Knee joint unloading and daily physical activity associate with cartilage T2 relaxation times 1 month after ACL injury

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Abstract

Osteoarthritis (OA) is prevalent after anterior cruciate ligament (ACL) injury, but mechanismsunderlying its development are poorly understood. The purpose of this study was to determine if gait biomechanics and daily physical activity (PA) associate with cartilage T2 relaxation times, a marker of collagen organization and water content, 1 month after ACL injury. Twenty-seven participants (15–35 years old) without chondral lesions completed magnetic resonance imaging, three-dimensional gait analysis, and 1 week of PA accelerometry. Interlimb differences and ratios were calculated for gait biomechanics and T2 relaxation times, respectively. Multiple linear regression models adjusted for age, sex, and concomitant meniscus injury were used to determine the association between gait biomechanics and PA with T2 relaxation times, respectively. Altered knee adduction moment (KAM) impulse, less knee flexion excursion (kEXC) and higher daily step counts accounted for 35.8%–65.8% of T2 relaxation time variation in the weightbearing and posterior cartilage of the medial and lateral compartment (all $p \leq .011$). KAM impulse was the strongest factor for T2 relaxation times in all models (all $p \leq .001$). Lower KAM impulse associated with longer T2 relaxation times in the injured

medial compartment (β = −.720 to −.901) and shorter T2 relaxation in the lateral compartment (β = .713 to .956). At 1 month after ACL injury, altered KAM impulse, less kEXC, and higher PA associated with longer T2 relaxation times, which may indicate poorer cartilage health. Statement of Clinical Significance: Gait biomechanics and daily PA are modifiable targets that may improve cartilage health acutely after ACL injury and slow progression to OA.

KEYWORDS
anterior cruciate ligament, biomechanics, cartilage, gait, osteoarthritis

1 | INTRODUCTION

Anterior cruciate ligament (ACL) injury is the most frequent intra-articular injury of the knee and occurs at an incidence of 68.6 per 100,000.[1,2] Young individuals participating in cutting and pivoting sports are at highest risk of ACL injury, and injury rates are on the rise.[2] The incidence of ACL injury increased by 74% in those under 25 years during a recent 15-year period.[3] An unfortunate but common consequence of ACL injury is the development of posttraumatic knee osteoarthritis (PTOA) at an early age. ACL injury increases the risk of future osteoarthritis (OA) by over eightfold within 11 years of injury.[4] Thus, the risk for total knee arthroplasty after ACL injury is 20 times greater during the third decade of life and 7.5 times greater during the fourth decade of life compared to the overall population.[5] The rapidly increasing incidence of ACL injuries in young populations will likely result in a greater burden of PTOA in young adults in the years ahead. Mechanisms underlying the early development of PTOA after ACL injury are not well understood. Thus, interventions to prevent or delay cartilage breakdown after ACL injury do not exist.

Articular cartilage is avascular, and chondrocytes and the extracellular matrix of articular cartilage are thus dependent on repetitive, cyclic loading to promote tissue health. Dynamic joint loading results in stronger collagen and increased proteoglycan concentrations in cartilage.[6] Meanwhile, inadequate joint loading results in cartilage that is thinner, softer and more susceptible to breakdown.[7] T2 relaxation time is a quantitative magnetic resonance imaging (qMRI) marker that provides an early trajectory of joint health before macroscopic MRI or radiographic changes occur after ACL injury. T2 relaxation times can detect changes in the water content and morphologic changes in collagen organization of the articular cartilage.[8,9] Thus, increased T2 relaxation times in the injured limb may indicate the potential for asymmetric chondral degradation over time. Other techniques, such as Th1rho and dGMERIC, have been established for quantitative evaluation of cartilage; however, these are based primarily on assessing proteoglycan content. Abnormal walking patterns have been linked to increasing T2 relaxation times after ACL injury.[10–15] Although preoperative changes in T2 relaxation time have been reported,[16] limited evidence exists regarding the relationship between walking patterns and T2 relaxation time before ACL reconstruction (ACLR). Due to the precedent for T2 relaxation in relation to physical activity (PA), this was selected over other techniques.

Although individuals spend less time in PA roughly 2–3 years (mean: 27.8 ± 17.5 months) after ACLR compared to uninjured matched controls,[17] our understanding of PA levels before ACLR is limited. It is also unknown if daily magnitudes of PA immediately after ACL injury are associated with change in T2 relaxation times in the cartilage of the injured knee. Because articular cartilage structure is dependent on repetitive and dynamic joint loading, an integrated approach using PA levels and walking biomechanics may provide an enhanced understanding of total daily knee joint loading. An understanding of the association between cumulative measures of joint loading (i.e., step counts and knee moments during gait) and measures of cartilage structure is needed to inform modifiable strategies to limit cartilage degeneration after ACL injury.

The purpose of this study was to determine if measures of knee joint loading (i.e., knee joint biomechanics during gait, PA levels) are associated with T2 relaxation times in the articular cartilage of the knee within 1 month of ACL injury. Because alterations in quantitative MRI markers of cartilage structure occur rapidly after ACL injury,[16] the 1-month time point was chosen to identify immediate changes in T2 relaxation time within a clinically reasonable period to recruit and enroll participants to inform the timing of future preventative interventions. We hypothesized that lower measures of knee joint loading would be associated with longer (worse) T2 relaxation times. A secondary aim was to determine if interlimb differences in gait biomechanics and cartilage T2 relaxation times are present immediately after ACL injury. We hypothesized that in the injured knee lower joint angles and moments but longer T2 relaxation times would be present.

2 | METHODS

2.1 | Participants

Participants between 15 and 35 years of age were enrolled within 1 month of ACL injury before ACLR for this ongoing, prospective cohort study (Level 2 evidence). Older individuals were excluded due to higher risk of baseline cartilage degeneration. Exclusion criteria

included a previous injury or surgery to either knee, concomitant Grade III tear to other knee ligaments, meniscus tear with anticipated meniscectomy by the treating orthopaedic surgeon, acute chondral lesions or degenerative cartilage changes identified on postinjury MRI, or open growth plates requiring altered ACLR technique (i.e., physeal-sparing). Additional exclusion criteria included history of inflammatory disease, immune compromise, chronic use of nonsteroidal antiinflammatory drugs, history of cortisone injection during the prior 3 months, current pregnancy, or contraindications to MRI. This study was approved by the Institutional Review Board at the University of Nebraska Medical Center. All participants provided written informed consent.

2.2 | Self-reported participant characteristics

Participants reported age, sex, race, and preinjury cutting and pivoting activity level (Level 1: soccer, basketball, etc.; Level 2: tennis, baseball, etc.[18,19]) in surveys within the REDCap electronic data capture tools hosted at the University of Nebraska Medical Center.[20] Height was measured using a portable stadiometer with shoes off.

2.3 | MRI acquisition and T2 relaxation time

Participants sat for 30 min before MRI acquisition to unload knee cartilage due to acute effects of loading on T2 relaxation time.[21] Each MRI scan began between 4:15–5:45 p.m. to control for the effect of daily activity on qMRI markers.[22] Bilateral MR image data (injured knee first) were acquired on a 3-Tesla Phillips Ingenia MRI scanner using a 16 channel transmit/receive knee coil (Phillips North America Corporation) in slight knee flexion and neutral rotation. For T2 mapping, a spin echo (SE) sequence with multiple echoes (MSE) was acquired with these parameters: TR = 2700 msec; 10 echoes with the echo times $TE_i = i \times 10$ msec (i = 1, ..., 10); FOV: 120 × 120 mm; acquisition matrix = 252 × 250; slice thickness = 3.0 mm; slice gap = 0.5 mm; range of slices = 23–31; pixel size = 0.3125 × 0.3125 mm; echo train length = 10; number of averages = 1. In addition to MSE, fat suppressed proton density weighted SE sequence in axial, coronal, and sagittal orientations and a sagittal T1 weighted SE were also included in the MRI protocol.

