INTRODUCTION: Over the past 20 years, numerous bone graft substitute materials have been developed in an effort to reduce the morbidity associated with the use of bone auto- and allografts. Among these materials, natural and synthetic bioceramics have received much attention because their composition is similar to that of natural bone (apatite). Despite encouraging results, these products too have their shortcomings, such as limited osteoconductivity. The purpose of this study was to compare the biological behavior of Conduit™ TCP Granules, a new medical grade synthetic tricalcium phosphate bone void filler (TCP), to that of a porous medical grade calcium carbonate-calcium phosphate bioceramic (ProOsteon-500R® - Interpose-Corex, Intl. [PO]). Bone ingrowth and implant resorption were compared over 24 weeks, using a rabbit tibial metaphyseal defect model. Our hypotheses were that 1) TCP would promote bone ingrowth without evidence of ongoing foreign body reaction, 2) that TCP would support bone ingrowth earlier than PO and 3) that by 24 weeks, TCP would exhibit resorption rates and bone ingrowth characteristics equivalent to those of PO.

METHODS: All procedures were approved by the Institutional Animal Care and Use Committee. Bilateral 5x12mm cortical defects were surgically created in the medial aspect of the proximal tibial metaphysis of mature, male, New Zealand White rabbits. Each defect was randomly implanted with PO or TCP, or was left empty (negative controls). Mean implant weights were 0.16kg (PO) and 0.146g (TCP). Nine rabbits were killed at 6, 12 and 24 weeks (n=6/treatment). Fresh cadavers were used to evaluate PO and TCP defect filling at time 0 (n=3/treatment). Radiographic and histologic evaluations were conducted at 0, 6, 12 and 24 weeks. High-resolution contact radiographs were obtained (Faxitron HP) to qualitatively evaluate implant resorption and defect mineralization at each time point. Quantitative histology and quantitative histomorphometry (Biomiquant™ TCW-98 image analysis) were performed on 3 undecalced, longitudinal sections per specimen at each time period. Sections were divided into cortical and marrow regions coinciding with the original defect. Regional bone ingrowth and overall implant resorption at each time period and over time were compared using one-way ANOVA followed by Tukey’s post-hoc test when significant differences (p<0.05) were found.

RESULTS: There was neither morbidity nor mortality during this study. Radiography: Empty. Despite a faint marginal increase in radiographic density, the defect silhouettes remained clearly visible at 24 weeks indicating incomplete bone healing. PO: Over time, there was no obvious resorption of PO granules, which retained their initial characteristic well-defined, porous appearance until 12 weeks. By 24 weeks, blurring of the defect margins and a subtle increase in radiographic density suggested moderate bone ingrowth. TCP: By 24 weeks, a gradual decrease in the TCP granules original sharp definition and porosity suggested ongoing implant resorption. Along with an even increase in defect radiographic density and progressive TCP granules coalescence, blurring of the defect margins and continuity between cranial cortex and TCP granules suggested ongoing bone ingrowth continuous with the cut edge of the host bone over time (Fig. 1).

Histology: By 24 weeks, while the cortical space of the empty defects contained immature trabecular bone, the defects had not yet fully healed; the marrow space remained filled with hematopoietic and adipose tissues. While regional cancellous bone ingrowth occurred on the surface of both TCP and PO materials over time, the greater osteoblastic activity seen with TCP resulted in more bone production at both 6 and 12 weeks compared to PO. By 24 weeks, cortical replacement was more mature (compact, lamellar bone) in the TCP group compared to the PO and empty groups (in which newly formed bone showed a more trabecular remodeling pattern). The PO and TCP resorption rates were minimal over time and by 24 weeks, residual implant material persisted in both cortical and marrow spaces of both groups. Although numerous multinucleated giant cells were seen on the PO implant surface, the absence of Howship’s lacunae and resorption pits suggested that PO degradation occurred via hydrolysis or dissolution. In contrast, TCP resorption seemed to occur via cell-mediated events as suggested by the marked and sustained osteoclastic activity noted on the ceramic surface throughout the study. Numerous osteoclasts and osteoblasts were also seen around the newly formed bone indicating ongoing bone formation and remodeling. The anticipated inflammatory response associated with implant resorption and debris removal was minimal in both PO and TCP groups, however, the number of foreign body giant cells was greater around the PO material.

Histomorphometry: While the overall amount of bone formed within the defects was similar in all groups at 24 weeks, TCP promoted significantly more bone formation than PO at both 6 (11.8% vs 4.3%) and 12 weeks (12.2% vs 4.1%) (Fig. 2A). Similarly, in the important cortical region of the defects, the mean bone fill in the TCP group at 6 weeks was approximately twice that of the PO specimens (26.7% vs 13%). This trend persisted at 12 weeks when bone fill was significantly greater in the TCP group than in the PO group (38.4% vs 13.7%). While the overall amount of residual implant was identical for both materials through 12 weeks, at 24 weeks, significantly less PO than TCP material remained in the defects (Fig. 2B), however, the total residual amounts of both materials were still quite small (7.4% vs 3.1%).

Fig. 2 - Bone ingrowth (A) and implant resorption (B) over time. Significantly more bone (#) formed with TCP than PO at 6 and 12 weeks. Significant resorption occurred after 12 weeks with PO (¥). There was significantly less residual PO than TCP at 24 weeks ($).

DISCUSSION: This study suggests that TCP is capable of supporting earlier cortical bone ingrowth than PO in a critical size metaphyseal defect model. Indeed, TCP implantation resulted in the production of a substantially equivalent or greater amount of bone in every defect region and at every time point when compared with either PO-filled or empty defects. In addition, histopathologic assessment of newly formed bone indicated that TCP implants contained cortical bone that was of greater maturity at 24 weeks than that observed in the PO group. Furthermore, while both implant degradation rates were identical during the first 12 weeks, TCP resorbed through cell-mediated events involved in normal bone remodeling, while PO appeared to be resorbed via simple dissolution. Interestingly, the more intimate and complete association between new bone and TCP may have reduced the exposed implant surface area making it less available for cellular resorptive interactions. This observation, along with the scant bone formation on PO material during the first 12 weeks of the study, may explain why by 24 weeks the amount of residual TCP was greater than that of the PO. The findings of this study suggest that TCP is an effective osteoconductive scaffold capable of enhancing bone healing in bone defects.

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