Patellofemoral Contact Forces and Knee Gait Mechanics 3 Months after ACL Reconstruction Are Associated with Cartilage Degradation 24 Months after Surgery

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Patellofemoral Contact Forces and Knee Gait Mechanics 3 Months After ACL Reconstruction Are Associated with Cartilage Degradation 24 Months After Surgery

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Objective
Evaluate patellofemoral cartilage health, as assessed by quantitative magnetic resonance imaging (qMRI) T2 relaxation times, 24-months after ACL reconstruction (ACLR) and determine if they were associated with patellofemoral contact forces and knee mechanics during gait 3 months after surgery.

Design
Thirty individuals completed motion analysis during overground walking at a self-selected speed 3 months after ACLR. An EMG-driven neuromusculoskeletal model was used to determine muscle forces, which were then used in a previously described model to estimate patellofemoral contact forces. Biomechanical variables of interest included peak patellofemoral contact force, peak knee flexion angle and moment, and walking speed. These same participants underwent a sagittal bilateral T2 mapping qMRI scan 24-months after surgery. T2 relaxation times were estimated for both patellar and trochlear cartilage. Paired t-tests were used to compare T2 relaxation times between limbs while Pearson correlations and linear regressions were utilized to assess the association between the biomechanical variables of interest and T2 relaxation times.

Results
Prolonged involved limb trochlear T2 relaxation times (vs uninvolved) were present 24-months after surgery, indicating worse cartilage health. No differences were detected in patellar cartilage. Significant negative associations were present within the involved limb for all the biomechanical variables of interest 3 months after ACLR and trochlear T2 relaxation times at 24-months. No associations were found in patellar cartilage or within the uninvolved limb.

Conclusions
Altered involved limb trochlear cartilage health is present 24-months after ACLR and may be related to patellofemoral loading and other walking gait mechanics 3 months after surgery.

Keywords
ACL Reconstruction; Patellofemoral; Biomechanics; Gait; T2 relaxation time
Introduction
Over 50% of individuals who undergo anterior cruciate ligament reconstruction (ACLR) develop post-traumatic knee osteoarthritis (OA) 10–20 years after surgery\(^1,2\). Many of the individuals who undergo this procedure are young, active, and otherwise healthy; consequently, many develop knee OA and suffer from its adverse consequences early in life\(^1,3\). Investigations regarding the pathogenesis of OA after ACLR have mostly been confined to the medial tibiofemoral compartment of the knee. Recent evidence indicates that patellofemoral OA after ACLR is at least as common as medial tibiofemoral OA and is associated with worse patient reported outcomes\(^4,5,6\). Despite this, few have investigated the mechanisms leading to OA within the patellofemoral compartment of the knee.

Advanced magnetic resonance imaging (MRI) techniques, such as quantitative MRI (qMRI), can monitor OA-related biochemical alterations that occur prior to morphometric alterations to cartilage\(^7\). One of the most commonly used qMRI techniques is T2 relaxation time, which provides insight into the collagen matrix structure of cartilage\(^7,8\). A prolonged T2 relaxation time is indicative of increased water content and collagen matrix degradation, both of which are hallmark signs of early knee OA\(^7,8\). There is limited information on patellofemoral T2 relaxation times after ACLR. In exploratory studies, Kim et al. and Li et al. both found prolonged involved limb femoral trochlear cartilage T2 relaxation times (vs uninvolved limb) 3 years after ACLR\(^9,10\). We previously reported no difference in trochlear cartilage T2 relaxation times between limbs 6 months after ACLR, however this may have been a result of analysis strategy\(^11\). Given the paucity of data, more investigations into patellofemoral T2 relaxation times after ACLR are needed as these could provide insights into cartilage health prior to morphometric alterations when potential rehabilitative interventions may be more viable.

