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EXTENDED REPORT

A novel method for bone area measurement provides new insights into osteoarthritis and its progression

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ABSTRACT

Background Modern image analysis enables the accurate quantification of knee osteoarthritis (OA) bone using MRI. We hypothesised that three-dimensional changes in bone would be characteristic of OA and provide a responsive measure of progression.

Methods 1312 participants with radiographic knee OA, and 885 non-OA controls with MRIs at baseline, 1, 2 and 4 years were selected from the NIH Osteoarthritis Initiative. Automated segmentation of all knee bones and calculation of bone area was performed using active appearance models. In a subset of 352 participants, responsiveness of bone area change was compared with change in radiographic joint space width (JSW) and MRI cartilage thickness over a 2-year period.

Results All OA knee compartments showed increased bone area over time compared with non-OA participants: for example, the 4-year percentage change from baseline in medial femur area for OA (95% CI) was 1.87(0.13), non-OA 0.43 (0.07); p<0.0001. Bone area change was more responsive than cartilage thickness or JSW; 2-year SRM for bone area in the medial femur was 0.83, for the most responsive cartilage thickness measure central medial femorotibial composite (cMFTC): 0.38, JSW: 0.35. Almost half of all knees had change greater than smallest detectable difference at 2 years. Body mass index, gender and alignment had only a small effect on the rate of change of bone area.

Conclusions Changes in bone area discriminated people with OA from controls and was more responsive than the current and impending standards for assessing OA progression. The shape change in OA bone provides a new window on OA pathogenesis and a focus for clinical trials.

INTRODUCTION

Osteoarthritis (OA) results in a massive burden for individuals, in terms of pain and reduced quality of life, and for health economies; this load is rising dramatically with ageing and increasingly obese populations.[1–3] Therapeutic interventions for OA have not progressed significantly for decades. Modern evidence-based guidelines recommend a range of symptom-modifying therapies, but the effect size of such therapies is often small.[4 5] There are no licensed disease-modifying drugs, and structure-modification trials have until recently focussed predominantly on cartilage progression, using radiographic joint space width (JSW) as a surrogate. The lack of sensitivity of this measure has resulted in a requirement for very large patient cohorts followed over long periods of time. This, in turn, has resulted in prohibitive expense and continues to discourage investment in the field.

MRI has, for over a decade, provided more information on OA structure than radiographs; however, this knowledge has not translated into new therapeutic options. With the exception of cartilage volume and thickness measures, we have not been able to quantitatively use much of the three-dimensional (3D) information provided by MRI. However, image analysis has progressed substantially, and active appearance models (AAM), a form of statistical shape modelling, can automatically identify ('segment') all bone surfaces in MR images,[6 7] and systematically align the segmented bones, allowing the study of temporal and spatial structural change in the population.

Bone has long been known to be integral to the OA process.[8 9] Despite this, changes in bone shape have received relatively little attention in OA studies, perhaps because until recently it was difficult to accurately identify and measure such changes, and also because the importance of this tissue as a therapeutic target is unknown. Bone is known to change with the progression of OA; the tibial condyles have demonstrated an increase in bone area,[10 11] and femorotibial area has been shown to be larger in OA knees than in healthy knees.[12]

We wanted to examine the usability of a potential new biomarker in the OA field. We hypothesised that the accurate measurement of bone provided by AAMs would demonstrate systematic patterns of change, and would provide novel measures for assessing OA and its progression.

We used change in the area of subchondral bone, similar to that designated as 'tAB' by a nomenclature committee.[13] Importantly, this definition was modified to include bone from around the cartilage plate—the 'peripheral osteophytes'.

We selected bone area as a feasible method for measuring summary change within a complex, undulating structure. We hypothesised that the rate of change of tAB in specific anatomical regions would differentiate between those with and without radiographic OA. We tested our hypothesis by examining tAB change, measured by AAMs, in a large longitudinal cohort, categorised according to the presence/absence of radiographic OA.

Additionally, we compared the responsiveness of this novel AAM bone measure with medial joint

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space width (mJSW), the standard radiographic measure used to assess OA progression and cartilage thickness, the most widely used quantitative MR measure, in a subset of the data.

