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Cartilage Subsurface Changes to Magnetic Resonance Imaging UTE-T2* 2 Years After Anterior Cruciate Ligament Reconstruction Correlate With Walking Mechanics Associated With Knee Osteoarthritis

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Abstract

Background—Anterior cruciate ligament (ACL) injury increases risk for posttraumatic knee osteoarthritis (OA). Quantitative ultra-short echo time enhanced T2* (UTE-T2*) mapping shows promise for early detection of potentially reversible subsurface cartilage abnormalities after ACL reconstruction (ACLR) but needs further validation against established clinical metrics of OA risk such as knee adduction moment (KAM) and mechanical alignment.

Hypothesis—Elevated UTE-T2* values in medial knee cartilage 2 years after ACLR correlate with varus alignment and higher KAM during walking.

Study Design—Cohort study (diagnosis); Level of evidence, 2.

Methods—Twenty patients (mean age, 33.1 ± 10.5 years; 11 female) 2 years after ACLR underwent 3.0-T knee magnetic resonance imaging (MRI), radiography, and gait analysis, after which mechanical alignment was measured, KAM during walking was calculated, and UTE-T2* maps were generated. The mechanical axis and the first and second peaks of KAM (KAM1 and KAM2, respectively) were tested using linear regressions for correlations with deep UTE-T2* values in the central and posterior medial femoral condyle (cMFC and pMFC, respectively) and central medial tibial plateau (cMTP). UTE-T2* values from ACL-reconstructed patients were additionally compared with those of 14 uninjured participants (mean age, 30.9 ± 8.9 years; 6 female) using Mann-Whitney *U* and standard *t* tests.

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Results—Central weightbearing medial compartment cartilage of ACL-reconstructed knees was intact on morphological MRI. Mean UTE-T2* values were elevated in both the cMFC and pMFC of ACL-reconstructed knees compared with those of uninjured knees ($P = .003$ and $P = .012$, respectively). In ACL-reconstructed knees, UTE-T2* values of cMFC cartilage positively correlated with increasing varus alignment ($R = 0.568$). Higher UTE-T2* values in cMFC and cMTP cartilage of ACL-reconstructed knees also correlated with greater KAM1 ($R = 0.452$ and $R = 0.463$, respectively) and KAM2 ($R = 0.465$ and $R = 0.764$, respectively) and with KAM2 in pMFC cartilage ($R = 0.602$).

Conclusion—Elevated deep UTE-T2* values of medial knee cartilage 2 years after ACLR correlate with 2 clinical markers of increased risk of medial knee OA. These results support the clinical utility of MRI UTE-T2* for early diagnosis of subsurface cartilage abnormalities. Longitudinal follow-up of larger cohorts is needed to determine the predictive and staging potential of UTE-T2* for posttraumatic OA.

Keywords

ACL reconstruction; osteoarthritis; biomechanics; gait; UTE-T2*; adduction moment

Anterior cruciate ligament (ACL) tear, one of the most common knee injuries, can lead to rapid onset of posttraumatic osteoarthritis (OA). ACL reconstruction (ACLR) has been successful in restoring knee stability and allowing patients to return to sports and physical activity but has failed to reduce the incidence of posttraumatic OA, with approximately 50% of patients progressing to symptomatic radiographic knee OA within 10 to 15 years of injury.^{6,21,22,34} This is likely because of the interaction between mechanical, biological, and structural changes that persist within the joint, leading to altered joint homeostasis and eventual onset of OA.^{4,10}

A major barrier to reducing OA risk after ACLR is the inability to accurately identify patients who are on an accelerated degenerative pathway before irreversible cartilage tissue breakdown. Changes in subsurface cartilage properties, particularly in cases where the articular surface remains intact, are difficult to identify using current clinical standards of radiography and morphological magnetic resonance imaging (MRI). Quantitative ultrashort echo time enhanced T2* (UTE-T2*) mapping has been shown to be sensitive to subsurface cartilage matrix changes occurring acutely after ACL injury that are undetectable with standard morphological MRI.¹² In this prior study, elevation of UTE-T2* values after injury to more than 50% greater than those of uninjured controls decreased to levels similar to uninjured controls by 2 years after ACLR in most, but not all, participants.¹² These data suggest that acute and persistent elevations to knee cartilage UTE-T2* values after ACL injury and reconstruction reflect potentially reversible cartilage matrix changes from injury or early degeneration.^{11,12} To further evaluate the diagnostic potential of UTE-T2* for identifying early cartilage abnormalities, this metric needs additional validation against clinical metrics of OA risk.

