American Society of Biomechanics Clinical Biomechanics Award 2015:
MRI Assessments of Cartilage Mechanics, Morphology and Composition Following
Reconstruction of the Anterior Cruciate Ligament

Jarred Kaiser, PhD.¹

Michael F. Vignos, MS¹

Fang Liu, PhD²

Richard Kijowski, MD.³

Darryl G. Thelen, PhD.*^{1,4,5}

1. Department of Mechanical Engineering, University of Wisconsin - Madison, 1513 University
Avenue, Madison, WI, USA 53706

2. Department of Medical Physics, University of Wisconsin - Madison, 1111 Highland Avenue,
Madison, WI, USA 53705

3. Department of Radiology, University of Wisconsin - Madison, 600 Highland Avenue,
Madison, WI 537924. Department of Biomedical Engineering, University of Wisconsin -
Madison, 1415 Engineering Drive, Madison, WI, USA 53706

5. Department of Orthopedics and Rehabilitation, University of Wisconsin - Madison, 1685
Highland Avenue, Madison, WI, USA 53705

(*) CORRESPONDING AUTHOR:

1513 University Avenue

Room 3039

Madison, Wisconsin, USA 53706

email: dgthelen@wisc.edu

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ABSTRACT

Background

The pathogenesis of osteoarthritis following anterior cruciate ligament (ACL) reconstruction is currently unknown. The study purpose was to leverage recent advances in quantitative and dynamic MRI to test the hypothesis that abnormal joint mechanics within four years of reconstruction is accompanied by evidence of early compositional changes in cartilage.

Methods

Static MR imaging was performed bilaterally on eleven subjects with an ACL reconstruction (1-4 years post-surgery) and on twelve healthy subjects to obtain tibial cartilage thickness maps. Quantitative imaging (mcDESPOT) was performed unilaterally on all subjects to assess the fraction of bound water in the tibial plateau cartilage. Finally, volumetric dynamic imaging was performed to assess cartilage contact patterns during an active knee flexion-extension task. A repeated-measures ANOVA was used to test for the effect of surgical reconstruction and location on cartilage thickness, bound water fractions, and contact across the medial and lateral tibia plateau.

Findings

No significant differences in cartilage thickness were found between groups. However, there was a significant reduction in the fraction of water bound by proteoglycan in the ACL reconstructed knees, most notably along the anterior portion of the medial plateau and the weight-bearing lateral plateau. During movement, reconstructed knees exhibited greater contact along the medial spine in the medial plateau and along the posterior aspect of the lateral plateau, when compared with their healthy contralateral knees and healthy controls.

Interpretation

This study provides evidence that abnormal mechanics in anterior cruciate ligament reconstructed knees are present coincidently with early biomarkers of cartilage degeneration.

Key Words: biomechanics; cartilage; anterior cruciate ligament reconstruction; dynamic MRI; thickness; biomarkers

1. INTRODUCTION

Early onset osteoarthritis (OA) is common in ACL-reconstructed (ACLR) knees, with greater than 50% of patients displaying some signs of radiographic OA within 20 years post-surgery (Liden et al., 2008). The underlying etiology of early OA in this patient population remains unknown, but identifying potential causes is important for establishing clinical management approaches that can best mitigate OA risk. However, investigating the pathogenesis of post-traumatic OA is challenging given the long time periods typically needed to detect clinical and radiographic manifestations of the disease. (Haughom et al., 2012).

Recent developments in quantitative magnetic resonance imaging (MRI) have enabled noninvasive evaluation of cartilage composition and ultra-structure. For example, T1rho relaxation rates have been correlated with proteoglycan content (Duvvuri et al., 2002), while T2 relaxation rates have been shown to be sensitive to changes in the collagen fiber network and water content (Mosher et al., 2000). A more recent bi-component T2 mapping technique, mcDESPOT (Deoni et al., 2008; Liu et al., 2014; Liu et al., 2015), can provide relative measures of the fractions of the fast and slow relaxing water components of cartilage which are thought to respectively represent water bound to proteoglycan (F_{PG}) and bulk water loosely associated with the cartilage macromolecular matrix (Reiter et al., 2009). Thus, quantitative MRI can potentially detect compositional changes in cartilage that occur early on in the development in OA (Haughom et al., 2012; Li et al., 2011). Indeed, abnormal T1rho and T2 relaxation rates have been detected in specific regions of the tibiofemoral cartilage within 1-2 years of ACL reconstructive surgery (Li et al., 2011). However, it remains unclear whether biomechanical factors contribute to the changes in MRI biomarkers of early cartilage degeneration.

