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ORIGINAL ARTICLE

Preclinical investigation of an innovative magnesium-based bone graft substitute for potential orthopaedic applications

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Summary Degradable or corrosive biometal is an attractive research and development (R&D) area in clinical orthopaedics. This study was designed to investigate biomechanical and biological properties of magnesium (Mg) and strontium (Sr) with a focus on Mg-based metals, including pure Mg and Mg–xwt% Sr ($x = 0.25$, $x = 1.0$, $x = 1.5$, $x = 2.5$) alloys, as potential bone graft substitutes in respect to their mechanical strength, corrosion resistance, and cytocompatibility for further optimization and establishing indications for relevant *in vivo* applications. Our data showed that the tensile and compressive strength increased with addition of Sr because of the $Mg_{17}Sr_2$ precipitation strengthen. Compared with commercially used bone graft substitutes, the mechanical properties of Mg–Sr alloys were close to those of cortical bone, and the compressive strength could reach 300 MPa, suggesting its potential application for load-bearing bone as bone defect filler. The corrosion rates of Mg–xwt% Sr alloys were controlled in the range of 0.05–0.07 mm/y, indicating feasibility of bone grafting and the *in situ* bone repair process. Moreover, Mg–Sr alloys also exhibit good cytocompatibility and antibacterial properties. Our innovation presented in this work supported *in vivo* clinical indication-based assessment of biodegradable Mg-based metals that could be potential candidates for bone graft substitutes for future orthopaedic applications.

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Introduction

The healing of bone fractures is a physiological process that results in bone union [1]. However, significant bone defects caused by a high-energy traumatic event or large bone resection may require bone grafting in order to fill the defects and provide support for biological repair of the defect. Bone grafting is a common surgical procedure, performed in approximately 10% of all skeletal reconstructive surgery cases [2]. It has been estimated that 2.2 million grafting procedures are performed worldwide each year [3,4].

The bone graft substitutes are characterized as a spectrum of products that have various effects on bone healing. The perfect bone substitute should be osteoconductive, osteoinductive, osteogenetic without risk of transferring infectious diseases, readily available, manageable, biocompatible, and bioresorbable [5]. Moreover, from a mechanical point of view, bone substitutes should have mechanical strength similar to that of the bone for replacement.

The gold standard for restoring bone defects has long been considered to be autologous bone grafting. However, donor-site complications have been shown to occur, clinical benefits are not guaranteed, and there is a high rate of associated complications [6]. Large amounts of alternative bone-graft substitutes are currently commercially available for orthopaedic use. Main products are made with calcium phosphate ceramics [hydroxyapatite (HA) and tricalcium phosphate (TCP)], calcium sulfate ($CaSO_4$), bioactive glasses, and biological/synthetic composites. They vary in composition, mechanical action, and special characteristics. The disadvantages encountered with those materials in clinical settings include low and unpredictable resorption, poor mechanical properties, and limited ability of osteoinduction [7,8].

Magnesium (Mg) and its alloys are promising novel metals as orthopaedic implants because of their satisfactory mechanical properties, attractive biological performance as well as their biodegradability *in vivo* [9]. In addition, the stress shielding effect might be avoided because the moduli of Mg and its alloys are closer to those of cortical bones [10]. Currently, the vascular stents and orthopaedic implants are two dominant medical applications for biodegradable Mg-based alloys. The advancement in tailoring controlled degradation rate, excellent mechanical property, and osteopromotion [11] inspire the development of the Mg alloys as potential bone graft substitutes.

Strontium (Sr) has been recently reported for its use in medical applications [12]. Sr is a component of human bones, and its role in bone is known to promote the growth of osteoblasts and prevent bone resorption [13]. Brar et al. [14] studied Mg—xwt% Sr ($x = 0.5$, $x = 1.0$, $x = 1.5$) alloys and found the lowest biodegradation rate in the Mg—0.5Sr alloy. Gu et al. [12] reported the Mg—Sr binary alloys with 1—4 wt% Sr and proved as-rolled Mg—2Sr alloy possessed the best combination of corrosion resistance, high strength, and *in vivo* biocompatibility.

As previously mentioned, pure Mg and Mg—Sr alloys were found to have combining properties of degradability, excellent mechanical properties, and biocompatibility, which may meet the clinical requirement for potential application for bone defect repair. Thus, in this work, the performance of pure Mg and Mg—Sr alloys with wt% Sr varying between 0.25 and 2.5 were studied as alternatives for bone substitutes. The mechanical and degradation properties of Mg-based metals were also compared with commercial products such as $CaSO_4$, HA, and β-TCP as positive controls. Such design would provide a solid basis for its translation toward further research and development (R&D) in establishing clinical indications for our Mg-based scaffold materials.

Materials and methods

Materials preparation

In the current study, pure Mg (99.9%) and Mg—Sr alloys were studied as the potential Mg-based bone graft substitutes. The binary Mg—xwt% Sr ($x = 0.25$, $x = 1.0$, $x = 1.5$, $x = 2.5$) alloys were fabricated using pure Mg (99.9%) and a Mg—30wt % Sr master alloy in a high-purity graphite crucible under the protection of a mixed gas atmosphere of SF_6 (1 vol%) and carbon dioxide (CO_2), (balance). The melting was held at 730°C for 30 minutes and stirred with a graphite rod. The melt was then poured into a steel mold preheated to 300°C. The binary Mg—Sr alloys were encapsulated in quartz tubes under vacuum for homogenization treatments at 500°C for 20 hours and quenched in water. The as-cast ingots were hot extruded into bars with extrusion ratio of 64:1 at 390°C. The as-extruded pure Mg was prepared following the aforementioned procedure. The samples were cut into pieces with dimensions of $\Phi 10 \times 2\ mm^3$ for microstructure characterization, corrosion experiments, and cytotoxicity tests. All samples were grounded with SiC paper up to 2000 grit, followed by ultrasonic cleaning in acetone, absolute ethanol, and distilled water for 10 minutes each and then sterilization with ethylene oxide. To compare the performances of bone substitutes, the $CaSO_4$ (Osteoset, Wright Medical Technology), HA (Pro-Osteon, Biomet Osteobiologics), and β-TCP (ChronOS, Synthes) were studied as the controls in this work.

Compositional analysis and microstructural characterization

The chemical compositions of the alloys measured by inductively coupled plasma atomic emission spectrometry (ICP-OES, Optima 7300DV, PerkinElmer, MA, USA) are listed in Table 1. The nominal composition of strontium content was designed in a range of 0.5—4.0 wt%; however, because of the high burning loss rate of Sr during the melting process, the actual composition was 0.25, 1.0, 1.5, and 2.5wt% Sr. The samples ($\Phi 10 \times 2\ mm^3$) for microstructural characterization were etched using acetic picral solution. The microstructure of the prepared samples was investigated

Table 1 Chemical composition of the Mg—Sr alloys (wt%).

Nominal composition	Mg—0.5Sr	Mg—1.5Sr	Mg—2.5Sr	Mg—4.0Sr
Actual Sr contents (wt%)	0.25	1.0	1.5	2.5

Mg = magnesium; Sr = strontium.