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The effect of anterior cruciate ligament injury on bone curvature: Exploratory Analysis in the KANON Trial.

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

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26

27

28 Abstract (249 words)**29 Objective**

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

32 Methods

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

41 Results

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

50 Conclusion

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

55

56 Introduction

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

63 More than 70% of formerly young and active individuals who sustain ACL injuries end up
64 with moderate to severe disabilities, like instability, meniscal and chondral surface damage
65 and osteoarthritis (OA) (3;4). OA changes occur in 15-70% of the patients at 10-15 years
66 following the injury (3-8). Evidence suggests that roughly 25% of the disease burden of knee
67 osteoarthritis could be prevented by preventing knee injuries among men (women, 14%)
68 (9).

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

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

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

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

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

109

110 **Materials and Methods**

111 *Study Design*

112 This is an ancillary analysis of data from a randomized controlled trial (the Knee Anterior
113 Cruciate Ligament, Nonsurgical versus Surgical Treatment [KANON] Study; Current
114 Controlled Trials ISRCTN 84752559) (11;12). The trial compared a treatment strategy of

115 structured rehabilitation plus early ACL reconstructive surgery (n=62) with a strategy of
116 structured rehabilitation plus optional delayed ACL reconstruction (n=59), in which those
117 with symptomatic instability were offered delayed ACL reconstructive surgery if needed and
118 if specific protocol guidelines were met (11). Over the 5 year period, a delayed ACL
119 reconstruction was performed in 30/59 patients initially assigned to rehabilitation; 29
120 patients were treated with rehabilitation alone (12). The study was approved by the ethics
121 committee of Lund University. At inclusion, participants were eighteen to thirty-five years
122 old, had a moderate to high activity level prior to their injury, and had an acute ACL injury to
123 a previously uninjured knee. Major exclusion criteria were total collateral ligament rupture,
124 full-thickness cartilage injury as visualized on initial MRI, and evidence of osteoarthritis on
125 weight-bearing radiographs. Inclusion and exclusion criteria, details of the recruitment
126 process, and the clinical outcome after two and five years have been reported
127 (11;12;14;31;32).

128

129 *Intervention*

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

139

140 *Study sample*

141 One hundred and eleven (92%) of the study participants had intact series of MR images
142 acquired at baseline (within 5 weeks of injury) and 5 years after injury and thus formed the
143 focus sample of this ancillary study. After 5 years, 59 of these had an early ACLR (performed

144 within 10 weeks after injury), 27 had a delayed ACLR and 25 were treated with rehabilitation
145 alone. Those treated with ACLR, performed early or as a delayed procedure, constituted the
146 ACLR group (n=86) and were compared to those treated with rehabilitation alone (n=25).
147 Data on patient demographics and characteristics were collected at the start of the trial.
148 Time from the date of the injury to the baseline MRI was recorded, as was time from injury
149 to surgery.

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

154

155 *MRI Acquisition*

156 MRI was performed with use of a 1.5-T magnet (Gyrosan Intera; Philips, Eindhoven, The
157 Netherlands) with a circular polarized surface coil; sequences were identical for all subjects
158 and all time points. The MRI scans consisted of sagittal three-dimensional, water excitation,
159 fast low-angle shot (FLASH) with TR/TE/flip angle of 20 ms/7.9 ms/25, and sagittal T2-
160 weighted three dimensional gradient echo with TR/TE/flip angle of 20 ms/15 ms/50. Both
161 series were acquired with 15 cm FOV, 1.5 mm slice thickness, and 0.29 x 0.29 mm pixel size.
162 In addition, sagittal and coronal dual-echo turbo-spin-echo (DETSE), both with TR/TE/TI of
163 2900 ms/15 ms/80 ms, 15 cm FOV, 3 mm slice thickness with 0.6 mm gap, and 0.59 x 0.59
164 mm pixel size and sagittal and coronal short tau inversion recovery (STIR) with TR/TE/TI of
165 2900 ms/15 ms/160 ms, 15 cm FOV, 3 mmslice thickness with 0.6 mm gap, and 0.29 x 0.29
166 mm pixel size were acquired. Quality control of the MRI scanner was performed at each
167 individual acquisition with use of volumetric phantoms attached to the knee and on a
168 monthly basis with use of a standardized and calibrated uniformity and linearity (UAL)
169 phantom (1;35).

170

171 *Quantification and Post-Processing of MR Images*

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

203 reported for the following regions of interest (ROI): entire femur (F), entire tibia (T), medial
204 femur (cMF), lateral femur (cLF), trochlea (TF), medial tibia (MT) and lateral tibia (LT).

