Interlimb differences in T1ρ MRI relaxation times linked with symptomatic knee osteoarthritis following anterior cruciate ligament reconstruction

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ABSTRACT

Background: Lower proteoglycan density, as estimated by greater T1ρ magnetic resonance imaging (MRI) relaxation times, may be an indicator of early osteoarthritis development. We examined associations between femoral cartilage inter-limb T1ρ MRI relaxation time ratios and clinically relevant knee symptoms at 12 months following anterior crucial ligament reconstruction (ACLR).
Methods: Twenty-nine individuals completed the Knee Osteoarthritis Outcome Score (KOOS) and underwent MRI 12 months following ACLR for this cross-sectional study. Participants were categorized as symptomatic or asymptomatic for clinically relevant knee symptoms consistent with osteoarthritis based on a standard KOOS classification. T1ρ MRI relaxation times were segmented in the weightbearing regions of lateral and medial femoral condyle (LFC and MFC). Inter-limb T1ρ MRI relaxation time ratios were calculated by normalizing the ACLR to the uninjured knee. T-tests were used to compare LFC and MFC interlimb T1ρ relaxation time ratios between individuals with and without knee symptoms. A Receiver Operating Characteristic (ROC) Curve analysis was used to determine a critical inter-limb T1ρ relaxation time ratio identifying symptomatic patients. Odds ratios (OR) and 95% confidence intervals (CI) estimated the association between the critical value and clinically relevant knee symptoms.
Results: Symptomatic individuals had significantly higher LFC inter-limb T1ρ MRI relaxation time ratios compared to asymptomatic individuals ($p = 0.04$). Individuals with an LFC inter-limb T1ρ MRI relaxation time ratio >1.11 were more likely to have symptoms (OR 8.5; 95% CI = 1.25–57.93).
Conclusion: Individuals with greater inter-limb LFC T1ρ MRI relaxation time ratios 12 months post-ACLR may be more likely to exhibit symptoms consistent with knee OA.

1. Introduction

Individuals who sustain anterior cruciate ligament (ACL) injuries often develop persistent long-term disability [1] and post-traumatic osteoarthritis (OA) [2] despite undergoing surgical reconstruction (ACLR). Approximately 36% of individuals

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with an ACL injury exhibit radiographic knee OA within 10 years of ACLR [2]. Given that ACL injuries typically occur in adolescent or young adults, many individuals may present with radiographic OA in their 30s when they are still engaging in higher level physical activity [3]. Therefore, it is important to identify individuals who demonstrate early markers of joint disease following ACLR, including imaging features, knee symptoms, and knee-related disability consistent with OA because they likely to have the greatest need for effective prevention strategies.

One barrier to effective OA prevention is identifying early joint tissue changes at time points when damage is still reversible. Articular cartilage compositional changes especially in the femur, including decreased proteoglycan density, may precede traditional radiographic changes [4]. Magnetic resonance imaging (MRI) T1ρ relaxation times associate with proteoglycan density in animal and human cartilage tissue, where greater T1ρ relaxation times reflect lesser proteoglycan density [2,5,6]. Inter-limb T1ρ MRI relaxation time ratios have been used as a within-patient estimate of the relative proteoglycan density loss in the ACLR limb compared to the normal proteoglycan density in the uninjured limb [7]. Unfortunately, the magnitude of change in T1ρ MRI relaxation time ratios that may indicate the development of OA remains unknown.

Greater lateral femoral inter-limb T1ρ MRI relaxation time ratios, indicative of less proteoglycan density in the ACLR limb, are associated with clinically relevant knee symptoms consistent with OA [7]. These symptoms can be quantified using the Knee Osteoarthritis Outcome Score (KOOS), which subjectively evaluates knee symptoms using five subscales: pain, symptoms, functions of daily life, function in sport and recreation, and quality of life [8]. Englund and colleagues validated a framework to classify individuals as presenting with clinically relevant knee related symptoms of OA [9] which has been applied to individuals with a history of ACLR by the Multicenter Orthopaedic Outcomes Network (MOON) [10].

