Changes to the articular cartilage thickness profile of the tibia following anterior cruciate ligament injury

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Objectives: We sought to determine if anterior cruciate ligament (ACL)-injured subjects demonstrated side-to-side differences in tibial cartilage thickness soon after injury, and if uninjured-control subjects displayed side-to-side symmetry in cartilage thickness. Second, we aimed to investigate associations between body mass index (BMI), cross-sectional area (CSA) of the proximal tibia, and articular cartilage thickness differences.

Methods: Bilateral Magnetic Resonance Images (MRIs) were obtained on 88 ACL-injured subjects (27 male; 61 female) a mean 27 days post-injury, and 88 matched uninjured control subjects. Within ACL-injured and uninjured control subjects, side-to-side differences in medial and lateral tibial articular cartilage thickness were analyzed with adjustment for tibial position relative to the femur during MRI acquisition. Associations between tibial CSA and cartilage thickness differences were tested within high and low BMI groups.

Results: Within the medial tibial compartment, ACL-injured females displayed significant increases: mean (confidence interval (CI)) = +0.18 mm (0.17, 0.19) and decreases: mean (CI) = −0.14 mm (−0.13, −0.15) in tibial cartilage thickness within the central and posterior cartilage regions respectively. Adjustment for tibial position revealed a decreased area of significant cartilage thickness differences, though 46% of points maintained significance.

In the lateral compartment anterior region, there was a significantly different relationship between cartilage thickness differences and CSA, within high and low BMI groups (BMI group*CSA interaction, P = 0.007). Within the low BMI group, a significant negative correlation between cartilage thickness and CSA was identified (P = 0.03).

Conclusions: ACL-injured females displayed cartilage thickness differences in the central, and posterior medial tibial cartilage regions. Tibial position effected thickness differences, but did not account for all significant differences.

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Introduction

Severe joint traumas, including injury to the anterior cruciate ligament (ACL), have lasting effects on joint health, and often result in the early onset of post traumatic osteoarthritis (PTOA). Though surgical reconstruction of the ACL has become the conventional way to improve patient function, it does not prevent the ultimate development of PTOA. Reports estimate the highest incidence of ACL-injury occurs in individuals between 15 and 26 years of age. As a consequence, many young and otherwise healthy individuals inevitably present with PTOA within 10–15 years of the index injury. Presently, little is known about the onset of cartilage degeneration after injury, though several studies...
suggest that the initial joint trauma and corresponding alterations in joint contact mechanics are paramount factors in the development of PTOA. Magnetic Resonance Imaging (MRI) studies of ACL-injured patients often reveal concomitant injuries within the tibiofemoral joint, that are indicative of the large shear and compressive loads developed across the joint at the time of injury. Though there might be an absence of gross defects within the articular cartilage surface, bone marrow lesions below the articular cartilage are common, and serve as evidence of the substantial forces transmitted through the cartilage at the time of ACL-injury. Transmitted forces of this magnitude are capable of disrupting the organization of the collagen matrix, and there is evidence to suggest that this initial impact could initiate a cascade of biological events culminating in chondrocyte necrosis, alterations in cell metabolism, loss of proteoglycan, and the ultimate development of MRI data in this study were originally collected as part of a larger longitudinal cohort study with a nested matched case-control design. The aforementioned study was designed to identify the risk factors for noncontact ACL-injury, and resulted in a multivariate model of risk. Additional details of the MRI cohort, including the recruitment protocol and subject demographics, have been previously described. 