Multi-echo MRI data at each pixel were fit to the signal equation $S_i = S_0\exp(-TE_i/T_2)$ to generate T2 maps using Levenberg-Marquardt nonlinear least squares algorithm (S_i = the signal at echo time TE_i, and S_0 = signal at TE = 0) within Interactive Data Language (Harris Geospatial Solutions Inc.). First echo data were not used in the fitting to minimize the errors due to stimulated echoes.[23]

Manual cartilage segmentation was completed in ITK-SNAP software[24] on reference images corresponding to TE = 40 msec from MSE data used for generating T2 maps for which we have demonstrated reliability (intrarater intraclass correlation coefficients [ICC] [n = 12]: femoral: 0.759; tibial: 0.775; interrater ICC [n = 12]: femoral: 0.949; tibial: 0.930). Before uninjured segmentation, a manual and affine registration technique was used to register the injured reference images to the uninjured knee using 3-D Slicer software.[25] The goal of this registration procedure was to provide an initial segmentation mask for the uninjured knee cartilage to reduce processing time. The combined registration was applied to the injured segmentation mask, overlaid on the uninjured reference images, and manually adjusted to anatomically match uninjured knee cartilage.

Lateral and medial compartments were defined using the center of the intercondylar notch for both the femur (LFC and MFC, respectively) and the tibia (LTC and MTC, respectively). Femoral and tibial cartilage in each compartment (LFC, MFC, LTC, MTC) were further divided into anterior, weightbearing, and posterior regions according to the location of the meniscus horns in the sagittal plane (Figure 1) using axial MR images to verify meniscus horn location. Anterior and posterior tibial cartilage was not analyzed due to few pixels in these regions. The patellar cartilage comprised a single region. A board-certified, fellowship-trained musculoskeletal radiologist confirmed accuracy of segmentation masks and region of interest (ROI) boundaries. Cartilage masks were overlaid on T2 maps to extract mean T2 relaxation time within each ROI (six femoral, two tibial, and one patellar). Pixels with T2 relaxation times less than 10 ms or more than 90 ms were excluded to remove outliers due to fitting errors.[26] A T2 relaxation time interlimb ratio (ILR) was

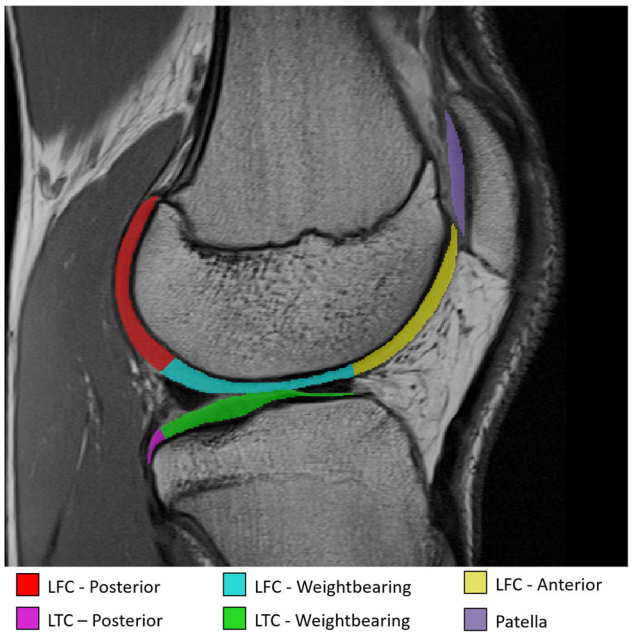

FIGURE 1 The femoral and tibial cartilage segmentation masks in each compartment (lateral compartment pictured above) were divided into anterior, weightbearing, and posterior regions as defined by the location of the meniscus horns in the sagittal plane. The anterior and posterior (not pictured) tibial cartilage was not used in analysis. Thus, analyses included three femoral regions (anterior, weightbearing and posterior) in each compartment (lateral and tibial) and a single weightbearing region in each compartment (lateral and tibial). The patellar cartilage comprised a single region. LFC, lateral femoral condyle; LTC, lateral tibial condyle [Color figure can be viewed at wileyonlinelibrary.com]

calculated in each ROI (T2 ILR = injured limb/uninjured limb).[13] Thus, an ILR more than 1.00 indicates longer T2 relaxation time in the injured compared to uninjured knee.

2.4 | Gait biomechanics

Three-dimensional motion capture data were collected using an 8-camera system (Qualysis AB) sampled at 120 Hz and two embedded force plates (Bertec Corporation) sampled at 1080 Hz. Passive, 14-mm retroreflective markers were placed on skeletal landmarks of the trunk, pelvis and lower extremities (Figure 2). Rigid shells each with four markers were placed at the lateral shanks and thighs.

Participants stood in anatomical position for a 1-s static trial. Markers at the first metatarsal heads, malleoli, femoral epicondyles, and anterior superior iliac spines (ASIS) were removed before gait trials. Participants completed five gait trials with valid kinematic and kinetic data on each limb at a self-selected, comfortable walking speed. Average gait speed was calculated along a 5.4 m walkway during the first three gait trials and maintained within 5% for all remaining trials.

Labeled marker data were exported to Visual 3D software (C-Motion, Inc.) for custom data postprocessing. Target and ground reaction force (GRF) data were low-pass filtered using a fourth-order bidirectional Butterworth filter with a cutoff frequency of 6 Hz. A cutoff frequency of 6 Hz was chosen after completing residual analysis of kinetic data as described by Winter.[27] Briefly, residuals were calculated for cutoff frequencies from 0.1 to 49.9 Hz at increments of 0.1 Hz using gait trials from the first ten participants in this study. Residuals were normalized to the maximum residual value. The linear section of high frequency residuals was defined as the collection of points where the values of the residuals' second discrete time derivative were below 0.0001. Using linear regression, the cutoff frequency was equal to the y-intercept of the linear regression line. The average cutoff frequency across both limbs was 4.5 ± 0.5 Hz. To account for two *SD*s of variance, a cutoff frequency of 6 Hz was chosen.

