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Comparative performance of three ceramic bone graft substitutes

Karin A. Hing, Bsc(Hon), PhD, CEng[a,*],
Lester F. Wilson, MB, BS, BSc(Hon)FRCS, FRCS(Orth)[b], Thomas Buckland, MEng, PhD[c]

[a]*IRC in Biomedical Materials, Queen Mary University of London, London, E1 4NS, United Kingdom*
[b]*Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP, United Kingdom*
[c]*ApaTech Ltd., 370 Centennial Avenue, Centennial Park, Elstree, Herts, WD6 3TJ, United Kingdom*

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Abstract

BACKGROUND CONTEXT: A number of different synthetic calcium-based bone graft substitutes (BGS) are currently available for clinical use. There is, however, a lack of comparative performance data regarding the relative efficacy of these materials when placed in an osseous defect site.

PURPOSE: To compare the rate, quality, and extent of osseous healing in a standard rabbit defect model for three commercially available BGS materials by measuring early bone formation and completion of defect healing and to identify whether rapid scaffold resorption stimulated or impaired bone healing.

STUDY DESIGN: Osteochondral defects, 4.8 mm in diameter and 6 to 7 mm deep, were made through the articular surface into the subchondral bone of the femoral condyle of New Zealand White rabbits and filled with cylindrical pellets of one of three commercially available BGS materials: dense calcium sulfate (DCaS), ultraporous tricalcium phosphate (β-TCP), and porous silicated calcium phosphate (Si-CaP). The repair response was examined at 1, 3, 6, and 12 weeks after surgery (n=4 per BGS per time point).

METHOD: Qualitative histological and quantitative histomorphometric (% new bone, % bone graft substitute, capillary index, and mineral apposition rates) analysis.

RESULTS: Rapid resorption of D-CaS, primarily through dissolution, elicited a mild inflammatory response that left the defect site empty before significant quantities of new bone were formed. Both β-TCP and Si-CaP scaffolds supported early bone apposition (<1 week). However, β-TCP degradation products subsequently provoked an inflammatory response that impaired and reversed bone apposition within the defect site. The Si-CaP scaffolds appeared to be more stable and supported further bone apposition, with the development of an adaptive bone-scaffold composite; cell-mediated resorption of scaffold and new bone were observed in response to local load and contributed to the production of a functional repair within the defect site.

CONCLUSIONS: Rapid BGS resorption impaired the regenerative ability of local bone via three pathways: 1) insufficient persistence of an osteoconductive scaffold to encourage bone apposition, 2) destabilization of early bony apposition through scaffold disintegration, and 3) stimulation of an inflammatory response by elevated levels of particulate degradation products. This had a significant impact on the ultimate rate of healing. D-CaS did not stimulate early bone apposition, but bone repair was more advanced in D-CaS–treated defects at 12 weeks as compared with those treated with β-TCP, despite the β-TCP supporting direct bone apposition at 1 week. Si-CaP appeared to provide a more stable osteoconductive scaffold, which supported faster angiogenesis and bone apposition throughout the defect site, with the development of a functionally adaptive trabecular structure through resorption/remodelling of both scaffold and new bone. There was rapid formation of

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* Corresponding author. IRC in Biomedical Materials/Department of Materials, Queen Mary University of London, Mile End Road, London, E1 4NS, United Kingdom. Tel.: (44) 0-207-882-7804; fax: (44) 0-208-983-1799.

E-mail address: k.a.hing@qmul.ac.uk (K.A. Hing).

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mineralized tissue at week 1 within the center of the defect and complete infiltration with dense, predominantly mature bone by weeks 3 to 6. The progressive remodeling of bone ingrowth and scaffold to reflect the distribution of local host tissue, combined with histological evidence of targeted osteoclastic resorption of both scaffold and bone, suggest that bone adaptation within the scaffold could be in response to Wolff's law. Although this model may not directly translate to a spinal fusion model and the products may vary according to the environment, these results suggest that, in patients in whom bone regeneration may be compromised, the degradation observed with some resorbable bone grafts may contribute to the decoupling of bone regeneration and resorbtion within the graft site, which may ultimately lead to incomplete bone repair.

