Bone Area Provides a Responsive Outcome Measure for Bone Changes in Short-term Knee Osteoarthritis Studies

Michael A. Bowes, Rose A. Maciewicz, John C. Waterton, David J. Hunter, and Philip G. Conaghan

ABSTRACT. ***Objective.*** To analyze the 3-D bone area from an osteoarthritis (OA) cohort demonstrating no change in cartilage thickness.

Methods. Twenty-seven women with painful medial knee OA had magnetic resonance images at 0, 3, and 6 months. Images were analyzed using active appearance models.

Results. At 3 and 6 months, the mean change in medial femoral bone area was 0.34% (95% CI 0.04–0.64) and 0.61% (95% CI 0.32–0.90), respectively. Forty-one percent of the subjects had progression greater than the smallest detectable difference at 6 months.

Conclusion. In this small cohort at high risk of OA progression, bone area changed at 3 and 6 months when cartilage morphometric measures did not. (J Rheumatol First Release October 1 2016; doi:10.3899/jrheum.151118)

Key Indexing Terms:
BONE KNEE OSTEOARTHRITIS

There is an urgent need for treatments to arrest structural progression in osteoarthritis (OA). However, we lack responsive measures (biomarkers) that could be used in early-phase evaluation of investigational therapies. Radiography and magnetic resonance imaging (MRI) offer many structural biomarkers, but currently these require larger sample sizes and longer duration of treatment than would be ideal in a phase II study.

Bone is integral to the OA pathological process, and a number of bony pathologies including subchondral bone thickening, trabecular morphometry, bone marrow lesions, and bone shape have been investigated[1]. There is likely to be considerable interplay between the subchondral bone and cartilage[2]. Changes in bone shape and area have been shown to be predictive biomarkers for the onset of knee OA[3,4], and can be accurately quantified using active appearance modeling (AAM), a form of statistical shape modeling that enables automatic segmentation (Figure 1)[5,6]. Recent studies in large cohorts have shown that change in 3-D bone area is specific for knee OA and more responsive than radiographic joint space width and cartilage thickness[7].

A previous study designed to assess the responsiveness of cartilage thickness in a small knee OA cohort enriched for known risk factors of progression including high body mass index (BMI), female sex, and varus alignment demonstrated no significant change in cartilage thickness at the group level in the medial femur (MF) or tibia at 3 or 6 months[8]. Our current posthoc study analyzed the changes in bone area of the femoral condyles in this cohort to determine the responsiveness of this novel bone biomarker.

MATERIALS AND METHODS

Twenty-nine participants were recruited in a multicenter, nonrandomized, observational cohort study at 4 sites in the United States[8]. Twenty-seven women had knee pain, a BMI ≥ 25 kg/m^2, radiographic evidence of medial OA, varus malalignment, and images at all timepoints; 2 did not have all images. A single knee was selected, being the knee with the highest Kellgren-Lawrence arthritis grading scale (KL) score, or the right knee if no difference.

MR images were acquired using 3T Siemens systems, using the dual-echo steady-state water excitation acquisition sequence previously used in the Osteoarthritis Initiative[9]. MR images were acquired at recruitment, with followup images at 1 week (providing a double baseline), 3 months, and 6 months. Ethics approval was obtained from the sites involved in the study and all participants gave informed consent.

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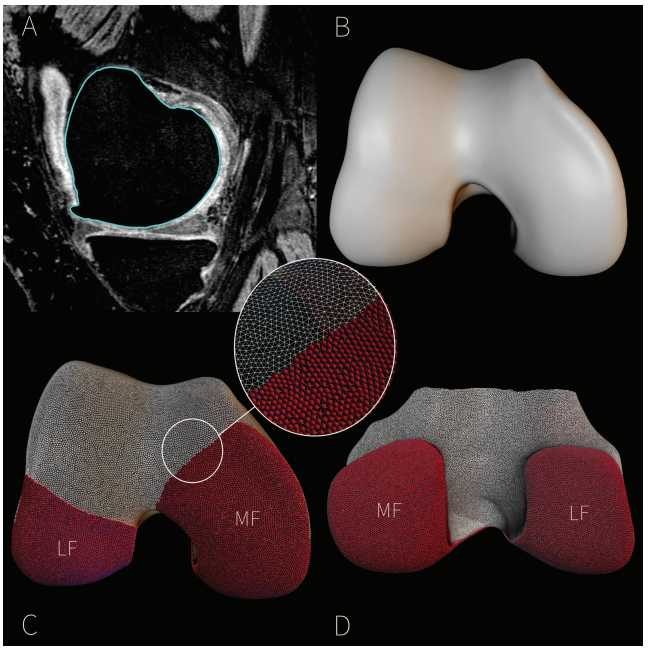


