# Remodeling of Settable, Weight-Bearing Polyurethane Composite Bone Grafts in a Tibial Plateau Defect Model in Sheep

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**Statement of Purpose:** Tissue engineering bone grafts for weight-bearing (WB) applications must precisely balance material resorption and bone regeneration to withstand mechanical loading of the defect site throughout healing. Poly(methyl methacrylate) (PMMA) bone cements have sufficient mechanical properties; however, these are non-degradable and integration with the host bone is limited. Calcium phosphate ceramics have also been investigated for WB applications but failed under the compressive loads of the tibial plateau defect model.[1] We have developed a moldable, settable, and resorbable nano-hydroxyapatite (nHA)-poly(ester urethane) (PEUR) polymer that when blended with either Mastergraft® (MG) ceramic particles or a blend of MG and bioactive glass (BG) particles achieves mechanical properties exceeding those of trabecular bone. In this proof-of-concept study, we implanted nHA-PEUR composites in a WB tibial plateau defect model in sheep to investigate their potential for remodeling in mechanically challenging applications where currently available bone grafts have not been successful.

**Methods:** nHA-lysine triisocyanate (nHA-LTI) prepolymer was synthesized by combining 65 wt% nHA in LTI in the presence of 0.025 wt% iron (III) acetylacetonate (FeAA) catalyst. nHA-PEUR composites were fabricated by hand-mixing the prepolymer and polycaprolactone (PCL) triol at an NCO:OH equivalent ratio of 1.4 with 55 wt% Mastergraft® (MG) ceramic granules or a 50:50 blend of MG with bioactive glass (BG) particles. Mechanical properties were investigated on cylindrical composites cured at room temperature for 1, 3, and 8 days to determine when the maximum moduli and strengths were achieved. Bilateral WB and non-WB defects were created in the hind limbs of 8 skeletally mature sheep. Non-WB 16 x 8 mm diameter drill holes were created in the medial and lateral femoral condyles using a surgical drill. WB slot defects that extended the medial-lateral width of the tibia and half of the anterior-posterior depth were created leaving a thin shelf of bone above the defect area. Composites of either MG or MG/BG blend were molded to fill each defect and cured within 10 minutes from the start of mixing. CT, µCT, and histology were used to evaluate healing and polymer degradation at 16 weeks.

**Results:** Both composites set to mechanical properties exceeding those reported for sheep trabecular bone (modulus = 589 ± 103 MPa, ultimate stress = 9.09 ± 2.21 MPa)[2] after only 24 hours cure lending their use in WB applications. Mechanical testing revealed an average modulus of 1300 MPa for MG composites and 1400 MPa for MG/BG blend composites and yield strengths of 76 and 63 MPa, respectively. Both CT and µCT showed maintenance of the tibial plateau defect spaces with MG formulations, and µCT images indicated infiltration of these grafts by cells and new bone. While both MG and MG/BG formulations stabilized the tibial plateau defects in a 2 week pilot study, fragmentation of the MG/BG group in the tibial defect was evident in CT and µCT images during the longer duration study. PUR/MG groups were well tolerated in the tibial plateau defects. Histological analysis verified that the material maintained the space of the defect and withstood mechanical loading at the defect site. A creeping substitution mechanism was evident at the periphery of the grafts where the material was well integrated with the host bone, and new bone (stained red, arrows) was formed throughout the volume of the graft (Fig 1). Histology of the grafts in the femur showed evidence of new bone growth (red) and cellular infiltration (blue) throughout the defect from the periphery to the core (Fig 2).

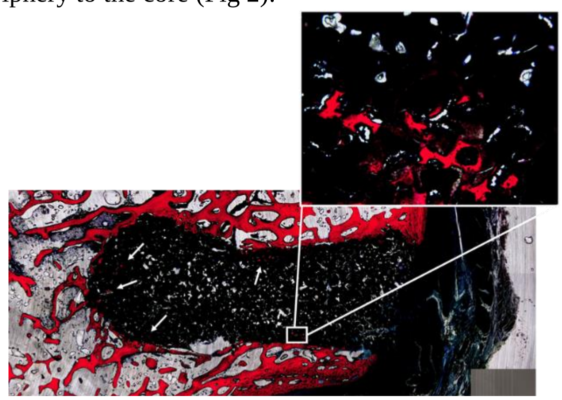

Figure 1. Sagittal view of MG composite in a tibial plateau defect at 16 weeks.

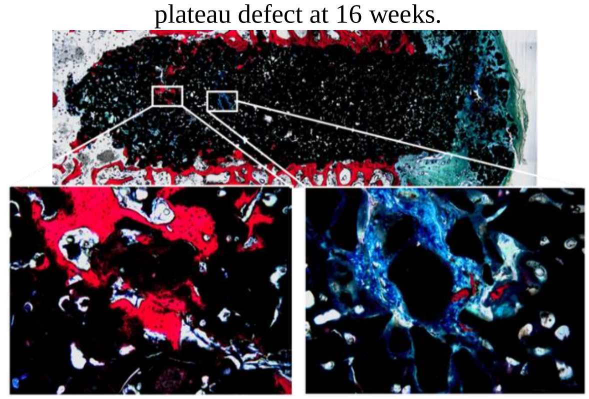

Figure 2. Transverse view of MG composite in a femoral condyle drill hole defect at 16 weeks.

**Conclusion:** nHA-PEUR composites exhibited mechanical properties exceeding those of trabecular bone. nHA-PEUR/MG composites supported appositional bone growth, provided mechanical stability, and infiltrated with cells and new bone at 16 weeks in a challenging weight-bearing *in vivo* model.

**References:** [1]Gisep A. J Biomed Mater Res A. 2003;66:532-540. [2]Wu Z. Med Eng Phys. 2008;30(9):1112-1118.