Both articular cartilage changes and clinically relevant knee symptoms develop within 12 months of ACLR. Increases in T1ρ MRI relaxation times preoperatively to 12 months post-ACLR [11,12] suggest articular cartilage compositional changes occur within the 12 months post-ACLR. Similarly, 42% of individuals present with clinically relevant knee symptoms consistent with OA development as early as 6 months following ACLR [13]. Yet, it remains unknown if there is an inter-limb T1ρ MRI relaxation time ratio threshold that would identify patients with clinically relevant knee symptoms 12 months after ACLR; thereby, providing important evidence regarding the magnitude of change in inter-limb T1ρ MRI relaxation time ratios that would associate with meaningful changes in knee joint health. An inter-limb T1ρ MRI relaxation time ratio threshold could allow for identification of early deleterious tissue changes and provide targets for future clinical trials.

Therefore, the purpose of this study is to determine the ability of inter-limb T1ρ MRI relaxation time ratios to identify patients with clinically relevant knee related symptoms 12 months following ACLR. We hypothesize that individuals with clinically relevant knee symptoms will have higher inter-limb T1ρ MRI relaxation time ratios (i.e., lesser proteoglycan density in the ACLR limb compared to the uninjured limb).

2. Materials and methods

This cross-sectional study was part of a larger longitudinal cohort study evaluating outcomes in individuals with ACL injuries at different time points post-ACLR (Level of Evidence: Level III). For the parent study, comprehensive demographic, clinical, MRI, biomechanical, and biomarker data were collected during research visits preoperatively, 6 months, and 12 months post-ACLR. In the current study, we utilized the 12-month follow up data for inter-limb T1ρ relaxation time ratios and KOOS scores to characterize patients with clinically relevant knee symptoms related to OA. The methods used in this study were approved by the Institutional Review Board at the University of North Carolina at Chapel Hill and all participants provided written informed consent prior to participating.

2.1. Participants

All participants were recruited between January 2014 and May 2016. Individuals between the ages of 16 and 35 years old that sustained an ACL injury within a preceding 14-day period were recruited into the study upon initial presentation to one of three sports medicine fellowship trained orthopaedic surgeons. Participants were excluded if they had a previous history of ACLR on the contralateral limb, a previous diagnosis of inflammatory arthritis or any joint disease, were pregnant or planned to become pregnant within the next 12 months or did not plan to undergo ACLR. Participants with a prior history of ACL injury or multi-ligament damage were also excluded. Participants with a cardiac pacemaker, cochlear implant, clinical hypertension, claustrophobia, hepatic disease, diabetes, or seizures were also excluded. Individuals with meniscal or chondral injuries were included in the study but were excluded if they had a lower extremity fracture or greater than one-third of their meniscus was removed during surgery (Figure 1).

2.2. MRI acquisition of tibiofemoral articular cartilage composition

T1ρ MRI was acquired using either a Siemens Magnetom TIM Trio 3-T scanner using a 4-channel Siemens large flex coil (516 × 224 mm; Siemens, Munich, Germany;) or a Siemens Magnetom Prisma 3-T PowerPack scanner with a XR 80/200 gradient coil (60 × 213 cm; Siemens). Inter-scanner reliability has previously been assessed using intra-class correlations (ICC), which was found to be within an acceptable range for the medial ($ICC_{2,1}$ = 0.99) and lateral ($ICC_{2,1}$ = 0.96) weight-bearing regions of the femoral condyle. Coefficient of variation values between scanners range from 1.46% to 5.02% according to