205

206 *Meniscal injury and cortical depression fractures*

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

218

219 *Statistical Analysis*

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

230 Relationships between change in bone curvature, treatment, presence of baseline
231 depression fracture, baseline meniscal injury and demographic characteristics were

232 compared using correlation analysis. Spearman's coefficients of correlations were calculated
233 for continuous variables, Kendall's tau-b coefficients of correlation - for categorical
234 variables/ binary outcomes in the 111 participants with complete baseline and 5 year data.

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

245

246 Results

247 The mean age of the 111 participants was 26 years, 27% were female and the mean BMI
248 was 24 kg/m² (**Table 1**). The characteristics of study participants who were assigned to
249 undergo rehabilitation alone approximated those that had an ACLR for age and BMI,
250 although appeared to differ for sex and injury to right knee.

251 Over the course of 5 years, the changes of values for curvature were statistically significant
252 in each region of the knee (i.e. convex shapes became flatter and concave shapes became
253 more concave, **Table 2, Figures 2 and 3**). The curvature values were averaged by ROI,
254 therefore the average ROI-curvature value represented a sphere that on average fit the ROI
255 surface. In that sense, we tested if the average ROI curvature fit a larger or smaller sphere.
256 For convex shapes the statistical test results indicated that on average the mean-curvature
257 was getting significantly smaller over time (Figure 3A and 3B). This implied that the
258 corresponding sphere that fit the ROI was getting larger, i.e. a flatter surface. On the other
259 hand, the concave tibia shape was getting significantly more concave over time. This
260 increase in concavity implied that the sphere that fit the tibia was getting smaller. In the
261 subsample with repeat visits over shorter time intervals (n=61), it is important to note these

262 changes were observable already by the 3 month visit (**Figure 3A**). Change to 3 months
263 (from baseline) in curvature was predictive of change at 5 years for both the femur
264 ($p=0.005$) and tibia ($p=0.006$).). The magnitude of the curvature change by 5 years was most
265 profound for the femur (standardized response mean, SRM $=-1.62$).

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

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

285

286 Discussion

287 Although the natural corollary of knee joint shape changes is not known, this study shows
288 that an acute ACL injury is associated with significant changes in bone curvature,
289 measurable within 3 months of the injury. Increased body mass index, meniscal injury and
290 surgical reconstruction of the ACL are associated with increased flattening (less convexity) of
291 the femur and increased depression (increased concavity) of the tibial surface. Bony shape

292 change was previously thought to be a late feature of OA pathogenesis but recent studies
293 suggest it is also seen in early OA (30;37). Whilst there is still considerable debate, many
294 studies suggest that alterations in bone may precede other structural changes in OA (38-41).
295 Consistent with prior literature on other structural changes following ACL injury (31;42), the
296 structural changes found for curvature in this study were more evident in the femoral
297 condyles than the tibial plateaus, however changes occurred both medially and laterally.

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

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

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

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

348 Our results support previous reports of trauma induced biological factors being important
349 for the longer term consequences of ACL injury (3;10;11;14;46). The shape changes found
350 here are likely to lead to less congruency of the joint surfaces and possibly higher stresses
351 on articular tissues during activity. Another important contributing factor may be the

352 “misalignment” between the condyles following an ACL tear resulting in changes in both
353 static and dynamic loading of joint surfaces leading to bone reaction (16;17). Studies that
354 include monitoring of the local structural and metabolic response to knee injury may shed
355 further light on this issue.

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

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

380 In sum, we have demonstrated that bone curvature changes occur within 3 months of acute
381 ACL injury and that the change is significant at 5 years. Our results support the importance

382 of trauma related factors for longer term structural change in the knee. Higher BMI,
383 concomitant meniscal injury and surgical reconstruction of the ACL predicted greater bone
384 curvature change.

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387 injuries and fractures, Björn Slaug for database extractions and Kerstin Åkesson for
388 coordinating study details.

389 Author Contributions

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

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411 manuscript writing, or the decision to publish this manuscript.

412

413 **Competing interest**

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

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

417

418 **Figure Legends**

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

426 **Figure 2. Cohort-based / population average maps.** Left Panel: Baseline measures for the
427 tibia and femur. Middle panel 2 year bone curvature change for femur (above) and tibia
428 (below). Right panel 5 year change for femur (above) and tibia (below). Maps are based on
429 93 of the 111 participants with both good reference atlas-segmentation and paired data at
430 baseline, 2 and 5 Years.

