Distinct Pathomechanics of Female Knees Compared to Males: A Population-Based In-Silico Analysis

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DISCLOSURES: Wheatley (N), Amirtharaj (N), Shamritsky (N), Pechstein (N), Zeitlin (N), Hirth (N), Nawabi (Arthrex, Gotham Surgical, Stryker, BetterPT, Engage Uni), Wickiewicz (Stryker), Pearle (MyGemini, Exactech, Smith & Nephew, Stryker, Zimmer, Arthrex, Engage Surgical, Knee Guardian, PerfectFit, Therma1), Beynnon (N), Imhauser (Corin)

INTRODUCTION: Young, female athletes are disparately vulnerable to first-time, noncontact anterior cruciate ligament (ACL) rupture with 2 to 6 times greater risk of injury than males [1]. These injuries impose a substantial physical and financial burden; therefore, significant effort has been devoted to identifying factors that predispose athletes, especially women, to this ailment. Clinical studies have revealed multiple sex-specific anatomic risk factors related to ACL injury including bone and soft tissue morphology and laxity of the knee. These factors impact knee biomechanics. However, the pathomechanics of the male and female knee in response to scenarios that place the ACL at risk of injury remain poorly understood. Without this knowledge, it is impossible to develop sex-specific, mechanism-driven strategies to prevent ACL injury. Combined compressive force, valgus torque, and anterior force preferentially load the ACL [2, 3]. Unfortunately, applying these potentially injurious loads to the knees of young athletes poses ethical challenges, while direct measurement of ACL force in vivo is technically difficult to accomplish in large populations. Thus, we developed a rapidly implementable, computational modeling pipeline [7] and leveraged a unique clinical data set of male and female high school and collegiate athletes [4] to investigate sex-specific knee biomechanics. We sought to address two research questions using our *in silico* pipeline: 1) Does ACL force differ between females and males when their knees are subjected to multiplanar loads known to stress the ACL? 2) Do tibiofemoral kinematics, including coupled internal tibial rotation (ITR) and valgus angulation, differ between females and males? We hypothesized that females would incur more ACL force, ITR, and valgus angulation than males. Second, we hypothesized that the females suffering a first-time, noncontact ACL injury would exhibit greater ACL force, ITR and valgus angulation compared to uninjured female controls.

METHODS: Magnetic Resonance Imaging (MRI) data of a cohort of high school and collegiate athletes consisting of 60 female (Age: 17.1 ± 2.3 years) and 24 male (Age: 18.0 ± 2.5 years) matched pairs of cases who suffered first-time noncontact ACL injury and uninjured controls matched by age, sex, and team were obtained under IRB approval. We then employed our previously published computational modeling pipeline to these MRI data [5]. This automated process consisted of first creating 3D renderings of the tibiofemoral bone, cartilage and meniscal geometries and then identifying ligament insertions and origins [6, 7]. Tissue stiffnesses were standardized via population means [5]. Ligament slack lengths were also standardized using a published optimization algorithm [5]. Loads were applied to the tibia in series and consisted of compression (100 N), then a valgus moment (8 Nm), and finally an anterior force (30 N) (ADAMS, Hexagon, Inc.). These loads increase ACL force and are key components of knee loading during clinical pivot shift and cutting maneuvers [2, 8]. This loading combination was applied at 15° of flexion to maximize ACL force. Primary outcomes measures included 1) resultant ACL force at the peak applied loads and 2) kinematic outcomes of ITR and valgus angulation, which were expressed in an anatomical coordinate system. Kinematic measures were calculated as the difference between the pose of the knee in unloaded passive flexion and at the peak applied loads. Outcomes were reported as means and standard deviations (SD). After confirming normality, unpaired t-tests were used to identify differences between male and female cohorts for ACL force (question 1) and ITR (question 2) ($\alpha = 0.05$). Subgroup analyses of differences in ACL force and ITR between ACL-injured females and uninjured female controls were performed using paired t-tests ($\alpha = 0.05$). Comparisons of valgus angulation between the all-male and all-female cohorts and for the subgroup analysis was performed via non-parametric Wilcoxon Sum Rank test and Wilcoxon Signed Rank test, respectively ($\alpha = 0.05$).

RESULTS: Regarding our first research question, female knees exhibited 35% greater ACL force than male knees at the peak applied loads (28.4 N, $p < 0.001$, Fig. 1A). ACL-injured females exhibited 26% greater ACL force than uninjured females, the subgroup with the second greatest force (24.9 ± 55 N, $p < 0.001$, Table 1). Regarding our second research question, female knees exhibited 38% greater ITR than males (2.9°, p = 0.01, Figure 1B) and 36% greater valgus angulation (1.3°, $p < 0.001$, Figure 1C). Females suffering first time non-contact ACL injury exhibited 44% greater ITR (3.7 ± 9°, p = 0.002, Table 1) and 18% greater valgus angulation (0.7 ± 2.1°, p = 0.008, Table 1) than uninjured females.

DISCUSSION: Combining a rapidly implementable computational modeling pipeline with a unique clinical, dataset of young male and female athletes revealed stark differences in the mechanics of the male and female knee. Our most important finding was that the knee models comprising the female cohort exhibited 35% greater ACL force and displayed not only 36% greater valgus angulation but also 38% greater coupled ITR compared to the male cohort. ACL-injured females exhibited significantly greater ACL force, coupled ITR, and valgus angulation compared to their matched, uninjured controls. These findings confirmed our hypotheses. The knee is known to exhibit coupled ITR with an applied valgus moment and that ACL force increases with ITR [2]. However, our findings reveal that the propensity of the female knee to exhibit increased kinematic coupling may be a key differentiator between sexes, especially for females at risk for ACL injury. Since ligament and meniscal properties were standardized in our model, differences between males and female knee geometries likely contribute to the observed differences in knee mechanics. Valgus moments preferentially load the lateral compartment and thus geometric factors such as lateral bony and articular slope may be important targets to help explain these differences. We speculate that our findings of increased ACL force in the female knee may help explain the increased injury rates in females compared to males even after controlling for sport and level of play [1].

SIGNIFICANCE: Our findings can inform mechanics-based injury screening tools and prevention protocols by targeting reduction in coupled internal tibial rotation with valgus loading to help address sex-based disparities in musculoskeletal care for females.

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ACKNOWLEDGEMENTS: Steers Family, Gosnell Family, Clark and Kirby Foundations, R21AR073388, R01AR050421

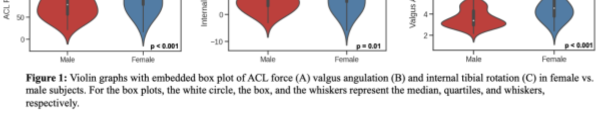

Figure 1: Violin graphs with embedded box plot of ACL force (A) valgus angulation (B) and internal tibial rotation (C) in female vs. male subjects. For the box plots, the white circle, the box, and the whiskers represent the median, quartiles, and whiskers, respectively.

Table 1: ACL Force, internal tibial rotation (ITR) and valgus angulation of ACL-injured and uninjured female subgroups. * signifies p < 0.001. ** signifies p = 0.002. *** signifies p = 0.001.

Cohorts	ACL Force (N)	ITR (°)	Valgus (°)
Injured Females	123.1 ± 37.9*	12.4 ± 6.5**	5.3 ± 1.8***
Uninjured Females	97.8 ± 41.4*	8.6 ± 7.2**	4.5 ± 1.5***