METHODS

Data used in the preparation of this article were obtained from the Osteoarthritis Initiative (OAI) database, which is available for public access at http://www.oai.ucsf.edu/. The OAI is a multicentre, longitudinal, prospective observational study of knee OA involving almost 5000 participants (http://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf).

Selection of participants is shown in figure 1; 2526 participants had images at baseline, 1, 2 and 4 years, using the same MRI scanner; MRI scanners were upgraded in the OAI centres as part of a rolling programme. The OA group was defined as all participants having Kellgren–Lawrence (KL) scores of 2 or more at baseline, who had not contributed a knee to the OA group. If more than one knee met these criteria, a single knee was selected being the knee for which cartilage and mJSW measures were available, or the knee with higher KL score, or right knee if KL scores were equivalent. The non-OA group was defined as all participants having KL scores of 0 at all time points; a randomly selected knee was used if both met this criterion.

Twenty-seven participants were excluded, as the knee had been used to build the AAM (see below); 13 participants were excluded for image quality.

A subset of the OA group, Method-OA, was used to assess the performance of tAB as a measure of progression when compared with mJSW and cartilage thickness. Method-OA was based on a group of 600 knees selected by the OAI as a 'core image assessment cohort' including only knees with frequent symptoms and KL grade of 2 or 3 at baseline[14–16]; we excluded those without mJSW readings and those which used both knees from the same participant. Only baseline, 1-year and 2-year cartilage thickness and JSW measures have so far been made publicly available for this subset.

Images for this study were acquired using Siemens 3T Trio systems using the double-echo-in-steady-state sequence (DESS-we).[17]

AAMs for the femur, tibia and patella were built from a training set of 96 examples acquired using the DESS-we sequence. The training set was chosen so as to contain examples from each stage of OA, and included approximately equal numbers of knees for each KL grade. Anatomical regions of tAB were outlined on the mean bone shape as previously described (figure 3).[18] In the femur, the medial femur/medial trochlear femur (MF/MedPF) and the lateral femur/lateral trochlear femur (LF/LatPF) boundary was defined as a line on the bone corresponding to the anterior edge of the medial or lateral meniscus, and extended smoothly to the edge of the tAB. The MedPF/LatPF boundary was defined as the centre of the trochlear groove.

During autosegmentation with AAMs, these regions are automatically propagated to each bone surface, allowing for the measurement of tAB, and the preparation of population maps (figure 3B).

Measurement error for each triangle area in a bone surface was defined as ±3 SD of the differences in area between the baseline and 1-year results of the non-OA group. Spatial distribution of change greater than measurement error was visualised using a colour scale displayed on the mean shape (figure 3C–D).

It was not possible to automatically segment the patella in all participants, as a result of some knees being too large for the imaging apparatus, leading to image aliasing; 43 knees could not be used from the OA group, and seven from the non-OA group.

KL and JSW scores were provided by the OAI; methodological detail for these assessments is available at http://oai.epi-ucsf.org/imageassessments.asp. mJSW is measured using a semiautomated tool shown to be as sensitive as manual measures.[19 20] Additionally, we selected the radiographic JSW measure for this dataset considered the most responsive by the authors of the method, medial JSW at $\times=0.225$ mm along the medial tibia (JSW_225).[21] MRI-based cartilage thickness measurements were computed from segmentations of the weight-

