

## Novel In-Situ Setting Bioglass based Calcium Phosphate Bone Cements.

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### Introduction:

Calcium phosphate cements (CPCs) have been widely used as an alternative to biological grafts as they present excellent biocompatibility and osteoconductive properties. An additional advantage is their self-setting nature, which makes them injectable and allows the use of a minimally invasive surgical procedure during clinical use. However, CPCs do not have sufficient intrinsic porosity to allow tissue ingrowth and are characterized by a very slow degradation rate. They also have poor setting characteristics and low compressive and flexural strength. Bioactive glasses (BGs) are synthetic silica-based bioactive materials that are biocompatible, resorbable and osteoinductive. They have the ability to bond to bone by forming a biologically active bone-like apatite layer on their surface that acts as a template for calcium phosphate precipitation and new bone formation. As a result, composite bioglass/calcium phosphate cements have been developed. Further *in vitro* studies have reported that fluoride-substituted hydroxyapatite augments osteoblastic activity and differentiation. In addition, studies have also shown that octacalcium phosphate (OCP) is more soluble when compared with calcium hydroxyapatite, and that the resorption of OCP is followed by new bone formation. Novel work previously performed by the authors, has successfully introduced BG into (i) hydroxyapatite, (ii) octacalcium phosphate and (iii) fluorohydroxyapatite cements without compromising the setting time. The aim of this study was to investigate bone formation and contact to these three novel BG/CPC cements following implantation in an ovine femoral condyle critical-sized defect. Our hypothesis was that the novel cements would augment bone formation to equal amounts when compared with a commercially available calcium phosphate cement (Hydroset™).

### Methods:

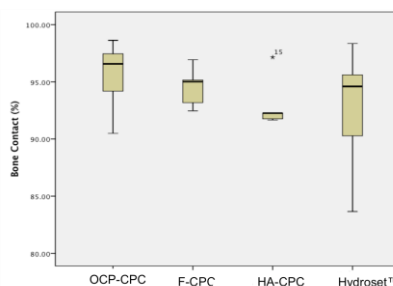
Twenty-four 8 x 15 mm deep defects were created in the medial femoral condyles of 6 female, skeletally mature commercially cross-bred sheep. Ethical approval was granted and all procedures were carried out in compliance with the UK's Home Office Regulations (Animal Scientific Procedures Act 1986). The cements investigated were BG/CPC composites, however the calcium phosphate component was composed of either (1) OCP/Brushite (OCP), (2) a fluorohydroxyapatite (FHA) or (3) hydroxyapatite (HA). Groups 1 – 3 were also compared with (4) Hydroset™, a commercially available calcium phosphate cement. Cements remained *in vivo* for 12 weeks (n=6). Fluorochrome markers (oxytetracycline and calcein green) were administered in order to measure bone apposition rates and following retrieval, specimens were processed for undecalcified histology. A thin histological section was made through the centre of each defect and image analysis techniques were used to quantify bone apposition rates and bone-implant contact at 12 weeks post surgery. The compressive strength (MPa) of each of the cements was tested using an indentation method (Zwick Proline 500) in two central positions (at least 2 mm apart) within the cement mantle following retrieval. Mann Whitney U tests were used for statistical analysis where  $p < 0.05$  was considered significant.

