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The effect of anterior cruciate ligament injury on bone curvature: The KANON Trial

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Abstract (249 words)

Objective

Investigate the 5-year longitudinal changes in bone curvature after acute anterior cruciate ligament (ACL) injury, and identify predictors of such changes.

Methods

In the KANON-trial (ISRCTN84752559), 111/121 young active adults with an acute ACL tear to a previously un-injured knee had serial 1.5T MR images from baseline (within 5 weeks from injury) to 5 years after injury. Of these, 86 had ACL reconstruction (ACLR) performed early or delayed, 25 were treated with rehabilitation alone. Measures of articulating bone curvature were obtained from computer-assisted segmentation of MR images. Curvature (mm^{-1}) was determined for femur, tibia, medial/lateral femur, trochlea, medial/lateral tibia. Age, sex, treatment, meniscal injury, osteochondral fracture on baseline MR images were tested for association.

Results

Over 5 years, curvature decreased in each region ($p<0.001$) suggesting flattening of convex shapes and increased concavity of concave shapes. A higher BMI was associated with flattening of the femur ($p=0.03$), trochlea ($p=0.007$) and increasing concavity of the lateral tibia ($p=0.011$). ACLR, compared to rehabilitation alone, was associated with flatter curvature in the femur ($p<0.001$), medial femoral condyle ($p=0.006$) and trochlea ($p=0.003$). Any meniscal injury at baseline was associated with a more flattened curvature in the femur ($p=0.038$), trochlea ($p=0.039$), lateral femoral condyle ($p=0.034$) and increasing concavity of the lateral tibia ($p=0.048$).

Conclusion

ACL injury is associated with significant changes in articulating bone curvature over a 5 year period. Higher BMI, baseline meniscal injury and undergoing ACL reconstruction (as distinct from undergoing rehabilitation alone) are all associated with flattening of the articulating bone.

Introduction

Rupture of the anterior cruciate ligament (ACL) is among the most frequent and serious musculoskeletal injuries affecting physically active men and women. ACL injuries occur with an annual incidence of at least 81 per 100 000 persons aged between 10 and 64 years (1), and are associated with both marked short-term morbidity and long-term consequences. It typically occurs in the younger population and as such leads to prolonged disability and increased economic cost (2); largely due to work loss.

More than 70% of formerly young and active individuals who sustain ACL injuries end up with moderate to severe disabilities, like instability, meniscal and chondral surface damage and osteoarthritis (OA) (3;4). OA changes occur in 15-70% of the patients at 10-15 years following the injury (3-8). Evidence suggests that roughly 25% of the disease burden of knee osteoarthritis could be prevented by preventing knee injuries among men (women, 14%) (9).

The acute ACL rupture is rarely isolated, often associated with injuries to the cartilage, subchondral bone, menisci and other ligaments (3). The precise pathogenesis behind why ACL ruptures lead to an increased risk of developing OA and why OA development can be accelerated in injured joints is unclear, but may be caused by the combination of an acute insult to the joint tissues, post traumatic alterations of the biochemical environment of the joint or chronic changes in dynamic loading of the knee joint surfaces. It was postulated that the majority of the tissue damage is related to the large forces required to injure the ACL (10). Identifying a biomarker predicting those at risk of poor long-term prognosis would greatly aid therapeutic development.

Early ACL reconstruction is currently the most frequently used treatment, mainly driven by the hypothesis that reconstruction improves instrumented laxity (11-13). However, evidence is inconclusive that ACL reconstruction facilitates return to previous activity level, reduces the likelihood of further injuries to the menisci or cartilage, or decreases the long-term risk of osteoarthritis (11;14). In fact, a recent randomized clinical trial presented evidence that early reconstruction may not alter short- or mid-term symptoms or structural outcomes significantly compared with those seen in subjects treated with delayed ACL reconstruction or rehabilitation alone (11;12).

Changes in the dynamic loading of the injured knee are also apparent and could drive OA development. There are significant differences in the tibiofemoral kinematics of ACL-deficient knees compared with healthy controls (15-18) but also between the ACL reconstructed and healthy contralateral knee (18).

One joint tissue that is pivotally involved in OA pathogenesis and responds promptly to altered load is the subchondral bone. Changes in subchondral bone in established OA include remodelling of the subchondral trabeculae (19), alterations in shape (20;21), thickening of the subchondral plate (22) and a steep stiffness gradient (23). Indeed, there does appear to be some bone changes that occur prior to cartilage destruction (24), including thickening of the subchondral cortical plate (25). With the exception of the shape of the femoral intercondylar notch (26) little heed has been paid to the bone shape in persons who have sustained an ACL injury. As bone is principally responsible for load distribution in the weight bearing knee (27) any kinematic change in loading is likely to lead to alteration in bone shape as it adapts to this changed load. Similarly, this responsive tissue may also demonstrate changes that are suggestive of deleterious progression towards an end stage osteoarthritic pathology (28). Previous studies suggest that subtle alterations in joint shape at both the hip and knee may be involved in the pathogenesis of OA (20;29;30). Due to the long lead time between knee injury and the development of radiographic OA, finding a more responsive biomarker that identifies those at risk of poor long term prognosis could aid therapeutic development.

The objective of this study was to investigate the 5-year longitudinal changes in bone curvature following an acute ACL tear, and to identify predictors associated with such changes.

Materials and Methods

Study Design

This is an ancillary analysis of data from a randomized controlled trial (the Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment [KANON] Study; Current Controlled Trials ISRCTN 84752559) (11;12). The trial compared a treatment strategy of structured rehabilitation plus early ACL reconstructive surgery (n=62) with a strategy of structured rehabilitation plus optional delayed ACL reconstruction (n=59), in which those with symptomatic instability were offered delayed ACL reconstructive surgery if needed and if specific protocol guidelines were met (11). Over the 5 year period, a delayed ACL reconstruction was performed in 30/59 patients initially assigned to rehabilitation; 29 patients were treated with rehabilitation alone (12). The study was approved by the ethics committee of Lund University. At inclusion, participants were eighteen to thirty-five years old, had a moderate to high activity level prior to their injury, and had an acute ACL injury to a previously uninjured knee. Major exclusion criteria were total collateral ligament rupture, full-thickness cartilage injury as visualized on initial MRI, and evidence of osteoarthritis on weight-bearing radiographs. Inclusion and exclusion criteria, details of the recruitment process, and the clinical outcome after two and five years have been reported (11;12;14;31;32).