Varsity athletes from 28 high schools and 8 colleges were monitored prospectively over a 4-year time interval for the occurrence of non-contact ACL-injuries. Non-contact ACL-injury was defined as: an ACL-injury that had occurred in the absence of a direct blow to the knee. 88 ACL-injured subjects (27 male, 61 female) who had sustained a first time, grade III, non-contact ACL-injury, during participation in organized high school or college sport were included in this study. Uninjured control subjects (27 males, 61 females), were recruited teammates of the ACL-injured subjects, who were matched on age, and sex. Case-control matching of subjects from the same sports team was performed to control for the type, amount, and level of activity of each case subject. Using the Phillips Achieva 3.0T Research MRI (Fletcher Allen Healthcare, Burlington, VT) bilateral MRI scans were obtained on both ACL-injured, and uninjured-control subjects. Subjects were positioned supine, with their knees in extension inside an 8-channel SENSE coil. Sagittal plane, T1 weighted, Fast-Field Echo (FFE) scans with a slice thickness of 1.2 mm, and a within-plane resolution of 0.3 mm by 0.3 mm, were obtained on all subjects. MRIs were acquired on ACL-injured subjects after injury, but preceding any surgical reconstruction (days post-injury: median 15, average 27, range 1–110). Using Osirix Software (Pixmeo, Geneva, Switzerland, version 3.6.1, open source) and a Cintiq 21 UK Digitizing tablet (Wacom Tech Corp, Vancouver, WA, USA), digital imaging and communications in medicine (DICOM) images were viewed and manually segmented. Medial and lateral compartments of the tibial plateau were segmented and considered separately. Articular cartilage surfaces were segmented in both the sagittal and coronal planes, from the edge of each compartment to the last slice on the tibial spine where the cartilage surface was discernable. Medial and lateral tibial plateau subchondral bone surfaces were segmented in the sagittal plane (Fig. 1 of Supplemental text). Intraclass correlation coefficient (ICC) values were obtained from an analysis of reliability between two separate time points, indicated a high level of cartilage thickness measurement reliability (Table I). Because MRI data were acquired in the coordinate system of the scanner, and the position of the tibia relative to the femur varied both within and between subjects, MRI data were transformed into three-dimensional bone based femoral and tibial coordinate systems [Fig. 1(A)]. Tibial and femoral coordinate systems were used to obtain measurements that were referenced to the anatomical planes of each bone, allowing for comparison of data both between, and within subjects. Methods used to establish and locate the coordinate systems have been described. 

### Table I

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<tr>
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<th>Regions</th>
<th>ICC</th>
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Building on prior research the objectives of this study were twofold. First, we sought to determine if ACL-injured subjects exhibited significant side-to-side differences in tibial plateau articular cartilage thicknesses within a short time interval after injury and, if uninjured control subjects displayed side-to-side symmetry in tibial cartilage thickness. Additionally, we aimed to determine if cartilage thickness differences were affected by the position of the tibia relative to the femur during MRI acquisition. Our second objective was designed to build on our first, by defining effects of overall subject size (body mass index (BMI)) and the size of a subject’s proximal tibia (defined by cross-sectional area (CSA)), on the measurement of cartilage thickness.

### Methods

Our Institutional Review Board gave approval for this study and all subjects provided written consent prior to their participation.

1. Previous research focused on cartilage status after ACL-injury and, if uninjured control subjects displayed side-to-side differences in tibial plateau regions.
2. These alterations are important to consider and, add to an understanding of the relationship between ACL-injury and subsequent PTOA development.
3. Our Institutional Review Board gave approval for this study and all subjects provided written consent prior to their participation.
4. Magnetic Resonance Imaging (MRI) studies of ACL-injured patients often reveal concomitant injuries within the tibiofemoral joint, that are indicative of the large shear and compressive loads developed across the joint at the time of injury.
5. Transmitted forces of this magnitude are capable of disrupting the organization of the collagen matrix, and there is evidence to suggest that this initial impact could initiate a cascade of biological events culminating in chondrocyte necrosis, alterations in cell metabolism, loss of proteoglycan, and the ultimate development of PTOA. Our second objective was designed to build on our first, by defining effects of overall subject size (body mass index (BMI)) and the size of a subject’s proximal tibia (defined by cross-sectional area (CSA)), on the measurement of cartilage thickness.
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### Methods

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1. Previous research focused on cartilage status after ACL-injury and, if uninjured control subjects displayed side-to-side differences in tibial plateau articular cartilage thicknesses within a short time interval after injury and, if uninjured control subjects displayed side-to-side symmetry in tibial cartilage thickness. Additionally, we aimed to determine if cartilage thickness differences were affected by the position of the tibia relative to the femur during MRI acquisition. Our second objective was designed to build on our first, by defining effects of overall subject size (body mass index (BMI)) and the size of a subject’s proximal tibia (defined by cross-sectional area (CSA)), on the measurement of cartilage thickness.