One mechanism thought responsible for OA development after ACLR is alterations in knee gait mechanics. These alterations are frequently observed after surgery and may represent an ideal target for explorative rehabilitative efforts, as gait mechanics may be modifiable\(^12,13,14,15,16\). Commonly reported alterations after ACLR that may influence the patellofemoral compartment include reduced involved limb knee flexion angles and knee flexion moments during gait\(^4,13,14,15,16,17,18\). These alterations are reported as early as 3 months after ACLR and persist past return-to-sport time points\(^13,14,15,16,17,18\). Mechanistically, these alterations may shift the location and magnitude of loading applied to the patellofemoral compartment which, given cartilage’s mechanosensitivity, may disrupt the biochemical and structural health of cartilage\(^19,20\). Previous work from our lab found no association between knee gait biomechanical variables 3 months after ACLR and trochlear cartilage T2 relaxation times 6 months after surgery\(^11\). We did, however, observe a significant negative association between participant walking speed and trochlear cartilage T2 relaxation times, indicating that slower walking speed 3 months after ACLR was associated with prolonged (worse) T2 relaxation times 6 months after surgery\(^11\). Recent evidence suggests that underloading of the involved limb’s patellofemoral compartment, compared to the uninvolved limb, is evident 3 months after surgery\(^21\). However, it is unknown if this underloading and other early gait alterations are associated with long-term signs of OA development within the patellofemoral compartment. Thus, the purpose of this exploratory study was (1) to examine patellofemoral cartilage T2 relaxation times 24-months after ACLR and (2) to investigate the association between knee gait biomechanical variables 3 months after ACLR and 24-month T2 relaxation times. We hypothesized that (1) the involved limb would display prolonged T2 relaxation...
times, compared to the uninvolved limb, in both patellar and trochlear cartilage and (2) that smaller values of the knee gait biomechanical variables of interest at 3 months would be associated with prolonged involved limb patellofemoral T2 relaxation times at 24 months (i.e., that a significant negative association would be present).

Methods

Participants

Thirty participants (Table I) from a larger longitudinal cohort study containing 60 subjects were included in this study. Enrollment criteria for the general study included: primary unilateral ACLR with no history of lower leg injury or surgery, no concomitant grade III ligament tears, no repairable meniscal injuries, no contraindications for MRI, and between 16 and 45 years old. Eligibility criteria specific to this study included: no patellofemoral osteochondral defects, completion of motion analysis 3 months after ACLR, and completion of an MRI 24 months after surgery. Patient reported outcomes, assessed with Knee Injury and Osteoarthritis Outcomes Scores (KOOS), were collected at both 3 and 24 months and are reported in Supplementary Table 1. All data were collected at the University of Delaware following approval from an Institutional Review Board. All participants granted written informed consent with both minor assent and parental consent obtained for individuals under the age of 18. Of the 30 individuals who signed informed consents as part of the larger study but were not included in this study: four did not provide demographic information nor complete gait analysis at the 3-month time point, an additional eight had incomplete gait data at the 3-month time point, two had patellofemoral osteochondral defects, and 16 were lost to follow-up. There were no differences in any variable of interest between those who were and were not included in this study (Supplementary Table 2).

Table I. Demographic characteristics of participants 3 months after ACLR (n = 30)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± standard deviation or number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23 ± 7</td>
</tr>
<tr>
<td>Sex</td>
<td>14 Female (47%), 16 male (53%)</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>77.1 ± 14.9</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.9 ± 3.8</td>
</tr>
<tr>
<td>Graft type</td>
<td>15 BPTB (50%), nine hamstring (30%), six allograft (20%)</td>
</tr>
<tr>
<td>Meniscal status</td>
<td>14 Meniscectomy (46%), 16 none (53%)</td>
</tr>
<tr>
<td>Walking speed (m/s)</td>
<td>1.55 ± 0.14</td>
</tr>
</tbody>
</table>

Motion analysis and musculoskeletal modeling

Participants completed motion analysis during overground walking at a self-selected speed 3 months (3.2 ± 0.6) after ACLR. Prior to walking, surface electromyography (EMG) electrodes (MA-300 EMG System, Motion Lab Systems) were placed over seven muscles of interest on each leg after shaving and cleaning the skin over each muscle belly. Muscles of interest included the rectus femoris, vastus medialis, vastus lateralis, medial and lateral gastrocnemii, semitendinosus, and the long head of the biceps femoris. After placement of the electrodes, participants completed maximal voluntary isometric contractions (MVICs) for each examined muscle group (quadriceps, gastrocnemii, and hamstrings). Retroreflective markers were then placed bilaterally on bony landmarks (first and
fifth metatarsal heads, malleoli, femoral epicondyles, greater trochanters, and iliac crest) and rigid shells with multi-marker groupings were fixed to the pelvis, thighs, and shanks with two additional markers attached to each calcaneus\textsuperscript{16}.