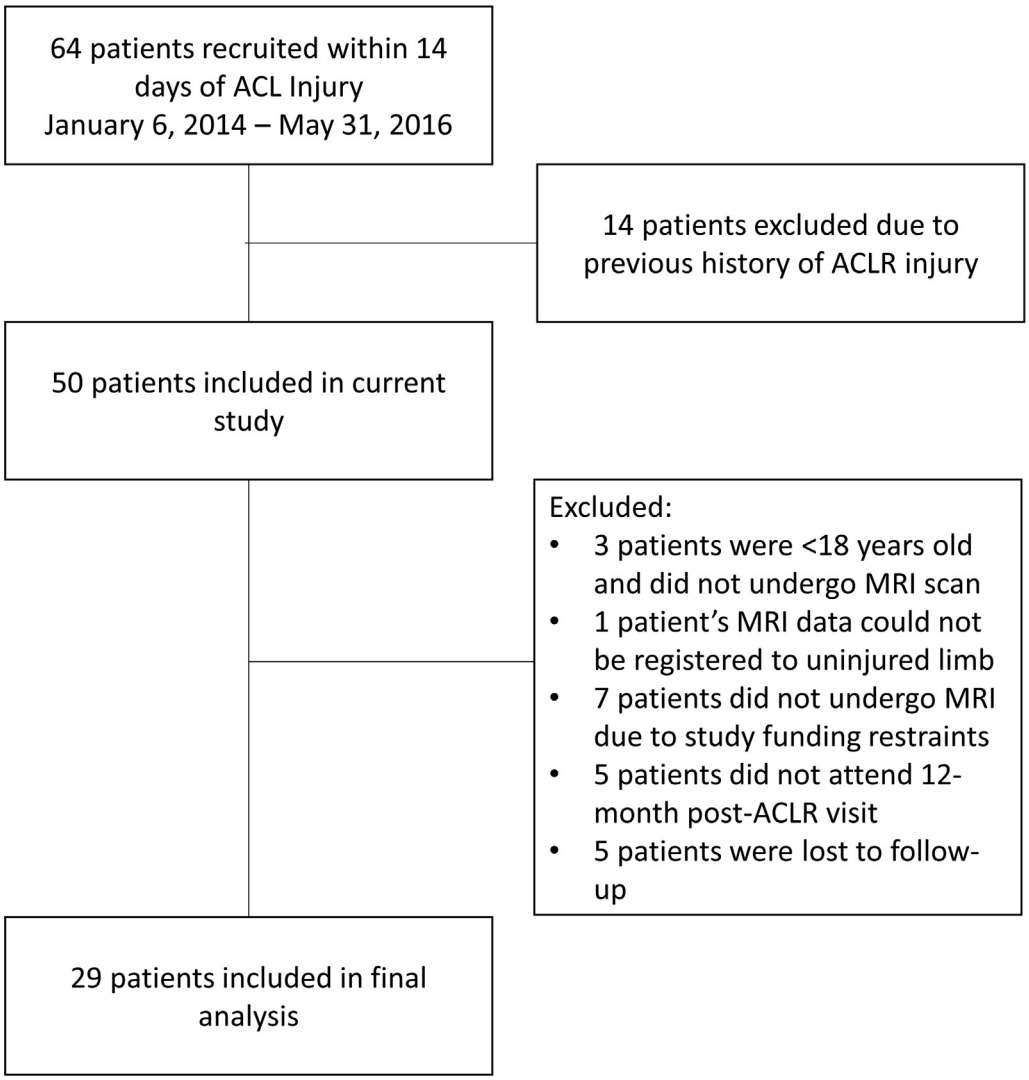

Figure 1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Flowchart of individuals included in the original prospective, longitudinal cohort study and reasons for exclusion from the current analysis.