Intervention

All subjects were treated according to an identical, goal-orientated rehabilitation program, initiated at the time of, or prior to randomization (11). All ACL reconstructions (early and delayed) were performed by one of four senior knee surgeons using single-bundle technique, either with a patella-tendon or hamstring-tendon procedure depending on the surgeon's preference (11). In randomised trials, these two methods have resulted in similar outcomes (33;34). Meniscal tears were treated with partial resection or fixation when indicated by MRI findings and clinical signs. Meniscocapsular separations of <10mm were treated with arthroscopic fixation, but fixation of larger meniscal tears resulted in exclusion from the study (11).

Study sample

One hundred and eleven (92%) of the study participants had intact series of MR images acquired at baseline (within 5 weeks of injury) and 5 years after injury and thus formed the focus sample of this ancillary study. After 5 years, 59 of these had an early ACLR (performed within 10 weeks after injury), 27 had a delayed ACLR and 25 were treated with rehabilitation alone. Those treated with ACLR, performed early or as a delayed procedure, constituted the ACLR group (n=86) and were compared to those treated with rehabilitation alone (n=25). Data on patient demographics and characteristics were collected at the start of the trial. Time from the date of the injury to the baseline MRI was recorded, as was time from injury to surgery.

In a further exploratory analysis, we investigated early bone shape changes in a sub-sample of 61 (48 treated with ACLR at 5 years) of the 111 individuals who had MR image acquisitions performed at 3, 6 and 12 months after injury in addition to the visits described above.

MRI Acquisition

MRI was performed with use of a 1.5-T magnet (Gyroscan Intera; Philips, Eindhoven, The Netherlands) with a circular polarized surface coil; sequences were identical for all subjects and all time points. The MRI scans consisted of sagittal three-dimensional, water excitation, fast low-angle shot (FLASH) with TR/TE/flip angle of 20 ms/7.9 ms/25, and sagittal T2-weighted three dimensional gradient echo with TR/TE/flip angle of 20 ms/15 ms/50. Both series were acquired with 15 cm FOV, 1.5 mm slice thickness, and 0.29 x 0.29 mm pixel size. In addition, sagittal and coronal dual-echo turbo-spin-echo (DETSE), both with TR/TE/TI of 2900 ms/15 ms/80 ms, 15 cm FOV, 3 mm slice thickness with 0.6 mm gap, and 0.59 x 0.59 mm pixel size and sagittal and coronal short tau inversion recovery (STIR) with TR/TE/TI of 2900 ms/15 ms/160 ms, 15 cm FOV, 3 mmslice thickness with 0.6 mm gap, and 0.29 x 0.29 mm pixel size were acquired. Quality control of the MRI scanner was performed at each individual acquisition with use of volumetric phantoms attached to the knee and on a monthly basis with use of a standardized and calibrated uniformity and linearity (UAL) phantom (1;35).

Quantification and Post-Processing of MR Images

Image administration and analysis was performed using CiPAS, a software platform for the automated segmentation of MRI images (Qmetrics Technology, Rochester, NY). The MRI data sets were segmented using a multi-atlas based method (36). An atlas-based segmentation approach uses an expert segmented subject as template to automatically segment MRI images. This multi-atlas approach mitigates template bias and improves segmentation precision (36). Segmentation errors of the multi-atlas based segmentation method are reduced by increasing the number of atlases (36). Experiments on Osteoarthritis Initiative (OAI) data sets showed that only five atlases provide good segmentation performance while keeping a reasonable computational workload (36). The imaging protocol of this study used lower resolution images than OAI; therefore, it was possible to add more atlases while keeping the same computational workload. In order to mitigate template bias, we used seven atlases (templates), two more than the original OAI experiment. The atlases used for segmentation of the SPGR Fast suppressed MRI set were selected from the KANON baseline and 6 month time points. The femur, the tibia, and the femur and tibia cartilage were segmented by an expert radiologist to create the atlases. The radiologist manually traced the five regions of interest: central medial, central lateral, posterior medial, posterior lateral, and trochlea. Once the seven atlases were created, each was used to perform the segmentation for each one of the KANON MRI sets. Each one of the atlas-based segmentations were then fused into a single labeled image that was used to quantify the bone-cartilage-interface (BCI) curvature as seen in **Figure 1**. The anatomic regions were identified in the atlases and therefore their locations did not vary between subjects or between different studies. The curvature was measured at each of several thousand polygons of the 3D rendered femur and tibia bone at the BCI. On average each one of the rendered surfaces had 6.1 polygons per square millimeter. We analyzed the global shape by using the average mean curvature of all fine scale measurements. The fine irregularities present in the bone did not affect the global averages, because the fine structural irregularities were composed of positive and negative curvatures, whose average represented the curvature of the sphere that fit the coarse resolution. The curvature was measured using inverse millimeters (mm^{-1}) to describe the radius of a sphere whose surface matched the local curvature at the polygon, with positive values for convex shapes (femur condyles) and negative values for concave shapes (tibia plateaus). Average values were reported for the following regions of interest (ROI): entire femur (F), entire tibia (T), medial femur (cMF), lateral femur (cLF), trochlea (TF), medial tibia (MT) and lateral tibia (LT).

Meniscal injury and cortical depression fractures

MR images were re-reviewed for meniscal injuries and osteochondral fractures after patient inclusion in the RCT by one experienced musculoskeletal radiologist (Torsten Boegård, MD, PhD). Images were classified for meniscal injuries and fractures blinded from other radiological, clinical and surgical information using described methods (1). In brief, a meniscal tear was defined as increased signal extending to at least one articular surface of the meniscal body in the medial and lateral meniscus separately. An osteochondral fracture was determined as either a trabecular fracture, defined as a line with low signal and parallel to the cortex, visualized on the DETSE sequences, and combined with a surrounding traumatic BML visualized on the STIR sequences indicating trabecular compression injury, or a cortical depression fracture, defined as a trabecular fracture combined with depressed cortical bone, with or without cortical discontinuity (1).