Keywords: Bone graft substitutes; Calcium sulphate; Tri-calcium phosphate; Silicated calcium phosphate; Osteoconductive; Resorption

Introduction

Bone grafting, first established in the 1800s, traditionally replaced missing bone with material from the body of either the patient (autograft) or a donor (allograft) [1,2] but has increasingly encompassed the use of processed or synthetic bone graft substitute (BGS) materials. The purpose of the graft, besides replacing the missing tissue, is to reinforce the repaired area by encouraging new bone ingrowth into the defect site. This new bone should ideally penetrate and replace the graft through sequential remodelling cycles, enabling the repair site to maintain an optimal balance between form and function. Although autografting is widely regarded as the ''gold standard,'' the volume of bone that can be safely harvested from the donor site is limited and can result in donor site pain and morbidity [3]. Modern allografting, using material stored within regulated bone banks, overcomes these complications; however, structure and healing can be unpredictable [4]; there are concerns regarding disease transfer [5,6] and demand outstrips supply. Consequently, there is a requirement for BGS materials free from these limitations of supply, inconsistency, and disease.

Bioceramics have been considered for use as synthetic bone graft substitutes for over 30 years [7], with two primary areas of research: 2) optimization of the bioceramic chemistry [8–10] and 2) optimization of the physical pore structure [11–14]. It has been shown that bioceramic chemistry is critical to the quality of repair, with ''bioactive'' materials, which support direct bonding of bone to its surface, greatly enhancing performance over those which are only bioinert or biocompatible [8,9]. ''Bioactive'' materials can be either osteoconductive, supporting the direct apposition of bone on their surfaces by mature osteoblasts, or intrinsically ''osteoinductive'' or ''osteoproductive,'' stimulating or accelerating bone apposition by influencing the recruitment, differentiation, and maturation of mesenchymal stem cells into committed osteoblasts [15].

Many bone graft substitutes are based on calcium salts, and these have a range of applications including posterolateral and anterior interbody spinal surgery [16–21], trauma [22], nonunion [23,24], fracture fixation [25], oncology [26,27], defect filling [28,29], tibial plateau fractures [30], maxillofacial/periodontal surgery [31,32], and as a carrier for antibiotics [33]. There is, however, a lack of comparative performance data regarding the relative efficacy of these materials either in clinical studies or in relevant animal models, with much dispute in the literature regarding the relative benefits of scaffolds that undergo resorption and are ultimately replaced by new bone as compared with those that persist. Resorption is a phenomenon routinely observed radiologically and histologically with both autograft and allograft [34] where persistence of graft material is often linked to poor clinical outcomes [4]. Hydroxyapatite (HA, $Ca_{10}[PO_4]_6[OH]_2$) is widely considered to be nonresorbable (ie, not subject to significant chemical dissolution or cell-mediated resorption in vivo), although there is some evidence to the contrary [21,35,36], whereas porous tricalcium phosphate (TCP, $Ca_3[PO_4]_2$) scaffolds and dense calcium sulfate (CS, $CaSO_4$) granules are stated to have high rates of resorption. In the case of TCP scaffolds, the combination of cell- and chemically mediated scaffold dissolution [26,37] can be controlled via structural parameters [38], with reports of 80% to 100% scaffold resorption occurring from 6 to more than 24 months, depending on porosity, species, and defect size [22,28,39–41]. These high rates of dissolution may, however, cause adverse biological reactions to the scaffolds via microparticle-induced inflammation [42], surface instability [43–45], and, for TCP, unpredictable [46] or uncoupled [28] resorption. Adverse inflammatory responses [23,47–49] and impaired healing [25,50] associated with rapid dissolution have also been reported for CS.

Silicate-substituted calcium phosphate (Si-CaP) is a new commercially available porous ceramic BGS whose crystal structure has been doped with silicate ions. The importance of low levels of silicon in stimulating bone metabolism has been established by dietary animal [51,52] and human [53] studies and numerous in vivo [54,55] and in vitro studies [56–60]. Si-CaP exhibits an increased in vivo resorption rate relative to traditional stoichiometric hydroxyapatites [61] and an upregulated healing response [62–64] because of the presence of trace levels of silicon both within its structure [65] and in the local bone-healing environment [66,67].

The aim of this study was to compare the rate, quality, and extent of osseous healing in an established defect