ACLR has not been shown to restore natural knee motion, as reflected by well-documented changes in walking mechanics.^{3,4,28,33,37} Despite the high rate of acute cartilage injury and/or bone bruising in the lateral compartment,²⁶ knee OA is more commonly observed

after ACLR in the medial compartment.⁶ A potential explanation for this observation is that altered loading across the medial knee after ACLR,³³ coupled with biological and structural changes persisting within the joint after injury, contributes to the initiation of a degenerative pathway.^{4,10} The mechanical metric of knee adduction moment (KAM) during walking has been associated with increased risk and progression of medial knee OA. Specifically, in patients with knee OA, a higher first peak of KAM (KAM1) during the stance phase of walking has been associated with a faster rate of medial knee OA progression,⁹ and a higher second peak of KAM (KAM2) has been associated with increased OA severity.²⁴ A recent study also showed that higher KAM during walking 2 years after ACLR correlated with lower patient-reported outcomes at 8-year follow-up.¹⁵

In addition to gait analysis, radiographic measurement of the mechanical axis is routinely used in orthopaedic clinical practice.¹⁹ Varus malalignment has also been associated with risk and progression of medial knee OA.^{8,19,30,31} As such, both KAM during walking and the mechanical axis have shown utility as noninvasive clinical metrics against which UTE-T2* values in medial knee cartilage can be evaluated. The objective of this study was to test the hypothesis that quantitative MRI UTE-T2* values in the medial compartment of the knee positively correlate with greater varus mechanical alignment and with higher KAM during walking 2 years after ACLR.

METHODS

Study Population

All patients were recruited and evaluated in accordance with institutional review board–approved protocols. Twenty ACL-reconstructed patients and 14 uninjured participants were evaluated. All participants provided informed consent.

ACLR Group—Inclusion criteria for the ACLR group included primary ACLR in either limb (no revision ACLR), age between 18 and 60 years, body mass index (BMI) <30 kg/m², no injections to knees or other joints in the preceding 6 months, self-reported knee stability, and an intact ACL graft (on morphological MRI and KT-1000 arthrometer side-to-side difference ≤ 5 mm).^{1,5} Twenty patients (11 female; mean age, 33.1 ± 10.5 years [range, 20–57 years]; mean BMI, 23.1 ± 2.4 kg/m² [range, 19.0–27.4 kg/m²]; mean Tegner activity level: 6.25 ± 1.65 [range, 3–10]) who underwent unilateral ACLR (2.25 ± 0.22 years after surgery; 11 Achilles tendon allografts, 4 patellar tendon autografts, 4 patellar tendon allografts, 1 quadriceps tendon autograft) and with no other history of lower limb injuries requiring crutches or surgery were recruited. Twelve patients had concomitant meniscal tears (3 medial meniscal tears and 9 lateral meniscal tears) at the time of ACLR. Of the patients with meniscal tears, 6 underwent partial meniscectomy (2 medial, 4 lateral), and 6 underwent meniscal repair (1 medial, 5 lateral) along with ACLR. Five patients had a concomitant medial collateral ligament tear.

Uninjured MRI Reference Group—Fourteen uninjured asymptomatic participants (6 female; mean age, 30.9 ± 8.9 years [range, 24–49 years]; mean BMI, 21.9 ± 2.8 kg/m² [range, 16.8–27.1 kg/m²]) with no history of injuries resulting in knee swelling or gait abnormalities as well as no surgery to their knees underwent knee MRI using the same

magnet as the ACL-reconstructed patients. The BMI and age of this reference group were similar to those of the ACLR group ($P = .52$ and $P = .18$, respectively). These participants provided reference UTE-T2* maps (Figure 1) and quantitative UTE-T2* values (Figure 3) only and did not undergo radiography or gait analysis.