Statistical Analysis

All statistical analyses were performed using the IBM® SPSS® Statistics v21 (*IBM Software Group, Chicago, IL, USA*). The five-year individual change and trajectory in bone curvature was presented as the mean crude change (and standard deviation) in curvature and the mean percentage change (and standard deviation) for each analyzed region of the knee in the 111 participants with complete baseline and 5 year data. Statistical comparisons between baseline and five-year bone curvature were made on crude values with use of the paired t-test. Levene's test for equality of variances was performed and the conditions of the assumption were met (i.e. assumption of homogeneous variance was evaluated using Levene's test and all these tests were statistically nonsignificant). No correction for multiple testing was made.

Relationships between change in bone curvature, treatment, presence of baseline depression fracture, baseline meniscal injury and demographic characteristics were compared using correlation analysis. Spearman's coefficients of correlations were calculated for continuous variables, Kendall's tau-b coefficients of correlation - for categorical variables/ binary outcomes in the 111 participants with complete baseline and 5 year data.

The association of longitudinal change of bone curvature with covariates including age at the time of injury, sex, treatment actually received (ACLR vs. rehabilitation alone), time between injury and ACLR, time between injury and baseline MRI, and osteochondral / meniscal injury at baseline with use of general linear models. Change of bone curvature at each anatomical site was used in a general linear model as a dependent variable and each explanatory was entered in to the model as an independent factor. Crude regression coefficients were recorded from these models. Fully fitted models were adjusted for baseline curvature measure of a corresponding anatomical site, baseline age and BMI and gender. A significance level of 0.05 was used and no adjustments for multiple comparisons were made.

Results

The mean age of the 111 participants was 26 years, 27% were female and the mean BMI was 24 kg/m^2 **(Table 1)**. The characteristics of study participants who were assigned to undergo rehabilitation alone approximated those that had an ACLR for age and BMI, although appeared to differ for sex and injury to right knee.

Over the course of 5 years, the changes of values for curvature were statistically significant in each region of the knee (i.e. convex shapes became flatter and concave shapes became more concave, **Table 2, Figures 2 and 3)**. The curvature values were averaged by ROI, therefore the average ROI-curvature value represented a sphere that on average fit the ROI surface. In that sense, we tested if the average ROI curvature fit a larger or smaller sphere. For convex shapes the statistical test results indicated that on average the mean-curvature was getting significantly smaller over time (Figure 3A and 3B). This implied that the corresponding sphere that fit the ROI was getting larger, i.e. a flatter surface. On the other hand, the concave tibia shape was getting significantly more concave over time. This increase in concavity implied that the sphere that fit the tibia was getting smaller. In the subsample with repeat visits over shorter time intervals (n=61), it is important to note these changes were observable already by the 3 month visit **(Figure 3A)**. Change to 3 months (from baseline) in curvature was predictive of change at 5 years for both the femur (p=0.005) and tibia (p=0.006).). The magnitude of the curvature change by 5 years was most profound for the femur (standardized response mean, SRM =-1.62).

The unadjusted non-parametric correlations between the predictors of interest (age at the time of injury, sex, treatment actually received, time between injury and ACLR, time between injury and baseline MRI, and osteochondral/ meniscal injury at baseline) and curvature by region are presented in **Table 3**. The results of the parametric regression before and after adjusting for baseline curvature value, age, BMI and gender are presented in **Table 4**. The results are broadly consistent between both tables. Of the demographic characteristics, age at injury did not affect curvature change whereas a higher BMI was significantly associated with curvature change in the femur, trochlea femur and lateral tibia. Participants who received surgery plus rehabilitation as opposed to rehabilitation alone were more likely to change curvature in a negative direction (flattening) in the femur (p<0.001), medial femur (p=0.006) and trochlea (p=0.003) with little change of these results after adjustment **(Figure 4)**. Time from injury to surgical reconstruction of the ACL (early or delayed) did not significantly affect curvature change.

Concomitant damage to the meniscus and tibial, but not femoral, osteochondral fractures also had effects on curvature change. Any meniscal injury (largely medial meniscus) diagnosed by MRI at the baseline examination was associated with lower curvature in the femur (p=0.038), trochlea (p=0.039), lateral femoral condyle (p=0.034) and lateral tibia (p=0.048). In contrast, a lateral tibial osteochondral fracture was associated with change to a more convex curvature in the lateral tibia (p=0.047).

Discussion

Although the natural corollary of knee joint shape changes is not known, this study shows that an acute ACL injury is associated with significant changes in bone curvature, measurable within 3 months of the injury. Increased body mass index, meniscal injury and surgical reconstruction of the ACL are associated with increased flattening (less convexity) of the femur and increased depression (increased concavity) of the tibial surface. Bony shape change was previously thought to be a late feature of OA pathogenesis but recent studies suggest it is also seen in early OA (30;37). Whilst there is still considerable debate, many studies suggest that alterations in bone may precede other structural changes in OA (38-41). Consistent with prior literature on other structural changes following ACL injury (31;42), the structural changes found for curvature in this study were more evident in the femoral condyles than the tibial plateaus, however changes occurred both medially and laterally.

What does this mean clinically? At this point this needs to be further examined as to how these changes in shape relate to pain, function and longer term radiographic changes. If we compare our findings with those of Neogi et al. (30), it does raise concerns that the changes we observe may be an early shape change predisposing to OA development. Whilst the methods of shape measurement in these studies are distinct, the findings of Neogi et al. of a wider and flatter femoral condyle predicting later onset of radiographic OA are provocative. Our findings of bone shape changes following ACL injury warrant replication, but these changes may offer an earlier and more responsive indicator of those with adverse long term prognosis for development of OA, in particular as changes at 3 months appear to be predictive of changes at 5 years.