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

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

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

442 **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/m², (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)

443

444

445

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

	Change in curvature (mm ⁻¹)		95%CI	p value	Standardised Response Mean
	Mean	SD			
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

448 p-values reflect difference between baseline and 5 years

449

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
<i>Unadjusted</i>							
<u>Treatment group</u>							
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
<u>Meniscal injury@ baseline (=Yes injury)</u>							
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
<u>Osteochondral fracture (=Yes Fracture)</u>							
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[#]
<i>Adjusted for Baseline curvature, age, BMI and gender</i>							
<u>Treatment group</u>							
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
<u>Meniscal injury@ baseline (=Yes injury)</u>							
Any	-0.000697[#]	-0.000626	-0.001231[#]	-0.000965[#]	-0.000977	-0.000594	-0.001557[#]
Medial	-0.001171[£]	-0.000712	-0.001319[#]	-0.001286[#]	-0.001277	-0.001475[£]	-0.001081
Lateral	-0.000403	-0.000651	-0.000554	-0.000710	-0.000909	-0.000327	-0.001673[#]
<u>Osteochondral fracture (=Yes Fracture)</u>							
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 ($p < 0.05$). §- $P < 0.001$; £ - $P < 0.01$; # - $P < 0.05$

Reference List

- (1) Frobell RB, Roos HP, Roos EM, Hellio le Graverand MP, Buck R, Tamez-Pena J, et al. The acutely ACL injured knee assessed by MRI: are large volume traumatic bone marrow lesions a sign of severe compression injury? *Osteoarthritis & Cartilage* 2008 Jul;16(7):829-36.
- (2) Yelin E, Callahan LF. The economic cost and social and psychological impact of musculoskeletal conditions. National Arthritis Data Work Groups [see comments]. [Review] [68 refs]. *Arthritis & Rheumatism* 1995 Oct;38(10):1351-62.
- (3) Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med* 2007 Oct;35(10):1756-69.
- (4) Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Annals of Internal Medicine* 2000 Sep 5;133(5):321-8.
- (5) Roos H, Adalberth T, Dahlberg L, Lohmander LS. Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. *Osteoarthritis & Cartilage* 1995 Dec;3(4):261-7.
- (6) Lohmander LS, Ostenberg A, Englund M, Roos H, Lohmander LS, Ostenberg A, et al. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis & Rheumatism* 2004 Oct;50(10):3145-52.
- (7) Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. *American Journal of Sports Medicine* 2008 Sep;36(9):1717-25.
- (8) Oiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. *Am J Sports Med* 2009 Jul;37(7):1434-43.
- (9) Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. [Review] [116 refs]. *Arthritis & Rheumatism* 1998 Aug;41(8):1343-55.
- (10) Buckwalter JA. Articular cartilage injuries. *Clin Orthop Relat Res* 2002 Sep;(402):21-37.
- (11) Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med* 2010 Jul 22;363(4):331-42.
- (12) Frobell RB, Roos HP, Roos EM, Roemer FW, Ranstam J, Lohmander LS. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. *BMJ* 2013;346:f232.
- (13) Spindler KP, Wright RW. Clinical practice. Anterior cruciate ligament tear. *N Engl J Med* 2008 Nov 13;359(20):2135-42.

- (14) Frobell RB, Le Graverand MP, Buck R, Roos EM, Roos HP, Tamez-Pena J, et al. The acutely ACL injured knee assessed by MRI: changes in joint fluid, bone marrow lesions, and cartilage during the first year. *Osteoarthritis Cartilage* 2009 Feb;17(2):161-7.
- (15) Chaudhari AM, Briant PL, Bevill SL, Koo S, Andriacchi TP. Knee kinematics, cartilage morphology, and osteoarthritis after ACL injury. *Med Sci Sports Exerc* 2008 Feb;40(2):215-22.
- (16) Scanlan SF, Chaudhari AM, Dyrby CO, Andriacchi TP. Differences in tibial rotation during walking in ACL reconstructed and healthy contralateral knees. *J Biomech* 2010 Jun 18;43(9):1817-22.
- (17) Zabala ME, Favre J, Scanlan SF, Donahue J, Andriacchi TP. Three-dimensional knee moments of ACL reconstructed and control subjects during gait, stair ascent, and stair descent. *J Biomech* 2013 Feb 1;46(3):515-20.
- (18) Hoshino Y, Fu FH, Irrgang JJ, Tashman S. Can Joint Contact Dynamics Be Restored by Anterior Cruciate Ligament Reconstruction? *Clin Orthop Relat Res* 2013 Jan 3;471(9):2924-31.
- (19) Messent EA, Ward RJ, Tonkin CJ, Buckland-Wright C. Tibial cancellous bone changes in patients with knee osteoarthritis. A short-term longitudinal study using Fractal Signature Analysis. *Osteoarthritis & Cartilage* 2005 Jun;13(6):463-70.
- (20) Haverkamp DJ, Schiphof D, Bierma-Zeinstra SM, Weinans H, Waarsing JH. Variation in joint shape of osteoarthritic knees. *Arthritis Rheum* 2011 Nov;63(11):3401-7.
- (21) Bredbenner TL, Eliason TD, Potter RS, Mason RL, Havill LM, Nicoletta DP. Statistical shape modeling describes variation in tibia and femur surface geometry between Control and Incidence groups from the osteoarthritis initiative database. *J Biomech* 2010 Jun 18;43(9):1780-6.
- (22) Grynblas MD, Alpert B, Katz I, Lieberman I, Pritzker KP. Subchondral bone in osteoarthritis. *Calcified Tissue International* 1991 Jul;49(1):20-6.
- (23) Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. *Clinical Orthopaedics & Related Research* 1986 Dec;(213):34-40.
- (24) Woloszynski T, Podsiadlo P, Stachowiak GW, Kurzynski M, Lohmander LS, Englund M. Prediction of progression of radiographic knee osteoarthritis using tibial trabecular bone texture. *Arthritis Rheum* 2012 Mar;64(3):688-95.
- (25) Buckland-Wright JC, MacFarlane DG, Jasani MK, Lynch JA. Quantitative microfocal radiographic assessment of osteoarthritis of the knee from weight bearing tunnel and semiflexed standing views. *Journal of Rheumatology* 1994 Sep;21(9):1734-41.
- (26) Stein V, Li L, Guermazi A, Zhang Y, Kent KC, Eaton CB, et al. The relation of femoral notch stenosis to ACL tears in persons with knee osteoarthritis. *Osteoarthritis Cartilage* 2010 Feb;18(2):192-9.
- (27) Hoshino A, Wallace WA. Impact-absorbing properties of the human knee. *J Bone Joint Surg Br* 1987 Nov;69(5):807-11.