Mechanical Axis

All ACL-reconstructed patients underwent radiographic examination including of a full-length standing anteroposterior radiograph for measurements of the mechanical axis using the method outlined by Brown and Amendola.⁷ With this method, the mechanical axis of the knee was defined in the frontal plane as the angle between a line passing through the center of the femoral head and the center of the knee and a line passing through the center of the ankle and the center of the knee.⁷ Data were recorded as degrees of varus (positive) or valgus (negative) from neutral alignment (0°).⁷

Magnetic Resonance Imaging

Thirty-four patients (20 in the ACLR group, 14 in the uninjured reference group) underwent an examination (ACL-reconstructed knee for the ACLR group and randomly selected knee for reference group) on a 3.0-T MRI scanner (MR750; GE Healthcare) with a transmit-receive 8-channel knee coil (GE Healthcare) at varying times when the magnet time was available. UTE-T2* maps were calculated via mono-exponential fitting on a series of T2*-weighted MRI images acquired at 8 echo times (TEs) (32 μ s to 16 ms; nonuniform echo spacing) using a radial out 3-dimensional (3D) cones acquisition. The cones sequence samples MRI data starting at the center of k-space and twisting outward along conical surfaces in 3D while allowing for anisotropic field of view and resolution.¹⁷ The UTE-T2* sequence was optimized through selection of TEs to assess deep articular cartilage, defined as the portion of cartilage extending from the bone-cartilage interface through half of the articular thickness. Prior UTE-T2* analyses have suggested that the range of TEs required to achieve this sensitivity include at least 1 ultrashort echo (TE <1 ms) and a longer echo (TE >10 ms).³⁶ The 3D cones sequence collects 4 echoes within a single acquisition. To obtain sufficient sampling of the relaxation curve to meet our goals, the sequence was acquired twice for a total collection of 8 echo images (first set's TEs = 0.032, 3.6, 7.2, and 16 ms; second set's TEs = 1, 4.7, 9, and 12.7 ms), with a repetition time of 22.5 ms and gain held constant between acquisitions. Three regions of weightbearing deep cartilage were chosen for analysis in the medial compartment: central and posterior medial femoral condyle (cMFC and pMFC, respectively) and central medial tibial plateau (cMTP) (Figure 1). MRI slice selection and region of interest (ROI) segmentation were manually performed by one experienced person (A.A.W.) according to published methods.³⁵ Briefly, full-thickness ROIs were drawn in the weightbearing zones of the cMFC and pMFC and the weightbearing zone of the cMTP for the midsagittal slice. Next, deep cartilage was assessed by further segmenting full-thickness cartilage into 2 approximately equal sections: a deep zone extending from the subchondral bone to the center of the tissue to encompass the bottom half of the tissue thickness (included in this study, Figure 1), and a superficial zone extending from the center to the articular surface (not included in this study). Mean UTE-T2* values for each deep cartilage ROI were recorded for analysis. A previous examination of this particular slice selection and cartilage segmentation technique indicated that mean

UTE-T2* quantitation errors associated with deep cartilage ROIs range from 13% to 16% for intersession precision repeatability and from 0.86 to 0.96 for interclass correlation of intraobserver segmentation reproducibility.³⁵

Morphological MRI was performed on ACL-reconstructed knees, consisting of sagittal, axial, and coronal proton density images with fat saturation, sagittal proton density images without fat saturation, and oblique sagittal 3D fast spin echo (CUBE) images, all of which were acquired in the same MRI sessions as the UTE-T2* images. An experienced musculoskeletal radiologist (G.E.G.), blinded to the UTE-T2* values and maps, graded the morphological MRI scans using the 5-point classification system of Outerbridge modified by Potter et al.²⁷

Gait Analysis

All subjects in the ACL reconstruction group underwent gait analysis, which included three 10-m walking trials at normal self-selected speed. A 10-camera optoelectronic system (Qualisys) and a force plate (Bertec) embedded in the floor were used to measure participants' motion at 120 Hz. The software application BioMove (Stanford University) was used to calculate knee kinematics and kinetics during the stance phase of walking using the point cluster technique.² The foot, shank, and thigh segments' anatomic reference frames were determined as previously described¹³ using a standing reference pose collected before the walking trials. Both peaks in the external KAM were normalized to the body weight and height of each participant (%BW*Ht).

Statistical Analysis

Normality in all data was assessed using Shapiro-Wilk tests. Standard *t* tests and Mann-Whitney *U* tests were used to assess differences in UTE-T2* values when data were normally and not normally distributed, respectively. The 2-tailed significance level was set at 5% and corrected for multiple comparisons (3 regions of cartilage) using the Bonferroni method ($\alpha = .017$). In the ACLR group, univariate linear regressions were used to correlate KAM1, KAM2, and knee alignment separately with UTE-T2* quantitative values in deep cartilage of the cMFC, pMFC, and cMTP regions. The effects of age, sex, and BMI were each tested by entering each one of these measures into a multiple linear regression model with KAM1, KAM2, or knee mechanical axis alignment. This method was preferred over including all three metrics in the same model to avoid an overfitted model with 4 independent measures. The univariate and multivariate regression models were considered statistically significant when the model's $P < .05$. Results for independent measures in each model are presented as standardized coefficients and *P* values to show their relative contribution to the overall model. Correlations between the independent measures and UTE-T2* values were considered statistically significant when $P < .05$.