Kinematic data during walking were captured using an eight-camera infrared Vicon system (Oxford Metrics Limited) at a sampling rate of 120 Hz. Kinetic data, recorded using a single embedded force plate (600 × 900 mm\textsuperscript{2}, Bertec Corporation), and EMG data were both sampled at 1080 Hz. Three trials for each leg were used for data analysis\textsuperscript{21,22}. Kinematic and kinetic variables of interest were calculated using inverse dynamics in Visual 3D (C-motion) after low-pass filtering the data at 6 Hz and 25 Hz, respectively. EMG data were high-pass filtered (30 Hz using a second order Butterworth filter), rectified, low-pass filtered (6 Hz), and then normalized to the subject’s MVIC values to create linear envelopes\textsuperscript{24,25}. Linear envelopes of the semimembranosus and the short head of the biceps femoris were set equal to those of the semitendinosus and long head of the biceps femoris, respectively\textsuperscript{24}. The linear envelope of the vastus intermedius was determined by averaging those of the vastus medialis and vastus lateralis\textsuperscript{24}. Following processes outlined in Buchanan et al., linear envelopes were transformed into muscle activations\textsuperscript{25}. These muscle activations, in turn, were used in a validated, subject-specific neuromusculoskeletal model to calculate muscle forces\textsuperscript{24,25}. These muscle forces were input into a previously described model to calculate patellofemoral contact forces\textsuperscript{21}. Briefly, a two-dimensional model of the patellofemoral compartment was scaled to each individual using subject-specific anthropometric data obtained during the motion capture process. This model was then used to estimate the patellofemoral contact force by quadriceps muscle force ratio. The net quadriceps muscle force, found by summing the muscle forces from the vastus medialis, vastus lateralis, rectus femoris, and vastus intermedius, was then multiplied by this ratio to determine patellofemoral contact force.

Variables of interest in this study included: peak patellofemoral contact force (pPCF), peak knee flexion angle (pKFA), external peak knee flexion moment (pKFM), and walking speed in both the involved and uninvolved limbs (Supplementary Table 3). Patellofemoral contact force was normalized by bodyweight (BW) and knee flexion moment was normalized to bodyweight and height (%BW $\times$ HT)\textsuperscript{16}.

Imaging

Twenty-four (24.6 ± 1.4) months after ACLR, these same participants underwent a supine bilateral knee MRI using a 3 T magnet (Siemens) and a 15-channel transmit/receive knee coil (Siemens). During the MRI scan, a sagittal bilateral T2 mapping sequence was performed [Field of View: 150 mm, Slice Thickness: 3 mm, Repetition Time: 3090 ms, Echo Times: 10–70 ms]\textsuperscript{26}.

Images were analyzed in 3D Slicer (https://www.slicer.org/\textsuperscript{27}). T2 maps were calculated using a monoexponential fit to a two-parameter model\textsuperscript{26}. During the calculation of the T2 map the first echo in each sequence was skipped in order to reduce stimulated echo artifacts\textsuperscript{28}. Three slices corresponding to the center of the patellar ridge and three slices corresponding to the center of the femoral trochlear sulcus were used for patellar and trochlear analyses, respectively. For each slice, the entire patellar or trochlear cartilage was initially segmented. Each segmentation was then further subdivided into equal deep and superficial layers to account for structural differences in those layers of cartilage\textsuperscript{7}.

T2 relaxation times were averaged across all three slices to provide an average patellar and trochlear T2 relaxation time within each limb for each subject. Analyses involving T2 relaxation times were done from both the total cartilage perspective and from the deep and superficial layer perspectives.
Statistical analysis

Statistical analyses were performed in JMP (SAS) with statistical significance defined as $\alpha = 0.05$. As this was an exploratory study, no adjustments for multiple comparisons were made\(^{29}\). Normality of the patellar and trochlear $T_2$ relaxation times in both limbs was assessed using a Shapiro–Wilks test. Two-tailed paired $t$-tests (for parametric data) or Wilcoxon Rank Sum tests (for nonparametric data) were used to compare $T_2$ relaxation times between limbs. Cohen’s $D$ was used as a measure of effect size when the difference in $T_2$ relaxation times between limbs was significant (small effect: $d = 0.2$, medium effect: $d = 0.5$, large effect: $d = 0.8$)\(^{30}\). The mean difference between limbs (involved limb value – uninvolved limb value) and 95% confidence intervals (CI) were also assessed. This was done for the entirety of the cartilage of interest as well as for the deep and superficial layers. Pearson correlation and simple linear regression were used to assess the association between each biomechanical variable of interest and the patellar and trochlear $T_2$ relaxation times. The assumptions of linear regression, (1) that the relationship is linear, (2) that the residuals are normally distributed, (3) residual homoscedasticity, and (4) independent observations, were confirmed valid for all tests. Effect sizes of the correlations were assessed using $R^2$ values and were described as small ($R^2 > 0.02$), medium ($R^2 > 0.13$), or large ($R^2 > 0.26$)\(^{30}\). Ninety-five percent confidence intervals for the $R^2$ values were also calculated.