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and females. These covariates in analyses. Evaluation of the in AP and ML tibial position (relative to the femur) were used as distribution. Therefore within each subject, the side-to-side differences of the joint would have an affect on the cartilage thickness distribution. Therefore within each subject, the side-to-side differences in AP and ML tibial position (relative to the femur) were used as covariates in analyses. Evaluation of the first objective included measurement of tibial plateau articular cartilage thickness within ACL-injured and uninjured-control subjects. Side-to-side differences in cartilage thickness were compared using a mixed model repeated measures of variance at each point on the aforementioned 1 mm by 1 mm grid. Comparisons were made in a region (anterior, central, posterior) and compartment (medial, lateral) specific manner, and the determined P-values were adjusted for a False Discovery Rate, using the Benjamini-Hochberg method. Our second objective aimed to evaluate if a relationship existed between measured cartilage thickness profile differences and subject size. Categorical BMI groups were defined based on the respective ranges of male and female subject BMI data. Median BMI values were used as the cut off for high and low BMI groups. Female subjects were considered to have low BMI if it was less than 22.5, or high BMI if greater than 22.5. Male subjects were considered to have a low BMI if it was less than 23.2 or high BMI if it was greater than 23.2. Analyses of variance (ANOVA) were used to test the associations between measurements of CSA, and magnitude of cartilage thickness change for each BMI group, and to test for differences in these associations between BMI groups. All statistical analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC).

Results

Summary statistics for measured articular cartilage thickness within each region of both the medial and lateral tibial compartments, including mean and 95% confidence intervals (CIs), are provided in Table II.

Analyses of within subject comparisons of cartilage thickness

Within ACL-injured females (n = 61), significant side-to-side differences in cartilage thickness were found in the central and posterior cartilage regions of the medial tibial compartment (Table III and Fig. 2). Specifically, significant cartilage thickness increases: mean (CI) = +0.18 mm (0.17, 0.19), were found within 15.9% of points in the central cartilage region, while significant cartilage thickness decreases: mean (CI) = −0.14 mm (−0.13, −0.15), were found within 28.5% of points in the posterior cartilage region of the medial compartment. Within ACL-injured females, no significant differences in lateral tibial cartilage thickness were seen in the anterior, central, or posterior cartilage regions. Further analyses of ACL-injured females that were adjusted for the AP and ML position of the tibia relative to the femur revealed a decrease in the area where cartilage where significant differences were found, though 46% of points in the central and posterior regions of the medial compartment maintained significance. Unadjusted analyses of ACL-injured females revealed no significant differences in cartilage thickness for any of the lateral compartment cartilage regions, though differences within the
Significant side-to-side (injured-to-uninjured knee) differences in medial tibial articular cartilage thickness within ACL-injured females (n = 61)

<table>
<thead>
<tr>
<th>Cartilage region</th>
<th>Mean (mm)</th>
<th>95% CI (mm)</th>
<th>Range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>+0.18</td>
<td>(+0.17, +0.19)</td>
<td>0.10 to 0.29</td>
</tr>
<tr>
<td>Central</td>
<td>-0.14</td>
<td>(-0.13, -0.15)</td>
<td>-0.27 to 0.07</td>
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ANOVA results for cartilage thickness difference vs categorical BMI, and mean CSA

Within the categorized high and low BMI groups, relationships within ACL-injured subjects between mean injured-uninjured side differences in cartilage thickness, and injured-uninjured side mean CSA were tested. A significant relationship was only found within female ACL-injured subjects, for the anterior cartilage region of the lateral compartment. Within the low BMI group, there was a significant negative correlation between cartilage thickness mean and CSA mean (P-value = 0.03; r = −0.39). There was also a nearly significant positively correlated relationship between mean cartilage thickness mean and CSA mean for the High BMI group (P-value = 0.08; r = 0.32). In addition, the BMI group×CSA mean interaction was significant (P-value = 0.007), indicating a significant difference in the thickness vs CSA relationships between BMI groups.