RESULTS

Morphological MRI

Subjects in the ACL reconstruction group did not have significant medial compartment cartilage abnormalities detectable by morphological MRI (Figure 2). All ACL-reconstructed

patients were assigned Outerbridge grade 0 (normal) to the cMFC, pMFC, and cMTP, except 1 patient with Outerbridge grade 1 (subsurface signal change) in the cMFC region and 3 patients with Outerbridge grade 2 (superficial surface disruption) in the pMFC.

Quantitative UTE-T2* MRI

Mean UTE-T2* values were 28% higher in both the cMFC and pMFC regions of ACL-reconstructed knees compared with uninjured reference knees ($P = .003$ and $P = .012$, respectively) (Figure 3). No differences were observed between ACL-reconstructed and reference patients in the cMTP region ($P = .306$).

Mechanical Axis

The mean ($\pm$ SD) mechanical axis of ACL-reconstructed knees was $0.8^\circ \pm 3.2^\circ$ (varus positive [range, 5.2° valgus to 6.5° varus]). UTE-T2* values in the cMFC were correlated with a more varus mechanical axis and increasing age ($R = 0.609$, $P = .049$) (Table 1). This correlation was primarily driven by alignment, with the univariate regression showing the strongest correlation with UTE-T2* values ($R = 0.568$, $P = .022$) (Table 1). Although not significant, the mechanical axis showed trends toward a positive correlation with higher pMFC UTE-T2* values ($R = 0.436$, $P = .091$) and cMTP UTE-T2* values ($R = 0.482$, $P = .058$). The mechanical axis also significantly correlated with KAM1 ($R = 0.621$, $P = .010$) and KAM2 ($R = 0.604$, $P = .013$).

Knee Adduction Moment

In ACL-reconstructed knees, higher UTE-T2* values correlated with higher KAM. Specifically, in the cMFC, UTE-T2* values positively correlated with higher KAM1 and increasing age ($R = 0.557$, $P = .042$) (Table 1). Despite the effect of age, KAM1 most strongly correlated with UTE-T2* values (univariate regression: $R = 0.452$, $P = .046$) (Table 1) and was the only significant independent measure in the model ($P = .025$) (Table 1). Additionally, KAM2 positively correlated with cMFC UTE-T2* values ($R = 0.465$, $P = .039$) (Table 1). The additions of sex and BMI to the model with KAM1 or age, sex, and BMI to the model with KAM2 did not yield any significant regression models for cMFC UTE-T2* values.

Deep UTE-T2* values in pMFC cartilage were not significantly correlated with KAM1 in the univariate regression ($P = .066$) but were significant with the addition of age to the model ($R = 0.555$, $P = .044$) (Table 1). Although the addition of age resulted in a significant correlation, KAM1 showed the strongest relationship with pMFC UTE-T2* values and was the only significant predictor in the model ($P = .033$) (Table 1). The additions of sex and BMI to the model with KAM1 did not yield significant regressions. Also, in the pMFC, KAM2 positively correlated with UTE-T2* values ($R = 0.602$, $P = .005$) and was the only significant measure in models with age, sex, and BMI ($P = .008$, $.017$, and $.034$, respectively) (Table 1).

In the cMTP, UTE-T2* values were positively correlated with KAM1 ($R = 0.463$, $P = .040$) (Table 1 and Figure 4). Multiple regressions of KAM1 and age, sex, and BMI were not significant. Also, in the cMTP, higher UTE-T2* values were correlated with KAM2 and age

($R = 0.780$, $P < .001$), KAM2 and sex ($R = 0.824$, $P < .0001$), and KAM2 and BMI ($R = 0.784$, $P = .001$). These regressions were driven by KAM2, which was the strongest independent measure in each model ($P < .0001$, $P < .0001$, and $P = .0001$, respectively) (Table 1) and also significant in the univariate regression with cMTP UTE-T2* values ($R = 0.764$, $P < .0001$) (Table 1 and Figure 4). Also noteworthy, in the regression with KAM2 and sex, sex was a significant independent predictor for cMTP UTE-T2* values ($P = .038$) (Table 1).