- (28) Kraus VB, Feng S, Wang S, White S, Ainslie M, Brett A, et al. Trabecular morphometry by fractal signature analysis is a novel marker of osteoarthritis progression. *Arthritis Rheum* 2009 Dec;60(12):3711-22.
- (29) Ganz R, Parvizi J, Beck M, Leunig M, Notzli H, Siebenrock KA. Femoroacetabular impingement: a cause for osteoarthritis of the hip. [Review] [30 refs]. *Clinical Orthopaedics & Related Research* 2003 Dec;(417):112-20.
- (30) Neogi T, Bowes MA, Niu J, De Souza KM, Vincent GR, Goggins J, et al. Magnetic resonance imaging-based three-dimensional bone shape of the knee predicts onset of knee osteoarthritis: data from the osteoarthritis initiative. *Arthritis Rheum* 2013 Aug;65(8):2048-58.
- (31) Frobell RB. Change in cartilage thickness, posttraumatic bone marrow lesions, and joint fluid volumes after acute ACL disruption: a two-year prospective MRI study of sixty-one subjects. *J Bone Joint Surg Am* 2011 Jun 15;93(12):1096-103.
- (32) Frobell RB, Lohmander LS, Roos EM. The challenge of recruiting patients with anterior cruciate ligament injury of the knee into a randomized clinical trial comparing surgical and non-surgical treatment. *Contemp Clin Trials* 2007 May;28(3):295-302.
- (33) Spindler KP, Kuhn JE, Freedman KB, Matthews CE, Dittus RS, Harrell FE, Jr. Anterior cruciate ligament reconstruction autograft choice: bone-tendon-bone versus hamstring: does it really matter? A systematic review. *Am J Sports Med* 2004 Dec;32(8):1986-95.
- (34) Biau DJ, Tournoux C, Katsahian S, Schranz PJ, Nizard RS. Bone-patellar tendon-bone autografts versus hamstring autografts for reconstruction of anterior cruciate ligament: meta-analysis. *BMJ* 2006 Apr 29;332(7548):995-1001.
- (35) Roemer FW, Frobell R, Hunter DJ, Crema MD, Fischer W, Bohndorf K, et al. MRI-detected subchondral bone marrow signal alterations of the knee joint: terminology, imaging appearance, relevance and radiological differential diagnosis. *Osteoarthritis Cartilage* 2009 Sep;17(9):1115-31.
- (36) Tamez-Pena JG, Farber J, Gonzalez PC, Schreyer E, Schneider E, Totterman S. Unsupervised segmentation and quantification of anatomical knee features: data from the Osteoarthritis Initiative. *IEEE Trans Biomed Eng* 2012 Apr;59(4):1177-86.
- (37) Reichenbach S, Guermazi A, Niu J, Neogi T, Hunter DJ, Roemer FW, et al. Prevalence of bone attrition on knee radiographs and MRI in a community-based cohort. *Osteoarthritis & Cartilage* 2008 Sep;16(9):1005-10.
- (38) Anderson-MacKenzie JM, Quasnicka HL, Starr RL, Lewis EJ, Billingham ME, Bailey AJ. Fundamental subchondral bone changes in spontaneous knee osteoarthritis. *Int J Biochem Cell Biol* 2005 Jan;37(1):224-36.
- (39) Hayami T, Pickarski M, Zhuo Y, Wesolowski GA, Rodan GA, Duong IT. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. *Bone* 2006 Feb;38(2):234-43.
- (40) Hutton CW, Higgs ER, Jackson PC, Watt I, Dieppe PA. 99mTc HMDP bone scanning in generalised nodal osteoarthritis. II. The four hour bone scan image predicts radiographic change. *Ann Rheum Dis* 1986 Aug;45(8):622-6.

- (41) Ding C, Cicuttini F, Jones G. Tibial subchondral bone size and knee cartilage defects: relevance to knee osteoarthritis. [Review] [63 refs]. *Osteoarthritis & Cartilage* 2007 May;15(5):479-86.
- (42) Lee YS, Jeong YM, Sim JA, Kwak JH, Kim KH, Nam SW, et al. Specific compartmental analysis of cartilage status in double-bundle ACL reconstruction patients: a comparative study using pre- and postoperative MR images. *Knee Surg Sports Traumatol Arthrosc* 2013 Mar;21(3):702-7.
- (43) Li X, Kuo D, Theologis A, Carballido-Gamio J, Stehling C, Link TM, et al. Cartilage in anterior cruciate ligament-reconstructed knees: MR imaging T1{rho} and T2--initial experience with 1-year follow-up. *Radiology* 2011 Feb;258(2):505-14.
- (44) Li RT, Lorenz S, Xu Y, Harner CD, Fu FH, Irrgang JJ. Predictors of radiographic knee osteoarthritis after anterior cruciate ligament reconstruction. *Am J Sports Med* 2011 Dec;39(12):2595-603.
- (45) Louboutin H, Debarge R, Richou J, Selmi TA, Donell ST, Neyret P, et al. Osteoarthritis in patients with anterior cruciate ligament rupture: a review of risk factors. *Knee* 2009 Aug;16(4):239-44.
- (46) Lohmander LS, Roos H. Knee ligament injury, surgery and osteoarthrosis. Truth or consequences? *Acta Orthop Scand* 1994 Dec;65(6):605-9.
- (47) Meuffels DE, Favejee MM, Vissers MM, Heijboer MP, Reijman M, Verhaar JA. Ten year follow-up study comparing conservative versus operative treatment of anterior cruciate ligament ruptures. A matched-pair analysis of high level athletes. *Br J Sports Med* 2009 May;43(5):347-51.
- (48) Potter HG, Jain SK, Ma Y, Black BR, Fung S, Lyman S. Cartilage injury after acute, isolated anterior cruciate ligament tear: immediate and longitudinal effect with clinical/MRI follow-up. *Am J Sports Med* 2012 Feb;40(2):276-85.
- (49) Theologis AA, Kuo D, Cheng J, Bolbos RI, Carballido-Gamio J, Ma CB, et al. Evaluation of bone bruises and associated cartilage in anterior cruciate ligament-injured and -reconstructed knees using quantitative t(1rho) magnetic resonance imaging: 1-year cohort study. *Arthroscopy* 2011 Jan;27(1):65-76.
- (50) Costa-Paz M, Muscolo DL, Ayerza M, Makino A, Aponte-Tinao L. Magnetic resonance imaging follow-up study of bone bruises associated with anterior cruciate ligament ruptures. *Arthroscopy* 2001 May;17(5):445-9.
- (51) Bullough PG, Jagannath A. The morphology of the calcification front in articular cartilage. Its significance in joint function. *Journal of Bone & Joint Surgery - British Volume* 1983 Jan;65(1):72-8.
- (52) Burr DB, Radin EL. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis?. [Review] [60 refs]. *Rheumatic Diseases Clinics of North America* 2003 Nov;29(4):675-85.