### Results:

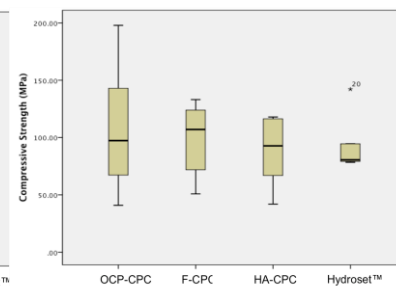
**Bone Apposition Rates:** Results are presented as mean and standard deviation. Results showed that greatest bone turnover rates were measured in the Hydroset™ group (mean,  $1.191 \pm 0.345 \mu\text{m/day}^{-1}$ ). Independent non-parametric analysis showed that significantly increased apposition rates were measured in the Hydroset™ group when compared with OCP filled (mean,  $0.740 \pm 0.156 \mu\text{m/day}^{-1}$ ) ( $p = 0.028$ ) and FHA defects (mean,  $0.839 \pm 0.141 \mu\text{m/day}^{-1}$ ) ( $p = 0.047$ ). No significant difference was found when Hydroset™ and HA samples were compared. Significantly increased bone turnover rates were measured adjacent to the HA cement specimens (mean,  $1.151 \pm 0.274 \mu\text{m/day}^{-1}$ ) when compared with OCP samples ( $p = 0.028$ ). No other significant differences were found.

**Bone-Implant Contact:** Extensive bone-cement contact was measured in all experimental groups however the greatest amount was measured in specimens in the OCP group (mean,  $95.47 \pm 3.22\%$ ). The lowest bone-cement contact values were measured in HA samples (mean,  $93.02 \pm 2.32\%$ ). Significantly less bone contact was measured in HA samples when compared with FHA samples (mean,  $94.55 \pm 1.77\%$ ) ( $p = 0.014$ ). No other significant differences were found (Figure 1). Qualitative evaluation using light and backscattered scanning electron microscopy showed mature lamellar bone in contact with all cement surfaces. In

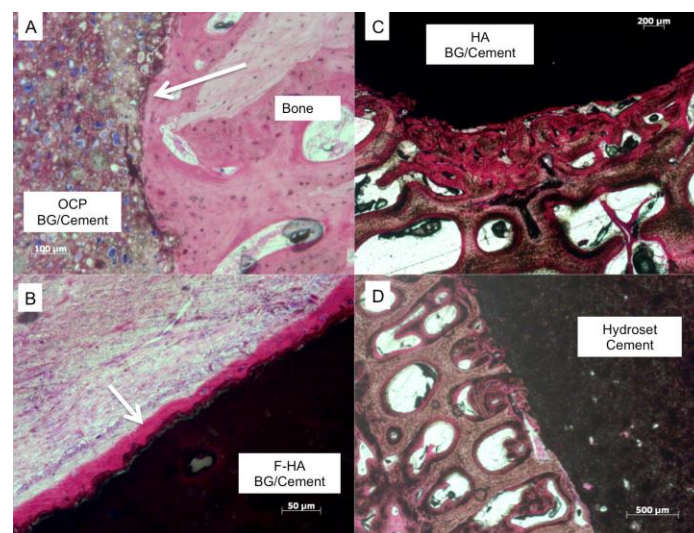
all groups and where pores were present within the cement mantle, new bone growth was seen growing preferentially along the cement surface. **Compressive Strength:** Mechanical testing showed the compressive strength of cements in each of the groups were similar. No significant differences were found when each of the groups were compared (Figure 2).



**Figure 1:** % Bone-Cement Contact In each of the experimental groups at 12 weeks.



**Figure 2:** Compressive Strength in each group at 12 weeks.



**Figure 3:** Photomicrographs showing bone remodeling adjacent to each of the groups investigated following 12 weeks *in vivo*. Arrows point to new bone formation at the bone-cement interface.

### Discussion

Excellent osteointegration was seen adjacent to all cement compositions with new bone formation seen surrounding implants in each group. Results from this study showed that the incorporation of fluoride within the hydroxyapatite lattice and the formation of OCP/Brushite BG/CPCs were as bioactive as the commercially available calcium phosphate cement Hydroset™. These cements are able to be injected and their compressive strength once set, and after 12 weeks *in vivo*, indicates that they may be excellent bone void fillers and may have potential uses for vertebroplasty applications. Further work is needed to assess the resorbability of the cements over time.

**Significance:** The use of OCP and fluorohydroxyapatite bioglass cements has the potential to be used clinically as bone void fillers.