DISCUSSION

The results of this study support the potential of UTE-T2* mapping for the early diagnosis of subsurface abnormalities in cartilage appearing structurally normal on morphological MRI. Specifically, elevations of UTE-T2* values in the medial compartment of the knee 2 years after ACLR correlated with 2 noninvasive clinical metrics of an increased risk for medial knee OA: a more varus knee mechanical axis and higher KAM during walking. This study also shows robustness of the UTE-T2* metric in that the UTE acquisitions were obtained using a different MRI magnet and sequence technology than a prior longitudinal UTE-T2* study of ACL-reconstructed participants.¹² Consistent with prior work, in which preoperative mean UTE-T2* values were elevated in the cMFC and pMFC while preoperative UTE-T2* values in the cMTP were shown to be similar to uninjured controls, this study showed that mean UTE-T2* values were elevated in the medial femur, but not the medial tibia in ACL-reconstructed knees compared with corresponding regions of uninjured participants (Figures 1–3).¹² Together with the findings from this earlier study showing arthroscopic softening to regions of elevated UTE-T2* values in the preoperative scans,¹² these results further support the clinical utility of UTE-T2* for noninvasive detection of cartilage subsurface matrix changes indicative of reduced cartilage health from injury or early degeneration.

The correlations between UTE-T2* values and mechanical metrics of increased OA risk also provide insight into the interplay between mechanics and structure in the pathogenesis of OA.¹⁰ In this study, Table 1 and Figure 4 show correlations between KAM and UTE-T2* values in deep cartilage of the medial compartment, a region especially prone to developing posttraumatic OA.⁶ Although the effects of age, sex, and BMI did produce significant regression models when combined with KAM and alignment, KAM and alignment were the driving factors in each regression tested. Given that higher KAM1 has been associated with worsening patient-reported outcomes at 8 years after ACLR¹⁵ and faster progression of medial knee OA,⁹ these findings support that subsurface elevations of UTE-T2* values in morphologically intact articular cartilage reflect early abnormalities that are not detected by conventional morphological MRI. These findings, and the prior UTE-T2* clinical study, are also consistent with those of a recent pilot study in 9 patients evaluated 1.5 years after ACLR, showing that patients with higher KAM during walking had elevated T2 and T1ρ relaxation times in their ACL-reconstructed knee.²⁰

The strong correlations observed between UTE-T2* values and KAM in both the femur and tibia of the ACL-reconstructed knee suggest that UTE-T2* changes reflect the mechanosensitivity of articular cartilage. Furthermore, regional variations in the observed

correlations between UTE-T2* values and KAM suggest that knee kinematics influence cartilage structure. Specifically, UTE-T2* values in the pMFC showed strong correlation with KAM2 and did not significantly correlate in univariate regression with KAM1. KAM2 occurs during late stance when the knee is more flexed and the loads are being applied more posteriorly to the femur. When KAM1 occurs in early stance, the knee is typically less flexed, and the pMFC is not as likely to be in contact with the tibia and thus would not be loaded as heavily. This coupling between kinematics, structure, and loading is further supported by reports suggesting that kinematic changes occurring after ACLR play a role in posttraumatic OA initiation by changing cartilage contact locations to regions that cannot adapt to changing loads.^{4,28,29,33}

Therefore, the results of this study also suggest potential intervention targets for reduction of OA risk after ACLR. The findings that UTE-T2* signals are lower in patients with lower KAM and less varus alignment suggest that reduction of KAM in patients showing elevated medial knee UTE-T2* values may improve cartilage health. This conclusion is supported by previous work showing that lower KAM and better alignment are associated with improved long-term patient-reported outcomes after ACLR¹⁵ as well as lower risk of OA progression.^{9,30} Thus, it is possible that some patients may either have valgus or neutral mechanical axis permitting lower KAM during walking that reduces risk for medial knee OA. While osteotomy to correct varus alignment is already used clinically to treat medial knee OA,^{23,25} the findings from this study showing elevated UTE-T2* values in ACL-reconstructed patients with higher KAM suggest that these patients may be targets for early interventions to reduce KAM, which has been shown to be modifiable through gait retraining¹⁶ and shoe design.¹⁴