Concomitant meniscal injury has in observational studies been demonstrated to be associated with adverse structural outcome in individuals with torn ACLs (42;43). Prior studies also suggest that an ACL reconstruction may not protect against the development of post-traumatic osteoarthritis (8;12;44-47). Our observation that those who received ACLR showed more marked changes in bone curvature compared to those who received rehabilitation alone was surprising to us, especially since the bone changes did not only occur in areas directly affected by surgery. Intriguingly, time from injury to surgery also had no effect on curvature change. This is surprising in that curvature change was essentially linear with time, and surgical reconstruction appeared to be one of the mediators of change, and thus should have an effect, although maybe not strong enough to show. The importance of early change in bone curvature after joint injury is not yet known, but if it reflects adverse long-term outcome after ACL rupture, then rehabilitation alone may be a preferred treatment option for these patients.

We did not have pre-injury MR images for comparison but the relation of osteochondral fracture to curvature change suggests that this immediate bone damage may lead to local remodeling of the plate/ region primarily affected. The overwhelming majority of osteochondral depression fractures occur in the lateral tibia and lateral femur as result of the impaction forces between the anterolateral femur and the posterolateral tibia that occur during the initial trauma (1). Of the predictor variables examined, this was the only one that consistently demonstrated a positive relation to curvature. That is, in persons with a depression fracture of the lateral tibia this leads to an increase in lateral tibial curvature (i.e. increasing joint surface convexity). This may be a consequence of local remodeling or healing but may also be a sign of adaptation to altered loading. The lack of curvature change in the area of the femoral osteochondral fracture may suggest that the cortical depression at this site does not undergo bone shape remodeling. Prior studies have demonstrated that an elevated lateral tibial plateau is associated with the presence of radiographic OA (20) and that the initial subchondral lesion (size, location, type) is associated with the location and occurrence of increased cartilage loss or increased T1rho values at follow-up (48-50). The present study is the first to our knowledge that examined the relation of osteochondral fractures to bone remodelling.

Our findings show that bone curvature change occurs already 3 months after an ACL injury and that surgical reconstruction of the torn ligament may not prevent such changes. Bone shape changes as measured here occur at several locations of the knee and reflect both the build of bone (potentially related to advancement of the tidemark (51)) and the removal of bone with consequent alteration in bone geometry (52). The shape changes depicted in curvature analyses are a complex 3D alteration. For example, the trochlea is largely a convex surface with a central concavity and the changes depicted here represent a flattening of the convex surface and thus on average curvature decreases. The curvature of osteophytes is positive (convex), therefore they could make curvature measurements more positive in affected areas.

Our results support previous reports of trauma induced biological factors being important for the longer term consequences of ACL injury (3;10;11;14;46). The shape changes found here are likely to lead to less congruency of the joint surfaces and possibly higher stresses on articular tissues during activity. Another important contributing factor may be the "misalignment" between the condyles following an ACL tear resulting in changes in both static and dynamic loading of joint surfaces leading to bone reaction (16;17). Studies that include monitoring of the local structural and metabolic response to knee injury may shed further light on this issue.

There are several important strengths of this study. Firstly, the study cohort and prospective design provides an unrivalled potential to examine serial MRI measures of structural change over time in an injured cohort exposed to a variety of important potential predictors including surgery and concomitant damage to meniscus and osteochondral fracture. The measures used demonstrate change within a short interval of the injury and may provide promise for an early marker of later disease. However, further analysis of bone curvature change, especially how it relates to clinical outcome and radiographic OA, is required before statements can be made about the value of this marker to predict likelihood or not of developing OA disease.

There are also a number of important limitations that warrant mention. Knee injury can lead to combined damage to both the meniscus and the subchondral bone. We do not have sufficient study power to look at interactions between these two predictor variables. In the group randomized to initial rehabilitation alone, about 50% went on to have a delayed ACLR over the five year period (12). Therefore, our study is underpowered to examine the influence of rehabilitation alone in subgroups of persons with meniscal injury. With regards to the method of measuring curvature, we used a multi-atlas approach with multiple subjects selected as templates, and any atlas bias was thus mitigated by considering the consensus segmentation created by fusing the individual segmentations into a single labeled image. The lack of an age, sex and BMI matched control group without ACL injury monitored together with the KANON group using the same MRI equipment and analysis technology, limits our ability to draw firm conclusions regarding the cause of our findings. The curvature changes observed here could thus, e.g., be a direct consequence of the ACL injury, represent natural joint remodeling in patients aged between 18 and 35 years, or be due to a combination of these causes.

In sum, we have demonstrated that bone curvature changes occur within 3 months of acute ACL injury and that the change is significant at 5 years. Our results support the importance of trauma related factors for longer term structural change in the knee. Higher BMI, concomitant meniscal injury and surgical reconstruction of the ACL predicted greater bone curvature change.

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Author Contributions

DJH conceived and designed the bone curvature ancillary study, supervised its conduct, drafted the manuscript and takes responsibility for the integrity of the work as a whole, from inception to finish. RF and SL were also involved in the design and conduct of the KANON study. JT, ST and ES were responsible for the bone curvature image analysis. All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

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None of the study sponsors had any role in data collection, storage or analysis, in manuscript writing, or the decision to publish this manuscript.

Competing interest

Ed Schreyer and Saara Totterman are both employees of QMetrics Technologies who conducted the image analysis.

Drs. Hunter, Lohmander and Frobell report no competing interest.

Figure Legends

Figure 1. Example image of one KANON study participant (study ID K-C-1052). Fat suppressed image at baseline and 5 year follow-up along with 3D bone surface models illustrating bone cartilage interface (BCI) curvature of the femur at baseline and 5 years. Notice the changes of the shape of the trochlea (long arrow at baseline and 5 years) and flattening of the articulating tibia and femur bone surfaces (short arrows at baseline and 5 years) shown in the MR images. The same curvature changes are depicted in the color coded curvature maps of the femur.

Figure 2. Cohort-based / population average maps. Left Panel: Baseline measures for the tibia and femur. Middle panel 2 year bone curvature change for femur (above) and tibia (below). Right panel 5 year change for femur (above) and tibia (below). Maps are based on 93 of the 111 participants with both good reference atlas-segmentation and paired data at baseline, 2 and 5 Years.

Figure 3. Trajectory of bone curvature over the five year follow-up period by anatomic location. Data points represent means with 95% confidence interval error bars.

