Increased Frequency of Running, Cutting, Deceleration and Pivoting Activities Associates with OA-like Changes to Femoral Bone Shape Following ACLR

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INTRODUCTION: Return to high demand sports and activities is a priority for many anterior cruciate ligament reconstruction (ACLR) patients. However, participation in intense physical activities that involve running, cutting, deceleration and pivoting within 3 years of ACLR has previously been linked to increased cartilage degeneration, and thus increased risk of knee osteoarthritis (OA).[1] While bone shape changes including flattening and spreading of weight-bearing surfaces and development of osteophytes at the joint periphery are hallmark features of osteoarthritis (OA),[2-4] similar albeit more mild bone shape changes have also been observed following ACLR.[5-7] The degree to which intense physical activity may influence bone shape changes following ACLR has not been widely examined. This study seeks to determine if and how intense physical activity in the first 2 years after ACLR impacts bone shape change. We hypothesize that patients who engage in more intense physical activity after ACLR will show more OA-like bone shapes 2 years following ACLR.

METHODS: Thirty-eight participants with unilateral ACL tear and reconstruction within 3 months of injury (17 females; mean[95%CI] age: 27.5 [25.3, 29.7] years; BMI: 25.3 [23.8, 26.8] kg/m^2; time to surgery 41 [36, 47] days) and 10 uninjured volunteers (7 females; age: 27.7 [25.5, 29.9] years; BMI: 24.6 [21.6, 27.5] kg/m^2) consented to participate in this IRB-approved study. "Six" weeks (7.4[6.2, 8.5] weeks), 1 year (11.9[11.1, 12.6] months) and again 2 years (23.0 [22.0, 24.0] months) after surgery, ACLR participants underwent 3T MRI of the reconstructed knee. Uninjured volunteers underwent MRI of the same knee twice with ~1 week between repeat scans. To quantitate bone shape, femurs from each patient or volunteer at each timepoint were first automatically segmented from a 3-D double-echo in steady state (DESS) MRI sequence (TR/TEs: 21/6.7, 34.8 ms; flip angle 20°, 0.42x0.42 mm resolution; 1.5 mm slice thickness) and scores representing femur bone shape (B-score) were calculated using a neural shape model (NSM) trained on 9,376 baseline DESS images from the OAI dataset.[8] Briefly, higher B-score indicates more OA-like shape features; 1 unit of B-score is equivalent to the standard deviation of healthy femur shapes. ACLR patients also completed Marx[9] surveys at each timepoint. The Marx questionnaire assesses participation level in activities that include running, cutting, deceleration and pivoting, and the instructions state "Please indicate how often you performed each activity in your healthiest and most active state, *in the past year*." *Statistical Analyses:* Shapiro-Wilks, histograms and Q-Q plots were used to assess normality. The smallest detectable difference (SDD) in NSM B-score was estimated as the limit of agreement from Bland-Altman (BA) analysis of test-retest scans in uninjured volunteers. Repeated measures ANOVA (or Friedman tests for non-normal data distributions) and post-hoc pairwise paired t-tests (or Wilcoxon Signed Rank tests) with adjustments for multiple comparisons assessed longitudinal changes in NSM B-score and Marx activity scores. Pearson correlations (or Spearman's *rho*, R_S) assessed univariate relationships between Marx score and NSM B-score. Relationships of patient factors (age, sex, BMI, height, meniscus tear) with NSM B-score were similarly assessed, and candidate factors with $p<0.25$ from univariate analyses were included along with Marx score in multivariable linear regression models. The ability for activity level to predict shape change (*i.e.* > NSM B-score SDD) was determined from receiver operating curve (ROC) analysis with a Marx score cut-off estimated from Youden's Index. Statistical analyses were performed with SPSS (IBM) and Excel (Microsoft) with a two-sided level of significance of 0.05.