The results of this study should be interpreted in light of limitations inherent to the cross-sectional design and the small numbers of participants. Because only 2 patients underwent medial meniscectomy, the small numbers prevented the evaluation of meniscectomy as a covariate, although it has been shown to influence KAM after ACLR.^{18,32} While a pilot study of a different cohort of uninjured participants showed no correlations between UTE-T2* values and KAM (data not shown), the absence of gait analysis and radiographs for the uninjured reference group limits the ability to determine whether the observed correlations with UTE-T2* values exist in the uninjured population. Nevertheless, the body of work to date showing elevations of UTE-T2* values acutely after ACL injury,¹² and these new data showing that higher medial knee cartilage UTE-T2* values correlate with 2 clinical metrics of greater medial knee OA risk, support the hypothesis that increased cartilage deep tissue UTE-T2* values reflect subsurface abnormalities. UTE-T2* mapping of articular cartilage is novel, and additional studies to evaluate its ability to predict longer term clinical and OA outcomes are needed. Additionally, the potential influence of age, sex, and BMI, all known risk factors for OA, on UTE-T2* observed in this study supports further investigations through the recruitment of larger cohorts for both cross-sectional and longitudinal studies.

This study showed that elevated UTE-T2* values in deep weightbearing regions of medial compartment knee cartilage appearing normal on morphological MRI correlate with 2 clinical metrics of increased risk for medial knee OA. These findings also suggest that a reduction of KAM may be a therapeutic target to reduce OA risk after ACLR and support

potential clinical investigations in this area. The new knowledge gained from this study supports continued evaluation of larger longitudinal cohorts to determine whether UTE-T2* mapping and gait mechanics early after ACLR are predictive of clinical outcomes and the eventual development of OA over a 10-year period, as well as whether UTE-T2* can be used to evaluate early intervention strategies to prevent or delay the onset of OA after ACLR.

References

1. Aglietti P, Buzzi R, Menchetti PPM, Giron F. Arthroscopically assisted semitendinosus and gracilis tendon graft in reconstruction for acute anterior cruciate ligament injuries in athletes. *Am J Sports Med.* 1996; 24(6):726–731. [PubMed: 8947392]
2. Alexander EJ, Andriacchi TP. Correcting for deformation in skin-based marker systems. *J Biomech.* 2001; 34(3):355–361. [PubMed: 11182127]
3. Andriacchi TP, Mündermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. *Curr Opin Rheumatol.* 2006; 18(5):514–518. [PubMed: 16896293]
4. Andriacchi TP, Mündermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Ann Biomed Eng.* 2004; 32(3):447–457. [PubMed: 15095819]
5. Bach BR, Jones GT, Sweet FA, Hager CA. Arthroscopy-assisted anterior cruciate ligament reconstruction using patellar tendon substitution. *Am J Sports Med.* 1994; 22(6):758–767. [PubMed: 7856799]
6. Barenus B, Ponzer S, Shalabi A, Bujak R, Norlen L, Eriksson K. Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: a 14-year follow-up study of a randomized controlled trial. *Am J Sports Med.* 2014; 42(5):1049–1057. [PubMed: 24644301]
7. Brown GA, Amendola A. Radiographic evaluation and preoperative planning for high tibial osteotomies. *Oper Tech Sports Med.* 2012; 20(1):93–102.
8. Cerejo R, Dunlop DD, Cahue S, Channin D, Song J, Sharma L. The influence of alignment on risk of knee osteoarthritis progression according to baseline stage of disease. *Arthritis Rheum.* 2002; 46(10):2632–2636. [PubMed: 12384921]
9. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. *Osteoarthritis Cartilage.* 2014; 22(11):1833–1839. [PubMed: 25211281]
10. Chu CR, Andriacchi TP. Dance between biology, mechanics, and structure: a systems-based approach to developing osteoarthritis prevention strategies. *J Orthop Res.* 2015; 33(7):939–947. [PubMed: 25639920]
11. Chu CR, Millis MB, Olson SA. Osteoarthritis: from palliation to prevention. *AOA critical issues. J Bone Joint Surg Am.* 2014; 96(15):e130. [PubMed: 25100783]
12. Chu CR, Williams AA, West RV, et al. Quantitative magnetic resonance imaging UTE-T2* mapping of cartilage and meniscus healing after anatomic anterior cruciate ligament reconstruction. *Am J Sports Med.* 2014; 42(8):1847–1856. [PubMed: 24812196]
13. Dyrby CO, Andriacchi TP. Secondary motions of the knee during weight bearing and non-weight bearing activities. *J Orthop Res.* 2004; 22(4):794–800. [PubMed: 15183436]
14. Erhart JC, Mündermann A, Elspas B, Giori NJ, Andriacchi TP. A variable-stiffness shoe lowers the knee adduction moment in subjects with symptoms of medial compartment knee osteoarthritis. *J Biomech.* 2008; 41(12):2720–2725. [PubMed: 18675981]
15. Erhart-Hledik JC, Chu CR, Asay JL, Andriacchi TP. Gait mechanics 2 years after anterior cruciate ligament reconstruction are associated with longer-term changes in patient-reported outcomes. *J Orthop Res.* 2017; 35(3):634–640. [PubMed: 27238273]
16. Guo M, Axe MJ, Manal K. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. *Gait Posture.* 2007; 26(3):436–441. [PubMed: 17134902]
17. Gurney PT, Hargreaves BA, Nishimura DG. Design and analysis of a practical 3D cones trajectory. *Magn Reson Med.* 2006; 55(3):575–582. [PubMed: 16450366]