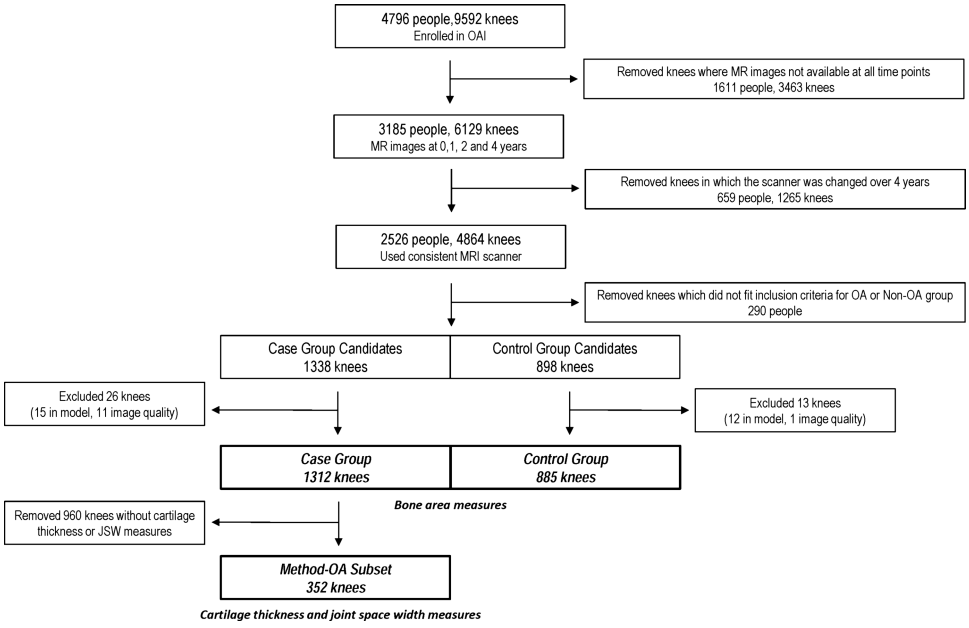

Figure 1 Selection of groups based on availability of images, MRI scanner use and radiographic OA; selection of a subgroup which have joint space width and cartilage measurements. MR scanners were upgraded in the Osteoarthritis Initiative (OAI) centres as part of a rolling programme. The MR scanner upgrade is recorded in the data provided by the OAI for each image.

bearing femorotibial cartilage plates performed by experienced operators blinded to the time of acquisition and to baseline radiographic readings.[16 22 23] We used the readings described in Project 09B (http://oai.epi-ucsf.org/datarelease/SASDocs/kMRI_QCart_Eckstein_Descrip.pdf), including the cMTMF regions identified by the authors as having the greatest sensitivity with this dataset.[24]

The significance of changes in tAB from baseline was determined using a pairwise Student t test.

We selected covariates considered as risk factors for OA,[2 25 26] namely age, body mass index (BMI) and knee alignment, together with KL grade at baseline. Their effects on the rate of change of tAB were examined using Analysis of Covariance (ANCOVA) models built from the OA and non-OA groups, using one model for each region. Assumptions of normality were explored graphically. Statistical analysis was performed on XLSTAT (Addinsoft).

The smallest detectable difference (SDD) and the root-mean-square (RMS) coefficient of variation (CoV) of the bone area and mJSW methods were calculated using baseline and 1-year images of the OAI non-exposed Control group ((http://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf)) which had not been used in the AAM (147 knees). This group did not have radiographic knee OA, and any changes within 1 year would be expected to be small with respect to the size of the measurement. SDD is defined as 1.96 times the SD of the measurement differences. SDD and CoV of cartilage thickness were not available, but have been recently published for a comparable dataset.[27]

RESULTS

Demographic information for the two groups and the subgroup is shown in table 1. A total of 1312 people met the inclusion criteria for the OA group, and 885 people for non-OA. This equates to 87% of all the participants with all images, and a consistent MRI scanner. The OA group were slightly older with a slightly higher BMI. Mean alignment was close to neutral in both groups. Average pain over the 4-year period was low in each group, though higher in the OA group. Cartilage and radiograph measures were available for 352 of the OA Group, and used for the Method-OA subgroup. The Method-OA subgroup was similar to the OA group, though with a greater percentage of KL3 knees, and no KL 4.

The repeatability of all bone area measurements was excellent, with typical CoV values of less than 1%. Radiographic JSW repeatability on this dataset was around 5%; cartilage thickness measures were not available.

There was a marked difference in the rate of change of tAB between the OA and non-OA groups in all knee compartments (table 1 and figure 2): the unadjusted mean change per annum for MF tAB was 0.48% and 0.13% in the OA and non-OA groups, respectively (unadjusted mean difference (95% CL) 0.35% (0.04%), p<0.0001). ANCOVA models of the OA group for rate of change in MF found the constant term to be 0.74% per annum (pa). The rate of change was 0.29% higher in females, 0.02% higher for each unit of increased BMI, and 0.02% higher for each degree of varus alignment. While MF increased over time (and hence with age), the rate of increase slowed by 0.01% for each additional year of age. In people with KL 3 or 4 knees, the rate of increase was faster compared to those with KL 2 by 0.31%.

The comparable equation for the non-OA group of MF alone was: 0.15+0.069 (if female)+0.003 (per degree of varus) +0.005(per unit of BMI −0.003 (per year of age) percent per annum. Similar results were obtained for the MT regions (data not shown). Standardised coefficients for the MF models are shown in figure 2.

Summary visual images of the areas which exhibited change in area greater than measurement error showed distinctive

Table 1 4-year changes in tAB from baseline, and demographics for OA and non-OA groups

	Non-OA	OA	Method-OA
Baseline demographics			
n	885	1312	352
Male (female) %	44.3 (55.7)	42.7 (57.3)	43.5 (56.5)
Age	59.0 (8.9)	62.4 (8.9)	60.6 (8.9)
BMI	27.0 (4.3)	29.1 (4.5)	29.6 (4.6)
KL Grade—baseline (% 0, 1, 2, 3, 4)	100, 0, 0, 0, 0	0, 0, 62, 32, 6	0, 0, 48, 51, 0
KL Grade—4 year (% 0, 1, 2, 3, 4)	100, 0, 0, 0, 0	0, 0, 54, 42, 18	0, 0, 41, 42, 18
Alignment	−0.4 (3.3)	−0.3 (3.9)	−0.4 (4.1)
Mean 4-year WOMAC pain	1.1 (1.5)	2.5 (2.6)	3.9 (2.9)

Bone	Region	Non-OA 4-year change (%)	OA 4-year change (%)
Femur	MF	0.50 (0.06)	1.91 (0.13)
	MedPF	0.52 (0.08)	1.62 (0.13)
	LF	0.59 (0.07)	1.35 (0.10)
	LatPF	0.41 (0.07)	1.05 (0.09)
	Notch	0.10 (0.08)	1.07 (0.11)
Tibia	MT	0.44 (0.08)	1.37 (0.12)
	LT	0.65 (0.08)	1.39 (0.11)
Patella (n=1 269 878)	MP	1.16 (0.1)	1.99 (0.16)
	LP	1.18 (0.11)	2.05 (0.16)

Alignment values are in degrees, with valgus negative. Demographic values are shown as mean (SD); 4-year change was calculated from baseline, using a pairwise Student t test, and is shown as percentage change (95% confidence limits).
Regions are displayed graphically in figure 3. All changes were highly significant (<0.0001).
BMI, body mass index; KL, Kellgren–Lawrence; LatPF, lateral femur (patellofemoral); LF, lateral femur (femorotibial); LP, lateral facet of patella; LT, lateral tibial condyle; MedPF, medial femur (patellofemoral region); MF, medial femur (femorotibial region); MP, medial facet of patella; MT, medial tibial condyle; Notch, femoral notch; OA, osteoarthritis.

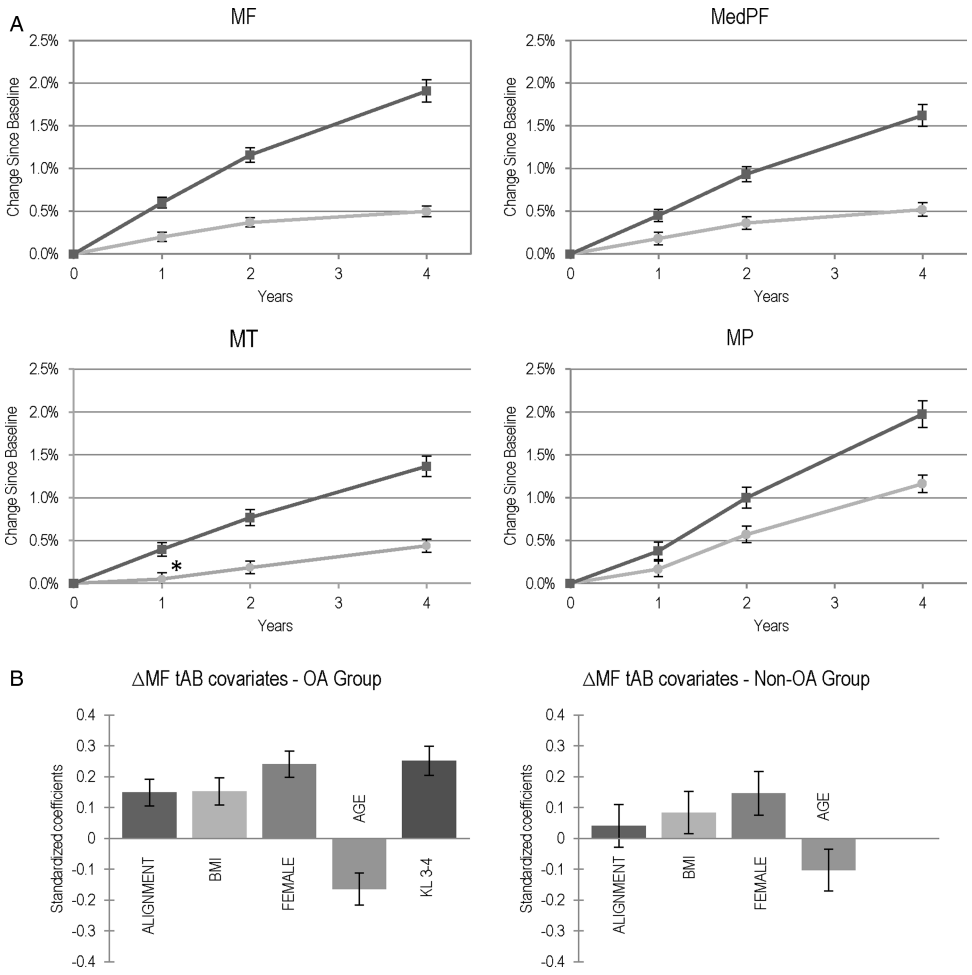

Figure 2 Percentage change in bone area (tAB) for medial regions in OA and non-OA groups, and effects of covariates on medial femur (MF) region. (A) shows percentage change from baseline for OA and non-OA groups (95% CI). All changes were highly significant ($p<0.0001$) except *. (B) shows standardised coefficients taken from analysis of covariance (ANCOVA) models of the non-OA and OA groups, with slope of change in MF tAB as the dependent variable, with the covariates shown here as explanatory variables.

spatial patterns of change in the OA group (figure 3C and D). In the femur and patella increase in area was seen most strongly around the edge of the cartilage plate, with smaller areas affected in the central articulating surfaces. In the tibia, change was more widespread across the whole plateaux, though more prominent around the edges.

Table 2 presents the comparative responsiveness for the different imaging measurements. Several anatomical regions showed superior responsiveness for change of tAB at 2 years compared with the most responsive cartilage thickness measure. In turn, the responsiveness of cartilage thickness was greater than the most responsive JSW measure, JSW-225. For example, the 2-year SRM for MF tAB was 0.83, central medial femorotibial composite (cMFTC) ThCtAB: 0.38, JSW-225: 0.35. Almost half the OA group showed change greater than measurement error for tAB, compared with 13% using mJSW as a measure. Data were not available for cartilage thickness.

DISCUSSION

This study has applied novel 3D image analysis to the investigation of joint structure in OA and, consequently, provided new insights into the pathogenesis of the disease as well as a new responsive biomarker for exploitation in OA clinical trials. This is the first study to examine longitudinal 3D changes in all the knee bones in large cohorts with and without radiographic knee OA. Change in tAB discriminated between OA and non-OA groups in all compartments of the knee.

Previous studies have assessed bone area, and reported that medial tibial bone area increased by 1.1% per annum in OA subjects,[10] and approximately 0.5% in healthy subjects.[28] Our study found a similar pattern, though of smaller magnitude (0.8% per annum vs 0.12% in MF). The methods are not directly comparable; the previous work measured area using outlines on two adjacent axial slices, while the current method uses the complete 3D bone surface.

We examined a number of covariates associated with progression of OA of the knee in the non-OA and OA groups. Female gender, BMI and varus alignment were associated with higher rates of change of tAB in the medial femur and tibia, however, these effects were smaller than the difference in rate of change between the non-OA and OA groups. These covariates were associated with greater change in the OA group than in the non-OA.

The effect of age was surprising: although tAB increased over time (and hence with age) the rate of increase was slower in older participants. It has been commonly understood that knees increase in size with age.[29] We were unable to find studies that corrected for the presence of radiographic OA when considering bone size.

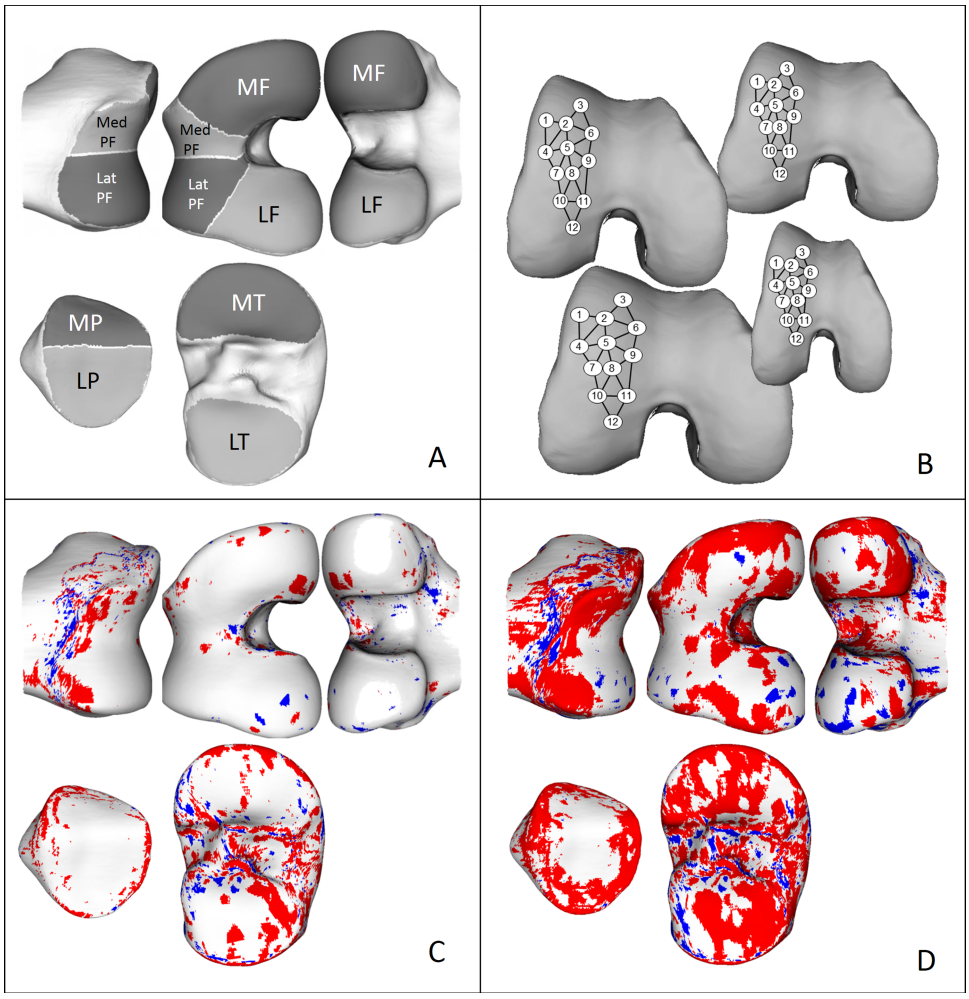

Figure 3 Selection of anatomical regions and location of 4-year change. (A) shows the regions used in this study, displayed on the mean shape for each bone. MF, medial femur; LF, lateral femur; MT, medial tibia; LT, lateral tibia; MedPF, medial trochlear femur; LatPF, lateral trochlear femur; MP, medial patella; LP, lateral patella. The MF/MedPF and the LF/LatPF boundaries were defined as a line on the bone corresponding to the anterior edge of the medial or lateral meniscus in the mean model. The MedPF/LatPF boundary was defined as the centre of the trochlear groove in the mean model. (B) shows schematic results for an active appearance model fit to 4 different femurs; each bone surface is fitted with a dense set of landmarks during autosegmentation, which corrects for individual shape differences. It is impractical to display the actual density of the model, for example, the femur model includes over 100 000 points. Location of 4-year change for the non-OA group is displayed in (C) and for the OA group in (D). Areas which increase in size more than measurement error are coloured red; those with a similar decrease are coloured blue.

It may be that the perceived change in bone size with age is actually caused by the presence of individuals with knee OA.

Previous studies have supported the importance of bone shape, using 2D shape taken from radiographic images in hip and knee OA.[30–32] These studies have established correlation between principal components of shape models of the hip and knee. However, these studies use only 2D information and are, therefore, prone to error. Apparent edges in radiographs are often composites of genuine shape change and projection artefacts. When comparing two radiographs it is not possible to determine with certainty that a knee has changed shape, rather than simply rotated or tilted.

All bones demonstrated an increase in area of all articulating surfaces (figure 3D), particularly on the medial side. This is accompanied by the development of a circumferential increase in area around each cartilage plate which, presumably, equates to the region in which osteophytes form. In the non-OA group, only small areas of bone increase in area, mostly within the osteophytic region of the bone. This may suggest that more than one mechanism is involved in the change in bone—the formation of osteophytes, and a general spreading of the 'normal' bone.

The biological mechanisms that cause the increase in bone area demonstrated in this study are not well understood.[33] Bone scintigraphy suggests that bone turnover is greater in OA subjects than controls.[34] The trabecular structure of bone in OA has recently been studied using fractal signature analysis, suggesting that changes in bone trabecular structure are associated with the presence and progression of OA.[35] It is noteworthy that recent clinical trials have demonstrated beneficial effects in OA using agents that have well-described effects on bone.[36–38]

We compared responsiveness of bone changes with the current radiographic standard and the standard MRI measure of cartilage. We used the Method-OA cohort which includes participants similar to those required for inclusion in modern clinical trials of structure modification. We selected the most responsive measures of JSW and MR cartilage thickness as suggested by the authors of the method,[21 24] and compared them with the most

Table 2 Comparison of responsiveness using method-OA subset (n=352)

Region	SRM 1:2 years	Type of Measure	2-year change	2-year change (%)	Smallest detectable difference (CoV)	Percentage >:<SDD at 24 months
MF	0.66:0.83	MRI bone area	38.40 (1.57) mm^2	1.57 (0.19)	1.4 (0.4)	50.0:2.0
MedPF	0.36:0.65	MRI bone area	8.68 (1.38) mm^2	1.24 (0.20)	1.9 (0.6)	30.7:3.1
LF	0.51:0.72	MRI bone area	20.54 (2.93) mm^2	1.18 (0.17)	1.8 (0.6)	31.3:2.0
LatPF	0.18:0.46	MRI bone area	8.40 (1.89) mm^2	0.66 (0.15)	1.8 (0.6)	20.2:2.8
Notch	0.37:0.55	MRI bone area	14.04 (2.65) mm^2	0.93 (0.18)	2.0 (0.6)	24.4:2.6
MT	0.35:0.56	MRI bone area	11.53 (2.12) mm^2	0.99 (0.18)	1.7 (0.6)	28.4:2.6
LT	0.34:0.57	MRI bone area	9.63 (1.76) mm^2	1.05 (0.19)	2.4 (0.8)	21.6:2.3
MP	0.15:0.37	MRI bone area	5.63 (1.56) mm^2	1.02 (0.28)	2.6 (0.8)	29.2:9.2
LP	0.17:0.45	MRI bone area	8.23 (1.92) mm^2	1.17(0.27)	3.0 (1.0)	21.7:4.2
mJSW	−0.19:−0.25	Radiographic JSW	−0.17 (0.07) mm	−4.27 (1.80)	16.7 (5.1)	13.6:4.0
JSW_225	−0.22:−0.35	Radiographic JSW	−0.21 (0.06) mm	−4.19 (1.18)	14.7 (4.7)	13.4:2.3
cMF ThCtAB	−0.28:−0.38	MRI cartilage thickness	−0.06 (0.02) mm	−3.26 (0.90)	n/a	n/a
MT ThCtAB	−0.20:−0.30	MRI cartilage thickness	−0.03 (0.01) mm	−1.54 (0.52)	n/a	n/a
cLF ThCtAB	−0.13:−0.09	MRI cartilage thickness	−0.01 (0.01) mm	−0.46 0.54)	n/a	n/a
LT ThCtAB	−0.33:−0.41	MRI cartilage thickness	−0.04 (0.01) mm	−1.92 (0.48)	n/a	n/a
cMFTC ThCtAB	−0.28:−0.38	MRI cartilage thickness	−0.06(0.02) mm	−3.26(0.90)	n/a	n/a