- **a.** Left panel. Intense follow-up group with repeat observations at multiple time points. Sample size at baseline (0 months) (n=64); 3 months (n=62); 6 months (n=61); 12 months (n=61); 24 months (n=61); 60 months (n=61)
- **b.** Right panel. Whole cohort follow-up with observations at baseline, 2 years and 5 years. Sample size at baseline (0 months (n=111); 24 months (n=111); 60 months (n=111).

Figure 4. Curvature change over 5 years by treatment group. Bars represent mean curvature change between baseline (0 months) and 5 years (n=111) with 95% confidence interval errors.

Table 1. **Demographic characteristics of study participants (n=111)**

	Total (N=111)	Rehab alone (N=25)	ACLR ALL (N=86)	Rehab + early ACLR (N=59)	Rehab + late ACLR (N=27)
Age in years (range)	26 (18-35)	25 (18-32)	26 (18-35)	27 (18-35)	26 (18-35)
Female sex-no. (%)	30 (27%)	8 (32%)	22 (26%)	12 (20%)	10 (37%)
BMI in Kg/m^2, (SD)	24.2 (2.9)	24.5 (2.9)	24.1 (2.9)	24.4 (3.2)	23.3 (2.1)
Injury to right knee-no (%)	60 (54%)	13 (52%)	47 (55%)	30 (51%)	17 (63%)
Days from injury to Baseline MRI: Mean(range)	19.4 (3-44)	20.4 (11-30)	19.1 (3-44)	19.6 (3-44)	18.2 (9-27)
Days from injury to ACLR: Mean(range)	-	-	190.6 (20-1714)	43.7 (20-72)	511.7 (186-1714)

Table 2. Change in bone curvature between baseline and five years for the whole cohort (n=111)

	Change in curvature (mm^{-1})				
	Mean	**SD**	**95%CI**	**p value**	**Standardised Response Mean**
Femur	-0.0028	-0.0087	-0.003178 -0.002516	<0.001	-1.62
Medial femur	-0.0041	0.0029	-0.004604 -0.003516	<0.001	-1.40
Lateral femur	-0.0044	0.0031	-0.004989 -0.003816	<0.001	-1.41
Trochlea	-0.0020	0.0025	-0.002459 -0.001508	<0.001	-0.78
Tibia	-0.0035	0.0031	-0.004121 -0.002954	<0.001	-1.14
Medial tibia	-0.0020	0.0037	-0.002665 -0.001277	<0.001	-0.53
Lateral tibia	-0.0036	0.0041	-0.00435 -0.002789	<0.001	-0.86

p-values reflect difference between baseline and 5 years

Table 3. Non-parametric correlations between change in bone curvature, treatment of the ACL, presence of baseline osteochondral fracture and demographic characteristics. Results presented as Spearman's coefficients of correlation for continuous variables and Kendall's tau-b correlation coefficients for categorical/ordinal variables or binary outcomes (n=111).

	Change in bone curvature						
	Femur Curvature	Medial femur	Lateral femur	Trochlea	Tibia Curvature	Medial tibia	Lateral tibia
Sex (Male=1; Female=2)	0.046	-0.144	0.116	0.018	0.038	-0.065	**0.200**[£]
Age (years)	-0.120	0.023	0.009	-0.155	0.120	0.095	0.054
BMI (kg/m^2)	**-0.206**[#]	-0.048	-0.116	**-0.256**[£]	0.024	0.037	**-0.241**[#]
ACL reconstruction (0=no; 1=yes)	**-0.282**[§]	**-0.183**[#]	-0.104	**-0.247**[£]	0.110	0.142	0.033
Treatment (1=Rehabilitation only; 2= Rehabilitation plus late ACL; 3= Rehabilitation plus early ACL)	**-0.462**[§]	**-0.368**[§]	-0.175	**-0.221**[£]	0.076	0.152	0.037
Time from injury to ACLR (days)	0.154	0.018	0.070	0.018	0.106	0.105	-0.020
Time from injury to MRI (days)	0.137	-0.046	0.108	-0.013	**0.194**[#]	0.134	0.025
Medial Meniscal injury@ baseline (=yes injury)	**-0.227**[£]	-0.050	-0.099	-0.131	-0.117	-0.062	-0.053
Lateral Meniscal injury@ baseline (=yes injury)	-0.114	-0.076	-0.073	-0.112	-0.105	-0.030	-0.134
Any Meniscal injury@ baseline (=yes injury)	**-0.159**[#]	-0.053	-0.144	-0.113	-0.103	-0.030	-0.123
Lateral Tibial Osteochondral fracture (=yes fracture)	0.003	-0.028	0.027	-0.114	**0.172**[#]	-0.002	**0.198**[#]
Lateral Femoral Osteochondral fracture (=yes fracture)	0.092	0.136	-0.022	0.018	-0.002	0.092	-0.147
Any Femoral Osteochondral fracture (=yes fracture)	0.011	0.062	0.059	-0.130	0.088	0.078	-0.008

Bold correlation coefficients indicate statistical significance ($p<0.05$)

§- P< 0.001; £ -P<0.01; # - P<0.05

Table 4. Factors tested for an association with bone curvature change over the five-year follow-up period (Fully fitted regression models were adjusted for baseline curvature, age, BMI and gender. Presented as Beta regression coefficients, n=111).