Figure 1. Automatic segmentation of MR images using active appearance models and generation of anatomical regions. Each image is automatically segmented using active appearance models, which produces a bone surface for femur and tibia. (A) An outline of the automated segmentation in 1 slice is illustrated. (B) The mean bone surface from multiple femurs is presented anatomically. (C and D) The mean bone surface is actually a triangulated mesh in which each vertex represents an anatomically corresponded point or landmark. The vertices contained within the chosen regions are in red. Inset shows closeup of landmarks indicating actual density of vertices. The boundary of the MF and LF regions were defined as a line on the bone corresponding to the anterior edge of the medial or lateral meniscus in the mean model. MR: magnetic resonance; MF: medial femur; LF: lateral femur.

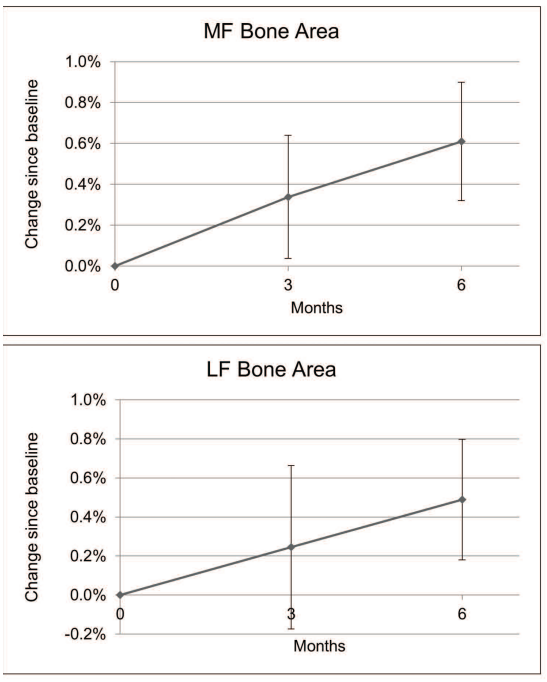
Images were automatically segmented using AAM of the femur, built using an unrelated training set[7], which has been shown to segment with point-to-surface accuracy of < 1 mm[10]. Two area measures (mm^2) were extracted from the bone surface produced by the AAM: the medial and lateral femorotibial regions of the femur (Figure 1), which were found to be the most responsive regions in a larger study[7].

Repeat baseline MRI scans were acquired a week apart[8], allowing estimation of repeatability by calculation of root-mean-square coefficients of variation (CV) and smallest detectable difference (SDD), defined as the mean of the differences ± 1.96 SD. Change over time was assessed using a paired Student t test of the ratio of the value of each timepoint against the baseline value using the geometric mean of the 2 baseline images. Spatial location of bone area change was visualized by color change maps, and displayed on the mean bone shape (Figure 2).

RESULTS

The mean age was 62 years (range 50–80), mean BMI at baseline was 35 kg/m^2 (31–44), and mean Western Ontario and McMaster Universities Osteoarthritis Index pain score was 7 (1–12). Mean knee alignment was 0.4° (–1.9° to 6.3°; varus positive). Twelve of 27 were left knees; 19 knees were KL grade 3 and the remainder were grade 2.

Repeatability for the MF region was 0.39% (CV) and 1.1% (SDD), and for the lateral femur (LF) region, 0.66% (CV) and 1.9% (SDD). At 3 months, the mean change in MF bone area was 0.34% (95% CI 0.04–0.64, p = 0.03), and at 6 months it was 0.61% (95% CI 0.32–0.90, p = 0.0002; baseline MF area was 2291 mm^2). In the LF region, the changes were not significant at 3 months (0.24%, 95% CI –0.17 to 0.66, p = 0.23), but became significant at 6 months (0.49%, 95% CI 0.18–0.80, p = 0.0021, baseline = 1527 mm^2; Figure 2). Standardized response mean (SRM) of MF at 3 months was 0.45 and at 6 months was 0.85, and for



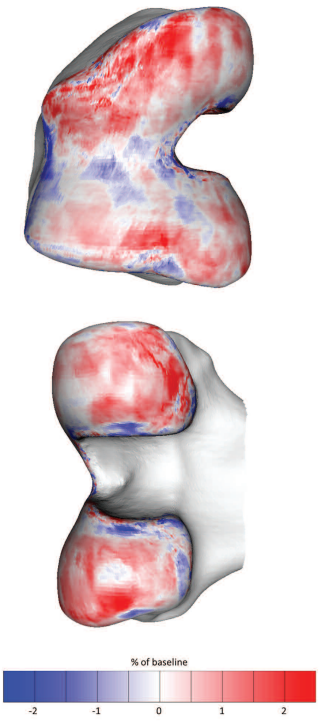


Figure 2. Bone area change at 3 and 6 months. Graphs show change from baseline using a pairwise Student t test with 95% CI. Illustration on right shows average change at each triangle in the mean bone shape at 6 months, expressed as percent of original area. MF: medial femur; LF: lateral femur.