Discussion

ACL-injured females displayed significant side-to-side differences in articular cartilage thickness within the medial compartment. Specifically, significant increases in tibial cartilage thickness were found within the central region of the medial tibial cartilage, while significant decreases in tibial cartilage thickness were found within the posterior cartilage region. Notably, within the current study ACL-injured males did not display significant side-to-side differences in cartilage thickness. The cartilage thickness data for male ACL-injured subjects was more variable than ACL-injured females. Greater variability within ACL-injured male data, in conjunction with a comparably smaller male sample size may have decreased the level of statistical power and obscured significant findings.

Measured cartilage thickness differences within ACL-injured females are biomechanically significant as they represent a magnitude of change that is more than 10% of the mean cartilage thickness within the medial compartment, and were not fully
explained by position of the tibia relative to the femur. Blunt impact forces to the articular cartilage, such as those produced at the time of ACL-injury, have been shown to alter the organization of the collagen matrix even in the absence of gross cartilage defects. Disruption of the cartilage matrix is a potential cause for the measured increase in cartilage thickness; increased thickness may be reflective of a shift in water content, created by an acute loss of proteoglycan from the cartilage. This notion is further supported by research that has employed the use of specialized MRI techniques to observe changes in both cell metabolism, and glycosaminoglycan indices of the cartilage within a short time interval after ACL-injury. Previous studies have revealed significant side-to-side differences in the delayed Gadolinium-Enhanced MRI Imaging of Cartilage (dGEMRIC) indices within the medial tibiofemoral compartment of ACL-injured subjects. Additionally, at one-year follow up after ACL-injury Li et al. described the prolongation of T1 rho, indicative of a loss of proteoglycan within a similar region of the tibial cartilage in the medial compartment.

Biomechanically, ACL-injury causes changes within the loading environment of the tibiofemoral joint. In the current study alterations in the position of the tibia relative to the femur at the time of MRI acquisition were found to be an important methodological factor to consider when making side-to-side comparisons of cartilage thickness. Statistical analysis with adjustment for the position of the tibia relative to the femur during MRI acquisition had a significant influence on the magnitude of side-to-side cartilage thickness differences. If the 3D position of the tibia relative to the femur were not considered in the statistical analysis, the magnitude of measured side-to-side differences would have been amplified. ACL-injury causes a shift in tibiofemoral contact mechanics to a more lateral and posterior location on the tibial plateau. Within the current study, the decreases in tibial cartilage thickness seen within the posterior cartilage region may be a result of increased load being transmitted through the posterior medial meniscus. Decreased cartilage thickness in this region could be further propagated by regional variations in the material and structural properties of the tibial cartilage; therefore loading cartilage unsuited to bear such loads. Conversely, the cartilage within the central cartilage region that is conditioned for functional weight bearing, but might be subjected to a decrease in load do to the more anterior position of the tibia relative to the femur.

Abnormal biomechanics and subsequent changes in the tibiofemoral joint loading environment have been proposed as a contributing factors for the progression of cartilage degeneration (PTOA). Altered orientations include a two-degree internal rotational orientation, a three-millimeter anterior shift, and a one-millimeter medial translation of the tibia relative to the femur within ACL-injured subjects performing a static lunge. The loading environment of tibial plateau articular cartilage is influenced by altered kinematics after an ACL-injury. In an ACL-injured knee, locations of highest contact stress transmission throughout gate can shift to thinner cartilage regions that are not conditioned to withstand such stress. Advancements of the study include its rigorous study design and highly standardized measurement methodology. Only subjects who had suffered their first ACL-injury (to either knee) were recruited for participation in this study. Uninjured controls were matched to the ACL-injured subjects on age, sex and participation on the same sports team. As such, there was control for the amount, level, and type of activity that subjects participated in prior to injury. A consistent definition of non-contact injury mechanisms was applied to all subjects, which avoided confounding results that may have been introduced by differences in joint biomechanics between contact and non-contact injury mechanisms. For each subject, bilateral MRI data were acquired in a consistent manner, with knees placed in extension, and patella aligned vertically, using the same 8-channel SENSE coil and MRI unit. Data analyses included the use of tibial and femoral coordinate systems that allowed us to establish the complete 6 degree-of-freedom position of the tibia relative to the femur during MRI acquisition and make reliable measures of cartilage thickness both within and between subjects.