Results

24-month $T_2$ relaxation times

The involved limb displayed significantly prolonged total trochlear cartilage $T_2$ relaxation times, compared to the uninvolved limb, 24-months after surgery ($P = 0.025$, $d = 0.57$, Involved: $49.64 \pm 3.85$ ms, Uninvolved: $47.57 \pm 3.40$ ms, mean difference $[95\% CI] = 2.07$ ms [0.27, 3.87] Fig. 1(A)). When further subdividing trochlear cartilage into deep and superficial layers, it was found that the involved limb displayed significantly prolonged $T_2$ relaxation times compared to the uninvolved limb only in the deep layer ($p_{T,\text{deep}} = 0.005$, $d = 0.69$, Involved$_{T,\text{deep}}$: $47.34 \pm 4.40$ ms, Uninvolved$_{T,\text{deep}}$: $44.40 \pm 4.17$ ms, mean difference $[95\% CI] = 2.94$ ms $[0.98, 4.90]$; $p_{T,\text{superficial}} = 0.245$, Involved$_{T,\text{superficial}}$: $51.76 \pm 4.19$ ms, Uninvolved$_{T,\text{superficial}}$: $50.57 \pm 3.28$ ms, mean difference $[95\% CI] = 1.19$ ms $[-0.85, 3.24]$; Fig. 1(B)). There was no significant difference between limbs in $T_2$ relaxation times within the total patellar cartilage ($P = 0.725$, Involved: $41.67 \pm 3.15$ ms, Uninvolved: $41.66 \pm 3.71$ ms, mean difference $[95\% CI] = 0.01$ ms $[-1.34, 1.36]$; Fig. 1(A)). Further subdividing the patellar cartilage into deep and superficial layers again revealed no significant differences between limbs ($P_{P,\text{deep}} = 0.712$, Involved$_{P,\text{deep}}$: $36.50 \pm 3.77$ ms, Uninvolved$_{P,\text{deep}}$: $36.25 \pm 3.73$ ms, mean difference $[95\% CI] = 0.25$ ms $[-1.13, 1.63]$; $p_{P,\text{superficial}} = 0.505$, Involved$_{P,\text{superficial}}$: $46.91 \pm 3.19$ ms, Uninvolved$_{P,\text{superficial}}$: $47.43 \pm 4.23$ ms, mean difference $[95\%] = -0.52$ ms $[-2.08, 1.04]$; Fig. 1(B)).
3 month gait mechanics vs 24-month T2 relaxation times – involved limb

Significant negative correlations existed between all the biomechanical variables of interest and 24-month involved limb total trochlea cartilage T2 relaxation times (Table II). There was a significant negative association with a large effect size between pPCF at 3 months and trochlear cartilage T2 relaxation times at 24 months (Fig. 2). Similarly, there was a significant negative association with a large effect size between pKFA at 3 months and trochlear cartilage T2 relaxation times at 24-months (Fig. 3). The association between 3-month pKFM and 24-month trochlear cartilage T2 relaxation times was similarly significant and negative but had a medium effect size (Fig. 4). Finally, the association between walking speed and trochlear cartilage T2 relaxation times was significant, was negative, and had a medium effect size (Fig. 5). These associations were mirrored within the deep and superficial layers, where every biomechanical variable of interest had a significant negative association with both deep (Table III) and superficial (Table IV) T2 relaxation times. The only exception to this was walking speed which was not significantly associated with deep layer trochlear T2 relaxation times ($P = 0.097$, Table III). No significant associations were seen between the biomechanical variables of interest and total patellar T2 relaxation times (Table II); however, small effect sizes were observed for the correlations involving pKFA and walking speed. When further subdivided into deep and superficial...
layers there was still no significant association between the biomechanical variables and patellar T₂ relaxation times (Table III, Table IV).