18. Hall M, Wrigley TV, Metcalf BR, et al. A longitudinal study of strength and gait after arthroscopic partial meniscectomy. *Med Sci Sports Exerc.* 2013; 45(11):2036–2043. [PubMed: 23657167]
19. Hunter DJ, Sharma L, Skaife T. Alignment and osteoarthritis of the knee. *J Bone Joint Surg Am.* 2009; 91(Suppl 1):85–89. [PubMed: 19182031]
20. Kumar D, Kothari A, Souza RB, Wu S, Benjamin Ma C, Li X. Frontal plane knee mechanics and medial cartilage MR relaxation times in individuals with ACL reconstruction: a pilot study. *Knee.* 2014; 21(5):881–885. [PubMed: 24993277]
21. 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; 35(10):1756–1769. [PubMed: 17761605]
22. Lohmander LS, Ostengren A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum.* 2004; 50(10):3145–3152. [PubMed: 15476248]
23. Marriott K, Birmingham TB, Kean CO, Hui C, Jenkyn TR, Giffin JR. Five-year changes in gait biomechanics after concomitant high tibial osteotomy and ACL reconstruction in patients with medial knee osteoarthritis. *Am J Sports Med.* 2015; 43(9):2277–2285. [PubMed: 26264767]
24. Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. *Arthritis Rheum.* 2005; 52(9):2835–2844. [PubMed: 16145666]
25. Noyes FR, Barber-Westin SD, Hewett TE. High tibial osteotomy and ligament reconstruction for varus angulated anterior cruciate ligament-deficient knees. *Am J Sports Med.* 2000; 28(3):282–296. [PubMed: 10843117]
26. Potter HG, Jain SK, Ma Y, Black BR, Fung S, Lyman S. Cartilage injury after acute, isolated anterior cruciate ligament tear. *Am J Sports Med.* 2012; 40(2):276–285. [PubMed: 21952715]
27. Potter HG, Linklater JM, Allen AA, Hannafin JA, Haas SB. Magnetic resonance imaging of articular cartilage in the knee: an evaluation with use of fast-spin-echo imaging. *J Bone Joint Surg Am.* 1998; 80(9):1276–1284. [PubMed: 9759811]
28. Scanlan SF, Chaudhari AMW, Dyrby CO, Andriacchi TP. Differences in tibial rotation during walking in ACL reconstructed and healthy contralateral knees. *J Biomech.* 2010; 43(9):1817–1822. [PubMed: 20181339]
29. Scanlan SF, Favre J, Andriacchi TP. The relationship between peak knee extension at heel-strike of walking and the location of thickest femoral cartilage in ACL reconstructed and healthy contralateral knees. *J Biomech.* 2013; 46(5):849–854. [PubMed: 23375789]
30. Sharma L, Song J, Dunlop D, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. *Ann Rheum Dis.* 2010; 69(11):1940–1945. [PubMed: 20511608]
31. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA.* 2001; 286(2):188–195. [PubMed: 11448282]
32. Sturniaks DL, Besier TF, Mills PM, et al. Knee joint biomechanics following arthroscopic partial meniscectomy. *J Orthop Res.* 2008; 26(8):1075–1080. [PubMed: 18327795]
33. Titchenal MR, Chu CR, Erhart-Hledik JC, Andriacchi TP. Early changes in knee center of rotation during walking after anterior cruciate ligament reconstruction correlate with later changes in patient-reported outcomes. *Am J Sports Med.* 2017; 45(4):915–921. [PubMed: 27881382]
34. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Ann Rheum Dis.* 2004; 63(3):269–273. [PubMed: 14962961]
35. Williams A, Qian Y, Chu CR. UTE-T2* mapping of human articular cartilage in vivo: a repeatability assessment. *Osteoarthritis Cartilage.* 2011; 19(1):84–88. [PubMed: 21035556]
36. Williams, AA; Chu, CR. Ultrashort and short T2 signal detection in cartilage and meniscus: how low do we need to go?. Presented at the Joint Annual meeting of the ISMRM and ESMRMB; Milan, Italy. May 2014; Available at: <http://dev.ismrm.org/2014/0306.html>
37. 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; 46(3):515–520. [PubMed: 23141637]

Figure 1.