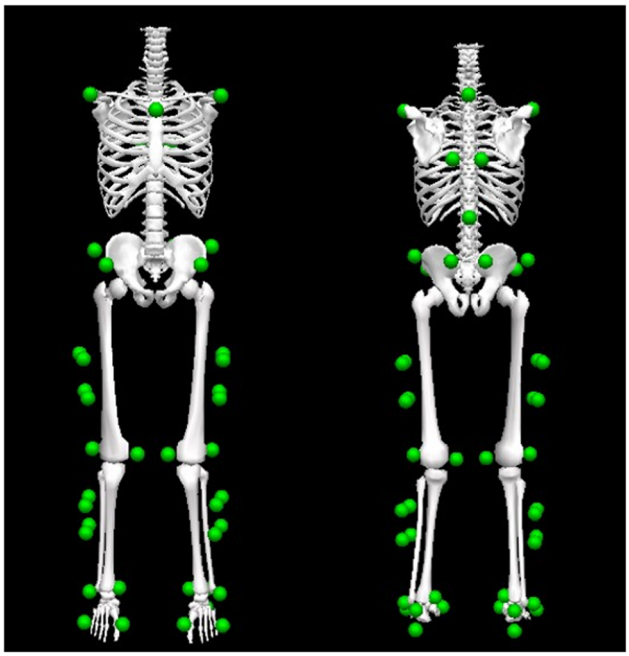

FIGURE 2 Individual markers (represented by green circles) were placed on bony landmarks of the trunk and lower extremities with rigid shells of markers placed at the thighs and shanks. Anterior view is on the left. Posterior view is on the right. Images generated in Visual 3D software [Color figure can be viewed at wileyonlinelibrary.com]

A subject-specific model was created using height (stadiometer) and mass (static trial) to determine segment lengths and joint centers. Virtual markers at bony landmarks were offset 9 mm toward the bone to account for half of the 14-mm marker and the 2-mm base.[28] The ankle and knee joint centers were defined as the mid-point of the virtual medial and lateral malleoli and virtual medial and lateral femoral epicondyles, respectively. A Visual 3D composite pelvis was built from virtual ASIS and PSIS landmarks. The hip joint center was defined using estimates described by Bell and colleagues.[29,30] Knee joint moments were calculated using an inverse dynamics approach.[27] The beginning and end of stance phase was determined using a 10 N threshold of the GRF. Variables of interest included the knee flexion angle (KFA) at initial contact, peak knee flexion angle (pKFA) and moment (pKFM) during loading response, and peak knee adduction moment (pKAM) during the first 50% of stance phase. Joint moments are reported as external moments. Knee excursion (kEXC) during loading response was defined by the difference in KFA from initial contact to pKFA. The impulse of the external KFM and KAM over the entire stance phase were calculated using the trapezoidal rule. External knee joint moments were normalized to mass (kilograms) and height (meters). Positive joint angles represent knee flexion. Positive joint moments represent knee flexion and adduction, respectively.

2.5 | Physical activity

PA was measured using a 3-axis accelerometer (wGT3X-BT; Actigraph Corporation) sampled at 100 Hz. This accelerometer reliably measures step counts across varying gait speeds.[31] Participants wore the accelerometer on the right iliac crest for 7 days beginning the day after MRI and biomechanics testing during all waking hours except when in water. Data were processed within Actilife 6 software (Actigraph Corporation).[32] Activity counts, which represent the weighted sum of the number of accelerations, were calculated for each 1-min interval to identify wear periods and calculate PA levels. A valid week of data required 4 days with at least 10 h of wear to provide a reliable estimate of PA behavior.[32–34] Nonwear periods were defined as intervals of at least 90 min with activity counts equal to zero with no more than 2 min of activity counts between 1 and 99.[33] The variable of interest was mean steps per day.

2.6 | Statistical analysis

Nominal data were described using counts and proportions. Continuous data were described using means, *SD*s, and 95% confidence intervals. Paired *t* tests were used to determine if gait biomechanics and cartilage T2 relaxation times differed between the injured and uninjured knee.

Hierarchical multiple regression models were used to determine the association between knee joint loading predictors (daily step counts, kEXC, and KAM impulse) with the outcome of T2 relaxation time ILR in each ROI. kEXC and KAM impulse parameters were defined as interlimb differences (injured minus uninjured). Daily step counts and kEXC were chosen because they represent global joint loading measures. KFM variables were not included because it demonstrated high collinearity with kEXC (peak KFM: $r = .711$; KFM impulse: $r = .590$). KAM impulse was chosen because it represents the relative joint loading balance in the frontal plane (i.e., relative loading between the medial versus lateral tibiofemoral compartment) throughout stance phase.[35] Age, sex (female = 0; male = 1), and the presence of meniscus injury (medial meniscus for medial compartment, lateral meniscus for lateral compartment, and any meniscus injury for patellar cartilage analyses) (n = 0; yes = 1) were entered as covariates in the first block, followed by the knee joint loading predictors in the second block. Age and concomitant meniscus injury were included as covariates because they increase the odds for developing knee OA earlier after ACL injury.[36,37] Multiple regression assumptions of independent observations, individual predictor linearity, collective predictor linearity and homoscedasticity of residuals, and residual normality were tested using the Durbin-Watson statistic, partial regression plots, scatterplots of unstandardized predicted values versus studentized residuals, and histograms and P-P plots, respectively. No outliers (standardized residual >3 *SD*s) were identified. A *p* value of less than .05 was set a priori.

3 | RESULTS

Descriptive statistics for age, race, mass, height, and sex are presented in Table 1. All but two participants participated in Level 1 cutting and pivoting activities (e.g., soccer, basketball) before ACL injury.[18,19] Participants were enrolled and completed MRI and biomechanical testing at an average of 25 days after injury (Table 1). Approximately one-quarter of participants had a concomitant medial meniscus tear and nearly one-half had lateral meniscus injury (Table 1). Accelerometer wear, daily steps counts, and gait speed during biomechanics testing are presented in Table 2.

3.1 | Gait biomechanics and T2 relaxation time

Compared to the uninjured limb, the injured limb demonstrated approximately 3° greater pKFA during loading response of gait (Table 3). However, this was accompanied by an average of 6° more knee flexion at initial contact resulting in less kEXC (Figure 3). A lower pKAM and KAM impulse was observed in the injured limb (Table 3 and Figure 4). However, no interlimb differences were present for sagittal plane knee moments. There were no significant interlimb differences in T2 relaxation times within any cartilage ROI (Table 4).

TABLE 1 Participant characteristics and concomitant meniscus injury is presented for all 27 participants

Variable	Mean (*SD*) or count (%)	95% CI
Age (years)	19.8 (5.0)	17.8–21.8
Race		
Asian	2 (7.4)	
Black or African American	2 (7.4)	
Hispanic, Latino or Spanish	3 (11.1)	
White	20 (74.1)	
Mass (kg)	74.4 (15.5)	68.3– 80.5
Height (m)	1.70 (0.09)	1.67–1.74
Sex (female)	15 (55.6)	
Preinjury activity level (Level 1)[18,19]	25 (92.6)	
Time From ACL injury (days)	24.6 (4.7)	22.8–26.5
Medial meniscus tear (Yes)	7 (25.9)	
Lateral meniscus tear (Yes)	12 (44.4)	
Medial or lateral meniscus tear (Yes)	14 (51.9)	

Note: Mean (*SD*) and 95% confidence intervals provided for continuous data. Counts (percentage) provided for categorical data. % = Percentage.
Abbreviations: CI, confidence interval; kg, kilograms; m, meters.

3.2 | Lateral tibiofemoral cartilage

After controlling for age, sex, and concomitant lateral meniscus injury in the full regression models, daily step counts, kEXC, and

TABLE 2 Accelerometer wear, daily steps counts, and gait speed during biomechanics testing is presented for all 27 participants

Variable	Mean (*SD*)	95% CI
Accelerometer wear (days)	5.6 (1.3)	5.1–6.2
Daily Accelerometer wear (min)	878.7 (145.7)	821.0–936.3
Daily step count	6274.6 (2500.7)	5285.4–7263.9
Gait Speed (m/s)	1.38 (0.21)	1.29–1.46

Note: Mean (*SD*) and 95% confidence intervals are provided.
Abbreviations: CI, confidence interval; m, meter; min, minutes; sec, second.