Regions of bone area are shown in figure 3A and table 1.[21] MRI cartilage thickness changes are mean thickness/area of bone (ThCtAB).
Mean 2-year change from baseline (95% confidence limit) is shown using the appropriate units, and as percentage of mean baseline value. SRM=(mean change from baseline/mean SD of change). All changes were highly significant ($p<0.0001$). Smallest detectable difference (SDD) and CoV are expressed as percentages of baseline to allow comparison of different measurement methods. See Discussion for SDD/CoV of MRI cartilage thickness measures. Note: 3 IDs from the JSW-225 measure had no value recorded for one time point, and were excluded. N for MP and LP bone area measures was 336 due to image aliasing in 16 cases.
cLF, central lateral femur; cMFTC, central medial femorotibial composite; JSW, joint space width; JSW_225, medial JSW at ×=0.225 mm; cMF, central medial femur; LatPF, lateral trochlear femur; LP, lateral patella; LT, lateral tibia; MedPF, medial trochlear femur; mJSW, medial minimum JSW; MP, medial patella; MT, medial tibia.

responsive tAB measure. The relationship between cartilage thickness and JSW in most of this cohort have recently been reported elsewhere; our results concur closely with the SRM values reported there.[24] It is important to recognise that we compared different measures assessing different OA pathologies. The authors of the previous publication considered this,[24] and concluded that different constructs were being evaluated.

The increased sensitivity of the method is, in part, due to the improved repeatability. AAM segmentations were highly repeatable, with CoVs of less than 1%, compared with around 5% for JSW (table 2). Cartilage thickness CoV has been reported from the group performing the measures at around 2–3%.[39] In a clinical trial expected to produce a 50% effect with a double-sided, 80% power, L=0.05 design, then the cohort size assuming a 1-year trial would be: JSW 225, 1298 patients per group, FTJ cartilage thickness: 459 patients, MF tAB: 149 patients.

There are limitations to our study. We have considered only one measure of 3D shape, namely the area of a triangulated surface. 3D shape is complex, and other measures may be more sensitive.

This study assumes that the material imaged in the DESS-we MR image sequence represents bone, rather than another tissue type. MR is unable to directly identify the presence of calcium, and further work is needed to establish that the surfaces are indeed bone. The method of segmentation is automated, and although shown to be accurate and repeatable may not identify all subtle detail involved in particular disease conditions.[10 11] Alignment values were recorded at enrolment, using a clinical goniometer; this is not a particularly reliable method of measurement.

Comparisons of responsiveness in this study used the SRM of the change. This measure is dependent on accurate determination of the SD of the change, and can be affected by small numbers of outliers.

This study has only provided information on the construct validity, reliability and responsiveness of a novel 3D bone biomarker—it has not addressed all the issues associated with biomarker validation. A recent publication has considered the validity of AAM-determined bone shape for predicting incident radiographic knee OA.[40]

It would be interesting to compare all three measures from this study in all OA and non-OA participants in our study; however, cartilage measures were not available for the non-OA group.

This is the first report of the use of bone area from 3D surfaces in all knee bones, and there is scope to improve the sensitivity and specificity of the method; technologies other than AAMs may provide similar or better measures of bone structures.

Change in bone area clearly delineated people with OA from controls and was more responsive than the current radiographic standard and the impending standard (MRI cartilage) for assessing progression. In order to be useful, a biomarker needs to be responsive, relatively absent in controls, and present in a large proportion of subjects in a clinical trial. Change in bone area measured using AAMs uniquely meets all these criteria. The change in bone found in this study provides an exciting new window on pathogenesis of the disease, and suggests that bone can now provide a new focus for clinical trials.

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Contributors MAB: contributed to study design, data analysis, data interpretation and writing. CBW: data analysis, data interpretation. GRV: data analysis, data interpretation. PGC: study design, data interpretation, writing.

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Competing interests MAB, GRV and CBW report that they are employees and shareholders of Imorphics Ltd. PGC has nothing to disclose.

Ethics approval The Osteoarthritis Initiative obtained ethics approval.

Provenance and peer review Not commissioned; externally peer reviewed.

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Notes