UTE-T2* map of the medial compartment of the tibiofemoral joint for an uninjured participant. The outlined regions of interest include the deep half of weightbearing cartilage on the central and posterior medial femoral condyle (cMFC and pMFC, respectively) and the central medial tibial plateau (cMTP). Low UTE-T2* values are shown as red. Note the laminar appearance in which a low signal is depicted as red in the deep layer of articular cartilage.

Figure 2.

Top: Morphological magnetic resonance imaging (sagittal proton density without fat saturation) of the medial compartment of the tibiofemoral joint of 2 anterior cruciate ligament–reconstructed patients: (A) 28-year-old female and (B) 27-year-old female. Both patients had Outerbridge grade 0 in the central and posterior medial femoral condyle and central medial tibial plateau regions of cartilage. Bottom: UTE-T2* maps of the same 2 patients. (C) The same patient from A had both a high knee adduction moment (KAM) and high UTE-T2* values. (D) The same patient from B had both a low KAM and low UTE-T2* values. Note that patient B demonstrates a similar laminar structure to articular cartilage as the uninjured participant (Figure 1), while patient A does not.

Figure 3.

Mean UTE-T2* values in deep weightbearing cartilage in the central and posterior medial femoral condyle (cMFC and pMFC, respectively) and central medial tibial plateau (cMTP) for the anterior cruciate ligament reconstruction group (dark gray) and the uninjured reference group (light gray). *Significant differences between knees ($P < .017$). Data reported as mean $\pm$ 95% CI.

Figure 4.

First and second peaks of knee adduction moment (KAM1 and KAM2, respectively) were positively correlated with UTE-T2* values in central medial tibial plateau (cMTP) weightbearing cartilage for anterior cruciate ligament–reconstructed patients. The plots show the univariate regression statistics for KAM1 and KAM2 with UTE-T2* values (Table 1). The results of the multiple regression analysis for all 3 regions (central and posterior medial femoral condyle and cMTP) are listed in Table 1.

Correlations Between KAM1, KAM2, and Knee Mechanical Axis Alignment and Deep UTE-T2* Values in the Weightbearing Regions of Cartilage in the cMFC, pMFC, and cMTP^a

TABLE 1

Cartilage Region	Independent Measures in Model			Overall Model	
	Name	Standardized Coefficient	P Value	R Value	P Value
cMFC deep UTE-T2*	KAM1	0.452	.046	0.452	.046
	KAM1	0.500	.025	0.557	.042
	Age	-0.330	.123		
	KAM2	0.465	.039	0.465	.039
	Alignment	0.568	.022	0.568	.022
	Alignment	0.545	.028	0.609	.049
pMFC deep UTE-T2*	Age	-0.220	.338		
	KAM1	0.473	.033	0.555	.044
	Age	-0.369	.088		
	KAM2	0.602	.005	0.602	.005
	KAM2	0.568	.008	0.634	.013
	Age	-0.202	.304		
cMTP deep UTE-T2*	KAM2	0.566	.017	0.607	.020
	Sex	0.081	.711		
	KAM2	0.514	.034	0.619	.016
	BMI	0.170	.457		
	KAM1	0.463	.040	0.463	.040
	KAM2	0.764	<.0001	0.764	<.0001
cMTP deep UTE-T2*	KAM2	0.791	<.0001	0.780	<.001
	Age	0.159	.316		
	KAM2	0.917	<.0001	0.824	<.0001
	Sex	-0.345	.038		
	KAM2	0.872	.0001	0.784	.001
	BMI	-0.206	.258		

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^aCorrelation was assessed using linear regression models with KAM1, KAM2, and alignment separately as independent measures. The addition of age, sex, and BMI to the models produced some statistically significant overall models in combination with KAM1, KAM2, and alignment, although only sex was a significant predictor within a model with KAM2 for the cMTP. Models are considered significant when the overall model's $P < .05$ (far right column), and independent measures are considered significant and are bolded when $P < .05$. BMI, body mass index; cMFC, central medial femoral condyle; cMTP, central medial tibial plateau; KAM1, first peak of knee adduction moment; KAM2, second peak of knee adduction moment; pMFC, posterior medial femoral condyle.