TABLE 3 Knee flexion angle and sagittal and frontal plane joint moments during gait is presented for the injured and uninjured limb for all 27 participants

	Injured	Uninjured	Difference	95% CI	*p*
KFA at IC (°)	6.7 (5.8)	0.2 (4.2)	6.4	4.4– 8.5	**<.001**
pKFA (°)	21.0 (5.9)	18.4 (6.5)	2.6	0.5–4.7	**.019**
kEXC (°)	14.3 (3.7)	18.2 (4.4)	−3.9	−5.5–−2.2	**<.001**
pKFM (N·m/kg·m)	0.36 (0.14)	0.40 (0.18)	−0.04	−0.10–0.02	.224
KFM impulse (N·m·s/kg·m)	0.056 (0.022)	0.057 (0.028)	−0.001	−0.010–0.007	.769
pKAM (N·m/kg·m)	0.21 (0.09)	0.28 (0.10)	−0.07	−0.12–−0.03	**.003**
KAM impulse (N·m·s/kg·m)	0.071 (0.043)	0.097 (0.044)	−0.026	−0.046–−0.006	**.012**

Note: Values in parentheses are *SDs*. The interlimb difference is presented with its 95% confidence interval. Boldface numbers indicate statistical significance (*p* values of <.05). ° = degrees.

Abbreviations: CI, confidence interval; IC, initial contact; KAM, knee adduction moment; kEXC, knee flexion angle excursion; KFA, knee flexion angle; kg, kilogram; KFM, knee flexion moment; m, meter; N, newton; *p*, *p* value; pKAM, peak knee adduction moment; pKFA, peak knee flexion angle; s, second.

KAM impulse accounted for an additional 35.8% of the variability in T2 relaxation time ILR's in the weightbearing LFC cartilage, 44.8% in the posterior LFC cartilage, and 64.5% in the weightbearing LTC cartilage (Table 5). KAM impulse was the only significant factor of T2 relaxation times in the weightbearing cartilage of the LFC ($\beta = .713$; $p = .001$). KAM impulse also most strongly associated with T2 relaxation times in the posterior cartilage of the LFC ($\beta = .799$; $p < .001$) and the weightbearing cartilage of the LTC ($\beta = .956$; $p < .001$). KAM impulse always positively associated with T2 relaxation times in the lateral compartment, indicating that asymmetrically lower KAM impulse in the injured knee was associated with asymmetrically shorter T2 relaxation time in the injured knee (ILR <1.00). Higher step counts (posterior LFC: $\beta = .478$; $p = .035$; weightbearing LTC: $\beta = .371$; $p = .025$) and less kEXC (posterior LFC: $\beta = -.481$; $p = .026$; weightbearing LTC: $\beta = -.403$; $p = .012$) also associated with longer T2 relaxation in the posterior LFC and weightbearing LTC of the injured knee.

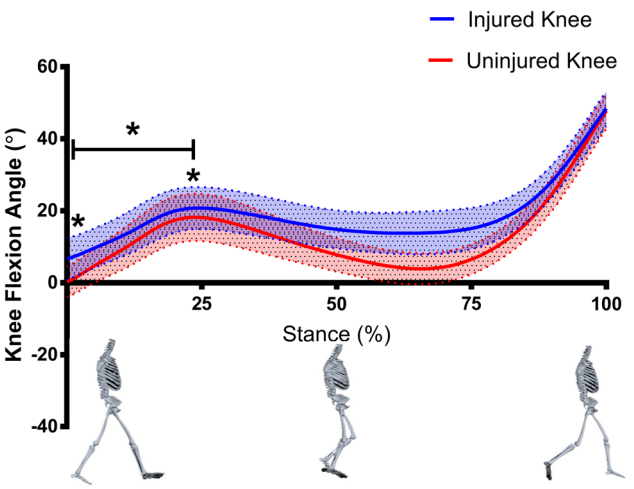

FIGURE 3 Mean knee flexion angle for all 27 participants during stance phase of gait. Participants walked with a statistically significant (asterisks) greater knee flexion angle at initial contact and at the end of loading response (~25% of stance phase) but less knee excursion in the injured limb compared to uninjured limb. The shaded regions represent ±1 *SD* of mean knee flexion angle at each percentage of stance phase. °, degrees; %, percentage [Color figure can be viewed at wileyonlinelibrary.com]

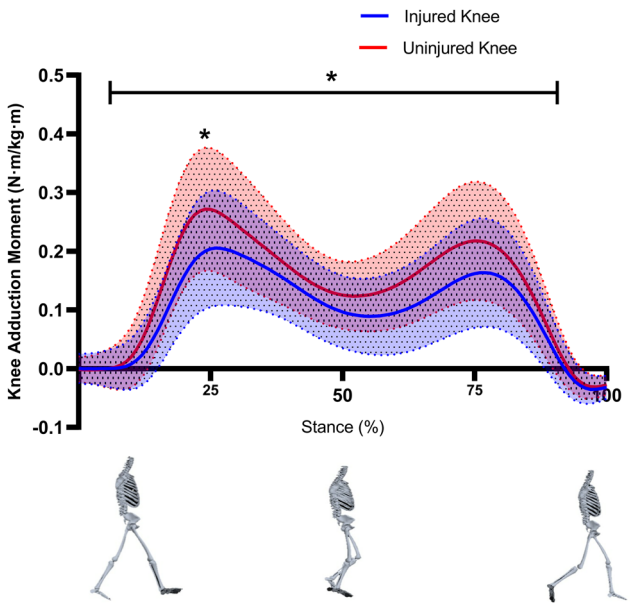

FIGURE 4 Mean external knee adduction moment for all 27 participants during stance phase of gait. Participants walked with a statistically significant (asterisks) smaller peak knee adduction moment during the first 50% of stance phase and a smaller knee adduction moment impulse over all of stance phase compared to uninjured limb. The shaded regions represent ±1 *SD* of the knee adduction moment at each percentage of stance phase. N, newton; m, meter; kg, kilogram; %, percentage [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Mean T2 relaxation time (milliseconds) in the cartilage of each region of interest is presented for all 27 participants

	Injured	Uninjured	ILR	95% CI	*p*
LFC—anterior	46.8 (2.9)	47.1 (2.7)	0.99	0.97–1.02	.624
LFC—weightbearing	46.9 (3.3)	47.5 (4.3)	0.99	0.96–1.03	.484
LFC—posterior	42.9 (4.4)	42.7 (5.2)	1.01	0.96–1.06	.897
LTC—weightbearing	41.7 (3.7)	42.6 (4.6)	0.99	0.94–1.04	.446
MFC—anterior	46.9 (3.7)	46.4 (3.6)	1.02	0.97–1.06	.608
MFC—weightbearing	46.7 (4.0)	46.9 (3.6)	1.00	0.96–1.04	.826
MFC—posterior	42.3 (5.6)	40.8 (4.5)	1.05	0.98–1.12	.300
MTC—weightbearing	43.0 (4.1)	42.3 (3.7)	1.02	0.97– 1.08	.611
Patella	39.0 (2.6)	39.4 (3.1)	0.99	0.97–1.02	.468

Note: Values in parentheses are *SD*s. The interlimb ratio (ILR) is presented with its 95% confidence interval.

Abbreviations: CI, confidence interval; LFC, lateral femoral condyle; LTC, lateral tibial condyle; MFC, medial femoral condyle; MTC, medial tibial condyle; *p*, *p* value.

