitskii et al. stated that the implantation of Mg into inflammatory tissues might lead to a neutralization of an acidic environment, and would thus positively stimulate the formation of fracture callus and facilitated in faster recovery in patients with osteomyelitis after implantations of Mg-based devices [23,26,27].

Although Mg based implants showed potential in surgical treatment of musculoskeletal diseases, more efforts have to be made for modification of Mg based orthopaedic devices prior to their applications in large-scale clinical trials due to the concerns of their poor corrosion resistance. Therefore, to develop Mg based devices with appropriate degradation rates remains a challenge.

2. The performance characteristic of Mg or its alloys as orthopaedic implants

Mg is the fourth most abundant cation in the human body, with approximately 1 mol (between 21 and 35 g) stored in the body of a healthy 70 kg adult [17,28–31]. Over half of the total physiological Mg is stored in bone, while 35–40% of Mg is found in soft tissues and less than 1% in serum [32,33]. In addition, Mg is the second most abundant intracellular divalent cation, which is involved in 300 known enzymatic reactions [31,34]. Apart from its important reaction with adenosine triphosphate (ATP), Mg plays important roles in protein and nucleic acid synthesis, the mitochondrial activity and integrity, ion channel modulation, plasma membrane stabilization and translational processes, as well as many other cellular functions [17].

2.1. Mechanical properties of Mg based implant materials

As shown in Table 1 [4,17,35,36], Mg and its alloys possess excellent and comprehensive mechanical properties. For example, Mg has a higher mechanical strength than biodegradable polymers while much lower modulus than permanent metals. As compared to bioceramics, Mg shows higher toughness. These indicate that Mg and its alloys may be suitable for developing into orthopaedic fixators in low load-bearing sites to prevent mechanical failure imposed to the implants and address concerns on potential stress shielding effects.

2.2. Chemical properties of Mg-based metals

Mg metals are known to degrade in aqueous environments via an electrochemical reaction, which produces $Mg(OH)_2$ and H_2. $Mg(OH)_2$ is deposited on the Mg matrix as a corrosion protective layer in water, but when the chloride ion (Cl^-) concentration in the corrosive environment reaches above 30 mM [37], $Mg(OH)_2$ starts to convert into highly soluble magnesium chloride ($MgCl_2$). Therefore, a continuous corrosion can be observed on Mg *in vivo* where the chloride content of the body fluid is about 150 mM [38–40]. The corrosion mechanism of Mg metals in aqueous condition could be demonstrated by following chemical reactions [14]: