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Marked and rapid change of bone shape in acutely ACL injured knees – an exploratory analysis of the Kanon trial

M.A. Bowes † *, L.S. Lohmander ‡, C.B.H. Wolstenholme †, G.R. Vincent †, P.G. Conaghan §, R.B. Frobell ‡

† Imorphics Ltd, Manchester, UK
‡ Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Orthopedics, Lund, Sweden
§ Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds, UK

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SUMMARY

Background: To investigate changes in knee 3D bone shape over the first 5 years after acute anterior cruciate ligament (ACL) injury in participants of the randomized controlled KANON-trial.
Methods: Serial MR images over 5 years from 121 young (32 women, mean age 26.1 years) adults with an acute ACL tear in a previously un-injured knee were analyzed using statistical shape models for bone. A matched reference cohort of 176 individuals was selected from the Osteoarthritis Initiative (OAI). Primary endpoint was change in bone area of the medial femoral condyle; exploratory analyses compared results by treatment and examined other knee regions. Comparisons were made using repeated measures mixed model ANOVA with adjustment for age, sex and body mass index (BMI).
Results: Mean medial femur bone area increased 3.2% (78.0 [95% CI 70.2 to 86.4] mm^2) over 5 years after ACL injury and most prominently in knees treated with ACL reconstruction (ACLR). A higher rate of increase occurred over the first 2 years compared to the latter 3-years (66.2 [59.3 to 73.2] vs 17.6 [12.2 to 23.0] mm^2) and was 6.7 times faster than in the reference cohort. The pattern and location of shape change in the extrapolated KANON data was very similar to that observed in another knee-osteoarthritis cohort.
Conclusion: 3D shape modelling after acute ACL injury revealed rapid bone shape changes, already evident at 3 months. The bone-change pattern after ACL injury demonstrated flattening and bone growth on the outer margins of the condyles similar to that reported in established knee osteoarthritis.

Introduction

Osteoarthritis (OA) is a multifactorial process that leads to joint-related pain and stiffness as well as decreased quality of life for those affected[1]. Curative or disease modifying treatments are lacking; symptomatic therapy often has modest efficacy and is commonly poorly tolerated. Recent estimates suggest that 250 million people worldwide suffer from OA of the knee[2], and that 15 million quality adjusted life years (QALYs) are lost over the remaining life span of US citizens diagnosed with knee OA[3].

Anterior cruciate ligament (ACL) injury is associated with a highly elevated risk of knee OA development, especially when associated with a meniscus tear[4,5]. The underlying mechanisms are not fully understood, but likely involve both the initial acute traumatic insult and long-term changes in dynamic joint loading. Surgical reconstruction of the torn ACL is performed with the aim of normalizing joint stability and kinematics and decreasing the risk of OA development. However, high quality trials have failed to present evidence in support of these aims[6–9]).

Plain X-ray examination is currently the gold standard to assess onset and progression of structural joint changes in OA[10]. However, the complexity of OA is highlighted in slow development of radiographic signs and the poor relation between typical radiographic manifestations (osteophytes and joint space narrowing) and symptoms reported by the patient. Finding a valid and early imaging biomarker to monitor and predict OA development is therefore important to facilitate research on disease modifying therapeutic OA interventions. Three-dimensional (3D) bone shape, derived from magnetic resonance imaging (MRI) using statistical

* Address correspondence and reprint requests to: M. A. Bowes, Worthington House, Towers Business Park, Wilmslow Road, Didsbury, Manchester, M20 2HY, UK.
E-mail address: mike@imorphics.com (M.A. Bowes).

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shape modelling (SSM) and measured as change in bone area, was recently proposed as a valid biomarker in OA intervention clinical trials since it was shown to be associated with radiographic OA progression[11]. Bone area has also been shown to predict subsequent radiographic OA[12], was larger in knees with radiographic OA compared to those without OA[13], and predicted the need for knee joint replacement[14]. In addition, 3D bone shape change was consistent over time[11]. Bone area has demonstrated greater responsiveness in small cohorts than the widely used MR outcomes of cartilage volume and thickness[13,15].

Given the strong relation between joint injury and a relatively rapid development of OA. The KANON-trial, involving patients with acute ACL-injury randomized to a surgical or a non-surgical treatment strategy, provided a relevant human model to explore early stages of OA development[6,7]. In the present explorative study, we used a novel, validated MRI analysis technique to investigate changes in knee 3D bone shape over the first 5 years after acute ACL injury in patients enrolled in the KANON-trial.

Methods

Material

Study group

The KANON-trial (ISRCTN 84752559) included 121 young (32 women, mean age 26.1 years) active adults with an acute ACL tear in a previously un-injured knee. Patients were randomized to rehabilitation plus early ACL reconstruction (ACLR, $n = 62$) or rehabilitation plus the option of having a delayed ACLR if needed ($n = 59$). Major exclusion criteria were: total collateral ligament rupture, full-thickness cartilage lesion seen on MRI, or inability to undergo an MRI examination; details of the recruitment process as well as the results after 2 and 5 years have been published[6,7,16].

During the 5 year follow up period, only one subject was lost to follow-up and 30 (51%) of those randomized to 'rehabilitation plus the option of having a delayed ACLR if needed' had a delayed ACLR[11]. All included patients had MRIs taken at baseline, 2 and 5 years; the first 63 recruited patients also had MRIs acquired at 3, 6 & 12 months. The baseline MRI acquisitions of three individuals could not be processed due to image quality issues and one lacked body mass index (BMI) values (needed for adjustment) leaving 117 participants in the acute ACL injury group (Table I). In agreement with previous publications from this trial[6,7], 3 individuals were excluded from the 'as treated' analysis due to lack of clinical follow up data at 5 years (1) and non-compliance to treatment (2) leaving 114 available for the as-treated analysis: 57 treated with rehabilitation plus early ACLR, 29 treated with rehabilitation plus delayed ACLR, 28 treated with rehabilitation alone.

Table I
Demographics and baseline bone areas of the KANON and reference groups

	KANON ($N = 117$)	Reference ($N = 176$)
Females, *n* (%)	31 (26%)	88 (50%)
Age, years, mean (SD)	26.2 (4.9)	47.9 (1.7)
BMI, kg/m^2, mean (SD)	24.1 (2.9)	27.2 (4.2)
Baseline bone areas, mm^2 *		
MF, mean (95% CI)	2334 (2220–2448)	2515 (2350–2681)
LF, mean (95% CI)	1674 (1581–1767)	1854 (1719–1988)
TrFMed, mean (95% CI)	668 (636–701)	705 (659–752)
TrFLat, mean (95% CI)	1264 (1203–1324)	1336 (1248–1424)
MT, mean (95% CI)	1139 (1083–1196)	1205 (1123–1288)
LT, mean (95% CI)	903 (859–947)	916 (852–980)
MP, mean (95% CI)	519 (492–546)	555 (516–594)
LP, mean (95% CI)	666 (631–702)	711 (659–763)

MF: Medial Femur; LF: Lateral Femur; TrFMed: Medial Trochlea Femur; TrFLat: Lateral Trochlea Femur; MT: Medial Tibia; LT: Lateral Tibia; MP: Medial Patella; LP: Lateral Patella. Baseline bone area is presented as mean value in mm^2 with 95% confidence limits.

* Adjustment for age, sex and BMI was performed since the reference cohort was significantly different to the Kanon cohort ($P < 0.05$).

Reference group

Age and gender matched healthy reference cohorts with similar activity level are scarce. Knee MRIs of the Osteoarthritis Initiative (OAI), an ongoing multi-centre observational cohort study of knee and hip OA (http://www.oai.ucsf.edu/) funded by the NIH and industry[17], have been analyzed using the same 3D shape modelling technique as used here[13]. The OAI enrolled 4796 subjects aged 45–79 at inclusion that have been followed for up to 8 years[17,18]. To form an OAI-based reference group comparing to the KANON group as closely as possible, we selected individuals of age 45 to 50 who were at risk for OA development but did not display signs of radiographic OA (i.e., Kellgren Lawrence [KL] scores of 0) at any imaging time-point and had MR images available for comparable time points as the KANON study cohort (0, 12, 24 and 48 months). If both knees of one individual fit these criteria, an index knee was chosen at random. A total of 176 knees met these criteria and thus constitute the reference group of this study.

MR image acquisition

In the KANON trial, MR images were acquired using a 1.5T Gyroscan Intera magnet (Philips) and a commercial circular polarized surface coil. The imaging protocol included a 3D Fast Low Angle Shot (FLASH), a T2* weighted 3D gradient-echo sequence (GRE), sagittal and coronal dual echo turbo spin echo (DETSE) and Short Tau Inversion Recovery (STIR) sequences as described[18].

In the OAI, 3T MRI systems (Trio, Siemens Healthcare, Erlangen, Germany) were used. The MRI pulse sequence protocol included a coronal two-dimensional (2D) intermediate-weighted (IW) turbo spin-echo, sagittal 3D dual-echo at steady-state, with water excitation (DESS-we), coronal and axial multiplanar reformations of the 3D DESS-we and sagittal IW fat-saturated turbo spin echo (TSE) sequences[18].

MRI image processing

Femur, tibia and patella bone surfaces were automatically segmented from the MR images (3D GRE and 3D DESS-we sequences in KANON and OAI knees, respectively) using active appearance models (AAMs), a form of SSM used for automated segmentation, provided by Imorphics (Manchester, UK). AAM search is a widely used method[19] and was performed as described[13]. Briefly, AAMs of the femur, tibia and patella were constructed from a training set of 96 knee MRIs from the OAI, using the DESS-we sequence. The training set was selected to contain examples across the range of radiographic OA. Anatomical regions were identified on the mean bone shape (regions shown in Fig. 1)[20]. We used a definition of the area of subchondral bone, or 'tAB', similar to that designated by a nomenclature committee[21], however, it was modified to also include bone (peripheral osteophytes) from around the cartilage plate as described (10).

Regions used in this study are presented in Fig. 1. The bone area of the medial femur region (MF) in mm^2 was used as the primary endpoint, as it has been shown to be the most responsive region in OA (10).

Shape change visualization

Shape differences between OA and non-OA knees were visualized using an "OA vector" of 3D shape, as previously described (10, 11). Using the training set of 96 individuals described above, which were selected to contain approximately equal numbers of OA and

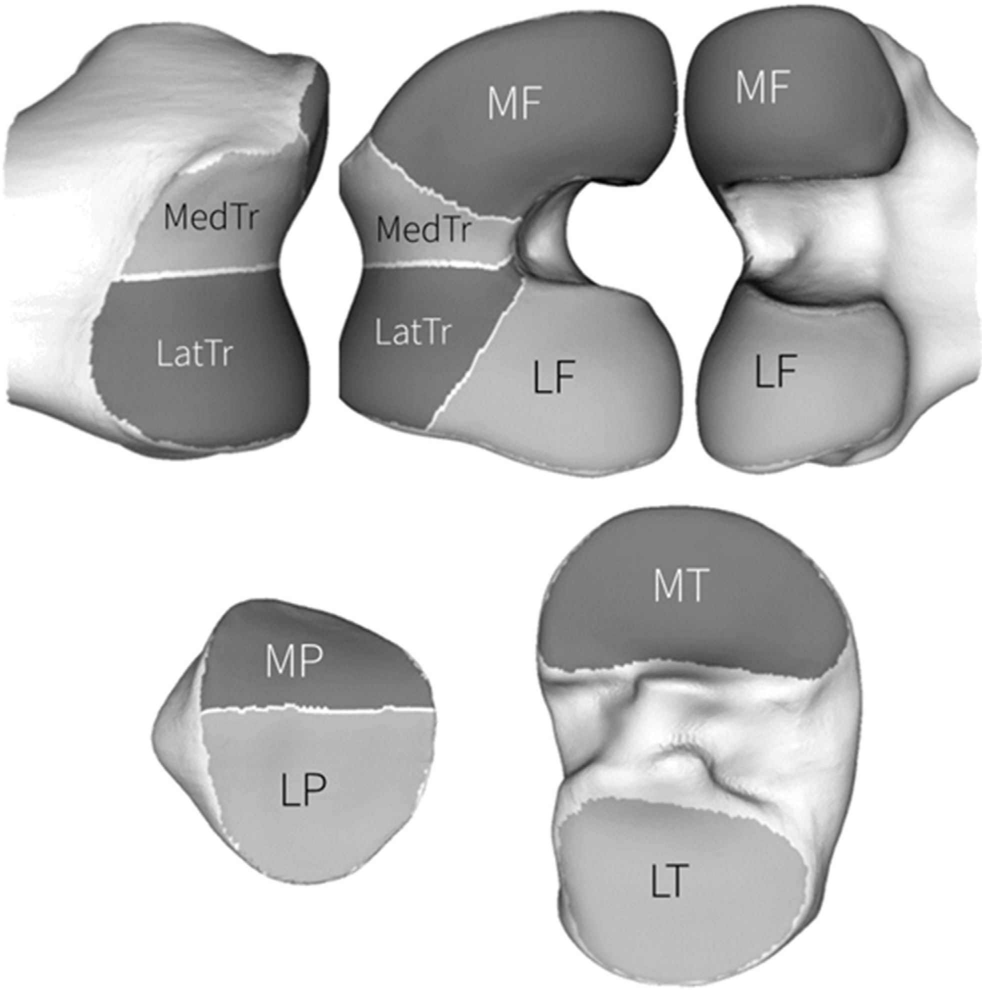

Fig. 1. The regions used in this study, displayed on the mean shape of each bone. medial femur region (MF), medial femur; LF, lateral femur; MT, medial tibia; LT, lateral tibia; MedTr, medial trochlear femur; LatTr, lateral trochlear femur; MP, medial patella; LP, lateral patella. The MF/MedTr and the LF/LatTr 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.

non-OA knees, the OA vector for each bone (i.e., femur and tibia) was calculated by taking the principal components of the mean non-OA shape, and the mean OA shape and drawing a straight line through them. This vector, showing the typical direction of change in bone shape as OA develops, has been used on a number of other cohorts to assess OA status where the distance along the vectors has been shown to be predictive of future onset of OA[12], and responsive to change in radiographic OA[11].

Realistic extreme shapes along the femur and tibia OA vectors (i.e., extreme non-OA shape and extreme OA shape) were identified from the distribution of individual bone shapes in the training set projected onto the OA vector. The 95% confidence limits of the distribution along the vector provided realistic estimates of the extreme OA and non-OA shapes, and allows visualization of the bone shapes at each of these two points using the shape model from the training set (Fig. 4). This analysis of shape is well-suited to visualize overall shape changes, as it includes all available 3D information, and is not affected by the size of the patient[22].

A comparable vector was constructed and calculated for the KANON cohort using the mean shape at baseline and at 60 months. We compared the amount of change in position along the femur and tibia OA vectors, with the bone area measures used in the KANON study. Change in the OA vector for the femur correlated well with change in MF bone area in the KANON dataset over 5 years ($r^2 = 0.63$).

As KANON patients were young and only had 5 years of follow up, any shape change was still small compared to the shape differences of the OA training set which included knees with no signs of radiographic OA and knees with end-stage OA. In order to visualize the small change at 5 years using a perspective of 20 years, we extrapolated the change 4-fold from the 60 month result (Fig. 4). This method cannot predict the rate of future shape change but does indicate whether 3D shape change occurs in a similar manner to OA, in a group of ACL ruptured knees.

Assessment of segmentation accuracy, and effects of notchplasty/metal artefacts

All baseline images were manually segmented by an experienced segmenter using specific software (EndPoint, Imorphics, Manchester, UK). In a second step, results of automated segmentation were compared to the reference manually-segmented bone surface. This method involves measuring the distance between the reference surface, and the automated segmentation surface, at each point of all of the model points (52,892 for the femur, 34,383 for the tibia, and 17,582 for the patella).

Specific effects of surgery were manually assessed by careful visual examination of images, overlaid with their associated segmentations, prior to and after ACLR to assess change in the bone surface identified by the method.

Statistical analysis

For the acutely ACL injured cohort (full study cohort), we investigated change in bone area using repeated measures mixed model ANOVA, with adjustment for baseline imbalance and using an unstructured variance-covariance matrix; all analyses were adjusted for age, sex and BMI in addition. The degrees of freedom were calculated using Satterthwaite's method. The primary region of interest was the medial femoral condyle; all other regions were of secondary interest in this exploratory analysis. Results are presented as adjusted means of change and 95% confidence intervals for different time periods over 5 years. Comparisons between the full study cohort and the reference cohort were made graphically without adjustments (Fig. 2); no hypothesis tests regarding identical parameters were performed since the two cohorts were not comparable in fundamental characteristics. Comparisons between the as-treated groups of the ACL injured cohort were made with adjustments and using the 95% CI of mean change. Statistics were calculated using Stata 14.

Results

Participants of the reference group were substantially older (mean age 47.9 [SD 1.7] vs 26.2 [4.9] years), had a higher proportion of females (88% vs 31%) and had a higher body mass index (BMI, mean BMI 27.2 [4.2] vs 24.1 [2.9] kg/m^2) than those of the KANON-study group. There were only minor, statistically non-significant, between group differences in adjusted baseline bone areas when comparing the reference and KANON-study groups (Table I). In the following, results are initially presented for the full KANON-study cohort, and then for the three ‘as treated’ patient groups: rehabilitation plus early ACLR, rehabilitation plus optional delayed ACLR, and rehabilitation alone. Given the statistically significant and clinically relevant differences in age, sex and BMI between KANON- and reference group, results were presented graphically without statistical comparisons between these two groups (Fig. 2).

Segmentation accuracy, and effects of notchplasty/metal artefacts

Mean automated segmentation accuracy of all three bones was −0.0009 mm, with ±95th percentiles of error of +0.34/−0.43 mm (a +ve error represents the automated surface being outside the reference surface. Visual examination of the automated segmentations showed no obvious effects of the metal artefacts in any of the images. Notchplasty (which would have affected only the lateral femur,LF) produced a small, albeit statistically non-significant, decrease in the rate of change of the LF region (corresponding to approximate 2 mm^2 slower change per annum). No other regions were affected by notchplasty or metal artefacts.

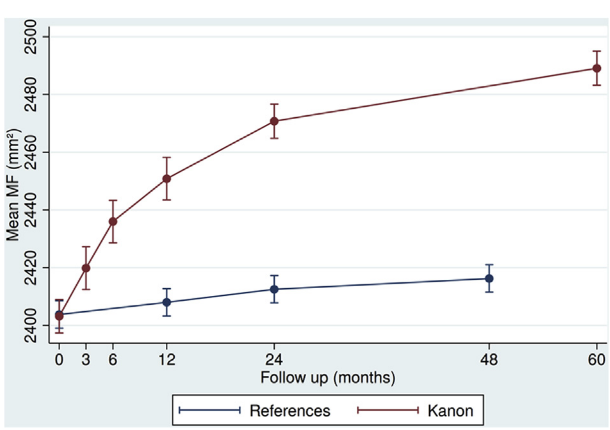

Fig. 2. The change over 5 years of bone area of the medial femur for the KANON study cohort ($n = 117$) and for the reference cohort over 4 years ($n = 176$). As opposed to tables and values in Fig. 3, symbols represent mean values without adjustment for baseline imbalance. Error bars represent 95% confidence intervals.

Overall results

After adjustment for differences in age, sex and BMI, the mean bone area of medial femur increased by 78.0 mm^2 (95% confidence interval 70.2 to 86.4, 3.2%) compared to baseline bone area over the first 5 years after acute ACL injury. The mean increase was highest over the first 2 years (66.2, 59.3–73.2 mm^2, 2.7%) with a lower rate of change over the next 3 years (17.6 [12.2 to 23.0] mm^2, 0.7%, Table II, Fig. 2). All other regions displayed changes of similar magnitude, with most prominent increases in patella, both medially and laterally, and the lateral tibia (Table II). The reference group also increased in bone area of the medial femur over a 4-year period but at a much slower pace. Over the first 2 years, the increase of medial femur bone area in the knees of the KANON cohort occurred 6.7 times faster than in the reference knees (Fig. 2).

The influence of treatment after acute ACL injury

Knees treated with ACLR, either performed early or as a delayed procedure, increased their bone area in medial femur at a higher rate and statistically significantly more than knees treated with rehabilitation alone over the 5 year period (Fig. 3). After 2 years and in medial femur, the mean increase of bone area in knees treated with early ACLR was 2.2 times higher compared to knees treated with rehab alone (78.2 mm^2 [67.9 to 88.8] vs 36.0 mm^2 [26.2 to 45.8], respectively, Table I, Supplementary Material). After 5 years, the mean difference was smaller (1.8 times) although still statistically significant (88.8 mm^2 [75.6 to 101.4] vs 48.6 mm^2 [37.2 to 59.4] respectively, Table II, Supplementary Material). A similar pattern of change was found for all investigated regions and most markedly in medial and lateral patella where the mean increase in bone area was 3.3 and 3.5 times larger in the early ACLR group compared to the rehab alone group after 2 years (Table I, Supplementary Material) and 2.8 and 3.0 times larger after 5 years (Table II, Supplementary Material).

Change in bone shape

A pictorial representation of the changes in bone shape (femur and tibia) for both OA and KANON cohorts is presented in Fig. 4. The OA changes demonstrated spreading of bone in the load-bearing regions and a peripheral change, that we have termed a 3D “pie-crust” shape, in the region in which osteophytes form in the OA knee. The extrapolated KANON data demonstrated patterns and locations of shape change very similar to those seen in a study of 3D bone shape in cohorts of OA knees[11] (Fig. 4).

Discussion

Rapid changes of bone area occurred after an acute ACL injury regardless of treatment. Visually, these shape changes were strikingly similar to overall shape changes caused by OA. Compared to a reference group of 45–50 year old individuals without OA, we found a more than 6-fold greater mean increase in the bone area of medial femur during the first 2 years after acute ACL injury; a marked difference towards the reference group was already evident after 3 months (Fig. 2). Compared to those treated with rehabilitation alone, reconstructive surgery of the torn ACL

Table II
Change in bone area for all regions of the knee in the KANON study group (full study cohort, $N = 117$)

Region	Change from BL to 2 years		Change from BL to 5 years		Change from 2 years to 5 years	
	mm^2 (%)	95% CI	mm^2 (%)	95% CI	mm^2 (%)	95% CI
MF	66.2 (2.7)	59.3 to 73.2	78.0 (3.2)	70.2 to 86.4	17.6 (0.7)	12.2 to 23.0
LF	30.2 (1.7)	25.2 to 35.3	47.4 (2.6)	42.0 to 53.4	19.4 (1.1)	14.8 to 23.8
TrFMed	13.9 (2.0)	12.0 to 15.8	16.8 (2.4)	14.4 to 19.2	4.3 (0.6)	2.5 to 6.1
TrFLat	13.7 (1.0)	11.0 to 16.6	17.4 (1.3)	14.4 to 20.4	4.3 (0.3)	2.2 to 6.5
MT	19.9 (1.7)	16.1 to 23.5	28.2 (2.4)	24.0 to 32.4	9.4 (0.8)	6.5 to 11.9
LT	21.1 (2.3)	18.2 to 24.0	27.6 (3.1)	24.0 to 30.6	7.6 (0.8)	5.4 to 10.1
MP	14.2 (2.6)	11.3 to 17.0	20.4 (3.8)	17.4 to 23.4	6.5 (1.2)	4.3 to 8.6
LP	18.7 (2.7)	15.1 to 22.3	27.0 (3.9)	23.4 to 30.6	8.6 (1.2)	6.1 to 11.5

Adjustment for age, sex and BMI was performed.
Change is presented as mean change in mm^2 (%) with 95% confidence limits. Baseline (BL).
MF: Medial Femur; LF: Lateral Femur; TrFMed: Medial Trochlea Femur; TrFLat: Lateral Trochlea Femur; MT: Medial Tibia; LT: Lateral Tibia; MP: Medial Patella; LP: Lateral Patella.

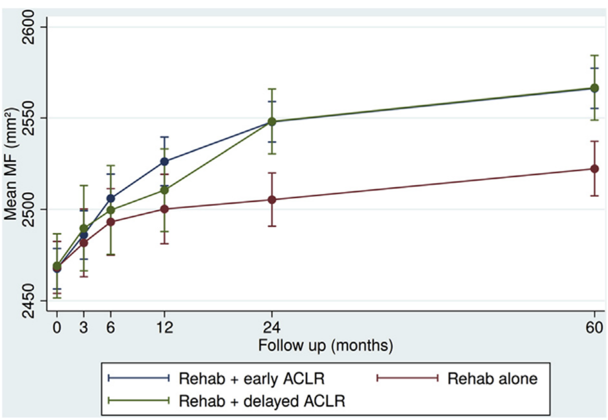

Fig. 3. The change over 5 years of bone area of the medial femur for the KANON study cohort ($n = 114$) separated for treatment actually received: Early anterior cruciate ligament (ACL) reconstruction ($n = 57$); Delayed ACL reconstruction ($n = 29$); Rehab alone ($n = 28$). As opposed to tables and values in Fig. 2, symbols represent mean values adjusted for baseline imbalance. Error bars represent 95% confidence intervals.

stimulated more rapid changes in bone shape irrespective of whether it was performed early or as a delayed procedure.

This study confirms previous suggestions that the medial femur displays marked bone changes over the first 5 years after ACL injury (24). Interestingly, the medial femur also showed significant cartilage thickening over the same period of time and in the same cohort[23–25]. Taken together, these results from the KANON-cohort suggest that bone and cartilage remodeling may occur simultaneously and in the same joint compartment during the initial years after ACL injury. Further analyses investigating both bone and cartilage change, preferably at the same location, would be of interest. Linking bone and cartilage structural changes to molecular biomarkers of joint tissue turnover may support a better understanding of these early features of the OA disease process and the identification of potential disease modification targets.

The accuracy of the automated segmentation was excellent, with a 95th percentile confidence interval of around 0.4 mm. The average voxel size in this dataset was 0.29 × 0.29 × 1.5 mm, giving an average voxel edge of 0.7 mm, which means that the 95% error of the automated segmentation was less than a single voxel edge. Further Active AAMs were not affected by the presence of metal artefacts, or surgical activity. AAMs fit the shape and texture of the whole 3D shape of the femur, tibia and patella, and are therefore relatively unaffected by small local differences in the image. There was a small, but non-significant, decrease in LF area with surgery (possibly due to notchplasty) however any effect caused by this small change would decrease bone area change in those treated with ACLR. For comparison with the changes found in this study, the test-retest repeatability of the MF region in a previous study[13] was 32.2 mm^2; the test-retest values for the other regions in this study are shown in Table III; Supplementary Materials.

Bone is intimately involved in the OA process[26,27]. Bone area of OA knees was found to be larger than in healthy knees in a cross-sectional analysis[13] and over time, changes of bone occur with OA progression[28,29]. Among recent publications on the relation between 3D bone area change and OA, we identified only one that addressed change in bone area among young, previously uninjured, individuals at high risk of developing OA due to an acute ACL injury (24). Using a different method (not including peripheral bone growth and focusing on shape characteristics) to the one used here, but in the same KANON sample, that study suggested early flattening of the convex condyle shape after ACL injury[30]. The current analysis included all 3-dimensional information (parameterized as principal components), and extends these results by visualizing that bone growth on the outer margins of the entire cartilage plates in the femur, tibia and patella (Fig. 4, shown in blue) occurs concurrently with flattening of convex surfaces (indicated by the borders of bone growth lying inside the baseline shape), and that these changes follow very soon after ACL injury.

A definite outer marginal osteophyte confirms the onset of radiographic OA disease according to the Kellgren–Lawrence classification system and is a required feature for all subsequent grades of radiographic OA progression using that system[31,32]. Interestingly, the outer marginal bone growth found in this study already at 3 months after injury, using a human model of individuals at high risk of rapid OA development, is located in areas of osteophyte formation. The concept that this bone expansion will evolve into osteophytes visible on plain radiographs is supported by reports suggesting that MRI-derived 3D bone shape predicts later radiographic OA development[11,12,14]. Based on the results of this and previous studies, we therefore introduce the hypothesis that 3D bone shape measures derived from MR images detect and identify longitudinal growth of osteophyte volumes at a much earlier stage than does the 2D area projection seen on plain X-ray images. However, to establish a firm relationship between MRI-detected early change in bone area, osteophyte growth, condyle shape and later development of symptomatic and radiographic OA, we need further long-term studies.

Similar to a previous study using a different analysis method of MRI data on the same study cohort[30], we confirmed a significant difference in time-related bone area change between knees that underwent ACLR, performed early or as a delayed procedure, and knees treated with rehabilitation. The surgical reconstruction of the ACL-injured knee apparently leads to an accelerated increase of bone area shortly after surgery (Fig. 3). Interestingly, knees

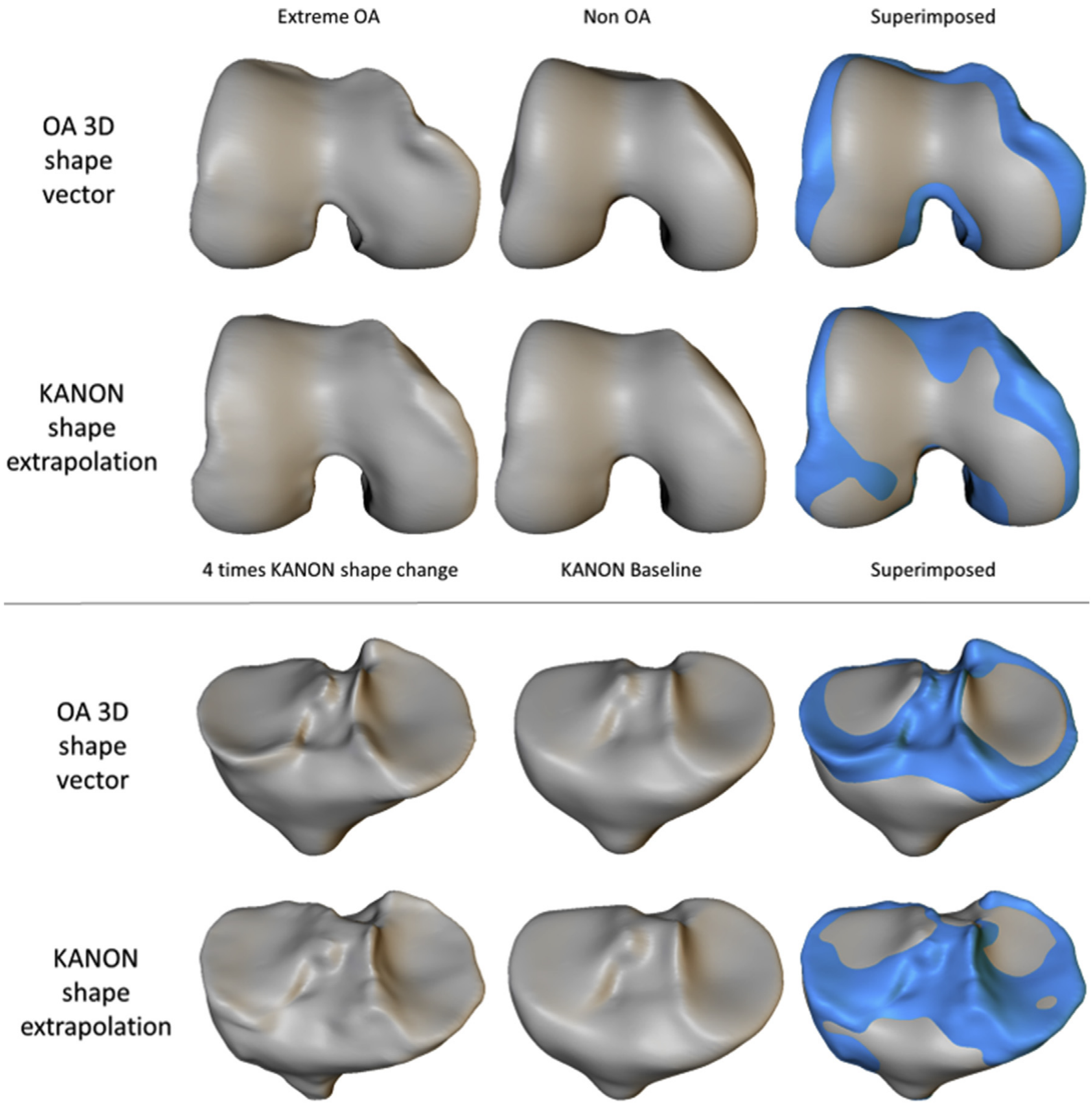

Fig. 4. Shape change in KANON study cohort ($n = 117$) compared with the extreme, but realistic, non-OA and OA shapes for the femur (top 2 rows) and tibia (bottom 2 rows) along an OA vector previously used to study 3D bone shape in cohorts of OA knees[13]. The left column shows the extreme-OA shape of the OAI training set, and the 4-fold extrapolation of the 5 year KANON study shape along the vector to simulate the shape 20 years after ACL injury. The middle column represents the non-OA shape of the OAI training set and the KANON baseline shape representing the mean baseline shape from MR images acquired within 4 weeks of ACL injury. The third column shows these shapes superimposed, with the shape change due to OA development coloured blue.

undergoing a delayed reconstruction of the ACL followed a similar pathway as knees with rehabilitation alone until the time of reconstruction, but then changed to follow the same path as knees that underwent early reconstruction. The rate of mean change in bone area between 2 and 5 years after ACL injury, where few surgeries were performed, was almost identical in all treatment groups.

Although using a different method for building and applying 3D SSM after ACL rupture, previous studies have suggested bone shape as a risk factor for ACL damage[33], a biomarker for accelerated cartilage degradation[34], and a predictor for abnormal kinematics following surgery[35]. Thus, it is possible that the early and consistent changes reported from this trial may represent features of early OA.

The mechanisms behind a surgery-induced increased rate of bone change in the ACL-injured knees are challenging to explain, but may include the added surgery-associated intra-articular trauma with local activation of inflammatory pathways (i.e., a 'second hit' phenomenon)[36]. The less treatment dependent longer-term changes may be explained by changes in dynamic joint loading where reconstructive surgery, as well as rehab alone, has been shown to fail in restoring normal kinematics[37]. The extent to which these early treatment-related differences in bone change following ACL injury are associated with later development of symptomatic and radiographic OA remains to be determined by continued follow-up of this and other post-injury cohorts.

This exploratory analysis of a randomised clinical trial had certain limitations. First, translating the complexity of three-dimensional shape into one numeric measure is difficult. We used triangulated surface area as the single measure in this study but there may be other measures, or combinations thereof, more sensitive to change. Second, MRI does not detect calcified tissue directly and further work is needed to confirm if the identified structures represent bone or mineralized cartilage. Mineralization of joint cartilage is associated with tidemark changes in OA disease and after joint injury. Thirdly, the reference cohort used for comparison was not matched for important variables such as age, gender, BMI and activity level. In consequence, we did not make statistical comparisons between the reference cohort and our study sample.

In summary, 3D shape modeling based on MR images in an ACL injury cohort with high risk of developing OA revealed rapid bone shape changes, detectable already at 3 months, of similar patterns as seen in established and advanced knee OA. Rapid increase of bone area and shape change occurs soon after ACL injury and is more prominent during the first 2 years and among those treated with surgical ACLR. Results from this and previous reports from the KANON-cohort suggest that flattening of bone surfaces, in combination with additional bone growth possibly representing early osteophyte formation, may be responsible for this change. The results of this study support ACL injury as an excellent human model of early OA development.

Author contributions

Bowes M.A* Conception and design, analysis and interpretation of the data, drafting of the article, analysis and interpretation of the data, final approval of submitted version.

Lohmander L.S.* Conception and design, analysis and interpretation of the data, drafting of the article, analysis and interpretation of the data, final approval of submitted version.

Wolstenholme, C.B. Analysis and interpretation of the data, image analysis methodology, final approval of submitted version.

Vincent G.R Analysis and interpretation of the data, image analysis methodology, final approval of submitted version.

Conaghan, P.G.* Conception and design, analysis and interpretation of the data, drafting of the article, analysis and interpretation of the data, final approval of submitted version.

Frobell R.B.* Conception and design, analysis and interpretation of the data, drafting of the article, analysis and interpretation of the data, final approval of submitted version.

* authors who take responsibility for the integrity of the work from inception to finished article (mike@imorphics.com, stefan.lohmander@med.lu.se, P.Conaghan@leeds.ac.uk, richard.frobell@med.lu.se).

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no conflicts of interest related to the work presented here.

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Ethics approval and consent to participate

The study was approved by the ethics committee of Lund University (LU-535). All patients gave written and informed consent.

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Supplementary data

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