Some limitations exist with the application of this study design. MRI data were acquired at a single time point after ACL-injury but prior to surgical reconstruction; a time interval which varied between ACL-injured subjects. However, the majority of subjects were recruited and evaluated within a short time interval (median 15 days) after ACL-injury. Consequently, this study should be considered to have focused on the response of articular cartilage to the trauma produced at the time of ACL disruption and its initial healing response. We were interested in determining if the time interval between ACL disruption and MRI data acquisition had an effect on cartilage thickness and consequently we performed post-hoc analysis. This revealed the time interval between injury and MRI acquisition was not significantly correlated with differences in articular cartilage thickness. Data collected from this unique patient demographic allowed for the investigation of the early traumatic effects of ACL-injury on cartilage thickness. However, without longitudinal data it is difficult to determine how the early changes in cartilage thickness are associated with the future onset and progression of PTOA. Future work is needed to characterize the progressive response of articular cartilage and bone. With such information, the time interval during which an intervention could be effective may be identified.

Additionally, leg axis and muscle forces could have an influence on articular cartilage thickness through alteration of contact stresses developed across the joint. Such measurements require data acquired with standing radiographs, which were not collected in this study. Recent work by Marsh et al. reported correlations between tibiofemoral joint space width measured off of weight-bearing X-ray, weight bearing MRI, and non-weight-bearing MRI. In addition, frontal plane (varus-valgus) alignment of the tibia was characterized in the current study through the orientation of the tibial coordinate system relative to the femoral coordinate system during MRI acquisition. No side-to-side differences in varus-valgus alignment within ACL-injured and uninjured control subjects were found. Consequently, limb alignment and muscle forces were thought to have minimal influence on both cartilage thickness or the within ACL-injured subject differences reported in this study. Other limitations of this study include the incomplete understanding of the effect of concomitant articular cartilage and meniscal injuries on the differences in cartilage thickness profile seen within ACL-injured females. Most ACL-injured subjects suffer some degree of bone marrow lesions and a large number suffer articular cartilage and meniscus lesions at the time of injury. Data on concomitant injury were not collected on all subjects. As a result, conclusions on their influence cannot be made. However, medical records including intra-operative arthroscopic documentation of meniscus and articular cartilage pathology were collected on a subset of 25 female subjects, 13 and 15 of which had a meniscus or cartilage injury diagnoses, respectively. Post-hoc analysis was completed to investigate potential effects. No significant differences in articular cartilage thickness were identified between groups based on meniscus or cartilage injury status. Consequently, the influence of such concomitant pathology may be small. Lastly, this study focused on characterizing changes in the tibial plateau articular cartilage. Changes in articular cartilage morphology throughout the femoral condyles, trochlea and patella may be equally, if not more, important. Future research should
investigate these anatomic structures with similar methodologies in order to obtain a more comprehensive understanding of the effects of an ACL-injury.

In conclusion, tibial plateau articular cartilage thickness differences were identified between the injured and uninjured legs of ACL-injured females. These differences were located within the tibial cartilage profile only, and were significant after adjustment for tibial position relative to the femur during MRI data acquisition. Consequently, differences seen within ACL-injured females represent a significant change in tibial plateau articular cartilage morphology as a result of ACL-injury. Quantification of these acute changes could act as a predictor for the progression of cartilage damage, and yield insight to the onset of PTOA, at a point in time where structural deterioration may be reversible.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2014.06.025.

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