RESULTS: ***Bone Shape Score Repeatability Estimate:*** The SDD of NSM B-score, estimated from test-retest scans in 10 uninjured volunteers, was 0.48, Figure 1. ***Longitudinal Bone Shape Change:*** Averaged across the 34 ACLR participants with MRI suitable for bone shape scoring at all 3 post-surgical timepoints, Repeated Measures ANOVA showed progressively increasing NSM B-scores from 6 weeks (mean[SD] B-score: 0.38[0.88]) to 1-year (0.67[0.90], $p<0.0005$) and 2-year follow-ups (0.88[0.91], $p=0.004$), Figure 2. Individually, nearly half (15/34, 44%) of participants demonstrated NSM B-score increases between 6 weeks and 2 years exceeding the SDD. ***Longitudinal Activity Level Change:*** Averaged across all 38 ACLR participants who completed Marx surveys at all post-surgical timepoints, the repeated measures Friedman test shows a significant decrease in Marx scores from 6-week values (which reflected pre-injury levels; mean[SD] Marx score: 10.4[5.6]) to 1-year follow-up (6.5[5.2], $p<0.0005$) followed by a non-significant recovery (7.3[4.8], $p=0.312$) at 2-years follow-up, Figure 2. Across individuals, Marx responses were highly variable between the 1- and 2-year follow-ups: 12/38 (32%) patients reported activity increases >2pts (the previously assumed clinically significant threshold[10]); 7/38(18%) reported activity decreases <-2pts. ***Activity Level vs Bone Shape:*** Higher Marx scores reported at 2 years post-ACLR, reflecting a greater frequency of intense physical activities in the previous year, significantly correlated with greater NSM B-score measured at 2 years post-ACLR ($R_S=0.439$, $p<0.007$), Figure 3a. The relationship remained significant when considered together in a model with sex and height, with parameter estimate (95%CI) suggesting that for each 1pt increase in Marx score (~equivalent to 1 additional bout of intense exercise per week) NSM B-score increases by 0.07(0.002,0.131), $p=0.007$. Youden's Index identified a Marx score cut-off of 8 points at 2 years post-ACLR as predictive of B-score *increase* between 6 weeks and 2 years post-ACLR exceeding the expected error in the metric and thus suggesting change toward more OA-like shape features (AUC = 0.68), Figure 3b.

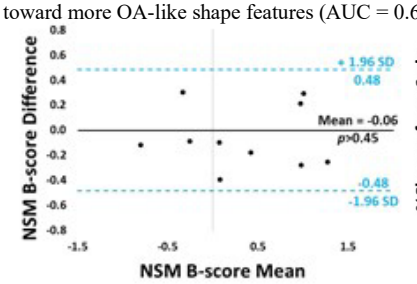

Figure 1. Bland-Altman analysis of test-retest MRI scans in 10 healthy volunteers shows good reliability of the NSM B-score metric with an SDD of 0.48 B-score units.

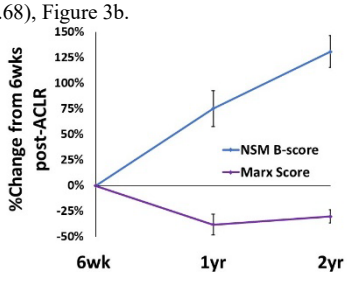

Figure 2. In the 2 years following ACLR, bone shapes become increasingly OA-like and activity only partially recovers toward pre-injury levels.

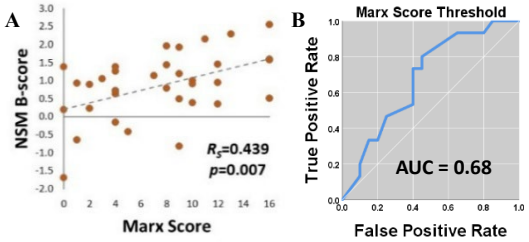

Figure 3. (A) Patients reporting more frequent intense physical activity (higher Marx Score) had more OA-like bone shapes (higher NSM B-score) 2 years after ACLR. Dotted line shows best linear fit. **(B)** ROC curve of sensitivity and specificity for Marx to predict B-score increase > SDD.

DISCUSSION: More than 30 years ago, Daniel *et al* expressed concern that ACLR may potentiate OA development by stabilizing a vulnerable knee to engage in higher levels of activity.[11] This work seems to support that concern as higher NSM B-scores, indicating more OA-like femur bone shapes, were detected in patients who reported more frequent participation in high intensity sports within 2 years of ACLR. Of note, a Marx score of 8 or higher, typically corresponding to intense physical activity (*e.g.* soccer) once or more times per week, was found to be a reasonable predictor of which ACLR patients developed more OA-like bone shapes following ACLR. In a previous bilateral examination of statistical shape modeling derived B-scores (SSM B-scores) after unilateral ACLR, greater interlimb differences associated with taller height, medial meniscus tear at the time of ACLR and decreasing age,[12] but comparisons with physical activity proved inconclusive. NSM B-scores out perform traditional shape modeling approaches (*e.g.* SSM) by capturing non-linear bone shape changes[8,13] and have detected femoral shape changes as early as 3 months after ACLR.[14] The degree to which activity-related bony remodeling trajectories of post-ACLR knees may differ from idiopathic OA requiring the added sensitivity of an NSM approach for detection is not yet fully understood.

SIGNIFICANCE: This study suggests that frequently engaging in high intensity physical activities within the first 2 years following ACLR may have negative consequences for bone shape remodeling leading to development of OA-like bone shape features.

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