Table II. Involved limb – association between 3-month walking gait mechanics and 24-month total patellar & trochlear cartilage T₂ relaxation times. Significant associations are **bolded**

<table>
<thead>
<tr>
<th>Gait variable</th>
<th>Region</th>
<th>R</th>
<th>Effect size (R²) [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pPCF</td>
<td>Patella</td>
<td>−0.089</td>
<td>0.008 [0.000, 0.155]</td>
<td>0.636</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.549</td>
<td>0.301 [0.052, 0.510]</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>pKFA</td>
<td>Patella</td>
<td>−0.158</td>
<td>0.025 [0.000, 0.200]</td>
<td>0.409</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.550</td>
<td>0.303 [0.053, 0.511]</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>pKFM</td>
<td>Patella</td>
<td>−0.063</td>
<td>0.004 [0.000, 0.128]</td>
<td>0.752</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.470</td>
<td>0.221 [0.016, 0.442]</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Walking speed</td>
<td>Patella</td>
<td>−0.318</td>
<td>0.101 [0.000, 0.317]</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.428</td>
<td>0.183 [0.004, 0.405]</td>
<td><strong>0.019</strong></td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.

Fig. 2. Association between 3-month peak patellofemoral contact force (pPCF) and 24-month total trochlear T₂ relaxation time. The dashed lines and shaded region represent the 95% confidence interval. A prolonged T₂ relaxation time is indicative of collagen matrix degradation. Trochlear cartilage T₂ relaxation time was negatively associated with pPCF, suggesting that smaller patellofemoral loads 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. Note: Y-axis begins at 40 ms rather than 0 ms.
Fig. 3. Association between 3-month peak knee flexion angle (pKFA) and 24-month total trochlear T₂ relaxation time. The dashed lines and shaded region represent the 95% confidence interval. A prolonged T₂ relaxation time is indicative of collagen matrix degradation. Trochlear cartilage T₂ relaxation time was negatively associated with pKFA, suggesting that smaller pKFAs 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. Note: Y-axis begins at 40 ms rather than 0 ms.

Fig. 4. Association between 3-month peak knee flexion moment (pKFM) and 24-month total trochlear T₂ relaxation time. The dashed lines and shaded region represent the 95% confidence interval. A prolonged T₂ relaxation time is indicative of collagen matrix degradation. Trochlear cartilage T₂ relaxation time was negatively associated with pKFM, suggesting that smaller pKFs 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. Note: Y-axis begins at 40 ms rather than 0 ms.
Fig. 5. Association between 3-month walking speed and 24-month total trochlear $T_2$ relaxation time. The dashed lines and shaded region represent the 95% confidence interval. A prolonged $T_2$ relaxation time is indicative of collagen matrix degradation. Trochlear cartilage $T_2$ relaxation time was negatively associated with walking speed, suggesting that slower walking speeds 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. Note: Y-axis begins at 40 ms rather than 0 ms and the X-axis begins at 1.3 m/s rather than 0 m/s.

Table III. Involved limb – association between 3-month walking gait mechanics and 24-month deep patellar & trochlear cartilage $T_2$ relaxation times. Significant associations are bolded

<table>
<thead>
<tr>
<th>Gait variable</th>
<th>Region</th>
<th>R</th>
<th>Effect size ($R^2$) [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pPCF</td>
<td>Patella</td>
<td>−0.052</td>
<td>0.003 [0.000, 0.099]</td>
<td>0.783</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.493</td>
<td>0.243 [0.024, 0.461]</td>
<td>0.006</td>
</tr>
<tr>
<td>pKFA</td>
<td>Patella</td>
<td>−0.110</td>
<td>0.012 [0.000, 0.168]</td>
<td>0.564</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.498</td>
<td>0.248 [0.026, 0.465]</td>
<td>0.005</td>
</tr>
<tr>
<td>pKFM</td>
<td>Patella</td>
<td>−0.061</td>
<td>0.004 [0.000, 0.132]</td>
<td>0.747</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.461</td>
<td>0.213 [0.013, 0.434]</td>
<td>0.010</td>
</tr>
<tr>
<td>Walking speed</td>
<td>Patella</td>
<td>−0.298</td>
<td>0.089 [0.000, 0.302]</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.309</td>
<td>0.095 [0.000, 0.311]</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.

