Knee cartilage transverse relaxation time (T2) in patients with anterior cruciate ligament injury treated conservatively with structured physical rehabilitation or standard of care

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INTRODUCTION: Magnetic resonance imaging (MRI) can be used to assess alterations in articular cartilage morphology (e.g., thickness) and composition (e.g., transverse relaxation time (T2)) implicated in osteoarthritis. Compositional cartilage changes after anterior cruciate ligament (ACL) rupture can potentially precede and even predict morphological changes, stressing their importance in the evaluation of early knee osteoarthritis. T2 is believed to reflect collagen integrity, orientation and hydration, and mechanical cartilage properties. ACL injuries can be treated surgically (e.g., ACL repair) or conservatively (e.g., physical rehabilitation), with both approaches yielding comparable clinical, functional and patient-reported outcomes longitudinally. Neuromuscular training can help restore muscular function by improving strength, dynamic stability, postural awareness, and muscular coordination, potentially reducing the risk of developing post-traumatic osteoarthritis. Yet, studies on the effects of different conservative treatment strategies on knee cartilage T2 after ACL rupture are lacking. This study aimed to examine the effects of a structured physical rehabilitation program on knee cartilage T2 in ACL rupture patients.

METHODS: This study was approved by the institution's research ethics board (# EA1/020/16) and participants provided written informed consent. ACL rupture patients and healthy control participants were studied. Patients were included in this analysis if they sustained a unilateral ACL rupture within 14 months of enrollment and sought conservative management for their injury. Exclusion criteria were previous knee injury/surgery, a pre-injury score of 0-2/10 (very low activity) or 10/10 (professional athlete) on the Tegner Activity Scale, and a body mass index (BMI) ≥35 kg/m^2. Upon enrollment, ACL injury patients were allocated to one of two groups based on their performance on the following clinical and physical performance criteria: ≥1 episode of giving way in the last 6 months; < 85/100 points on the Lysholm Knee Score; and a limb symmetry index <85% for a single leg jump for distance. Patients who tested positive for at least two of the three criteria were deemed to have reduced knee function and symptomatic instability, and thus were assigned to the physical training group [+TRAINING: n=11; 9 women; age of 45.2 ± 8.7 years; BMI of 24.8 ± 3.6 kg/m^2; time between baseline and follow-up of 12.4 ± 0.4 months; time between injury and baseline of 5.5 ± 3.6 months]. Patients who tested positive for one or none of the three criteria were considered to have adequate knee function and dynamic stability, and thus were assigned to the standard of care group [-TRAINING: n=13; 5 women; age of 35.5 ± 8.5 years; BMI of 24.7 ± 2.2 kg/m^2; time between baseline and follow-up of 12.4 ± 0.7 months; time between injury and baseline of 5.7 ± 2.9 months]. Furthermore, healthy control participants without past lower-limb injury/surgery or known lower-limb musculoskeletal conditions were used as a reference group [CONTROL: n=14; 10 women; age of 42.6 ± 9.2 years; BMI of 24.9 ± 2.9 kg/m^2; time between baseline and follow-up of 12.2 ± 0.4 months]. After baseline assessment, the +TRAINING group completed a 24-session supervised, structured, physical training program over roughly 12 weeks. The training program comprised progressive lower-limb strengthening and neuromuscular re-education exercises with the aim of restoring knee muscular strength and neuromuscular control. The -TRAINING group received routine clinical care and managed their injury conservatively as recommended by their healthcare provider. At baseline and ~1-year follow-up, sagittal multi echo spin echo (MESE) images were acquired (1.5 T, Avanto, Siemens; 3.5 mm slice spacing; 0.31 mm in-plane resolution). The weight-bearing tibiofemoral cartilage plates were manually segmented by experienced readers, and quality assurance done by an expert. Superficial and deep tibiofemoral cartilage T2 (50% each) were extracted from the segmentations for the medial tibia, lateral tibia, medial femur and lateral femur, resulting in eight quantitative cartilage measures. Repeated measures analyses of covariance were used to test the effects of treatment (+TRAINING, -TRAINING, CONTROL), time (baseline, 1-year) and treatment*time interaction across cartilage T2 outcomes, after adjusting for baseline age and sex. Ultimately, no treatment*time interaction was significant; thus, these were removed from the models. Paired t-tests were used to examine pairwise comparisons when main effects were significant. Normality and sphericity were confirmed, and outliers scrutinized. No outliers were deemed to critically distort the results, thus, all observations were analyzed. Statistical significance was set at α=0.05 (without adjusting for multiplicity).