Pfeiffer and colleagues [14] which were similar to Li and colleagues [15], who reported coefficient of variation values ranging from 3.0% to 6.4% in similar regions of interest. Upon arrival to the imaging center, participants remained seated for 30 minutes to unload their knees in an extended position [14]. We used a T1ρ prepared three-dimensional fast low-angle shot with a spin-lock power at 500 Hz, five different spin-lock durations (40, 30, 20, 10, and 0 ms) and a voxel size of 0.8 × 0.4 × 3 mm (field of view, 288 mm; slice thickness, 3.0 mm; repetition time, 9.2 ms; echo time, 4.6 ms; averaging, 1; bandwidth, 350 Hz; acquisition time range, 700–900 s (depending on the number of slices); range of number of slices acquired, 28–36 slices; 160 × 320 matrix; gap, 0 mm; flip angle, 10°; echo-train duration time, 443 ms; phase encode direction of anterior/ posterior). Prior to segmentation, ACLR limb images were registered to the uninjured limb image using 3-D Slicer software [16]. The registration process included a manual affine registration as well as a nonrigid deformable, voxel-by-voxel intensity-based registration technique which were applied to account for specific interlimb differences of specific tissues (e.g., bone and cartilage) [14].

2.3. Tibiofemoral articular cartilage segmentation

Articular cartilage in the medial (MFC) and lateral femoral (LFC) condyles was manually segmented by trained investigators using ITK-SNAP software from images collected from the 0-ms spin-lock duration. Our laboratory has previously established excellent intra- (ICC = 0.80–0.97) and inter-segmentor reliability (ICC = 0.75–0.98) for manual segmentation of femoral cartilage [7]. Anatomical accuracy of the segmentations was confirmed by a fellowship trained radiologist.

Weightbearing tibiofemoral regions of interest, used for analysis, were defined in the sagittal plane as articular cartilage residing between the posterior edge of the posterior horn of the meniscus and the anterior edge of the anterior horn of the meniscus, as previously described [7]. These regions were used to calculate mean inter-limb T1ρ MRI relaxation times for the LFC and MFC global weightbearing regions in both the injured and uninjured limbs. The lateral femoral condyle weightbearing region was subsequently broken down into its anterior, central, and posterior subregions [17]. T1ρ MRI relaxation time values for injured limbs were normalized to the T1ρ relaxation time values of the non-injured limb by dividing the injured limb value by the uninjured limb value for each region to account for normal variation in articular cartilage proteoglycan density between participants [18].

2.4. Patient reported outcomes

Participants were evaluated for clinically relevant knee symptoms using the KOOS, which includes five subscales: pain, symptoms, functions of daily life (ADL), function in sport and recreation (sports/rec), and quality of life. Participants rated their knee function on each subscale on a 5-point Likert scale, which is then transformed to a 0–100 scale (lower values indicate worse knee function and symptoms). These subscales were used to classify individuals as symptomatic or asymptomatic for clinically relevant knee symptoms based on a classification created by Englund and colleagues [9] and applied to individuals with a history of ACLR by the Multicenter Orthopedic Outcome Network (MOON) [10]. Individuals were classified as having clinically relevant knee symptoms if Quality of Life score <87.5, and two or more of pain <86.1, symptoms <85.7, ADL <86.8, sports/rec <85.8.

2.5. Statistical analysis

Descriptive statistics (means, standard deviations, and frequencies) were calculated for participant characteristics and inter-limb T1ρ MRI relaxation time ratios. Assumptions of normality and equal variance were analyzed using the Shapiro-Wilk tests and the Levene tests for Equality of Variances. Independent t-tests were used to compare inter-limb T1ρ MRI relaxation time ratios between individuals with and without clinically relevant knee symptoms. An ROC analysis was used to determine whether a critical inter-limb T1ρ MRI relaxation time ratio indicates clinically relevant knee symptoms. Inter-limb T1ρ MRI relaxation time ratios that maximized the combination of sensitivity and specificity for clinically relevant knee symptoms were identified as critical points. Participants were then either classified as having inter-limb T1ρ relaxation time ratios as greater or less than the critical point. Unadjusted logistic regression models were used to estimate odds ratios and 95% confidence intervals for the association between clinically relevant knee symptoms and inter-limb T1ρ MRI relaxation ratios.

