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Novel strategy for mechanically tunable and bioactive metal implants

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ABSTRACT

Metals have been used as biostructural materials because of outstanding mechanical reliability. However, low bioactivity and high stiffness in biological environments have been major issues of metals, causing stress shielding effects or foreign body reactions after implantation. Therefore, in this study, densified porous titanium has been introduced to achieve comparable mechanical properties to hard tissues and bioactivity that promote a better interface between the implant and bone. Porous titanium scaffolds were successfully fabricated through dynamic freezing casting, and were densified, controlling the degree of densification by applied strain. During densification, structural integrity of porous titanium was well maintained without any mechanical deterioration, exhibiting good pore connectivity and large surface area. Densified porous titanium possesses two important features that have not been achieved by either dense titanium or porous titanium: 1) mechanical tunability of porous scaffolds through densification that allows scaffolds to be applied ranging from highly porous fillers to dense load-bearing implants and 2) improved bioactivity through bioactive coating that is capable of sustainable release through utilizing high surface area and pore connectivity with controllable tortuosity. This simple, but effective post-fabrication process of porous scaffolds has great potential to resolve unmet needs of biometals for biomedical applications.

1. Introduction

Metallic biomaterials have been widely used as load-bearing implants and internal fixation devices such as orthopedic, dental implants, and even vascular/non-vascular stents depending on design because of their excellent mechanical strength and resilience [1–3]. Despite the progress in load-bearing metal implant research, fixation of implants to the host tissue remains a problem. The mismatch between the elastic modulus of the implant material and that of the bone is the main reason that causes the stress to be shielded from reaching the bone in addition to low bioactivity of metallic materials that often leads to poor interface between the implant and biological tissues [4–6]. To overcome these problems, porous structures are being extensively investigated, since a reduction in elastic modulus can be coupled with bone integration through tissue ingrowth into pores to promote healthy recovery [7–9]. Various porous metals such as NiTi, titanium and tantalum have been proved to exhibit strong bone-implant contact and excellent bone ingrowth without signs of loosening from the surgical sites [8,10,11]. Moreover, recent studies have proposed various surface modification methods of metallic surface in order to improve biological activities, e.g., coating the metal surface with bioactive molecules (e.g., growth factors) or drugs (e.g., vancomycin, tetracycline) [12–14]. As compared to bare metals, the bioactive coating layer on a metal surface with or without drugs has shown accelerated healing processes of the implanted region or suppressed undesirable reactions between surrounding tissues and the implant [12,15,16]. These include titanium (Ti) ring implant with recombinant human bone morphogenetic protein (rhBMP-2), e.g., Ti alloy conjugated with synthetic peptide, and Ti screw coated with rhBMP-2 [17–19].

However, introduction of pores to metals has been found to come up with a tradeoff in the mechanical properties besides the reduction of stiffness. Although a porous structure facilitates bone

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ingrowth, uncontrolled or undesirable pores often result in significant decreases of the mechanical properties due to inherent structural instability associated with irregular, inhomogeneous pore structures and defects [20,21]. Moreover, chemical contamination during the fabrication of porous metals has been found to cause embrittlement of the materials with decreased compressive strength [22–24]. Therefore, development in a fabrication method of porous metals that is able to provide mechanical tunability of a porous scaffold associated with various porosity features (e.g., pore fraction, shape, size, distribution, connectivity and gradient) and material properties (e.g., metallic phase and impurity) has been one of key challenges in order to achieve a balance between biological performance and mechanical stability [10,25].

On the other hand, sustainable release of coating layers on metallic surface has been regarded as an issue of surface modification. Porous metallic implants have been considered as better drug carrier candidates as compared to dense metals because of large surface area. However, porous materials coated with substances experience burst effects in physiological environments, thus methods to control the rate of release is under much research. For example, in attempts to control the initial burst and to sustain the release of substances, nanopores are formed on the surface of implants or polymers with a low degradation rate is used to coat the implants [13,26–28]. However, there are still some room for improvement such as controlling the side-effects caused by the coated polymers, reducing the additional processes needed to form nanopores, and fabricating uniform pore structures [29–31].

In this study, we have proposed densified porous Ti scaffolds as a drug carrier as well as load-bearing implants. The large surface area of the porous scaffolds is capable of loading significantly increased amount of drugs on the metal surface as compared to dense metal body of the same weight [32,33]. In addition, microstructural modification associated with porosity and pore structures of the scaffolds provides mechanical tunability as well as controllable drug release behavior. To demonstrate the potential of porous scaffolds as a drug-loaded metal implant, we have coated porous titanium (Ti) scaffolds with one of well-known bone growth factors, BMP-2. BMP-2 is known to accelerate bone regeneration in the body so it has been widely applied in treatment of bone defects, and also as bioactive coating agents for orthopedic and dental implants [32,34,35]. However, negative side effects including heterotopic bone formation, retrograde ejaculation and osteoclast activation have also been reported with supraphysiologic doses of rhBMP-2 over relatively short periods [31,36–38]. Therefore, many studies have tried to develop a carrier system which is capable of sustained and controlled release of rhBMP-2 over a prolonged period with the bioactivity of the growth factor still maintained [39–41]. Here, we have fabricated porous Ti scaffolds through a dynamic freeze casting process, and coated the scaffolds with rhBMP-2 varying the amount of rhBMP-2 loading with initial porosity. Through densification of the porous scaffolds, modified porosity and pore structures were evaluated in terms of mechanical properties as well as drug release behavior. Moreover, herein, we report for the first time *in vitro* rhBMP-2 release studies for a prolonged period in parallel to *in vivo* study in order to prove biological improvement of rhBMP-2-coated Ti samples.