	Change in bone curvature						
	Femur Curvature	**Medial femur**	**Lateral femur**	**Trochlea**	**Tibia Curvature**	**Medial tibia**	**Lateral tibia**
Unadjusted							
Treatment group							
Rehabilitation plus early ACL	**-0.002141**§	**-0.003000**§	-0.001425	-0.001278	0.000367	0.001210	0.00412
Rehabilitation plus late ACL	**-0.001754**§	**-0.003262**§	-0.001106	-0.000211	-0.000761	-0.000107	0.000356
Rehabilitation only (reference group)	0	0	0	0	0	0	0
Meniscal injury@ baseline (=Yes injury)							
Any	**-0.000723**$^{\#}$	-0.000540	-0.001132	-0.000781	-0.000599	-0.000274	-0.001058
Medial	**-0.001050**$^{\#}$	-0.000460	-0.000996	**-0.001089**$^{\#}$	-0.000977	-0.000724	-0.000604
Lateral	-0.000508	0.000692	-0.000511	-0.000590	-0.000572	-0.000194	-0.001261
Osteochondral fracture (=Yes Fracture)							
Any Femoral	0.000467	0.001029	-0.00042	-0.000119	-0.000076	0.000849	**0.001777**$^{\#}$
Lateral Tibial	0.000034	-0.000292	0.00019	0.000258	**0.001315**$^{\#}$	-0.000095	**0.001983**$^{\#}$
Lateral Femoral	0.000467	0.001029	-0.00042	-0.000119	-0.000076	0.000849	**-0.001777**$^{\#}$
Adjusted for Baseline curvature, age, BMI and gender							
Treatment group							
Rehabilitation plus early ACL	**-0.002245**§	**-0.003304**§	-0.001566	-0.001083	0.000280	0.001071	0.000313
Rehabilitation plus late ACL	**-0.001908**§	**-0.003530**§	-0.001328	-0.000721	-0.000703	-0.000275	-0.000113
Rehabilitation only	0	0	0	0	0	0	0
Meniscal injury@ baseline (=Yes injury)							
Any	**-0.000697**$^{\#}$	-0.000626	**-0.001231**$^{\#}$	**-0.000965**$^{\#}$	-0.000977	-0.000594	**-0.001557**$^{\#}$
Medial	**-0.001171**$^{\pounds}$	-0.000712	**-0.001319**$^{\#}$	**-0.001286**$^{\#}$	-0.001277	**-0.001475**$^{\pounds}$	-0.001081
Lateral	-0.000403	-0.000651	-0.000554	-0.000710	-0.000909	-0.000327	**-0.001673**$^{\#}$
Osteochondral fracture (=Yes Fracture)							
Any Femoral	0.000248	0.000474	0.000136	-0.000346	0.000468	0.000650	-0.000078
Lateral Tibial	0.000140	0.000028	-0.000081	0.000050	0.001169	0.000239	**0.001603**$^{\#}$
Lateral Femoral	0.000598	0.001057	-0.000246	0.000086	0.000077	0.000665	-0.001066

Bold regression coefficients indicate statistical significance ($p<0.05$). §- $P< 0.001$; £ -$P<0.01$; # - $P<0.05$

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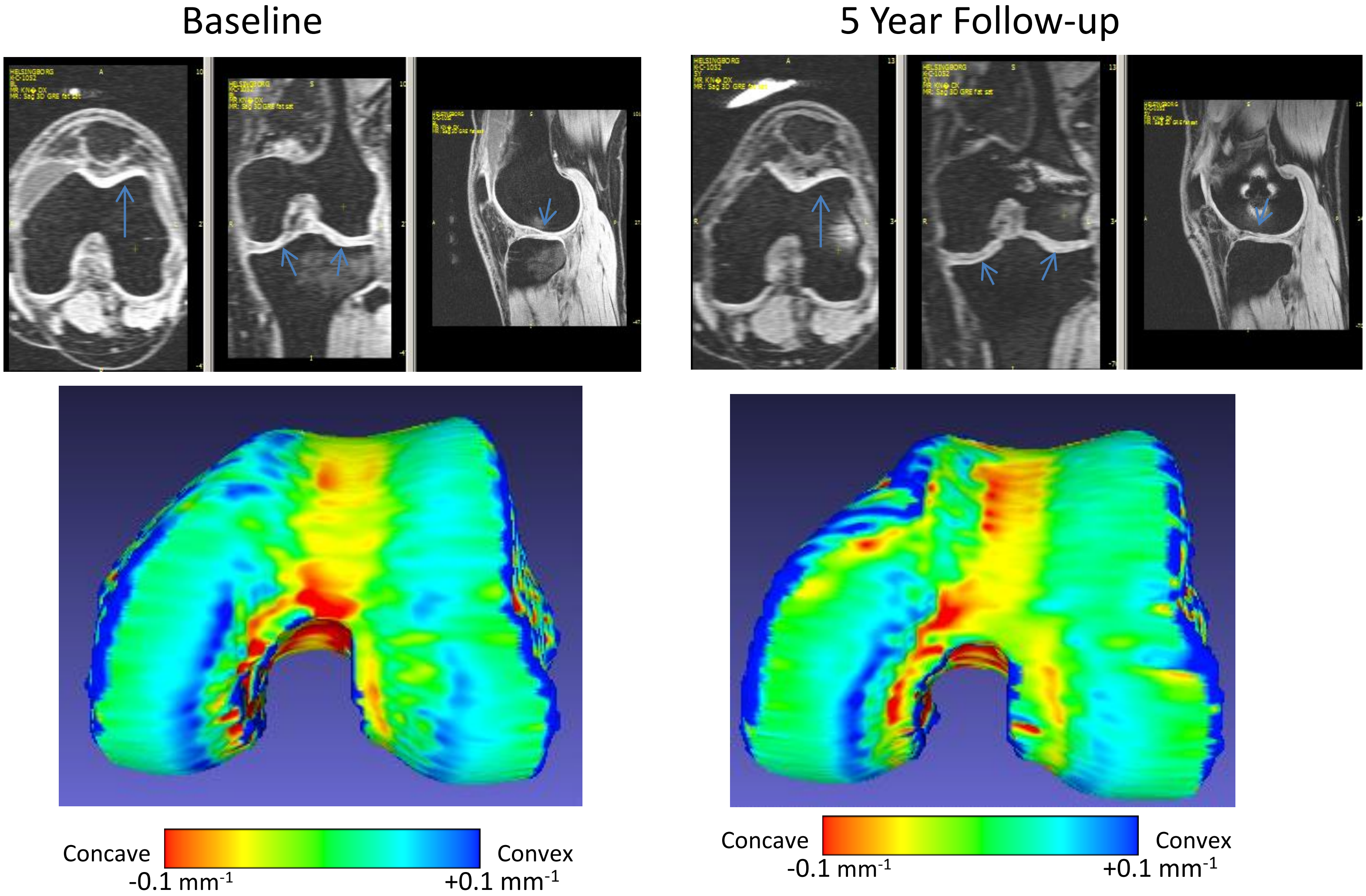
Figures for curvature paper

Figure 1


Baseline
5 Year Follow-up
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Convex
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+0.1 mm^{-1}
Concave
Convex
-0.1 mm^{-1}
+0.1 mm^{-1}