LF at 6 months was 0.66. There were no significant differences between the KL2 and the KL3 groups, for example, MF region changed by 0.32 (–0.01 to 0.65) at 3 months and 0.57 (0.25–0.89) at 6 months in the KL3 group, and by 0.34 (–0.18 to 0.50) at 3 months and 0.63 (0.5–0.76) at 6 months in the KL2 group (all values are percent).

Previously reported[3] cartilage thickness change was not significant at any timepoint, and showed no trend with time. Mean change at 3 months for medial femoral cartilage was –1.3% (range –2.9 to 0.3), and at 6 months was 0.8% (range –1.4 to 3.0, baseline = 1.54 mm). Mean change at 3 months for medial tibial cartilage was 1.3% (range –3.9 to 1.7), and at 6 months was –1.0% (range –3.2 to 1.2, baseline = 2.27 mm). There were no differences between the KL2 and the KL3 groups for cartilage change; for example, the medial femoral cartilage region changed by –1.73 (–4.1 to 0.6) at 3 months and 1.12 (–2.4 to 4.7) at 6 months in the KL3 group, and by –0.62 (–3.5 to 2.5) at 3 months and –0.27 (–2.3 to 2.9) at 6 months in the KL2 group (all values are percent).

Graphs of change with time for each participant are shown in Figure 3, together with the SDD for each measure. Bone area measures showed increasing numbers of progressors (those with change greater than the SDD) with time, and progressors outnumbered regressors at each point. Forty-one percent of subjects progressed more than SDD using the MF bone area measure at 6 months (11 subjects) compared with 15% who lost cartilage greater than SDD in the medial tibia region (4 subjects).

The spatial pattern of change was similar to that reported in a larger study[7]. Increase in area was seen in articulating tibiofemoral surfaces, together with a circumferential increase in bone area around the cartilage plate, in the osteophytic region (Figure 2).