2. Materials and methods

2.1. Fabrication of densified porous titanium coated with biomolecules

The schematic of sample preparation was illustrated in Fig. 1. In this study, porous Ti scaffold coated with rhBMP-2, a bone growth factor, was studied as a model system for orthopedic applications. Porous Ti scaffolds were fabricated by dynamic freeze casting [42], which enables production of mechanically stable metal scaffolds with 3-dimensionally interconnected porous channels. All samples were sterilized in an autoclave for 15 min at 121 °C. Following the sterilization, the scaffolds were immersed in green fluorescent protein (GFP) or rhBMP-2 solution that had been fabricated using *Escherichia coli* (*E. coli*) [32,43]. Immersed specimens were put into a vacuum desiccator connected to a rotary pump for 10 min, incubated overnight at room temperature (RT), washed with DPBS twice and dried. Subsequently the drug-loaded porous samples were uniaxially compressed in a mold. The initial porosity and degree of densification were major processing parameters used to vary the mechanical properties and to control drug release rates as well as the amount of drug loading.

2.2. Characterization of densified porous titanium

The structures of the dense Ti scaffolds were characterized by scanning electron microscopy (FE-SEM, JSM- 6330, JEOL Techniques, Tokyo, Japan) and μ-computed microtomography (Skyscan 1173 X-ray μ-tomography System, Skyscan, Kontich, Belgium) with the following parameters: 1.0 mm aluminum filter, 180° rotation, 4-frames averaging, 0.2° rotation step, 7.5 μm resolution, 130 kV voltage, and 60 μA current. The pore size was measured and averaged from the SEM images of the samples prepared by filling the porous Ti scaffolds with an epoxy resin (Spurrs epoxy Polysciences Inc., Warrington, PA). The porosity was measured using the volume and mass of the samples in the following equation:

$$p = 100\left(1 - \frac{m_S/V_S}{\rho_{Ti}}\right)$$

where p is the total porosity percentage, ρ_{Ti} is the theoretical density of the titanium and m_S/V_S is the measured density of the sample calculated using the mass (m_S) and volume (V_S). In addition, porosity and pore size were analyzed using computed

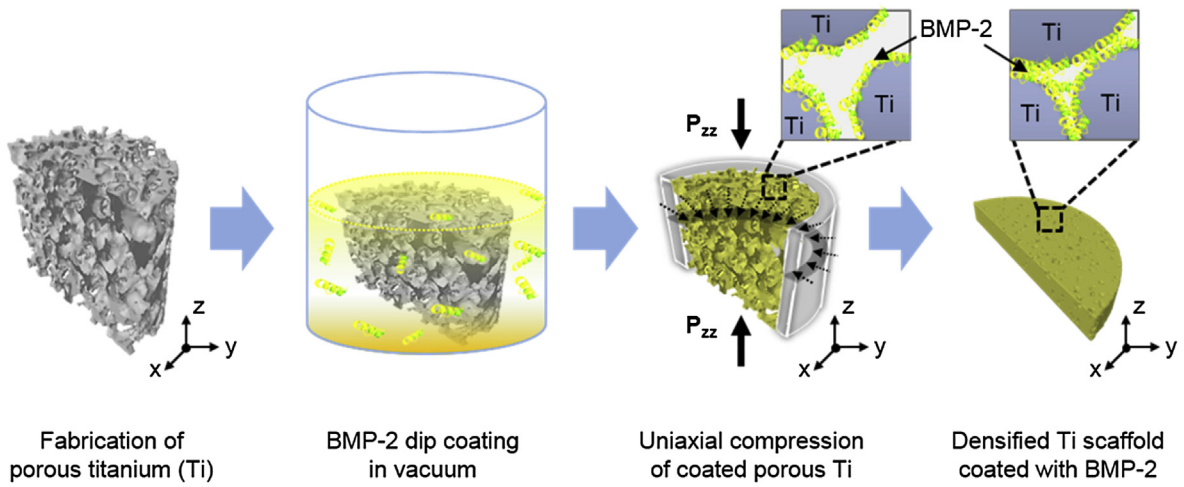

Fig. 1. Schematic illustration of the fabrication process of a densified porous metallic scaffold (Ti) coated with a growth factor (BMP-2). The porous scaffold was compressed under triaxial compression conditions.

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