2.6. Post hoc analysis

If differences in inter-limb T1ρ relaxation ratios were identified in the LFC or MFC global weightbearing cartilage regions between individuals with and without clinically relevant knee symptoms, then the global weightbearing region was separated into its anterior, central, and posterior subregions to identify which subregion(s) most strongly associated with these symptoms using odds ratios and 95% confidence intervals.

3. Results

A total of 7 and 22 participants were classified as symptomatic and asymptomatic for clinically relevant knee symptoms, respectively. All inter-limb T1ρ MRI relaxation time ratio outcomes were normally distributed and demonstrated equal variance between symptomatic and asymptomatic groups. No participants with clinically relevant knee symptoms had a chondral injury while 57.14% of participants without clinically relevant knee symptoms had a chondral injury ($p = 0.01$). There were no other statistically significant differences (p *range = 0.32–1.00*) in participant characteristics between those with and without clinically relevant knee symptoms (Table 1).

3.1. Comparison of T1ρ relaxation time ratios between individuals with and without clinically relevant symptoms

Individuals with clinically relevant knee symptoms demonstrated higher inter-limb T1ρ MRI relaxation time ratios than individuals without clinically relevant knee symptoms in the LFC global weightbearing region ($p = 0.04$) but there were no differences in the MFC global weightbearing region (Table 2).

3.2. Association of T1ρ relaxation time ratios with clinically relevant knee symptoms

LFC inter-limb T1ρ MRI relaxation time ratios also identified whether an individual had clinically relevant knee symptoms based on the ROC analysis (Table 3; AUC = .75, $p = 0.047$). An LFC inter-limb T1ρ MRI relaxation time ratio of >1.11 was identified as the critical value that maximized the sensitivity (85.7%) and specificity (68.2%) for identifying those with

Table 1
Participant Characteristics at 12 months Post-ACLR (Mean ± Standard Deviation).

Participant Characteristics	Total Sample (N = 29)	Asymptomatic (N = 22)	Symptomatic (N = 7)	*p*-value†
Age (years)	21.86 (3.87)	22.27 (4.23)	20.57 (2.15)	0.32
Sex (% Female)	48.28%	50.00%	42.86%	1.00
BMI (kg/m^2)	24.00 (2.53)	24.25 (2.51)	23.24 (2.82)	0.38
Meniscal injury (%)	78.57%	76.19%	85.71%	1.00
Chondral Injury (%)	42.86%	57.14%	0.00%	0.01*

* indicates statistical significance (p = 0.05), †indicates p-values for comparisons between asymptomatic and symptomatic participants; Abbreviations: BMI = body mass index.

Table 2
Comparison of Medial and Lateral Femoral Cartilage Inter-limb T1ρ Relaxation Time Ratios between Asymptomatic and Symptomatic Participants (Mean ± Standard Deviation).

Cartilage Region	Asymptomatic	Symptomatic	*p*-value†
Lateral Femoral Condyle Global Weight Bearing Region	1.086 ± .081	1.161 ± .080	0.040*
Medial Femoral Condyle Global Weight Bearing Region	1.271 ± .102	1.341 ± .106	0.126

* indicates statistical significance (p = 0.05); †indicates p-values for comparisons between asymptomatic and symptomatic participants.

clinically relevant knee symptoms. Individuals with LFC inter-limb T1ρ MRI relaxation time ratios greater than the critical value were 8.5 times more likely to demonstrate clinically relevant knee related symptoms (95%CI: 1.25–57.93).

3.3. Post-hoc analysis

When analyzing the LFC weightbearing subregions, individuals with clinically relevant knee symptoms had statistically significant higher inter-limb T1ρ MRI relaxation time ratios only anteriorly (Table 4). Furthermore, only anterior LFC inter-limb T1ρ relaxation time ratios identified whether individuals were symptomatic (AUC = 0.84, p = 0.007) (Table 5). Individuals with anterior LFC inter-limb T1ρ relaxation time ratios >1.23 were 25 times more likely to have clinically relevant knee symptoms (95% CI: 2.79–223.67) with a sensitivity of 71.4% and specificity of 90.9% (Table 5).