3.3 | Medial tibiofemoral cartilage

After controlling for age, sex, and concomitant lateral meniscus injury in the full regression models, daily step counts, kEXC, and KAM impulse accounted for an additional 58.3% of the variability in T2 relaxation time ILR's in the weightbearing MFC, 45.1% in the posterior MFC, and 65.8% weightbearing MTC (Table 6). KAM impulse was the only loading factor of T2 relaxation times in these ROIs (weightbearing MFC: $\beta = -.848$, $p < .001$; posterior MFC: $\beta = -.720$, $p = .001$; weightbearing MTC: $\beta = -.901$, $p < .001$). Unlike the lateral compartment, KAM impulse always negatively associated with T2 relaxation times in the medial compartment, indicating that asymmetrically lower KAM impulse in the injured knee was associated with asymmetrically longer T2 relaxation time in the injured knee (ILR >1.00). The opposite relationship between the KAM impulse and T2 relaxation times in the medial compared to lateral compartment is illustrated in Figure 5. Older age was associated with longer T2 relaxation time in the injured weightbearing MFC ($\beta = .349$; $p = .017$) and MTC ($\beta = .278$; $p = .039$).

3.4 | Patellar cartilage

After controlling for age, sex, and concomitant lateral or medial meniscus injury in the full regression model, daily step counts, kEXC, and KAM impulse were not associated with T2 relaxation times in in the patellar cartilage (R^2: .303, R^2 change: .050, $p = .700$). Patellar cartilage findings were consistent with the absence of T2 association with knee joint loading factors in the cartilage of the anterior LFC and anterior MFC (Tables 5 and 6).

4 | DISCUSSION

The primary aim of this study was to determine if measures of knee joint loading (i.e., PA levels, knee joint biomechanics during gait) were associated with T2 relaxation times in knee cartilage within 1 month of ACL injury. Our findings partially support our hypothesis that lower measures of knee joint loading are associated with longer cartilage T2 relaxation times. Lower KAM impulse in the injured knee associated with longer T2 relaxation times in the medial femoral and tibial cartilage but shorter T2 relaxation times in the lateral femoral and tibial cartilage. Less kEXC associated with longer T2 relaxation times in the lateral posterior femoral and weightbearing tibial cartilage. However, higher daily step counts associated with longer T2 relaxation times in the injured lateral posterior femoral and weightbearing tibial cartilage.

Our findings demonstrate the acute association between knee joint loading patterns and cartilage structure after ACL injury. Participants in this study walked with a 25% lower pKAM ($p = .003$) and a 27% lower KAM impulse ($p = .012$) compared to the uninjured knee within 1 month of ACL injury. The KAM impulse demonstrated a differential relationship with T2 relaxation times in the medial compared to lateral weightbearing and posterior regions of both femoral and tibial cartilage (Figure 4). Participants who walked with lower KAM impulse in the injured knee (relatively lower medial loading, greater lateral loading[38]) demonstrated T2 relaxation times that were longer in the medial compartment but shorter in the lateral compartment when compared to the uninjured knee. The relationship was opposite in those that walked with higher KAM impulse (relatively greater medial loading, lower lateral loading). Although walking requires limited knee flexion during stance phase (21.0 ± 5.9° in the current cohort), the reduced KAM present during gait in this study may reflect knee joint unloading tendencies previously reported after ACL injury during movement patterns that require greater knee flexion, such as sitting and standing from a chair or navigating stairs.[39,40] Knee joint unloading patterns during daily activities that require greater weightbearing knee flexion than normal gait may explain the relationships between knee joint biomechanics and T2 relaxation times in the posterior regions of the femoral cartilage.

Longer T2 relaxation times indicate increased water content and disorganization of the collage matrix and is a sensitive marker for symptomatic and structural progression of knee OA.[41–43] However, changes in cartilage qMRI markers, including T2 relaxation time, may also reflect temporary acute changes after ACL injury and subsequent healing in addition to altered movement mechanics.[44–46] Our cohort taken together did not show significantly different T2 relaxation times within any femoral, tibial or patellar ROI (Table 4). The longer T2 relaxation times in some, but not all, individuals in this study may have been influenced from variations in severity of injury. For example, bone marrow edema patterns that are common after ACL injury are associated with increased cartilage loss up to 3 years later.[47] Klocke and colleagues reported longer T2 relaxation times in the tibiofemoral cartilage of 13 participants 7–136 days after ACL injury.[16] They concluded that these acute changes may reflect elevated fluid content in the articular cartilage associated with the inflammatory response from the traumatic nature of ACL injury. Other evidence suggests that

TABLE 5 Results of linear regression models with daily physical activity (step counts), interlimb difference in knee flexion angle excursion, and interlimb difference in knee adduction moment impulse as independent variables and interlimb ratios in T2 relaxation times in the lateral tibiofemoral regions of interest as the outcome of interest, after adjusting for age, sex, and concomitant meniscus injury

Cartilage region	R^2	R^2 change	*p*	Factor	Unstandardized *B*	*β*	*p*
LFC—anterior	0.265	0.246	.116				
				Age	<0.001	.033	.877
				Sex	−0.008	−.063	.754
				Meniscus injury	−0.029	−.239	.255
				Daily PA	<0.001	.159	.550
				kEXC	−0.001	−.045	.859
				KAM impulse	0.670	.554	.026
LFC—WB	0.507	**0.358**	**.011**				
				Age	−0.003	−.156	.375
				Sex	−0.018	−.101	.540
				Meniscus injury	0.032	.183	.286
				Daily PA	<0.001	.318	.153
				kEXC	−0.005	−.226	.278
				KAM impulse	1.250	**.713**	**.001**
LFC—posterior	0.517	**0.448**	**.004**				
				Age	−0.008	−.320	.074
				Sex	−0.040	−.159	.331
				Meniscus injury	−0.017	−.069	.682
				Daily PA	<0.001	**.478**	**.035**
				kEXC	−0.015	**−.481**	**.026**
				KAM impulse	2.028	**.799**	**<.001**
LTC—WB	0.747	**0.645**	**<.001**				
				Age	−0.006	−.232	.074
				Sex	−0.005	−.019	.872
				Meniscus injury	0.007	.026	.827
				Daily PA	<0.001	**.371**	**.025**
				kEXC	−0.013	**−.403**	**.012**
				KAM impulse	2.545	**.956**	**<.001**

Note: The *p* values represent statistical significance of the R^2 change and Beta coefficient, respectively. Boldface numbers represent statistically significant predictor variables in regression models with statistically significant changes in R^2.

Abbreviations: KAM, knee adduction moment; kEXC, knee flexion angle excursion; LFC, lateral femoral condyle; LTC, lateral tibial condyle; MFC, medial femoral condyle; MTC, medial tibial condyle; *p*, *p* value; PA, physical activity.

qMRI markers of ultrashort echo time (UTE)-T2* mapping, which may be more sensitive to deep cartilage health and correlated to injury severity, were 45% higher in the deep medial femoral cartilage compared to the uninjured knee before ACLR.[45] However, higher UTE-T2* resolved by 2 years after ACLR in patients with intact menisci, indicating the potential for healing. Longitudinal study of acute changes in T2 relaxation time is needed to determine if alterations are transient or predictive of future cartilage degeneration.

