Article:
Bowes, MA, Maciewicz, RA, Waterton, JC et al. (2 more authors) (2016) Bone area provides a responsive outcome measure for bone changes in short-term knee osteoarthritis studies. Journal of Rheumatology, 43 (12). pp. 2179-2182. ISSN 0315-162X

https://doi.org/10.3899/jrheum.151118

The Journal of Rheumatology

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Journal:	*The Journal of Rheumatology*
Manuscript ID	2015-1118.R2
Manuscript Type:	Brief Communication
Date Submitted by the Author:	n/a
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Keywords:	Bone, Osteoarthritis, Knee

Bone area provides a responsive outcome measure for bone changes in short-term knee osteoarthritis studies

Michael A Bowes[1], Rose A Maciewicz[2], John C Waterton[3], David J Hunter[4], Philip G Conaghan[5]

Abstract

Objective: This post-hoc study analyzed 3D bone area from an osteoarthritis (OA) cohort demonstrating no change in cartilage thickness.

Methods: 27 women with painful medial knee OA had MRI at 0, 3 and 6 months. Images were analysed 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% [CI 0.32, 0.90]. 40% of subjects had progression > SDD 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.

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Running Head

OA bone area change

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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 osteoarthritis (3, 4), and can be accurately quantified using active appearance modelling (AAM), a form of statistical shape modelling that enables automatic segmentation.(Figure 1) (5, 6). Recent studies in large cohorts have shown that change in 3D 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 BMI, female gender and varus alignment demonstrated no significant change in cartilage thickness at the group level in the medial femur or tibia at 3 or 6 months (8). The current post-hoc study analysed the changes in bone area of the femoral condyles in this cohort to determine the responsiveness of this novel bone biomarker.

Materials and Methods

29 participants were recruited in a multi-centre, non-randomized, observational cohort study at four sites in the USA (8). 27 females had knee pain, a body mass index (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 highest 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 (DESS-we), previously used in the Osteoarthritis Initiative (9). MR images were acquired at recruitment, with follow-up images at 1 week (providing a double baseline), 3 and 6 months. Ethics approval was obtained from the sites involved in the study and all participants gave informed consent.

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Repeat baseline MRI scans were acquired a week apart (8), allowing estimation of repeatability by calculation of root-mean-square coefficients of variation (CoV), and smallest detectable difference (SDD), defined as the mean of the differences ±1.96 standard deviations. Change over time was assessed using a paired 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 visualised by colour 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); mean WOMAC pain score was 7 (1-12). Mean knee alignment was 0.4° (-1.9° to +6.3°) (varus positive); 12 of 27 were left knees. 19 knees were Kellgren Lawrence Grade 3; the remainder were Grade 2.

Repeatability for the MF region was 0.39% (CoV) and 1.1% (SDD), and for the LF region was 0.66% (CoV), 1.9% (SDD). At 3 months the mean change in MF bone area was 0.34% [95% confidence

interval (CI) (0.04, 0.64), p=0.03] and at 6 months 0.61% [CI 0.32, 0.90, p=0.0002]; baseline MF area = 2291 mm^2. In the LF region, the changes were not significant at 3 months 0.24% [CI -0.17%, 0.66, p=0.23], but became significant at 6 months 0.49% [CI 0.18, 0.80, p=0.0021] (Figure 1); baseline = 1527 mm^2. Standardised Response Mean (SRM) of MF at 3:6 months were 0.45:0.85 and for LF at 6 months was 0.66. There were no significant differences between the KL 2 and KL3 groups, for example, MF region changed 0.32 (-0.01,0.65) at 3 months, and 0.57 (0.25,0.89) in the KL3 group, and 0.34(-0.18,0.50) at 3 months, 0.63(0.5,0.76) at 6 months in the KL2 group (all values in percent).

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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, but progressors outnumbered regressors at each point. 41% 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 MT region (4 subjects).

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In this small, short-term study of people with OA knee selected for high risk of structural progression, 3D bone area using AAMs 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 this study, the change shows a clear trend in bone area change, with 3-month change about half that at 6 months. Rates of area change per bone region were also similar to those reported from a large OA longitudinal dataset, which showed annual change of 0.75% in the MF region, as compared to 1.2% in this study (3), 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 This 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, one-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, 13). These studies have primarily considered tibial rather than femoral bone, and use 2D methods of identification of area. The repeatability of AAMs resulted in an SDD of approximately 1% compared to 4% in these previous studies.

There are limitations to this work. It is reasonable to expect that there may be some relationship between changes in bone and cartilage, but no relationship was seen in this admittedly small study. While this analysis was based on an appropriately collected, well designed study, it does represent a post-hoc analysis. The MRI scanners and imaging sequences employed in this study were as used in

the Osteoarthritis Initiative (9). The images derived from these MRI scans were not optimised to visualise bone, so further responsiveness may be possible with dedicated bone sequences. We have only provided data on one 3D bone shape biomarker (bone area) and other measures, such as those that measure other regions within the subchondral bone, may be more responsive.