There is ample evidence that ACLR knees often exhibit subtle abnormalities in knee motion when compared to the contralateral uninjured knee. For example, a small, but significant, shift toward external tibia rotation and medial tibia translation has been observed during locomotion in ACLR knees (Carpenter et al., 2009; Scanlan et al., 2010; Tashman, 2004), along with a potential progressive increase in anterior tibia translation (Hofbauer et al., 2014). It has been theorized that these abnormal kinematic patterns may alter cartilage loading patterns and thereby initiate a cyclic catabolic response that eventually leads to OA (Andriacchi and Mündermann, 2006; Chaudhari et al., 2008). New dynamic MRI sequences can be coupled with high resolution cartilage imaging to investigate whether abnormal kinematics influence cartilage contact patterns during motion (Borotikar and Sheehan, 2013; Kaiser et al., 2013). Further, quantitative MRI can then be used to investigate the association between changes in cartilage contact patterns and the onset of early cartilage degeneration in ACLR knees.

The goal of this study was to use static, dynamic and quantitative MRI to investigate whether abnormal knee mechanics is linked to the pathogenesis of early post-traumatic cartilage degeneration. To do this, we compared images of tibial cartilage morphology, composition, and contact patterns between healthy and ACLR knees within four years of reconstructive surgery. We hypothesized that ACLR knees would display different cartilage contact patterns than their contralateral knees and healthy control knees. Further, we hypothesized ACLR knees would exhibit no change in cartilage morphology but would exhibit region specific reductions in bound water.

2. METHODS

2.1. Subjects

The bilateral knees of eleven subjects with a primary unilateral, isolated ACL-reconstruction (6 F, 24.7 (SD: 4.7) yrs, 83.9 (SD: 17.8) kg, 2.1 (SD: 0.7) years since surgery, 6 patellar tendon grafts, 5 hamstrings grafts, 1 partial lateral meniscectomy, 1 subject with small, stable medial and lateral meniscal tears) and the dominant knees of twelve healthy controls (5F, 24.5 (SD: 4.7) years, 74.9 (SD: 10.0) kg) were tested after obtaining informed consent according to an IRB-approved protocol. Control subjects and the contralateral knees of ACLR subjects had no history of knee pain, injury or surgery and no history of septic, inflammatory or crystalline induced arthritis. ACLR subjects had no history of septic, inflammatory or crystalline induced arthritis, and no post-operative complications. Leg dominance of the control subjects was determined by a self-report of the leg with which they would kick a ball.

2.2. Static and Quantitative MRI

Subjects underwent a static MR protocol consisting of an axial fat-suppressed three-dimensional spoiled gradient recall-echo (3D SPGR) sequence (TR/TE = 10.48/2.24 ms, in-plane resolution = 0.37x0.37 mm, slice thickness = 0.90 mm resolution, image matrix size = 512x512x304 pixels) and a sagittal three-dimensional fast spin-echo (3D FSE Cube) sequence (TR/TE = 2066.7/19.8 ms, in-plane resolution = 0.39x0.39 mm, slice thickness = 1.0 mm resolution, acquisition matrix size = 384x384 pixels) (Fig. 1). These sequences were performed bilaterally for patient subjects and unilaterally for control subjects. A mcDESPOT sequence, consisting of twenty five (8 spoiled gradient echo SPGR, 1 inversion recovery SPGR and 16 balanced steady-state free precession bSSFP) steady-state image sequences with varying flip angles, was performed on the reconstructed knee of the patient subjects and the dominant knee of the control subjects (in-plane resolution = 0.62x0.62 mm, slice thickness = 3.0 mm, image matrix size = 256x256 pixels, (Liu et al., 2014)). The mcDESPOT sequence was only performed

unilaterally due to limitations in scanning time. All static scans were performed in a 3.0T clinical MR scanner (Discovery MR750, GE Healthcare, Waukesha, WI, USA) using an 8-channel phased array extremity coil (InVivo, Orlando, FL, USA). Foam padding was used to firmly secure the knee within the coil to minimize subject motion during the static MR examination.