4. Discussion

The most important findings of the present study are that inter-limb T1ρ MRI relaxation time ratios were associated with clinically relevant knee symptoms consistent with OA in individuals 12 months post-ACLR and critical threshold values for inter-limb T1ρ MRI relaxation time ratios are capable of identify individuals with and without clinically relevant knee symptoms. Our findings are significant as critical threshold values for inter-limb T1ρ MRI relaxation time ratios provide evidence for the magnitude of inter-limb differences in T1ρ MRI that are clinically relevant and may be indicative of early OA development. Future studies may use these thresholds to identify patients at greatest risk for OA development and for inclusion of high-risk patients into clinical trials.

Individuals with clinically relevant knee symptoms (based on the Englund classification [9]) had higher LFC global weightbearing region inter-limb T1ρ MRI relaxation time ratios compared individuals without clinically relevant knee symptoms, (Table 2), and post-hoc analysis showed this association was even stronger in the anterior lateral region (p = 0.001; Table 4). Our novel finding was the identification of an LFC global weightbearing region critical inter-limb T1ρ MRI relaxation time ratio (1.12) associated with an 8.5-fold increased likelihood of demonstrating clinically relevant knee symptoms. Post hoc analysis narrowed and strengthened the association by showing an individual with an anterior LFC inter-limb T1ρ relaxation time ratio >1.23, has a 25x greater likelihood of demonstrating clinically relevant knee symptoms. This anterior LFC critical value identified clinically relevant knee symptoms consistent with early OA with equal sensitivity

Table 3
Lateral and Medical Femoral Cartilage Receiver Operating Characteristic Curve Analysis to Identify Critical Threshold Inter-limb T1ρ Relaxation Time Ratios.

Cartilage Region	Area Under Curve	*p*-value	Critical Threshold for Inter-Limb T1ρ Relaxation Ratio (Sensitivity, Specificity)
Lateral Femoral Condyle Global Weight Bearing Region	0.753*	0.047	1.118 (0.714, 0.773)
Medial Femoral Condyle Global Weight Bearing Region	0.708	0.103	1.3939 (0.571, 0.864)

* indicates statistical significance (p = 0.05).

Table 4
Comparison of Lateral Femoral Condyle Subregions Cartilage Inter-limb T1ρ Relaxation Time Ratios between Asymptomatic and Symptomatic Participants (Mean ± Standard Deviation).

Lateral Femoral Cartilage Subregion	Asymptomatic	Symptomatic	*p*-value†
Medial	1.056 ± .131	1.144 ± .139	0.139
Central	1.110 ± .116	1.165 ± .106	0.271
Anterior	1.274 ± .108	1.344 ± .086	0.001*

* indicates statistical significance (p = 0.05); †indicates p-values for comparisons between asymptomatic and symptomatic participants.

Table 5
Lateral Femoral Condyle Sub-Region Receiver Operating Character Curve Analysis to Identify Critical Inter-limb T1ρ Relaxation Time Ratios.

Lateral Femoral Cartilage Subregion	Area Under Curve	*p*-value	Predictive Inter-limb T1ρ Relaxation Ratio (Sensitivity, Specificity)
Medial	0.675	0.169	1.074 (0.714, 0.636)
Central	0.643	0.262	1.164 (0.571, 0.773)
Anterior	0.844	0.007*	1.234 (0.714, 0.909)

* indicates statistical significance (P = 0.05).

(71.4%) and higher specificity (90.9%) compared to that of the entire LFC global weightbearing region (specificity = 77.3%). There were no differences between those with and without clinically relevant knee symptoms in the medial femoral condyle.

