Approach to Evaluate Femoral Cartilage Thickness Based on Patient Geometry

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INTRODUCTION: Loss of tibiofemoral cartilage is a hallmark feature of posttraumatic osteoarthritis progression (PTOA) following anterior cruciate ligament (ACL) injury and subsequent ACL reconstruction surgery (ACLR);[1,3] however, biological sex-based differences in cartilage thickness are known to exist.[2] As these baseline characteristics could contribute to the varied sequelae observed following ACLR, we sought to test whether cartilage thinning was sex-dependent in a subset of patients participating in a longitudinal clinical trial evaluating outcomes after ACLR (NCT00434837). To do so, we developed an approach to quantify sub-regional medial femoral condyle (MFC) cartilage thickness that could be scaled to account for differences in knee size. We hypothesized that: 1) MFC cartilage in uninjured female controls would be thinner than in uninjured male controls; and 2) MFC cartilage thickness in ACLR patients (10-15 years post-surgery) would be thinner than uninjured controls.

METHODS: Nine ACLR patients (4M/5F; 10-15 years post-surgery; mean age 34±10.5 years) and 12 uninjured controls (7M/5F; no history of knee injury; mean age 38±7.4 years) participated in this IRB-approved study. Tibiofemoral cartilage was segmented from magnetic resonance (MR) images acquired using a 3D fast low angle shot (FLASH) sequence (RT/ET/FA: 20ms/7.6ms/12°; slice thickness/gap: 1.5/0mm; 0.313x0.313x1.5mm voxel size). Femoral bony geometry was segmented from images acquired from computerized tomography (CT) scans (80kV, smart mA, 0.293x0.293x0.625mm voxel size). The cartilage and bone segmentations were used to generate 3D mesh models that were smoothed and remeshed using commercial software (Mimics; Materialise, Geomagic Wrap; 3D Systems). A local coordinate system was generated from the femoral geometry using an established approach.[4] The cartilage models were aligned in the femoral coordinate system using an iterative closest point algorithm (RMS error: 1.53±0.33mm). Cartilage thickness was mapped from the subchondral bone surface to the articular surface using a k-nearest neighbor search algorithm (MATLAB R2022b; Mathworks). The location of the femoral notch was used to delineate medial and lateral condyles. Based on the width and curvature of the condylar cartilage, 24 proportionally distributed MFC sub-regions were generated (mean sub-region size across patients: 2.72±0.46mm^2; Fig 2). Mixed models were used to test the study hypotheses. Pairwise comparisons were conducted via orthogonal contrasts. The Holm test was used to maintain a two-tailed familywise alpha at 0.05.

RESULTS: Cartilage thickness was not different (p=0.069) between female and male healthy controls (2.13mm, 95% CI=1.83-2.43 versus 2.54mm, 95% CI=2.22-2.87); however in a pooled analysis of both ACLR and Controls, females had significantly (p=0.004) thinner MFC cartilage (2.26mm, 95% confidence interval (CI)=1.99-2.54 versus 2.76mm, 95% CI = 2.57-2.95) with a trend towards a group X sex interaction [F(1, 483)=0.23, p=0.063] (Fig 1). A significant interaction effect between sex and location was detected in both the Control-only [F(10, 230)=2.83, p=0.003] and pooled analyses [F(19, 437)=22.05, p<.0001]. In the pooled analysis, females had thinner cartilage across 13/24 sub-regions which were primarily coincident with the weight-bearing region of the condyle (sub-regions #7-18). ACLR patients tended (p=0.056) to have thicker MFC cartilage (2.68mm, 95% CI=2.42-2.95 versus 2.34mm, 95% CI=2.10-2.57), with a significant interaction effect between group and sub-region [F(19, 437)=22.05, p<.0001; Fig 3). Although limited by statistical power, 7/24 sub-regions were significantly different between ACLR and Controls before adjusting for multiple comparisons; these regional trends in thickened cartilage coincided with the anterolateral region of the femoral notch (sub-regions #3 & 6) and central weight-bearing regions (sub-regions #14, 17, 19 20, 24).