Table IV. Involved limb – Association between 3-month walking gait mechanics and 24-month superficial patellar & trochlear cartilage $T_2$ relaxation times. Significant associations are bolded

<table>
<thead>
<tr>
<th>Gait variable</th>
<th>Region</th>
<th>R</th>
<th>Effect size ($R^2$) [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pPCF</td>
<td>Patella</td>
<td>−0.100</td>
<td>0.010 [0.000, 0.162]</td>
<td>0.598</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.485</td>
<td>0.235 [0.021, 0.454]</td>
<td>0.007</td>
</tr>
<tr>
<td>pKFA</td>
<td>Patella</td>
<td>−0.166</td>
<td>0.028 [0.000, 0.207]</td>
<td>0.380</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.492</td>
<td>0.242 [0.024, 0.460]</td>
<td>0.006</td>
</tr>
<tr>
<td>pKFM</td>
<td>Patella</td>
<td>0.032</td>
<td>0.001 [0.000, 0.040]</td>
<td>0.866</td>
</tr>
<tr>
<td></td>
<td>Trochlea</td>
<td>−0.382</td>
<td>0.146 [0.001, 0.368]</td>
<td>0.037</td>
</tr>
<tr>
<td>Walking speed</td>
<td>Patella</td>
<td>−0.231</td>
<td>0.053 [0.000, 0.252]</td>
<td>0.220</td>
</tr>
</tbody>
</table>
3 month gait mechanics vs 24-month T2 relaxation times – uninvolved limb

There were no significant associations between any biomechanical variable of interest and uninvolved limb total T2 relaxation times, regardless of region of cartilage (Supplementary Table 4). When further subdivided into deep and superficial layers, there was still no significant associations between any of the variables assessed (Supplementary Table 5).

Discussion

The purpose of this study was to examine patellofemoral cartilage health, as assessed by T2 relaxation times, 24-months after ACLR and to determine if these measures of cartilage health were associated with patellofemoral load and other knee gait mechanics 3 months after surgery. We found that individuals displayed prolonged T2 relaxation times in the trochlear cartilage of the involved limb 24-months after surgery, indicating worse cartilage health. We also found that patellofemoral loading and other knee gait mechanics 3 months after surgery were negatively associated with 24-month femoral trochlear cartilage T2 relaxation times. This is one of only a few studies that have examined patellofemoral T2 relaxation times after ACLR9, 10, 11. Additionally, to the best of our knowledge, this is the first study to examine how patellofemoral loading is associated with cartilage degradation after ACLR. Altogether these results add to the growing body of literature surrounding patellofemoral OA after ACLR and provide insight into how potentially modifiable mechanisms for disease development early after surgery are associated with long-term cartilage health.

Our first hypothesis, that the involved limb would display significantly prolonged patellofemoral T2 relaxation times (vs uninvolved) 24 months after ACLR, was partially supported. T2 relaxation times were significantly prolonged within trochlear cartilage but not in patellar cartilage. These results agree with the findings of Kim et al. and Li et al., both of whom observed prolonged T2 relaxation times only within trochlear cartilage 3 years after surgery9, 10. These results also align well with reports that morphometric signs of patellofemoral OA after ACLR originate within trochlear cartilage31. While there were no differences between limbs in patellar cartilage, 23% of individuals displayed involved limb total T2 relaxation times at least 2 ms greater than the uninvolved limb (equivalent to the average difference in trochlear cartilage). This may suggest that at least a subset of these individuals are at risk of long-term patellar cartilage degradation, however future follow up is needed to examine this possibility. When cartilage was further subdivided into deep and superficial layers, a significant difference between limbs was only present within the deep layer of trochlear cartilage. This contradicts the findings of Kim et al. who found significant differences between limbs only in the superficial layers9. The average T2 relaxation times found in this study were also shorter than those found by Kim et al.. This could be due to a variety of reasons including that our sample was younger (23 ± 7 years vs 34 ± 8 years), had an earlier follow up (2 years vs 3 years), had more participants (30 vs 10), utilized different acquisition and processing techniques, and were analyzed using different slices of cartilage9. Comparisons with the magnitudes of Li et al. were not possible as they only reported the interlimb differences in T2 relaxation times10. Overall, the results of this study provide new insights into the timeline of OA development after surgery and align well with reports of increased risk of OA.
development within trochlear cartilage following ACLR. Future work should examine longitudinal changes in patellofemoral T2 relaxation times after ACLR and include longer-term follow-up.

Our second hypothesis, that smaller values of the knee gait biomechanical variables of interest at 3 months would be associated with prolonged involved limb patellofemoral T2 relaxation times at 24 months, was largely supported.