Distal femur and proximal tibia bone geometries were manually segmented from the 3D SPGR images. Femoral and tibial articular cartilage surfaces were manually segmented (MIMICS, Materialise Group, Leuven, Belgium) from the 3D FSE Cube images (Fig 1), smoothed and then described by polygon meshes (approximately $0.33 \text{ mm}^2/\text{triangles}$) that were registered to the bone models. Anatomical coordinate systems were determined for each bone independently using the bones' inertial and geometric properties (Miranda et al., 2010). Cartilage thickness was defined as the normal distance from each face of the cartilage mesh to the underlying bone.

The mcDESPOT series was used to reconstruct maps of F_{PG} using a custom Matlab routine (MathWorks, Natick, MA, USA) (Liu et al., 2014). Image registration (FLIRT, Functional Magnetic Resonance Imaging of the Brain Analysis Group, Oxford University, UK) was used to align the static and mcDESPOT image sequences. Cartilage masks, segmented from the 3D FSE Cube images, were then interpolated to the mcDESPOT images to separate the articular cartilage from the surrounding tissues. The F_{PG} of three ACLR and one control subjects were omitted from analysis due to substantial motion artifacts.

2.3. Dynamic MRI

Immediately following the static MRI protocol, subjects were positioned supine with their lower leg secured on a MRI-compatible loading device. Cyclic knee flexion and extension was performed at 0.5 Hz with the rate maintained via an audible metronome. An inertial loading

device induced eccentric quadriceps contraction with knee flexion, similar to the load-acceptance phase of gait (Kaiser et al., 2013). During this open-chained task, subjects reached $\sim 35^\circ$ of knee flexion with a peak extension moment of ~ 0.5 Nm/kg. A 3D SPGR sequence with vastly-undersampled isotropic projections (SPGR-VIPR, 1.5 mm isotropic resolution, pulse repetition time/echo time = 4 ms/1.4 ms, flip angle = 8° , receiver bandwidth = 32.5 kHz, unique radial lines = 93,922, field of view = 48 cm, scan time = 5 min) was used to continuously collect volumetric image data over five minutes of continuous motion (Fig. 1). A MR-compatible rotary encoder (MR310, Micronor, Newbury Park, CA, USA) mounted on the device was used to monitor knee flexion angle. The encoder data (collected at 50 Hz) was used retrospectively to bin the SPGR-VIPR projections into 60 equal duration intervals over the motion cycle. Sixty SPGR-VIPR images were then reconstructed offline with no view-sharing between frames. We dynamically imaged both the reconstructed and contralateral knees in the subjects who previously underwent ACL-reconstructive surgery. Dynamic imaging was only performed on the dominant knee of healthy control subjects.

Femoral and tibial bone segments and cartilage surfaces were registered to each frame of the dynamic images. Registration was achieved by using numerical optimization to position and orient the bone segments in a way that minimized the sum squared intensities of the dynamic images at the outer bone model vertices (Powell, 1964). This numerical routine drives the bone models to the dark bone outlines in the dynamic images, and yields the bone 3D translations and rotations in space. Tibiofemoral kinematics were defined as the position and body fixed rotations (flexion-adduction-internal rotation) of the tibia relative to the femur (Grood and Suntay, 1983). Tibiofemoral kinematics were low pass filtered with a third-order bidirectional Butterworth filter with a cut-off frequency of 5 Hz. Contact patterns were characterized by the proximity between

the undeformed tibial and femoral cartilage surfaces. Proximity was calculated at each face of the tibial mesh by projecting along the normal direction to determine the closest femoral mesh face. Positive proximity was indicative of cartilage contact at that location. Tibial cartilage proximity through flexion and extension was re-zeroed such that at least one mesh triangle remained in contact in both the medial and lateral compartments at each frame (Borotikar and Sheehan, 2013). Tibial plateau proximity maps were presented for those faces in contact or within 3 mm of the femoral cartilage surface. A tibial plateau proximity map was then defined as the closest proximity of each face throughout the motion cycle (Fig 2).

