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Design and characterization of calcium phosphate ceramic scaffolds for bone tissue engineering

Isabelle Denry[a,*], *Liisa T. Kuhn*[b]

[a] *Department of Prosthodontics, University of Iowa College of Dentistry, 801 Newton Road, Iowa City, IA 52242-1010, USA*

[b] *Department of Reconstructive Sciences, UConn Health, 263 Farmington Avenue, MC 1615, Farmington, CT 06030-1615, USA*

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ABSTRACT

Objectives. Our goal is to review design strategies for the fabrication of calcium phosphate ceramic scaffolds (CPS), in light of their transient role in bone tissue engineering and associated requirements for effective bone regeneration.

Methods. We examine the various design options available to meet mechanical and biological requirements of CPS and later focus on the importance of proper characterization of CPS in terms of architecture, mechanical properties and time-sensitive properties such as biodegradability. Finally, relationships between *in vitro* versus *in vivo* testing are addressed, with an attempt to highlight reliable performance predictors.

Results. A combinatory design strategy should be used with CPS, taking into consideration 3D architecture, adequate surface chemistry and topography, all of which are needed to promote bone formation. CPS represent the media of choice for delivery of osteogenic factors and anti-infectives. Non-osteoblast mediated mineral deposition can confound *in vitro* osteogenesis testing of CPS and therefore the expression of a variety of proteins or genes including collagen type I, bone sialoprotein and osteocalcin should be confirmed in addition to increased mineral content.

Conclusions. CPS are a superior scaffold material for bone regeneration because they actively promote osteogenesis. Biodegradability of CPS via calcium and phosphate release represents a unique asset. Structural control of CPS at the macro, micro and nanoscale and their combination with cells and polymeric materials is likely to lead to significant developments in bone tissue engineering.

Contents

* Corresponding author. Tel.: +1 319 335 7369; fax: +1 319 335 8895.
E-mail address: Isabelle-Denry@uiowa.edu (I. Denry).

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1. Introduction

Autologous bone grafts remain the gold standard in bone replacement procedures with the highest success rates for bone regeneration [1]. It is well established, however, that harvest of bone tissue is associated with several clinical drawbacks, including limited availability of healthy bone, secondary surgery cost and burden, harvest site morbidity and long-term pain issues [2]. There is therefore a critical need for synthetic bone graft materials capable of promoting successful bone regeneration. Indeed the past two decades have been associated with sustained interdisciplinary efforts to design and develop synthetic scaffolds encompassing a wide range of materials from ceramics [3] to polymers, including composite scaffolds, cell-bearing, protein-loaded or growth factor-carrying scaffolds mixing both inorganic and organic phases [4–7].

Amongst available scaffold materials, calcium phosphate-based ceramics represent a unique avenue based on tunable similarities in both crystalline structure and chemistry between calcium phosphate ceramics and bone apatite, the mineral phase of bone tissue that is similar, albeit distinct, from hydroxyapatite (HA) due to its carbonate content and reduced or absent hydroxyl groups [8]. A literature search associating the terms “calcium” and “phosphate” and “scaffolds” returned a total of more than 7000 articles. This interest appears to have gathered momentum in the past 15 years, although HA, and more generally calcium phosphate-based ceramics have long been the focus of extensive research [9–13]. Calcium phosphate ceramics have been shown to enhance bone formation depending on crystallinity, crystalline phase and Ca/P ratio, which results in calcium and phosphate ion release needed for bone mineralization [14,15]. This characteristic uniquely differentiates them from other metal oxide ceramics used in orthopedics, such as alumina or zirconia that are considered chemically inert. The importance of a scaffold-type architecture stems from the fact that interconnected porosity is a condition for osteoconductivity and promotes angiogenesis. Furthermore, there is ample literature showing that calcium phosphate bioceramic scaffolds promote both osteogenesis and osseointegration, which are directly related to surface charge, chemistry and topography. However, it should be noted that the target application for calcium phosphate scaffolds (CPS) is transient bone replacement. Therefore, the degree of mimicry with regard to bone does not extend beyond chemistry, surface topography and architecture. Bone becomes stiffer and stronger as it matures while CPS should biodegrade and become weaker, with the end point of being completely replaced by newly formed bone.

CPS are manufactured using a palette of techniques from polymer foam replication to ceramic foaming, inclusion of porogens, 3D printing and gel casting. This variety of manufacturing techniques illustrates the difficulty of producing ceramic scaffolds with controlled pore size, porosity and mechanical integrity. Regardless of manufacturing technique, the last step is a thermal treatment or sintering step. This high temperature step has traditionally triggered design issues due to the competition between the high temperatures required for sintering and crystalline phase thermal decomposition. Additionally, for bioactive glass-ceramics, competition between sintering and crystallization processes renders sintering to full density difficult to achieve.

Our goal is to review design strategies for the fabrication of CPS, in light of their transient role in bone tissue engineering and associated requirements for effective bone regeneration. We later focus on the importance of proper characterization of CPS in terms of architecture, mechanical properties and time-sensitive properties such as biodegradability. Finally, relationships between *in vitro* versus *in vivo* testing are addressed, with an attempt to highlight reliable performance predictors.

1.1. *Design requirements for CPS as bone graft substitutes*

As mentioned earlier, an ideal scaffold material for synthetic bone grafts should be osteoinductive, osteoconductive, promote osseointegration, be able to deliver osteogenic agents, anti-infectives and stem cells, and degrade at the same rate as new bone forms [16]. Calcium phosphate ceramic scaffolds are therefore excellent candidates, offering a large palette of design options as detailed below.

1.1.1. *Osteoinduction and biodegradation*

Osteoinduction can be defined as the chemical stimulation of human mesenchymal stem cells into bone-forming osteoblasts, thereby inducing osteogenesis [17]. Osteoinduction is best demonstrated by the ability of a material to form bone in an ectopic site [18]. Calcium phosphate ceramics have been shown to be osteoinductive [19]. It is postulated that osteoinductivity of CPS stems from the combination of micro and macroporosity capable of entrapping and concentrating growth factors that are directly involved in mesenchymal stem cell differentiation into an osteoblastic lineage [20]. The