This study compared bone area with one specific method of cartilage measurement; other methods, and other variables such as volume may provide better responsiveness. However, we are not aware of any method showing significant cartilage change in less than 30 people in 6 months.

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, such as those with a treatment likely to affect bone.

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References

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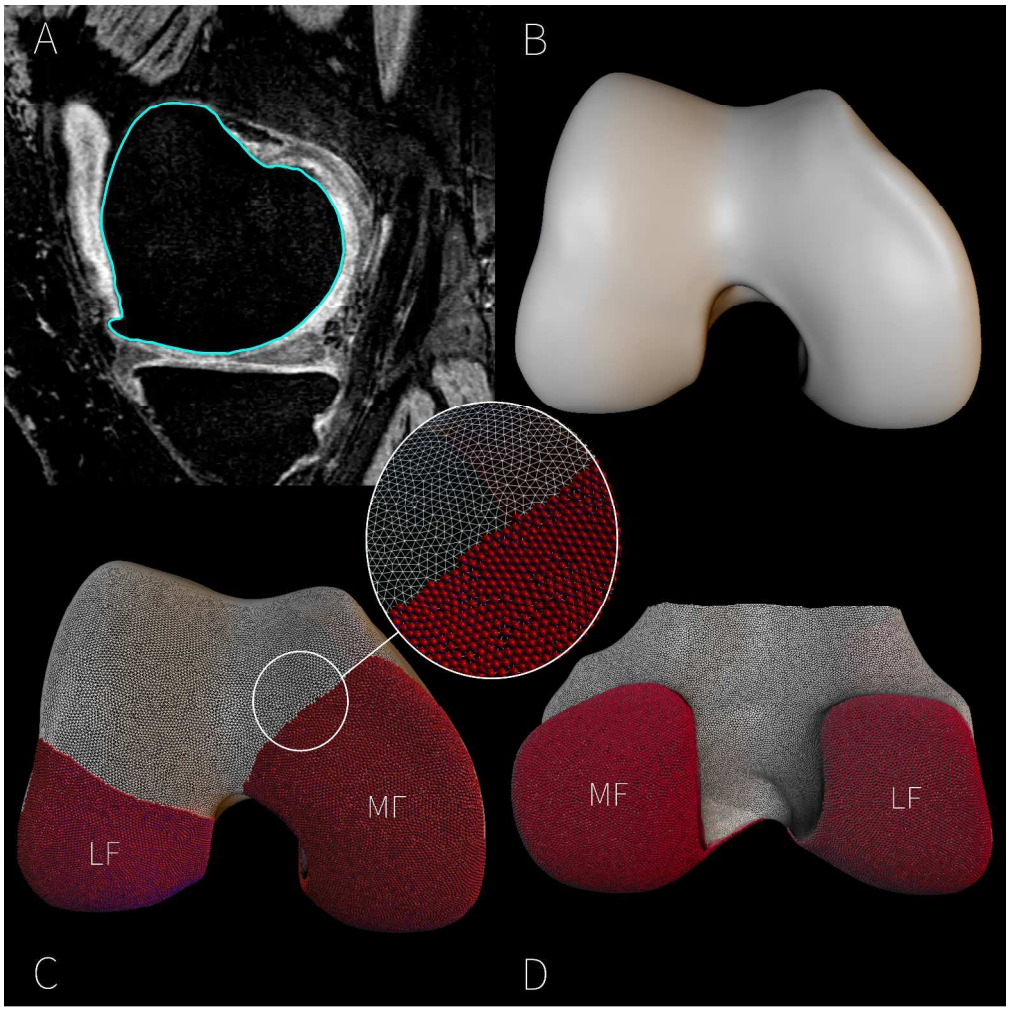

Figure 1: Automatic segmentation of MR images using active appearance models, and generation of anatomical regions

Each image is automatically segmented using active appearance models, which produces a bone surface for femur and tibia. An outline of the automated segmentation in one slice is illustrated (A). The mean bone surface from multiple femurs is presented anatomically in B. The mean bone surface is actually a triangulated mesh (C and D) in which each vertex represents an anatomically corresponded point, or landmark. The vertices contained within the chosen regions are coloured in red. Inset shows close up of landmarks indicating actual density of vertices. MF: medial femur, LF: lateral femur. 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.