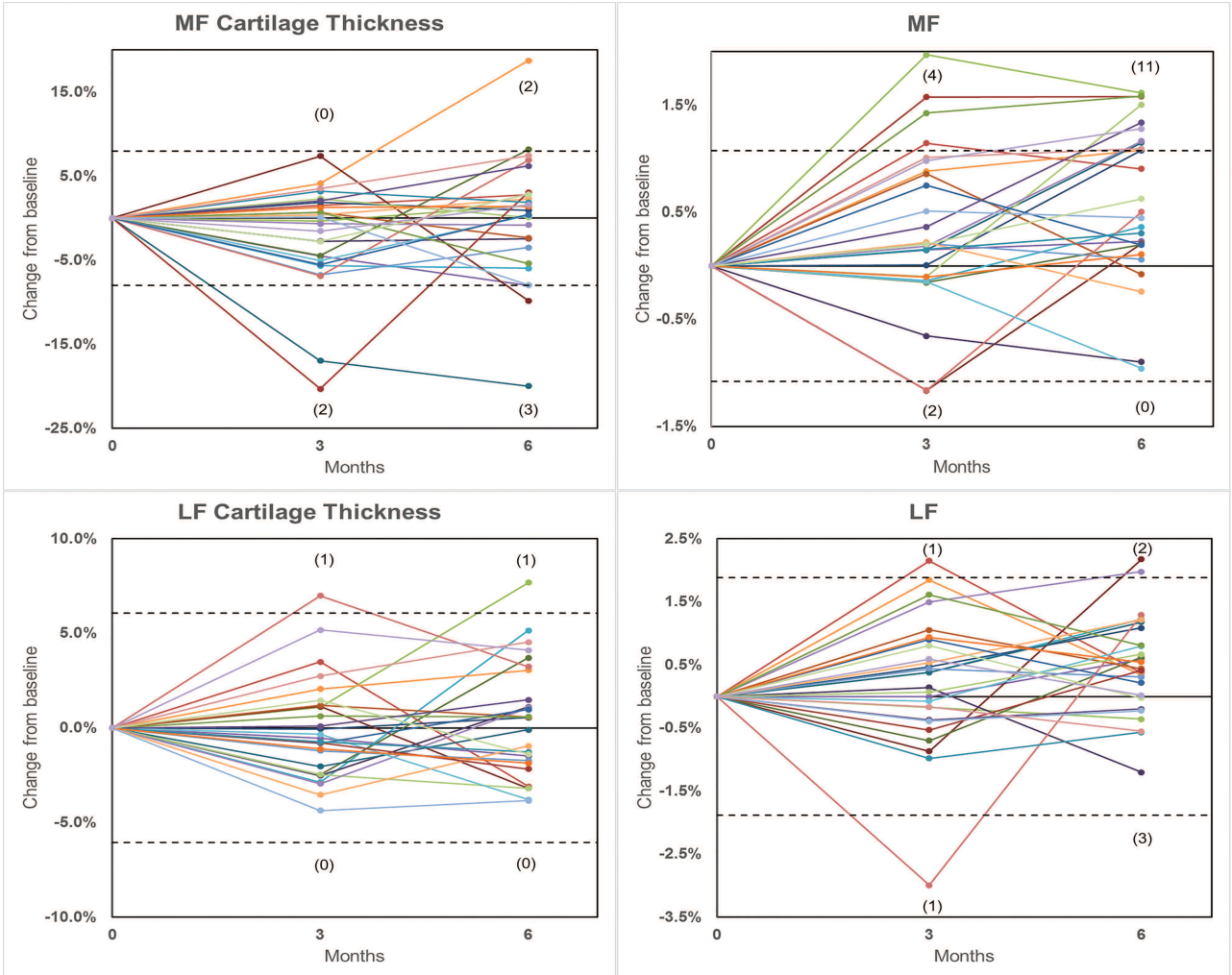


Figure 3. Individual change of bone area and cartilage thickness. Change from baseline was determined using pairwise Student t tests and is expressed as percentage of baseline value. Bone regions are as specified in Figure 1. SDD was calculated from the double baseline results, and is shown as a dotted line on each graph. At the 6-month timepoint for the MF region, several of the lines are overlaid, making it difficult to see directly how many individuals have reached the SDD. The number of individuals with change greater or less than SDD at each timepoint are therefore shown in brackets. SDD: smallest detectable difference; MF: medial femur; LF: lateral femur.

DISCUSSION

In our small, short-term study of people with OA knee selected for high risk of structural progression, 3-D bone area quantified using AAM demonstrated change in 3 months for the medial femoral region, and for both femoral regions at 6 months. Previous analysis of this dataset did not demonstrate significant change in cartilage thickness[1], one of the most promising MRI biomarkers of OA progression to date[11].

Though the participant numbers were small in our study, the change shows a clear trend in bone area change, with 3-month change about half that of 6 months. Rates of area change per bone region were also similar to those reported from a large OA longitudinal dataset[3], which showed annual change of 0.75% in the MF region, as compared with 1.2% in our study, further supporting the validity of these findings.

The structural endpoints in most clinical trials in the musculoskeletal area, such as those for rheumatoid arthritis where good treatments and patient responses are common, are driven by a few percent of progressors (change greater than SDD) because of the relationship between small changes and large measurement noise. Our study is notable, both because significant change is detected in the population, but also because the change shows a clear trend with time, and is greater than SDD in a significant number of participants.

Power calculations, using an SRM of 0.85, the value for change in MF region at 6 months, assuming intervention had 50% reduction, 1-sided, 80% power, L = 0.05%, show that cohorts of ~80 persons would be needed for each arm of an intervention study.

Longitudinal change in bone area has been reported elsewhere[12]. These studies have primarily considered tibial rather than femoral bone, and use 2-dimensional methods of area identification. The repeatability of AAM resulted in an SDD of about 1% compared with 4% in these previous studies.

There are limitations to our work. It is reasonable to expect that there may be some relationship between changes in bone and cartilage, but no relationship was seen in our admittedly small study. While our analysis was based on an appropriately collected, well-designed study, it does represent a posthoc analysis. The MRI scanners and imaging sequences used in our study were as used in the Osteoarthritis Initiative[9]. The images derived from these MRI scans were not optimized to visualize bone, so further responsiveness may be possible with dedicated bone sequences. We have only provided data on one 3-D bone shape biomarker (bone area), and other measures, such as those that measure other regions within the subchondral bone, may be more responsive.

Our study compared bone area with 1 specific method of cartilage measurement; other methods, and other variables such as volume may provide better responsiveness. It may also be possible to enrich a patient group to increase the likelihood of cartilage change, allowing for detection of cartilage change in a small cohort. However, we are not aware of any method showing significant cartilage change in < 30 people in 6 months.

In this small cohort selected for high risk of OA progression, bone area changed in a nearly 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, such as those with a treatment likely to affect bone.

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