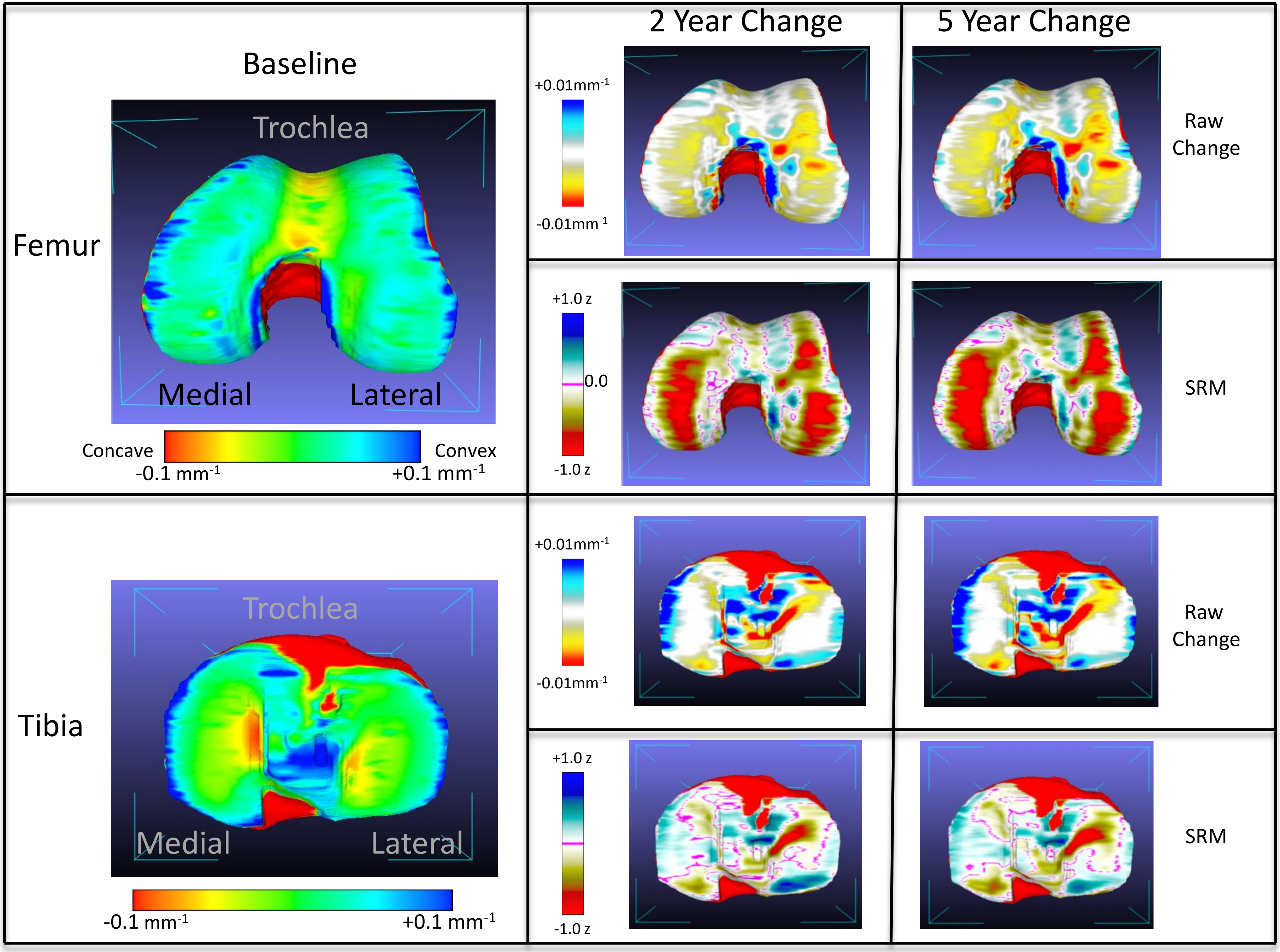


Figure 2. Population Average: Left, Baseline Average. Middle, 2 year average change. Right, 5 Year average changes