To the best of our knowledge, this is the first study to examine the association between patellofemoral loading, as assessed by patellofemoral contact force, and knee cartilage health after ACLR. While many assume OA development stems from overloading of the joint, there is a growing body of evidence suggesting that underloading may be equally detrimental. Within the medial tibiofemoral compartment, underloading of the involved limb 6 months after ACLR is associated with radiographic osteoarthritis development 5 years after surgery. Limited evidence suggests that underloading of the patellofemoral compartment occurs during everyday tasks, such as walking, and during more dynamic activities such as running and single leg hopping. The results of this study indicate that underloading of the patellofemoral compartment during walking gait 3 months after ACLR is associated with worse trochlear cartilage health 24-months after surgery. This may be explained by the fact that cartilage is a mechanosensitive tissue, with many critical processes within the joint dependent on the loading environment. For example, chondrocytes, which are essential for cartilage matrix synthesis, rely on mechanical stimuli. Without proper loading chondrocyte function could be disrupted leading to alterations in collagen matrix synthesis and consequently degradation. Studies investigating cartilage immobilization in animal models support this notion as immobilization was associated with both structural and biochemical alterations typically seen in the initial stages of OA. Thus, underloading of the patellofemoral compartment after ACLR, as seen here, has the potential to disrupt and degrade the biochemical and structural components of cartilage. It should be noted that this study did not examine the influence of loading history on long-term cartilage degradation. Cumulative load over time may provide important insights into the mechanisms for OA development; thus, future work should examine this potential variable.

Smaller involved limb pKFAs during gait, compared to the uninvolved limb and healthy controls, are commonly reported after ACLR. Our results suggest that smaller involved limb pKFAs 3 months after ACLR are associated with worse trochlear cartilage health 24-months after surgery. In the context of the patellofemoral compartment, alterations in pKFA could shift where load is applied to patellar and trochlear cartilage. Altered load location is hypothesized to be a potential mechanism for OA development as this may load cartilage not capable of sustaining typical day-to-day forces. This, in turn, could result in a repeated relative overloading of patellofemoral cartilage that could lead to cartilage degradation. These results seemingly contradict the findings of AA Williams et al. who found that greater knee flexion angle at heel-strike 2 years after surgery was associated with worse patellofemoral qMRI measures at the same time point. However, given differences in where knee flexion angle was examined in these two studies (pKFA vs KFA at heel-strike), our results may actually be representative of the same phenomenon. Reduced pKFAs and greater knee flexion angles at heel-strike are both likely emblematic of reduced range of motion during gait (i.e., a “stiff-knee” gait), which is commonly reported after ACLR. Thus, their observation at heel-strike
may be in line with our observation at pKFA, suggesting that truncated sagittal plane range of motion during gait is associated with worse trochlear health 2 years after ACLR.

Alterations in knee flexion moment are also commonly reported after ACLR. The results of our study indicate that a smaller pKFM during gait 3 months after ACLR is associated with prolonged trochlear T2 relaxation times 24 months after surgery. This contradicts the findings of AA Williams et al. who found that greater pKFM was associated with qMRI measures of trochlear degradation 2 years after surgery. The disagreement of our results may stem from the differences of when pKFM was observed (3 months vs 24 months). Early reductions in pKFM are common after ACLR and are thought to be adopted as a pain avoidance mechanism. Conversely, evidence indicates that those with existing patellofemoral OA typically display increased pKFM. Thus, greater pKFM at 24 months may be a consequence of, rather than a mechanism for, patellofemoral OA development.

Given reports of MRI defined trochlear OA development as early as 1 year after ACLR, it is possible that Williams et al. were observing OA driven pKFM rather than pKFM driven signs of OA degradation. It should also be noted that some argue that KFMs are reflective of knee extensor muscle forces and thus may be proportional to patellofemoral joint contact forces. This assumption fails to account for neuromuscular phenomena such as knee muscle co-contraction, which is commonly reported after ACLR. This, in turn, has the potential to underestimate quadriceps muscle forces and patellofemoral loading. Nonetheless, reductions in pKFM 3 months after ACLR were associated with worse cartilage health 2 years after surgery, suggesting that pKFM may play an important role in the onset of eventual disease development.

Previous work from our lab found that walking speed 3 months after surgery was the sole biomechanical predictor of trochlear cartilage T2 relaxation times 6 months after surgery. The results of the present study reinforce this finding, as walking speed 3 months after ACLR was significantly associated with trochlear cartilage T2 relaxation times 24-months after surgery. Some believe walking speed is an important measure of function and that, given the relative ease in which it can be measured, it may be an ideal initial target in explorative rehabilitation efforts. While slower walking speed was associated with prolonged T2 relaxation times this does not necessarily mean that having individuals walk with increased speed after ACLR will preserve long-term cartilage health. In fact, increased speed may also be detrimental to cartilage. Numerous studies indicate that faster walking speed after ACLR is associated with increased biomechanical asymmetry between limbs. Asymmetries in knee biomechanics are linked to prolonged tibiofemoral T2 relaxation times after ACLR. While walking speed may represent an easy to measure and modifiable mechanical feature of movement, more work is needed to fully understand its role in OA development after ACLR and its viability as a rehabilitation target.