DISCUSSION: Trends in our results were consistent with the literature describing females having thinner tibiofemoral cartilage than males,[2] but did not warrant separate analyses for male and females as we originally hypothesized. Also contrary to our hypothesis, our results highlighted a trend towards ACLR patients having thicker cartilage than healthy controls. These results suggest that even 10+ years after ACLR surgery, these patients present with cartilage swelling rather than thinning at this stage. Cartilage thickness significantly differed by sub-region in all analyses. While raw p-values suggested that some sub-regions were preferentially affected in ACLR patients, we were limited by statistical power. Nevertheless, the sub-regional approach used to quantify cartilage thickness differences revealed potentially clinically relevant cartilage thickening that likely would have been overshadowed if expressed as a mean of the entire surface. Further, the detected regional trends in cartilage thickening align with those previously reported,[5] giving some confidence in the trends.

SIGNIFICANCE/CLINICAL RELEVANCE: Coupled with AI-based algorithms for automatic cartilage model generation, the approach could be applied to larger cohorts to monitor cartilage changes earlier in the disease trajectory when interventions may be more effective.

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ACKNOWLEDGEMENTS: NIH NIAMS K99/R00-AR069004; R01-AR047910; R01-AR074973; NIGMS P30-GM122732; Lucy Lippitt Endowment

IMAGES AND TABLES:

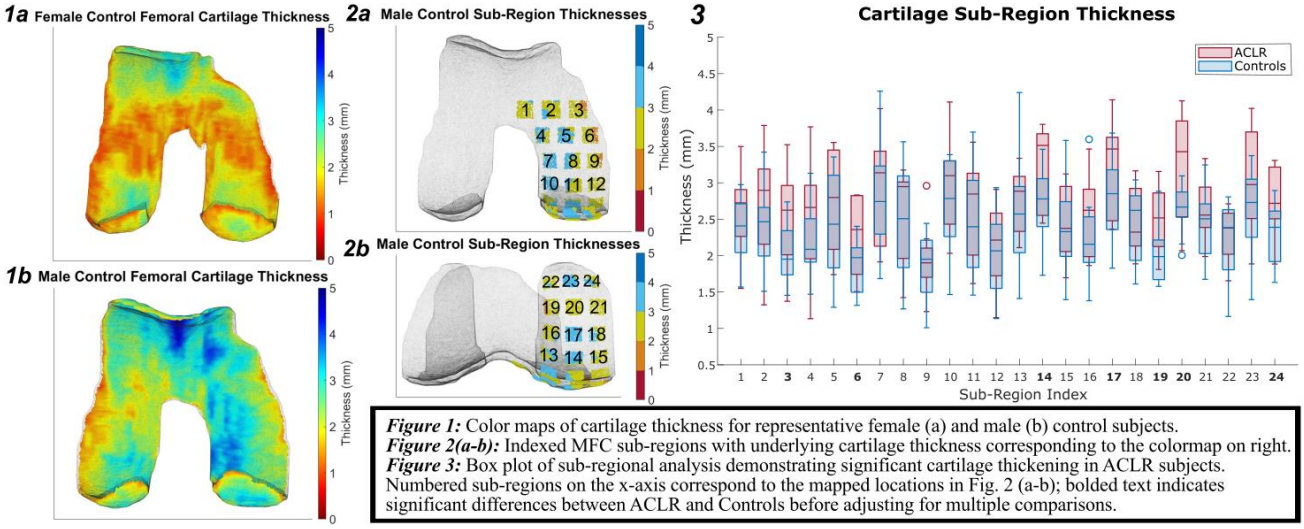

Figure 1: Color maps of cartilage thickness for representative female (a) and male (b) control subjects.
Figure 2(a-b): Indexed MFC sub-regions with underlying cartilage thickness corresponding to the colormap on right.
Figure 3: Box plot of sub-regional analysis demonstrating significant cartilage thickening in ACLR subjects. Numbered sub-regions on the x-axis correspond to the mapped locations in Fig. 2 (a-b); bolded text indicates significant differences between ACLR and Controls before adjusting for multiple comparisons.