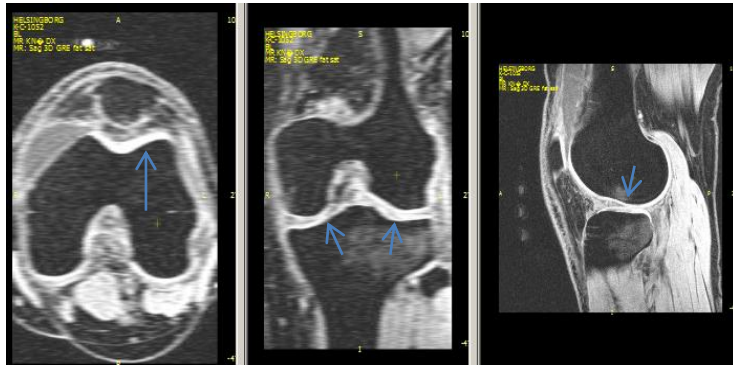
Figure

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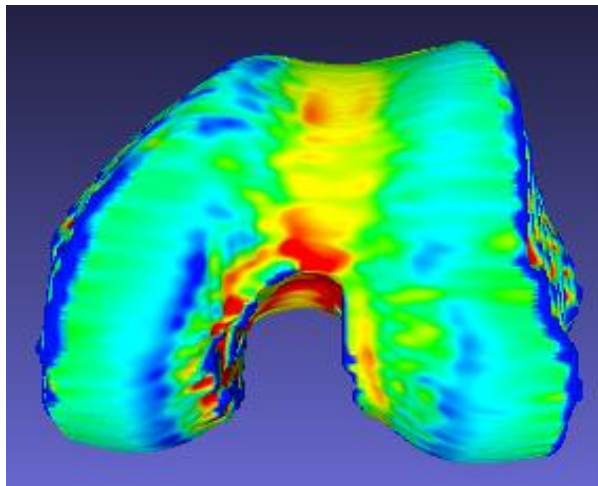
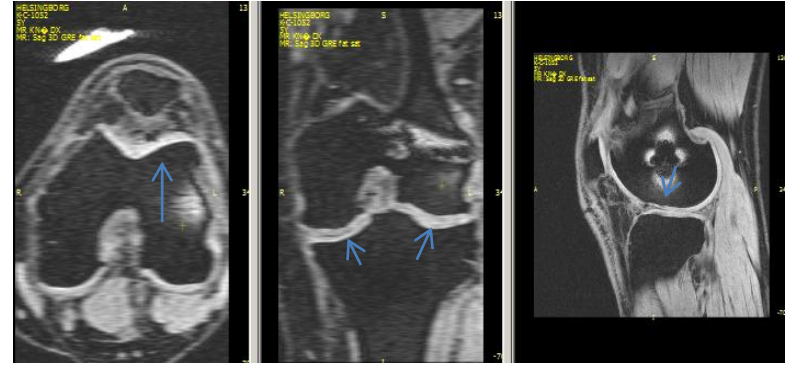
Figures for curvature paper