Figure 3

Click here to download Figure: Figure 3AB Hunter et al.EPS

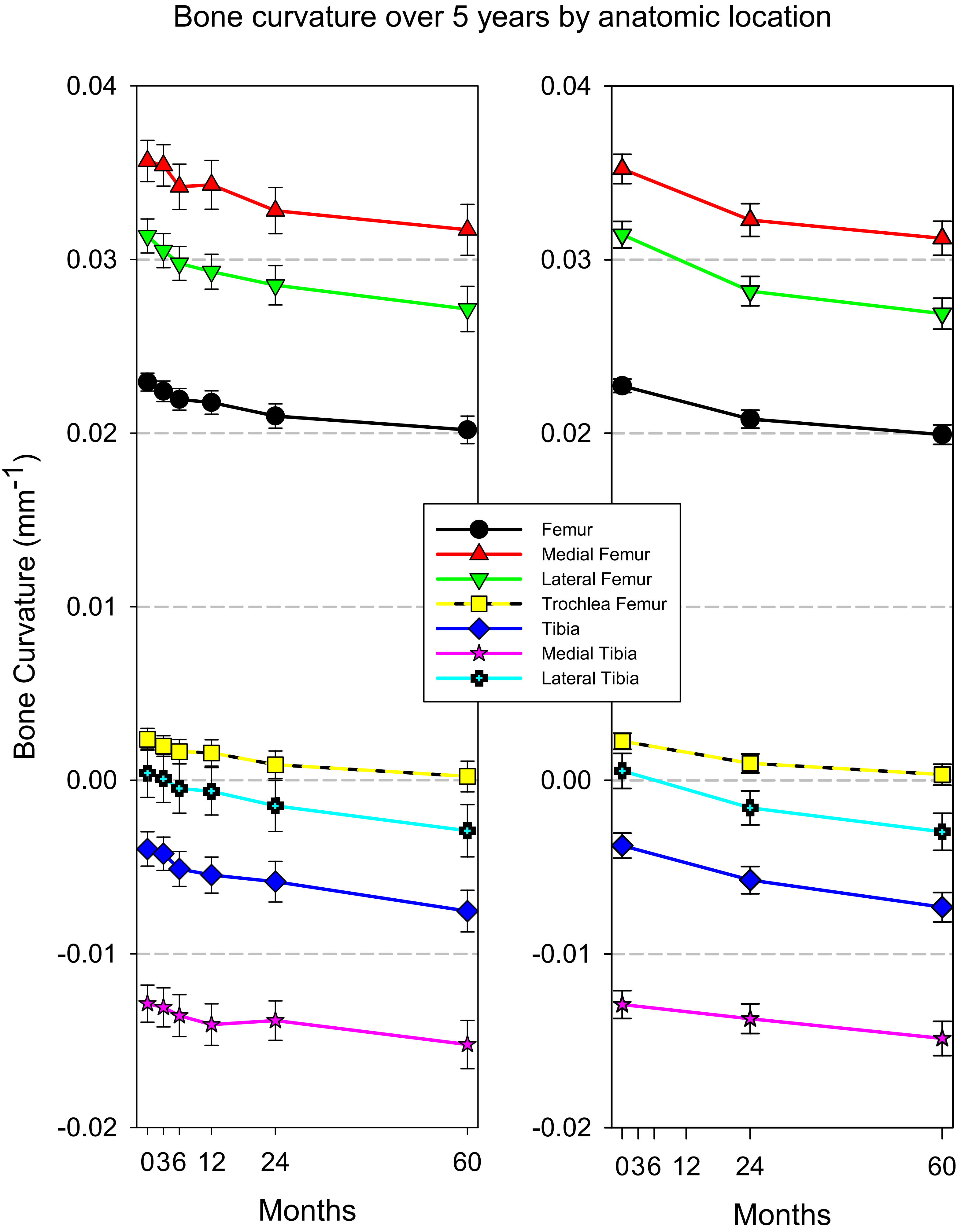
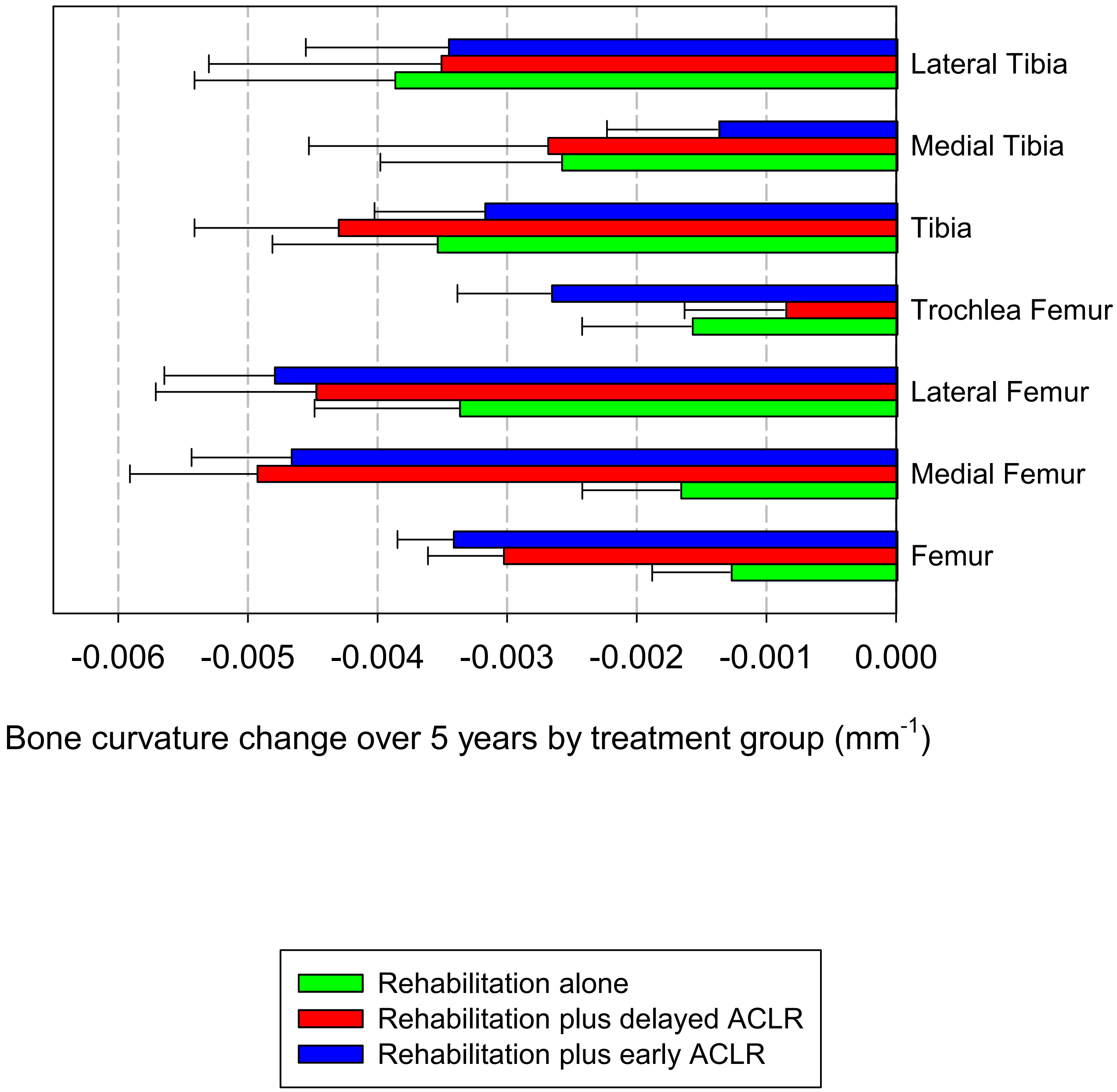


Figure 4


Lateral Tibia
Medial Tibia
Tibia
Trochlea Femur
Lateral Femur
Medial Femur
Femur
-0.006
-0.005
-0.004
-0.003
-0.002
-0.001
0.000
Bone curvature change over 5 years by treatment group (mm^{-1})
Rehabilitation alone
Rehabilitation plus delayed ACLR
Rehabilitation plus early ACLR