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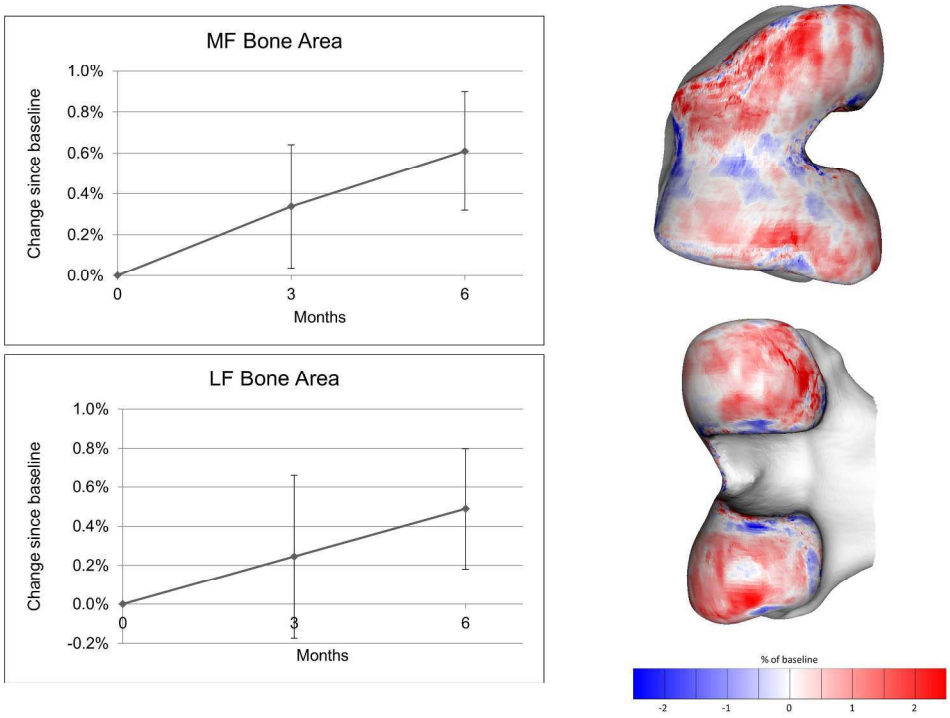

Figure 2: Bone area change at 3 and 6 months
Graphs show change from baseline, using a pairwise Student's t-test, with 95% confidence limits. Figure on right shows average change at each triangle in the mean bone shape at 6 months, expressed as percent of original area).

231x190mm (300 x 300 DPI)

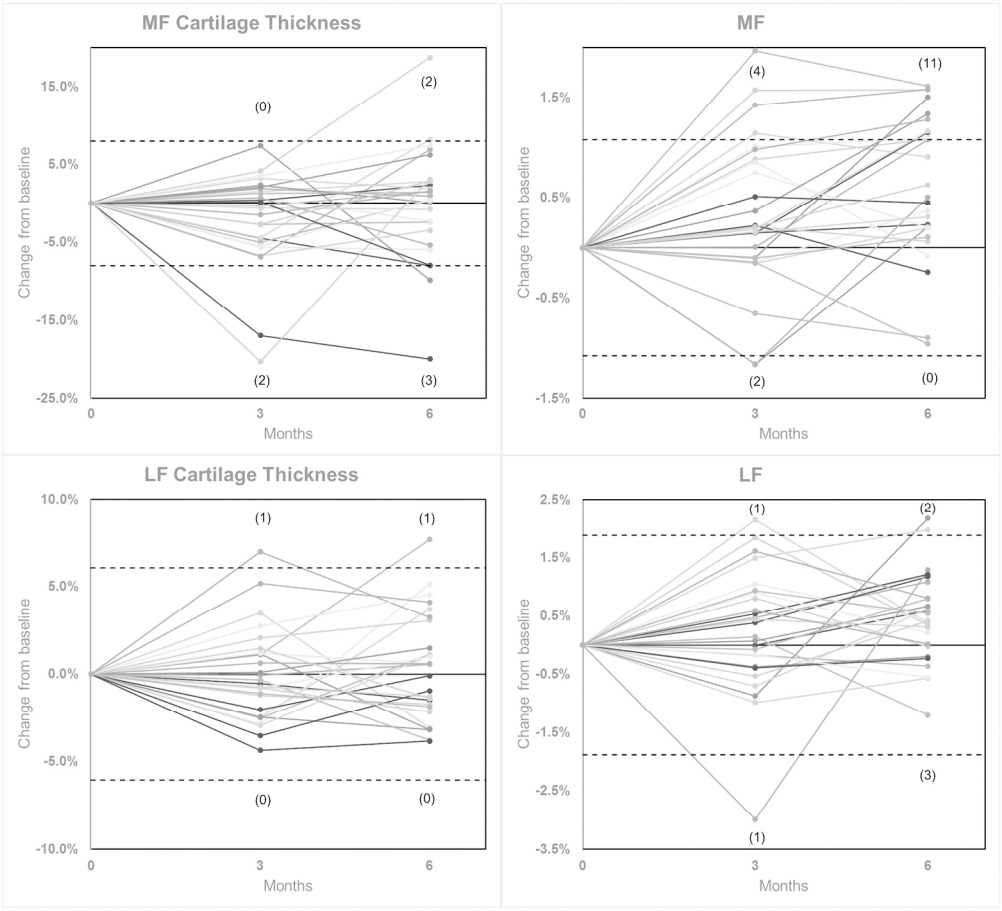

Figure 3: Individual change of bone area and cartilage thickness
Change from baseline was determined using pairwise t-tests, and is expressed as percentage of baseline value. Bone regions are as specified in Figure 1. Smallest detectable difference (SDD) was calculated from the double baseline results, 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.

209x190mm (300 x 300 DPI)

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OA bone area change

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