RESULTS: Groups were not different in terms of sex (p=0.066), BMI (p=0.987), time between baseline and follow-up (p=0.518), and time between injury and baseline (+TRAINING vs. -TRAINING only, p=0.854); however, the +TRAINING group was older than the -TRAINING group (p=0.031). No significant treatment (group) effects were noted for any of the cartilage T2 outcomes (p>0.05). Conversely, significant main effects of time were noted for the lateral tibia superficial T2 (p=0.039); lateral femur deep T2 (p=0.005); and lateral femur superficial T2 (p=0.017). Post hoc analyses revealed that T2 increased over 1 year in the superficial cartilage layer of the lateral tibia in the -TRAINING group (p=0.028). Moreover, T2 increased over 1 year in both the deep and superficial cartilage layers of the lateral femur in the CONTROL group (p=0.017 and p=0.009, respectively) (Table 1).

DISCUSSION: This work assessed between-group (at baseline and 1-year follow-up) and within-group (1-year change) differences in layer-specific knee cartilage T2 in (1) ACL injury patients treated conservatively with structured physical rehabilitation, (2) ACL injury patients treated conservatively with standard of care, and (3) healthy (non-ACL-deficient) controls. No differences in deep and superficial cartilage T2 were noted between groups at baseline and follow-up, suggesting that the initial group differences in clinical, functional and knee stability status had little-to-no impact on cartilage T2. Conversely, T2 increased over 1 year in the superficial cartilage layer of the lateral tibia in the -TRAINING group. This finding may reflect early signs of cartilage degeneration, preceding cartilage matrix loss. However, this borderline significant finding should be interpreted cautiously as no statistical adjustment was made for multiplicity. Further, the findings of increased T2 over 1 year in both the deep and superficial cartilage layers of the lateral femur in the CONTROL group are not easily interpretable, and may simply be the result of multiple comparisons and/or a small sample size. Further limitations of this study include unknown knee osteoarthritis status and a heterogeneous age range (up to 56 years old). In conclusion, ACL rupture patients treated conservatively with standard clinical care displayed an increase in T2 over 1 year in the superficial cartilage layer of the lateral tibia. Further studies comparing the influence of different ACL injury management strategies on knee tissue integrity are needed to improve our understanding of post-traumatic, degenerative joint changes.

SIGNIFICANCE: Knee function/dynamic stability status after ACL rupture seemingly has little-to-no impact on knee cartilage T2. The conservative management approach used after ACL rupture may influence knee cartilage composition in the initial 1-2 years after injury: patients treated with standard of care displayed increased T2 in the superficial cartilage layer of the lateral tibia, while patients treated with neuromuscular training showed no changes in T2.

Table 1. Summary of statistically significant findings. Values (ms) are mean ± SD. An asterisk indicates an increase between baseline & follow-up (p<0.05).

	+TRAINING		-TRAINING		CONTROL	
Cartilage Outcome	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
Lateral tibia superficial T2	49.7 ± 2.9	49.8 ± 2.1	49.6 ± 2.4	**50.4 ± 2.5***	50.3 ± 2.2	50.9 ± 2.2
Lateral femur deep T2	43.3 ± 2.7	43.8 ± 2.6	43.9 ± 3.2	44.9 ± 2.8	42.4 ± 1.9	**44.0 ± 2.4***
Lateral femur superficial T2	52.5 ± 2.6	52.6 ± 3.0	53.5 ± 3.9	54.0 ± 3.6	52.9 ± 2.5	**54.0 ± 2.1***