Figure 1

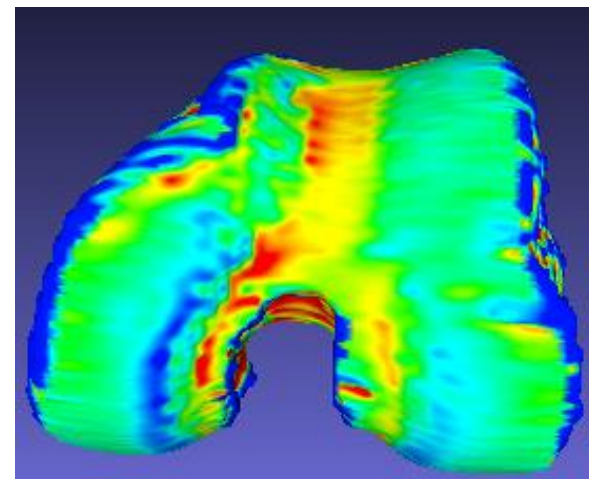
Baseline



5 Year Follow-up



Concave  Convex
-0.1 mm⁻¹ +0.1 mm⁻¹



Concave  Convex
-0.1 mm⁻¹ +0.1 mm⁻¹

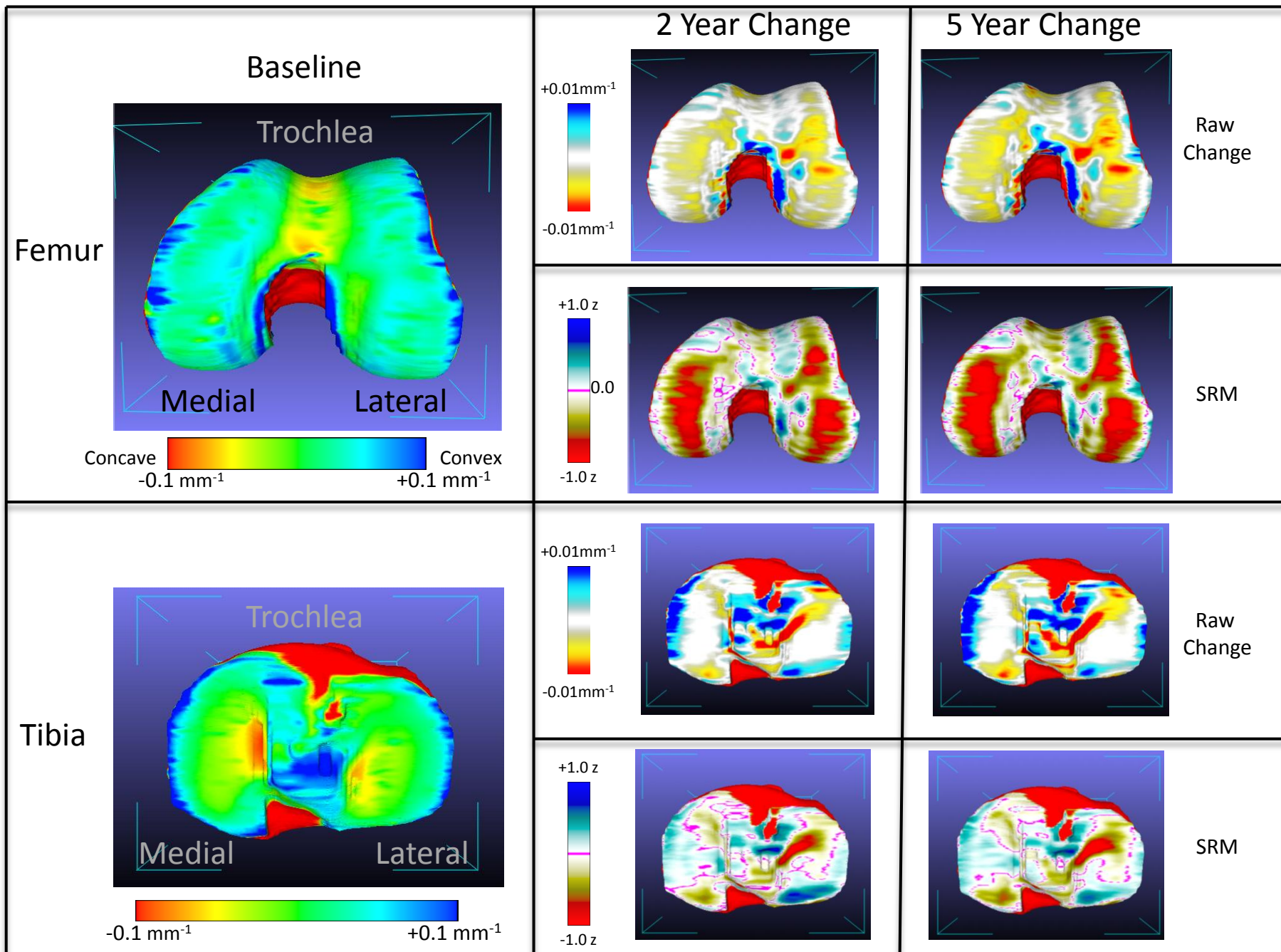


Figure 2. Population Average: Left, Baseline Average. Middle, 2 year average change. Right, 5 Year average changes

Figure 3

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Bone curvature over 5 years by anatomic location