There are several limitations that need to be considered when interpreting the results of this study. The presence of significant associations between these variables does not necessarily imply cause and effect. Other underlying factors within the knee, such as the inflammatory response after surgery, may be responsible for the mechanics and relaxation times observed. We are not able to determine why patellar cartilage did not exhibit signs of degradation or associations with gait variables. It could be that the thicker patellar cartilage, compared to trochlear, may provide the patella with more protection from post-surgical biomechanical and biochemical alterations. These results align well with prior
work from Culvenor et al. who found that trochlear cartilage was the most affected region after ACLR\textsuperscript{31}. Future work needs to explore these region-specific differences. It is possible that individuals had elevated/altered T\textsubscript{2} relaxation times prior to injury/surgery. Future work should collect pre-surgical T\textsubscript{2} relaxation times as a reference value for later time points to more accurately quantify post-surgical joint health on a subject-by-subject basis. Additionally, patellofemoral cartilage was not divided into medial and lateral subregions. Future work utilizing axial scans of the knee may allow for a more detailed examination of T\textsubscript{2} relaxation times including how they differ between medial and lateral regions of the knee. Given the challenges of three-dimensional modeling of the patellofemoral compartment using traditional motion capture techniques, we are unable to assess potential alterations in patellar tracking and how these could influence load location and magnitude. It is possible, given the reduced knee flexion angles observed, that the patella has minimal-to-no engagement with the trochlear groove, which may support the notion that reduced load could be a mechanism for long-term alterations to cartilage. Characterizing how patellar tracking is altered during day-to-day walking gait after ACLR remains an area of high interest for future work. Additionally, few hip spanning muscles were measured as part of this study. Altered hip muscle function can influence the quadriceps-angle (Q-angle) as well as the positioning of the femur relative to the tibia, both of which can alter patellofemoral contact forces. Future work incorporating more hip-spanning muscles in conjunction with three-dimensional modeling of the patellofemoral compartment may increase the accuracy of the calculated patellofemoral contact forces. Linear regression is susceptible to outliers in data. We assessed the influence of outliers on the associations examined and found that they did not meaningfully change the results, hence they were not removed (See Supplementary Text 1 for further details). It should be noted that no a priori power analysis was performed for this study as these analyses were secondary to those of the primary study from which subjects were taken. Thus, areas where no significant differences were detected may be do so due to inadequate power rather than lack of true statistical difference. Participant surgical and rehabilitation factors, such as graft type, presence of meniscectomy, and rehabilitation approach were not controlled for in this study. While ideal, controlling for these variables across the broader ACLR population is not feasible and thus the results of our study may be more generalizable. We would like to note that participants with meniscal repairs were excluded from this study as this procedure is associated with a prolonged period of non-weight bearing post-surgery that would strongly influence the knee mechanics observed at 3 months. Finally, we did not collect MRI scans designed to assess morphological signs of alterations within the knee. Future work incorporating both semi-quantitative and quantitative approaches to assess knee health could address this limitation.

In conclusion, alterations in involved limb femoral trochlear cartilage T\textsubscript{2} relaxation times are detectable 24-months after ACLR. Patellofemoral loading and other knee mechanics during walking gait 3 months after surgery were strongly associated with these T\textsubscript{2} relaxation times, where smaller loads, smaller knee flexion angles and moments, and slower walking speeds were all associated with worse cartilage health. This suggests that how an individual walks early after ACLR may influence the long-term health of their patellofemoral cartilage. Future studies should explore the viability of these potentially modifiable variables in rehabilitative efforts aimed at preventing long-term post-traumatic knee osteoarthritis.
Author contributions
JRW contributed to research design, data acquisition, analysis, and interpretations, drafting of the manuscript, and incorporation of revisions. KN, AA, JJC, and AK contributed to data acquisition, interpretation, and critical review. KM contributed to data interpretation and critical review. LSM and TSB contributed to research design, funding acquisition, data interpretation, and critical review. All authors have read and approved the manuscript prior to submission. JRW takes full responsibility for the integrity of the work as a whole, from inception to finished article.

Declaration of competing interest
None.

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