Our findings that KAM impulse and kEXC associate with longer cartilage T2 relaxation times are consistent with previous studies correlating joint unloading to negative qMRI markers early after ACL injury and ACLR. Lower GRF, KAM and medial compartment contact forces during walking in the ACL-injured limb have been associated with worse cartilage T1ρ relaxation time and radiographic knee OA after ACLR.[15,48] However, other studies have reported that higher or increasing parameters of knee joint loading are associated with

TABLE 6 Results of linear regression models with daily physical activity (step counts), interlimb difference in knee flexion angle excursion, and interlimb difference in knee adduction moment impulse as independent variables and interlimb differences in T2 relaxation times in the medial tibiofemoral regions of interest as the outcome of interest, after adjusting for age, sex, and concomitant meniscus injury

Cartilage region	R^2	R^2 change	*p*	Factor	Unstandardized *B*	*β*	*p*
MFC—anterior	0.409	0.257	.060				
				Age	0.003	.153	.425
				Sex	−0.069	−.326	.079
				Meniscus injury	−0.015	−.063	.729
				Daily PA	<0.001	.024	.917
				kEXC	<0.001	−.015	.948
				KAM impulse	−1.069	−.504	.019
MFC—WB	0.701	**0.583**	**<.001**				
				Age	0.007	**.349**	**.017**
				Sex	−0.023	−.111	.387
				Meniscus injury	0.004	.015	.908
				Daily PA	<0.000	−.210	.213
				kEXC	0.007	.284	.086
				KAM impulse	−1.762	**−.848**	**<.001**
MFC—posterior	0.523	**0.451**	**.003**				
				Age	0.009	.236	.178
				Sex	−0.045	−.124	.443
				Meniscus injury	0.006	.016	.924
				Daily PA	<0.000	−.091	.665
				kEXC	0.009	.204	.317
				KAM impulse	−2.630	**−.720**	**.001**
MTC—WB	0.734	**0.658**	**<.001**				
				Age	0.008	**.278**	**.039**
				Sex	−0.021	−.075	.535
				Meniscus injury	0.004	.013	.915
				Daily PA	<0.000	−.220	.170
				kEXC	0.009	.246	.113
				KAM impulse	−2.588	**−.901**	**<.001**

Note: The *p* values represent statistical significance of the R^2 change and Beta coefficient, respectively. Boldface numbers represent statistically significant predictor variables in regression models with statistically significant changes in R^2.

Abbreviations: KAM, knee adduction moment; kEXC, knee flexion angle excursion; LFC, lateral femoral condyle; LTC, lateral tibial condyle; MFC, medial femoral condyle; MTC, medial tibial condyle; *p*, *p* value; PA, physical activity.

worsening markers of cartilage health.[10,11,14] Three factors may explain these discrepancies. First, in studies where increases in joint loading correlate with worsening qMRI markers (e.g., longer T2 relaxation/T1rho times), it is unknown whether the initial underloading, the progressive increase in loading, or both factors influence qMRI changes. Second, knee joint angles and moment change over time after ACL injury. A knee stiffening and unloading strategy early after ACL injury and ACLR often progresses to more symmetrical gait patterns 1–2 years later.[49] It is possible that both lower and higher magnitudes of knee joint loading are harmful to articular cartilage depending on circumstances such as time from injury. Third, comparisons of only the injured limb without normalization to the uninjured limb may negate individual variation in both walking patterns and cartilage markers. For example, an increased KFA may initially appear to represent a more normal gait pattern, but if it coincides with limited kEXC, as demonstrated in the current study, it may instead indicate an abnormal loading strategy. Comparison of injured limb biomechanics to the uninjured limb provides greater

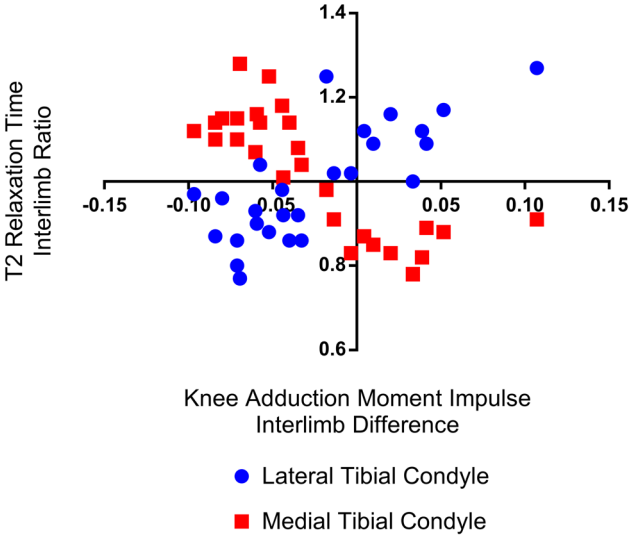

FIGURE 5 Interlimb differences in knee adduction moment impulse (N·m·s/kg·m) were positively associated with interlimb ratios of T2 relaxation time (milliseconds) in the lateral femoral and tibial cartilage but negatively associated with interlimb ratios of T2 relaxation time in the medial femoral and tibial cartilage. Data for the weightbearing lateral and medial tibial cartilage are presented here. Lower knee adduction moment impulse in the injured limb (i.e., lesser medial loading vs. greater lateral loading) was associated with longer (i.e., worse) T2 relaxation time (ILR >1.00) in the medial tibial condyle and shorter T2 relaxation time (ILR <1.00) in the lateral tibial condyle. Greater knee adduction moment impulse in the injured limb (i.e., greater medial loading vs. lesser lateral loading) was associated with shorter T2 relaxation time (ILR <1.00) in the medial tibial condyle and longer T2 relaxation time (ILR >1.00) in the lateral tibial condyle. ILR, interlimb ratio [Color figure can be viewed at wileyonlinelibrary.com]

context of the loading environment than analysis of only the injured limb.

Participants in this study walked with 3° greater pKFA and symmetrical pKFM in the ACL-injured knee compared to the uninjured knee, but with 6° less kEXC during loading response. The association between less kEXC and longer T2 relaxation times in the posterior lateral femoral and weightbearing lateral tibial cartilage supports previous evidence suggesting that changes in cartilage contact points not accustomed to these changing loads may influence initiation of PTOA.[50–52] The greater injured pKFA and symmetric KFM within 1 month of injury represents a stiffened knee gait pattern that is observed from initial contact and continuing through stance phase with a more flexed knee. Although joint angles and moments are commonly reduced during the first postoperative year and are used as a recovery target of normal gait patterns,[49] elevations in pKFA acutely after ACL injury may not be optimal and minimize normal joint loading within some regions of the knee.

KAM impulse and kEXC were not related to T2 relaxation times in the anterior femoral or patellar cartilage. These findings are consistent with Capin et al. reporting weak to absent associations with walking mechanics and T2 relaxation times in the trochlear cartilage 6 months after ACLR.[12] However, Culvenor et al. reported that individuals with MRI-defined patellofemoral cartilage lesions 1–2 years after ACLR hopped with a smaller KFA and KFM.[53] Indeed, the odds for developing patellofemoral OA increase after ACL injury.[54] Sagittal plane joint angles and moments may not be sensitive enough to the patellofemoral loading environment early after ACL injury. Instead, models of patellofemoral joint contact stress that incorporate joint moments, estimated muscle forces, and patellofemoral joint contact area may be required to sufficiently characterize patellofemoral joint loading within the context of PTOA development.