The cause of the lesser proteoglycan density in the anterolateral femoral region is not clear but we hypothesize that femoral bone bruising at the time of injury may play a role in the localized proteoglycan deficits in the anterolateral femoral region [19]. Additionally, it may be due to increased inflammatory signals, as both MCP-1 (a chemokine associated with OA pathogenesis) and COMP (an articular cartilage extracellular matrix protein associated with articular cartilage degeneration) have been shown to rise with LFC, but not MFC, articular cartilage degeneration following ACLR [17]. The LFC proteoglycan changes demonstrated here reflect previous work by Pietrosimone and colleagues [7] who found that LFC articular cartilage degeneration correlated with KOOS symptoms one year following ACLR, Lisee and colleagues [17] who found increased LFC T1ρ relaxation times 12 months after ACLR in patients with increased MCP-1 and COMP, and Su [20] who found that articular cartilage degeneration occurs laterally 2 years following ACL injury.

Our study is the first to identify an inter-limb T1ρ relaxation time ratio threshold that corresponds to clinically relevant knee symptoms related to OA development. Critical values provide an objective datapoint to clinically identify high risk individuals with early reversible cartilage changes who may develop symptomatic knee OA. While there is currently no cure or preventative treatment for post-traumatic OA, identifying these individuals before irreversible changes occur would allow them to focus on modifiable risk factors. Known OA risk factors include weak quadriceps muscles [21], obesity, high-impact sports, and high occupational loading [22]. Therefore, individuals with increased inter-limb T1ρ MRI relaxation time ratios may benefit from quadriceps strengthening, weight loss and activity modification to modify the rate of disease progression.

These critical values could aid in the selection of patients for disease modifying OA interventions. OA is a heterogeneous disease with varying pathophysiology including cartilage, bone, and inflammatory phenotypes, all of which may be modified by distinct pharmacotherapies [23]. Therefore, clinical trial participants may be more effectively selected based on phenotype. Increased inter-limb T1ρ MRI relaxation time ratios reflect articular cartilage proteoglycan density changes [5] and therefore critical ratios may identify individuals at risk for OA due to cartilaginous changes. Hence, our findings may be applied to identify participants best suited to study the effects of disease modifying osteoarthritis drugs that target articular cartilage degradation such as MMP inhibitors [23].

Due to the cross-sectional study design, our findings cannot demonstrate a causative link between cartilage composition and knee symptoms. Additionally, the lack of preoperative imaging prevents the evaluation of how the cartilage composition changed over time. It is also possible that some individuals may have different proteoglycan densities than others. We minimized this potential inter-subject difference by calculating the inter-limb T1ρ relaxation time ratios with the uninjured limb serving as a control. We also evaluated associations between inter-limb T1ρ MRI relaxation time ratios and outcomes related to symptomatic OA, but future studies need to determine if inter-limb T1ρ MRI relaxation time ratios associate with disease related OA outcomes (e.g., radiographic changes). Furthermore, the current study included a modest sample size that was powered to detect a large effect (d = 1.7, power = 0.80, alpha = 0.05) for differences in inter-limb T1ρ relaxation time ratios between the asymptomatic and symptomatic groups. A study with a larger sample size is warranted to further investigate whether MFC inter-limb T1ρ relaxation time ratios may also identify the development of post-traumatic OA, as our results suggested a relationship in that direction.

5. Conclusion

This study provides evidence that decreased proteoglycan density in the ACLR knee based on T1ρ MRI is associated with clinically relevant knee symptoms consistent with OA 12 months following ACLR. Longitudinal analysis is necessary to

identify whether T1ρ MRI can predict post-traumatic OA following ACLR, but our research suggests that individuals with increased LFC inter-limb T1ρ MRI relaxation time ratios 12 months following ACLR may require close follow-up and examination. Furthermore, these individuals may represent an ideal clinical trial population to research the efficacy of different interventions to slow or prevent cartilage breakdown and OA onset following ACL injury.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Level of Evidence: Level III.

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