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Bone Area Demonstrates Change in 3 Months in a Very Small OA Cohort

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Purpose: In order to stimulate the production of novel drugs and treatments of osteoarthritis (OA), responsive measures of structural progression are required. Ideally, proof of concept studies would take no longer than 6 months and require small cohorts. Changes in bone shape and size show promise as a potential progression biomarker, which can be accurately measured using modern magnetic resonance imaging (MRI) analysis. This post-hoc study analysed the changes in bone area of knee OA, using a convenience cohort selected for high risk of OA progression, with MR images acquired at 3 months and 6 months. A previous study using this cohort demonstrated no significant change in cartilage thickness in the medial femur or tibia at either time point [1].

Methods: 27 females with knee pain, a body mass index (BMI) $\geq$ 25 kg/m2, radiographic evidence of medial compartment OA and varus mal-alignment, were recruited in a multi-centre, non-randomized, observational cohort study at four sites in the US. MR images were acquired using 3T Siemens systems, using the Dual Echo Steady State water excitation acquisition sequence. Images were automatically segmented using active appearance models (AAMs) of the femur. The primary endpoint for this study was change of the area of subchondral bone in the medial femorotibial region (MF), with a secondary endpoint of change in the lateral femur (LF) area. Repeatability of the AAM method was assessed using double baseline images, using root-mean-square coefficients of variation (CoV), and smallest detectable difference (SDD), defined as the 95% limits of agreement; the mean of the differences $\pm$1.96 standard deviations. Change was assessed using a paired t-test of the change at each time point, compared with the average of the 2 baseline images.

Results: Repeatability for the MF region was 0.39% (CoV) and 1.1% (SDD), and for the LF region was 0.66% (CoV) and 1.9% (SDD). Change in bone area of the MF region (the primary endpoint) was statistically significant at both 3 months and 6 months, with the 6 month change being almost twice that seen at 3 months. At 3 months, mean change was 0.29% [95% confidence interval (CI) (0.57%, 0.02%)], and at 6 months 0.58% [0.30%, 0.85]. In the LF region, the changes were not significant at 3 months 0.24% [-0.81%, 0.66], but became significant at 6 months 0.51% [0.21%, 0.81] (see figure 1 for comparison with previous cartilage study).

Conclusions: In this small cohort selected for high risk of OA progression, bone area changed in an approximately linear manner at 3 and 6 months from baseline. Bone area shows promise as a highly sensitive biomarker of OA progression, detecting change when current imaging outcomes are unable to do so, and provides a potential tool for small short-duration proof of concept studies.
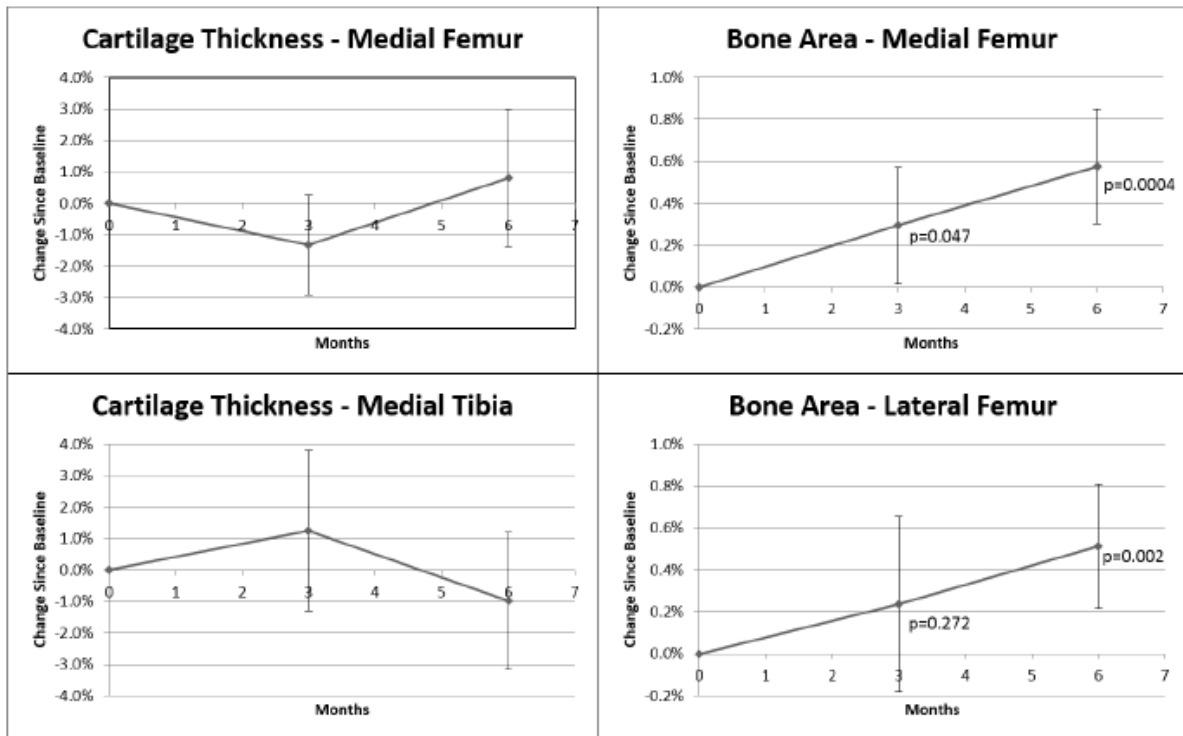
Figure 1 – Comparison of bone area change at 3 and 6 months with cartilage thickness change. Change from baseline was determined using pairwise t-test, and expressed as percentage of baseline value. P-values obtained from t-test are shown where p<0.05

[1] Hunter DJ, Bowes MA, Eaton CB, Holmes AP, Mann H, Kwoh CK, et al. Can cartilage loss be detected in knee osteoarthritis (OA) patients with 3-6 months' observation using advanced image analysis of 3T MRI? Osteoarthritis Cartilage. 2010;18(5):677-83.