Participants walked an average of 6275 steps per day (range: 900–11,960) at 1 month after ACL injury. This is the first study to objectively measure PA levels before ACLR. Higher daily steps were associated with longer T2 relaxation times in the posterior lateral femoral and weightbearing lateral tibial cartilage. qMRI cartilage markers increase after a day of normal activity.[22] Thus, our PA findings may not indicate a detrimental cartilage response to higher PA but rather a normal physiological response. Data from the osteoarthritis initiative suggests that participation in moderate and vigorous PA by middle- and older-aged adults does not alter risk for development or progression of knee OA.[55] However, extreme levels of low PA (i.e., nonweightbearing activity) results in cartilage thinning and atrophy.[56] Optimal PA levels after ACL injury to cyclically load the articular cartilage and maintain structural health is unknown. However, it likely resides somewhere between extremely low and high PA levels.

The cross-sectional design of this study prohibits determination whether: (a) knee joint unloading patterns led to longer T2 relaxation times, (b) severity of ACL injury influenced T2 relaxation times and resulted in altered joint loading or (c) changes in joint loading and T2 relaxation times occurred independently of each other. However, the strong and consistent relationships between KAM impulse, kEXC and PA levels provides further evidence that modifiable walking patterns play an important role in PTOA pathogenesis. The sample size was relatively small for the multiple analyses completed and use of multiple covariates and variables of interest. Despite the consistent relationships between measures of knee joint loading and T2 relaxation times, the risk of some false positives is present. The covariates used in these analyses were chosen based on previous evidence to their link to knee OA, and the variables of interest were chosen to represent different aspects of knee joint loading. However, there is risk that the regression models were over-fit. To test, we examined the model for weightbearing MTC ILR because it had the greatest R^2 change of .658 with an R^2 of the overall model of .734. The predicted R^2 value for this regression model was .455. Additional limitations exist. Accelerometry-based PA levels were measured for 1 week following MRI data acquisition and may differ from PA behaviors before MRI. Lower extremity alignment was not measured, but is associated with compositional articular cartilage changes after ACLR.[14] Slower walking speed is associated with qMRI markers of articular cartilage 6–12 months after ACLR.[12,13] Walking speed was not adjusted for within regression models, but its influence was likely mitigated by maintaining gait speed within 5% across limbs. The age of the current cohort was relatively young (19.9 ± 5.2 years). Although the incidence of ACL injury is highest among adolescents and young adults,[2] our findings may limit comparison to other similar studies in populations with older and more variable age.[10–12] In this study, age was a significant

covariate of T2 relaxation times in some cartilage regions indicating biological and nonmodifiable factors also likely influence PTOA development after ACL injury.

In conclusion, altered KAM impulse, less kEXC, and higher daily PA are associated with longer cartilage T2 relaxation times 1 month after injury. The most significant finding was that lower KAM impulse in the injured knee associated with longer T2 relaxation times in the medial femoral and tibial cartilage but shorter T2 relaxation times in the lateral femoral and tibial cartilage. Gait biomechanics and daily PA are modifiable targets that may improve cartilage health acutely after ACL injury and slow progression to OA.

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AUTHOR CONTRIBUTIONS

Elizabeth Wellsandt, Yvonne Golightly, Kaleb Michaud, Matthew Tao, Balasrinivasa Sajja, and Melissa Manzer had substantial contributions to the research design of this study. All authors had substantial contributions to the acquisition, analysis or interpretation of data. All authors contributed to the drafting of the paper or revising it critically. All authors have read and approved the final submitted manuscript.

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REFERENCES

1. Majewski M, Susanne H, Klaus S. Epidemiology of athletic knee injuries: a 10-year study. *Knee*. 2006;13(3):184-188.
2. Sanders TL, Maradit Kremers H, Bryan AJ, et al. Incidence of anterior cruciate ligament tears and reconstruction: a 21-year population-based study. *Am J Sports Med*. 2016;44(6):1502-1507.
3. Zbrojkiewicz D, Vertullo C, Grayson J. Increasing rates of anterior cruciate ligament reconstruction in young australians, 2000-2015. *Med J Aust*. 2018;208(8):354-358.
4. Snoeker B, Turkiewicz A, Magnusson K, et al. Risk of knee osteoarthritis after different types of knee injuries in young adults: a population-based cohort study. *Br J Sports Med*. 2020;54(12):725-730.
5. Abram SGF, Judge A, Khan T, Beard DJ, Price AJ. Rates of knee arthroplasty in anterior cruciate ligament reconstructed patients: a longitudinal cohort study of 111,212 procedures over 20 years. *Acta Orthop*. 2019;90(6):568-574.
6. Sanchez-Adams J, Leddy HA, McNulty AL, O'Conor CJ, Guilak F. The mechanobiology of articular cartilage: bearing the burden of osteoarthritis. *Curr Rheumatol Rep*. 2014;16(10):451.
7. Arokoski JP, Jurvelin JS, Vaatainen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. *Scand J Med Sci Sports*. 2000;10(4):186-198.
8. Taylor C, Carballido-Gamio J, Majumdar S, Li X. Comparison of quantitative imaging of cartilage for osteoarthritis: T2, T1rho, dGEMRIC and contrast-enhanced computed tomography. *Magn Reson Imaging*. 2009;27(6):779-784.
9. Burstein D, Gray M, Mosher T, Dardzinski B. Measures of molecular composition and structure in osteoarthritis. *Radiol Clin North Am*. 2009;47(4):675-686.
10. Kumar D, Su F, Wu D, et al. Frontal plane knee mechanics and early cartilage degeneration in people with anterior cruciate ligament reconstruction: a longitudinal study. *Am J Sports Med*. 2018;46(2):378-387.
11. Teng HL, Wu D, Su F, et al. Gait characteristics associated with a greater increase in medial knee cartilage T1rho and T2 relaxation times in patients undergoing anterior cruciate ligament reconstruction. *Am J Sports Med*. 2017;45(14):3262-3271.
12. Capin JJ, Williams JR, Neal K, et al. Slower walking speed is related to early femoral trochlear cartilage degradation after ACL reconstruction. *J Orthop Res*. 2020;38(3):645-652.
13. Pfeiffer S, Harkey MS, Stanley LE, et al. Associations between slower walking speed and T1rho magnetic resonance imaging of femoral cartilage following anterior cruciate ligament reconstruction. *Arthritis Care Res (Hoboken)*. 2018;70(9):1132-1140.
14. Titchenal MR, Williams AA, Chehab EF, et al. Cartilage subsurface changes to magnetic resonance imaging UTE-T2* 2 years after anterior cruciate ligament reconstruction correlate with walking mechanics associated with knee osteoarthritis. *Am J Sports Med*. 2018;46(3):565-572.
15. Pfeiffer SJ, Spang J, Nissman D, et al. Gait mechanics and T1rho MRI of tibiofemoral cartilage 6 months after ACL reconstruction. *Med Sci Sports Exerc*. 2019;51(4):630-639.
16. Klocke NF, Amendola A, Thedens DR, et al. Comparison of T1rho, dGEMRIC, and quantitative T2 MRI in preoperative ACL rupture patients. *Acad Radiol*. 2013;20(1):99-107.
17. Bell DR, Pfeiffer KA, Cadmus-Bertram LA, et al. Objectively measured physical activity in patients after anterior cruciate ligament reconstruction. *Am J Sports Med*. 2017;45(8):1893-1900.
18. Hefti F, Muller W, Jakob RP, Staubli HU. Evaluation of knee ligament injuries with the IKDC form. *Knee Surg Sports Traumatol Arthrosc*. 1993;1(3-4):226-234.
19. Daniel DM, Stone ML, Dobson BE, Fithian DC, Rossman DJ, Kaufman KR. Fate of the ACL-injured patient. A prospective outcome study. *Am J Sports Med*. 1994;22(5):632-644.
20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
21. Souza RB, Stehling C, Wyman BT, et al. The effects of acute loading on T1rho and T2 relaxation times of tibiofemoral articular cartilage. *Osteoarthritis Cartilage*. 2010;18(12):1557-1563.
22. Taylor KA, Collins AT, Heckelman LN, et al. Activities of daily living influence tibial cartilage T1rho relaxation times. *J Biomech*. 2019;82:228-233.
23. Milford D, Rosbach N, Bendszus M, Heiland S. Mono-exponential fitting in T2-relaxometry: Relevance of offset and first echo. *PLoS One*. 2015;10(12):e0145255.
24. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage*. 2006;31(3):1116-1128.

25. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D slicer as an image computing platform for the quantitative imaging network. *Magn Reson Imaging*. 2012;30(9):1323-1341.
26. Williams A, Winalski CS, Chu CR. Early articular cartilage MRI T2 changes after anterior cruciate ligament reconstruction correlate with later changes in T2 and cartilage thickness. *J Orthop Res*. 2017; 35(3):699-706.
27. Winter DA. Kinetics: Forces and moments of force. *Biomechanics and motor control of human movement*. 4th ed. John Wiley & Sons, Inc; 2009:107-138.
28. Fiorentino NM, Kutschke MJ, Atkins PR, Foreman KB, Kapron AL, Anderson AE. Accuracy of functional and predictive methods to calculate the hip joint center in young non-pathologic asymptomatic adults with dual fluoroscopy as a reference standard. *Ann Biomed Eng*. 2016;44(7):2168-2180.
29. Bell AL, Brand RA, Pedersen DR. Prediction of hip joint centre location from external landmarks. *Hum Movement Sci*. 1989;8(1):3-16.
30. Bell AL, Pedersen DR, Brand RA. A comparison of the accuracy of several hip center location prediction methods. *J Biomech*. 1990; 23(6):617-621.
31. Chow JJ, Thom JM, Wewege MA, Ward RE, Parmenter BJ. Accuracy of step count measured by physical activity monitors: the effect of gait speed and anatomical placement site. *Gait Posture*. 2017;57:199-203.
32. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the united states measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181-188.
33. Song J, Semanik P, Sharma L, et al. Assessing physical activity in persons with knee osteoarthritis using accelerometers: data from the osteoarthritis initiative. *Arthritis Care Res (Hoboken)*. 2010; 62(12):1724-1732.
34. Dunlop DD, Song J, Semanik PA, et al. Objective physical activity measurement in the osteoarthritis initiative: are guidelines being met? *Arthritis Rheum*. 2011;63:3372-3382.
35. Wellsandt E, Khandha A, Manal K, Axe MJ, Buchanan TS, Snyder-Mackler L. Predictors of knee joint loading after anterior cruciate ligament reconstruction. *J Orthop Res*. 2017;35(3):651-656.
36. Johnson VL, Roe JP, Salmon LJ, Pinczewski LA, Hunter DJ. Does age influence the risk of incident knee osteoarthritis after a traumatic anterior cruciate ligament injury? *Am J Sports Med*. 2016;44(9): 2399-2405.
37. Poulsen E, Goncalves GH, Bricca A, Roos EM, Thorlund JB, Juhl CB. Knee osteoarthritis risk is increased 4-6 fold after knee injury—a systematic review and meta-analysis. *Br J Sports Med*. 2019;53(23): 1454-1463.
38. Telfer S, Lange MJ, Sudduth ASM. Factors influencing knee adduction moment measurement: a systematic review and meta-regression analysis. *Gait Posture*. 2017;58:333-339.
39. Chan MS, Sigward SM. Loading behaviors do not match loading abilities postanterior cruciate ligament reconstruction. *Med Sci Sports Exerc*. 2019;51(8):1626-1634.
40. Thambyah A, Thiagarajan P, Goh Cho Hong J. Knee joint moments during stair climbing of patients with anterior cruciate ligament deficiency. *Clin Biomech (Bristol, Avon)*. 2004;19(5):489-496.
41. Baum T, Stehling C, Joseph GB, et al. Changes in knee cartilage T2 values over 24 months in subjects with and without risk factors for knee osteoarthritis and their association with focal knee lesions at baseline: Data from the osteoarthritis initiative. *J Magn Reson Imaging*. 2012;35(2):370-378.
42. Joseph GB, McCulloch CE, Nevitt MC, et al. Medial femur T2 Z-scores predict the probability of knee structural worsening over 4-8 years: data from the osteoarthritis initiative. *J Magn Reson Imaging*. 2017;46(4):1128-1136.
43. Joseph GB, Baum T, Alizai H, et al. Baseline mean and heterogeneity of MR cartilage T2 are associated with morphologic degeneration of cartilage, meniscus, and bone marrow over 3 years—data from the osteoarthritis initiative. *Osteoarthritis Cartilage*. 2012;20(7):727-735.
44. Palmieri-Smith RM, Wojtys EM, Potter HG. Early cartilage changes after anterior cruciate ligament injury: evaluation with imaging and serum biomarkers-A pilot study. *Arthroscopy*. 2016;32(7):1309-1318.
45. 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.
46. Pedoia V, Su F, Amano K, et al. Analysis of the articular cartilage T1rho and T2 relaxation times changes after ACL reconstruction in injured and contralateral knees and relationships with bone shape. *J Orthop Res*. 2017;35(3):707-717.
47. Potter HG, Jain SK, Ma Y, Black BR, Fung S, Lyman S. Cartilage injury after acute, isolated anterior cruciate ligament tear: immediate and longitudinal effect with clinical/MRI follow-up. *Am J Sports Med*. 2012;40(2):276-285.
48. Wellsandt E, Gardinier ES, Manal K, Axe MJ, Buchanan TS, Snyder-Mackler L. Decreased knee joint loading associated with early knee osteoarthritis after anterior cruciate ligament injury. *Am J Sports Med*. 2015;44(1):143-151.
49. Hart HF, Culvenor AG, Collins NJ, et al. Knee kinematics and joint moments during gait following anterior cruciate ligament reconstruction: a systematic review and meta-analysis. *Br J Sports Med*. 2016;50(10):597-612.
50. 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.
51. Andriacchi TP, Mundermann 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.
52. 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.
53. Culvenor AG, Perraton L, Guermazi A, et al. Knee kinematics and kinetics are associated with early patellofemoral osteoarthritis following anterior cruciate ligament reconstruction. *Osteoarthritis Cartilage*. 2016;24(9):1548-1553.
54. Lie MM, Risberg MA, Storheim K, Engebretsen L, Oiestad BE. What's the rate of knee osteoarthritis 10 years after anterior cruciate ligament injury? an updated systematic review. *Br J Sports Med*. 2019;53(18):1162-1167.
55. Jayabalan P, Kocherginsky M, Chang AH, et al. Physical activity and worsening of radiographic findings in persons with or at higher risk of knee osteoarthritis. *Arthritis Care Res (Hoboken)*. 2019;71(2):198-206.
56. Souza RB, Baum T, Wu S, et al. Effects of unloading on knee articular cartilage T1rho and T2 magnetic resonance imaging relaxation times: a case series. *J Orthop Sports Phys Ther*. 2012;42(6):511-520.

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