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The effect of anterior cruciate ligament injury on bone curvature: exploratory analysis in the KANON trial

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SUMMARY

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 (ISRCTN 84752559), 111/121 young active adults with an acute ACL tear to a previously un-injured knee had serial 1.5 T 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, BMI, 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 (LT) ($P = 0.011$). 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 LT ($P = 0.048$).
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 OA 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

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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 OA[11,12,14]. 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 remodeling 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 ACL, Nonsurgical vs 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 OA 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 preference11. In randomized 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 <10 mm 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 ACL reconstruction (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 × 0.29 mm pixel size. In addition, sagittal and coronal dual-echo turbo-spin-echo (DETSE), both with TR/TE/TI of 2,900 ms/15 ms/80 ms, 15 cm FOV, 3 mm slice thickness with 0.6 mm gap, and 0.59 × 0.59 mm pixel size and sagittal and coronal short tau inversion recovery (STIR) with TR/TE/TI of 2,900 ms/15 ms/160 ms, 15 cm FOV, 3 mm slice thickness with 0.6 mm gap, and 0.29 × 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[35,36].