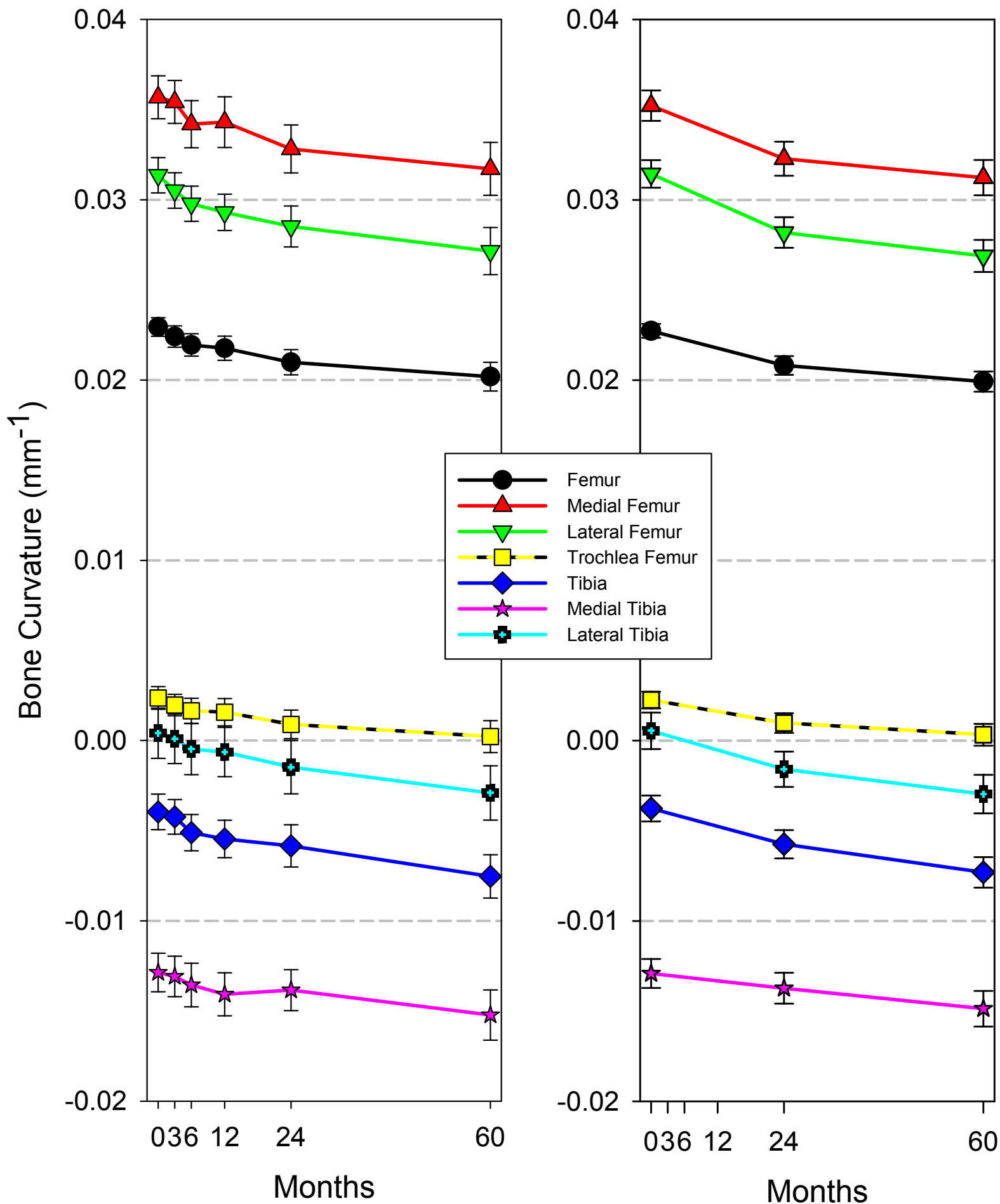
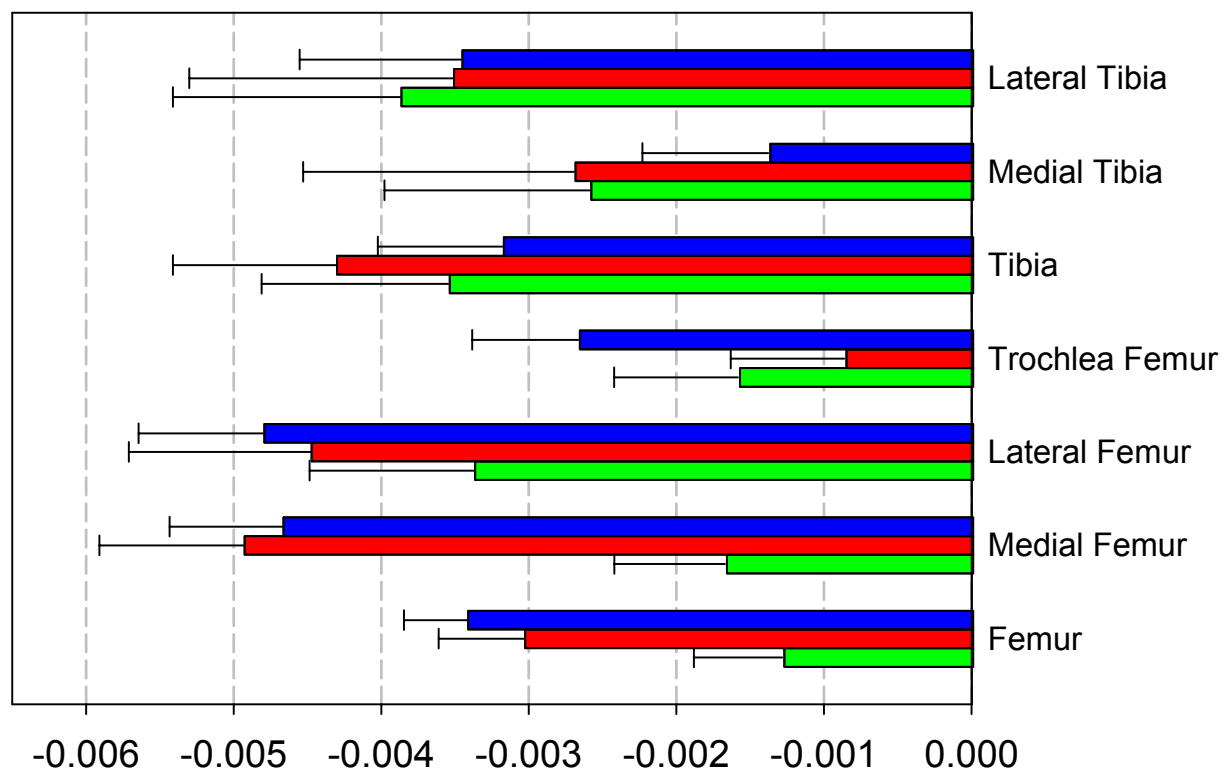


Figure 4

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Bone curvature change over 5 years by treatment group (mm⁻¹)