2.6 Statistical Analysis

Our primary metrics were cartilage thickness, F_{PG} and proximity over the tibial plateau surface. Regional analysis was performed by equally dividing a bounding box of the medial and lateral compartments of the tibial plateau cartilage into 20 rectangular regions of interest (ROIs). The anterior-posterior and medial-lateral directions were determined from the tibial anatomical coordinate systems, described above. Each of the primary metrics were averaged for all cartilage surface pixels within the ROI. F_{PG} measures were averaged through the cartilage thickness. The most lateral and medial ROIs were excluded for the F_{PG} comparisons due to significant partial-volume fractioning at these locations.

A repeated measures ANOVA tested the effect of surgery (between-group factor) and location (within-group factor) on thickness, F_{PG} , and contact between the ACLR knees and the control subject knees. A repeated measures ANOVA was used to compare the cartilage thickness and contact of the ACLR knees to the contralateral knees of the same subjects. If a significant difference was found ($P < 0.05$), a post-hoc Tukey test was performed to identify the location of group differences ($P < 0.05$).

3. RESULTS

The thickest cartilage regions were found in the middle regions of the medial (ACLR: 3.4 (SD: 0.9) mm, contralateral: 3.4 (SD: 0.8) mm, control: 3.1 (SD: 0.7) mm) and lateral (ACLR: 4.5 (SD: 1.0) mm, contralateral: 4.6 (SD: 0.8) mm, control: 4.6 (SD: 0.7) mm) compartments of the tibial plateau (Fig. 3). There were no significant differences in cartilage thickness between any groups (Fig. 4, Fig. 5).

The average F_{PG} in the tibial plateau cartilage ranged from 15.3%-38.5% and 11.3%-37.8% in the control and ACLR knees, respectively. There was a significant decrease in the F_{PG} in the ACLR knees (25.5% (SD: 1.5%)) when compared with the control knees (27.5% (SD: 1.6%)). These differences were apparent in the anterior portion of the medial tibia plateau and the medial portion of the lateral tibial plateau (Fig 5).

Cartilage proximity over the tibial plateau cartilage was significantly greater in the ACLR knee when compared to both the control (-0.4 mm average difference) and contralateral (-0.3 mm) knees. In the post-hoc analyses, significantly greater contact in the ACLR knees was observed along the medial ridge of the medial tibial plateau and the posterior aspect of the lateral tibial plateau (Fig. 4, Fig. 5).

4. DISCUSSION

It has been speculated that abnormal knee mechanics can contribute to the development of early OA in ACL-reconstructed knees (Andriacchi et al., 2009). However, direct links between abnormal mechanics and early manifestations of OA are lacking. In this study, we leveraged advances in dynamic and quantitative MRI techniques to test the hypotheses that ACLR knees will exhibit evidence of abnormal cartilage loading and cartilage composition within four years of surgery. Our hypotheses were supported, with ACLR knees exhibiting

greater contact in characteristic regions of both the medial and lateral tibial plateau. Further, despite no evidence of cartilage thinning, we noted a decrease in the fraction of bound water in the ACLR knees. Thus, this study provides evidence that early MRI biomarkers of cartilage degeneration coincide with the time point at which abnormal knee mechanics can be detected in ACL reconstructed knees.

To our knowledge, this is the first study to show that abnormal tibiofemoral cartilage contact patterns can be detected in reconstructed knees with dynamic MRI. Prior studies using biplanar fluoroscopy have identified greater joint sliding in the medial tibiofemoral compartment during downhill running (Hoshino et al., 2013). A posteriolateral shift in contact in the medial plateau and a posteriomедial shift in the lateral plateau were also found during a single leg quasi-static lunge (Hosseini et al., 2012). Similarly, we observed a significant lateral shift in contact on the medial compartment and a posterior shift on the lateral compartment in the ACLR knees. The similarity of these results suggests that there may be systematic differences in the passive restraint provided by an ACL graft, relative to the native ACL. It is noteworthy that we observed such systematic shifts despite the study population having mixed clinical presentation, graft types and meniscal conditions. This would suggest that other surgical factors, such as graft placement (Abebe et al., 2011; Bedi et al., 2011) and pre-tensioning (Brady et al., 2007; Melby et al., 1991), may contribute to the altered knee mechanics. While greater subject numbers are needed to better test the effects of surgical factors, ultimately computational knee models are important to establish causal relationships between surgical factors and functional knee behavior (Lenhart et al., 2015; Pena et al., 2006; Salehghaffari and Dhaher, 2014; Smith et al., 2015).

The absence of changes in cartilage thickness in the ACLR knees within 4 years is consistent with prior studies suggesting that longer time frames are needed for cartilage thinning

to be visible. For example, (Andreisek et al., 2009) found a very small amount of cartilage thinning (on average <0.1 mm) in the lateral aspect of the lateral tibial compartment seven years following ACLR surgery. Additional studies have shown either longitudinal increases in cartilage thickness in ACLR knee over a 2 year follow-up period (Frobell, 2011) or no changes in cartilage thickness in ACLR knees when compared to the contralateral healthy knees at 7 year follow-up (Andreisek et al., 2009).

In contrast, quantitative MRI is able to detect potential evidence of altered cartilage composition within 1-2 years of reconstruction (Li et al., 2011; Tiderius et al., 2005). Quantitative MRI also has the benefit of providing a laminar analysis of cartilage (Li et al., 2011), potentially providing additional information on the depth-dependent changes of early post-traumatic cartilage degeneration. In this study, we found a decrease in the fraction of water bound by proteoglycan. Proteoglycan is necessary to produce the hydrostatic compressive stiffness of cartilage (Buschmann and Grodzinsky, 1995) and the loss of proteoglycan has been identified as a critical event in OA (Rizkalla et al., 1992; Sandy et al., 1992). While quantitative MRI has been directly linked to histological changes evident in OA (Regatte et al., 2006), further study is still needed to see whether changes in these MRI parameters are associated with *in vivo* cartilage loss over time and the development of joint pain and radiographic OA.

Interestingly, we found no direct correspondence between the regions of abnormal cartilage contact and lower F_{PG} . While reductions in bound water were evident in the reconstructed knees, significant differences were found in cartilage adjoining the higher contact regions. This could be due to several factors. First, all metrics were averaged within ROIs on the order of 60 mm^2 . While the ROIs simplify the analysis, it also significantly reduces the quantitative detail available with our methodology. Other studies have shown interesting

information exists not only in the magnitude of individual voxels of relaxation rates maps, but also in the spatial distribution of relaxation rates (Blumenkrantz et al., 2008; Li et al., 2009). A voxel-based analysis therefore may further elucidate the relationship between contact, morphology, and composition in the ACLR knees. Furthermore, changes in knee biomechanics may not be the only cause of early cartilage degeneration in ACLR knees. Other factors not investigated in our study including meniscus tears (Li et al., 2011; Neuman et al., 2011), acute cartilage injury sustained at the time of joint trauma (Bolbos et al., 2008) and post-traumatic synovial inflammation (Elsaid et al., 2008; Marks and Donaldson, 2005), all of which may have played a role in reduction in bound water seen in our patient population.

We also recognize that our cartilage contact metric may not fully capture the abnormal mechanical environment of the cartilage tissue. Cellular mechano-transduction is one potential mechanism controlling the catabolic response of cartilage post-ACLR and is influenced by changes in fluid flows and pressures (Mizuno et al., 2002), osmotic levels (Hopewell and Urban, 2002), and changes in pH (Halloran et al., 2012). At a tissue scale, these signals are altered by differing compressive and shear strains (Guilak and Hung, 2005), which are further influenced by cartilage thickness, stiffness, and sliding friction. Our proximity metric likely best reflects compressive pressure and perhaps could be used within a computational model of the cartilage tissue to more fully characterize factors that can regulate mechano-biological responses. Further, emerging imaging techniques for measuring *in vivo* cartilage tissue strain (Coleman et al., 2013; Neu and Walton, 2008) may provide greater insights into functional cartilage tissue behavior.

Our study was limited to an ROI analysis of only the tibial plateau, though early OA has been found in all articular cartilages of the tibiofemoral (Kessler et al., 2008; Meunier et al., 2007; Sward et al., 2010) and patellofemoral (Neuman et al., 2009) joints in ACLR knees.

SPGR-VIPR and the mcDESPOT sequences provide a large enough field of view (40x40x40 cm) to enable kinematic and compositional information of all three joints, allowing us to perform a similar analysis of the femoral and patellar cartilages in the future. Additionally, the complete mcDESPOT analysis was available for only a subset of subjects (8/11 patient subjects, 11/12 control subjects). While the flexion-extension task performed used in this study is not weight-bearing, the loading paradigm was designed to induce eccentric quadriceps loads of comparable magnitudes to that seen in walking (Kaiser et al., 2013). It is notable that the abnormalities in cartilage contact in the ACLR knees are comparable to that seen during lunges while using biplane fluoroscopy (Hosseini et al., 2012). This result is important since it means that morphology measures, functional behavior and biomarkers of cartilage degeneration can all potentially be assessed with clinical MRI scanners. Finally, our dynamic MRI methodology acquires image data over many repeat motion cycles, which necessitates the repeatability of the task. Our prior study shows that subjects can closely replicate the desired cycle period when undergoing an inertial loading (Kaiser et al., 2013).

In summary, we found evidence of a shift in the location of contact in the medial and lateral tibial plateaus following ACL-reconstruction surgery. We also identified significantly lower fractions of bound water in the tibial cartilage, which may reflect early cartilage degeneration. Future work will try to explore potential links between surgical factors, cartilage contact and MRI biomarkers following ACLR.

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Figure 1. Experimental Protocol. Subjects underwent a MR protocol consisting of two static sequences (IDEAL SPGR, FSE Cube), a quantitative sequence (mcDESPOT) and dynamic imaging (SPGR-VIPR) of a knee flexion-extension task. The static images were used to create subject-specific models of the bone and cartilage geometries. mcDESPOT was used to compute maps of the fraction of water bound by proteoglycan (F_{PG}). Finally, the bone and undeformed cartilage models were registered to the dynamic images, providing a quantitative characterization of the tibiofemoral contact patterns.

Figure 2. Dynamic cartilage contact. Tibiofemoral kinematics were used to characterize regions of proximity between the tibial and femoral cartilage. Contact maps for each subject were created by identifying the greatest proximity of each face of the cartilage mesh over a flexion-extension motion cycle.

Figure 3. Example maps of cartilage thickness, F_{PG} , and thickness. Representative thickness, fraction of water bound by proteoglycan (F_{PG}), and proximity maps for the tibial plateau of one control subject, an ACL-reconstructed knee and their healthy contralateral knee. Note the greater contact along the medial spine of the medial plateau, and the posteriolateral tibia of the reconstructed knee, when compared to the contralateral and control knees. The subject also exhibits lower fraction of bound water relative to the control, particularly in the lateral tibia plateau.

Figure 4. ROI comparison with contralateral knees. Region of interest comparisons of average cartilage proximity and thickness between reconstructed and contralateral knees of the

subjects who underwent unilateral ACL reconstructive surgery. Asterisks denote areas of significantly larger contact along the medial spine and on the posterior portion of the lateral tibial plateau.

Figure 5. ROI comparison with control knees. Region of interest comparisons of average cartilage proximity, thickness and fraction of water bound by proteoglycan (F_{PG}) between reconstructed knees and healthy control knees. Asterisks denote areas of significant difference between groups. There were no significant differences in cartilage thickness, but there were regions of significantly greater magnitudes of cartilage contact and lower fractions of bound water on both the medial and lateral tibia plateaus.

Figure 1

Setup

Images

IDEAL SPGR

FSE Cube

mcDESPOT

SPGR-VIPR

Outcomes

Bone Models

Cartilage Surfaces

Fraction of Water Bound by PG

Tibiofemoral Kinematics

Figure 2

Figure 3

Figure 4