A Sex-Stratified Multivariate Risk Factor Model for Anterior Cruciate Ligament Injury

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Anterior cruciate ligament (ACL) injuries produce significant joint trauma and have been implicated as the inciting event for both short-term and long-term changes within the articular structures of the knee.[1–8] Regardless of whether a patient chooses surgical or nonsurgical treatment, ACL injury is associated with the onset of posttraumatic arthritis.[9] Consequently, recent researchers have focused on understanding the mechanisms and factors that place individuals at increased risk for sustaining this severe injury. However, variations in study designs and methods have led to conflicting reports regarding these relationships. For example, exclusion criteria used for control participants (eg, combining control participants who have a history of knee pain with those who have normal, pain-free knees) and the approaches used to match case and control participants vary widely among studies. In addition, previous authors have obtained data from the affected knees of ACL-injured patients after the injury. This approach does not take into consideration that the ACL injury itself is capable of producing both short-term and long-term changes in knee-joint geometry.[1,5] Furthermore, few investigators have used measurement techniques with established interobserver and intraobserver measurement reliability.[10] Finally, many researchers have evaluated men and women as a combined group. However, in light of the disparities that exist between the sexes in ACL injury rates, knee-joint geometry, anatomical alignment, joint laxity, demographic characteristics, and strength, male and female models of injury risk should be considered separately.[11]

This keynote presentation provided a summary of findings from our group's previous and ongoing research efforts that have focused on identifying the factors associated with increased risk of ACL injury. For clarity, the findings are organized in 3 sections: “Epidemiology of ACL

Injury,” “Evaluation of ACL Injury Screening Tools,” and “Development of ACL Injury Risk Models.”

Epidemiology of ACL Injury

Our epidemiology investigation evaluated the independent effects of athlete sex, level of competition, and sport on the risk of sustaining an ACL injury.[11] We prospectively followed athletes from 26 institutions (8 colleges, 18 high schools) over 4 years to determine the incidence of first-time, noncontact ACL injuries.

After controlling for differences in level of play and sport, we found that an athlete's sex had an independent influence on the risk of injury: female athletes' risk of experiencing a noncontact ACL injury was 2.10 times greater than that of their male counterparts.[11] When athlete sex and sport were controlled, collegiate athletes were at greater risk for incurring a noncontact ACL injury than were high school athletes (relative risk [RR] = 2.38).[11] When controlling for athlete sex and level of play, we observed that the risk of sustaining a noncontact ACL injury was greatest in soccer (RR = 1.77) and rugby (RR = 2.23) compared with all other sports studied.[11] Of note, collegiate female soccer athletes had the greatest overall risk of experiencing a noncontact ACL injury among all the sports and levels of competition investigated.

To our knowledge, this was the first study to reveal that the risk of incurring a first-time noncontact ACL injury was independently influenced by an athlete's sex, level of competition, and sport. These findings help to describe the population at greatest risk for ACL injury and could enable us to identify the individuals who should be targeted with injury-prevention strategies.

Evaluation of ACL Injury Screening Tools

Two screening tools, the Landing Error Scoring System (LESS) and a predictive algorithm for the probability of high knee-abduction moment (pKAM), were evaluated for their capacity to identify individuals at increased risk for ACL injury.[12,13] Evaluations of the LESS and pKAM were done using data collected from the same prospective study with a nested case-control analysis.

For the LESS, we used video data collected from 3876 high school and collegiate athletes (2021 young men; 1855 young women) during preseason screenings; participants were directed to perform the drop vertical-jump test in accordance with the LESS protocol.[13] Over the 3-year study period, 28 participants sustained a first-time, noncontact ACL injury. The LESS data obtained from ACL-injured participants were then compared with data from 64 uninjured control participants matched for age, sex, involvement with the same team, and screening day. Analyses of these data revealed that the LESS was unable to predict which athletes were at increased risk for a first-time, noncontact ACL injury. Analysis of female and male athletes as separate groups yielded the same findings as an analysis of both sexes considered as a combined group.

Because the pKAM clinic-based algorithm created by Myer et al[14,15] was originally developed for females, our second study applied the algorithm to 65 of the female participants

(20 cases, 45 controls) in the LESS study.[12,13] Measurements of knee-valgus motion, knee-flexion range of motion, and tibial length were obtained from the drop vertical-jump video. We entered video-based measurements, participant mass, and a surrogate measure of the quadriceps-to-hamstrings ratio[15] into the algorithm as described by Myer et al to determine the pKAM. Analysis of these data revealed no significant relationship between the algorithm-calculated pKAM values and the risk of sustaining an ACL injury.[12]

Development of ACL Injury Risk Models

This investigation comprised 2 phases with shared hypotheses: that a diverse set of risk factors exists for first-time, noncontact ACL injury and that these factors differ between females and males. The first phase consisted of a comprehensive, multivariate evaluation of all risk factors thought to be associated with ACL injury (ie, demographic characteristics, joint laxity, lower extremity alignment, strength, personality characteristics, and sex-hormone concentrations). The second phase focused on a multivariate evaluation of knee-joint geometry and its effect on the risk of ACL injury.[16–21] Detailed results from the first phase are currently under review for publication and, consequently, we can provide only an overview of the study design, but we encourage the reader to consider the detailed findings once they have been published. The findings from the multivariate work in the second phase have been published.[16–21]

Athletes from 36 institutions (8 colleges, 28 high schools) were monitored prospectively over 4 years for the occurrence of ACL injuries. A total of 109 case participants (70 females, 39 males) who sustained a first-time grade III noncontact ACL injury during involvement in a school-organized sport were enrolled in the study. Concurrently, 227 control participants matched for age, sex, and involvement on the same sport team were recruited. We recruited case and control participants from the same team to control for athlete-exposure (eg, exposure to the same types of activities, training, coaching, and extrinsic risk factors).

During phase 1, we obtained measurements of potential risk factors including demographic characteristics, joint laxity, lower extremity alignment, strength, and personality characteristics from case and control participants soon after injury. Our prior work established a relationship between ACL injuries and sex-hormone concentrations based on analysis of sera collected at the time of ACL disruption.[22] However, because the recruitment procedure for the current study identified athletes throughout Vermont and upstate New York, we were unable to obtain serum samples from participants on the day of injury. With this in mind, we initially planned to evaluate menstrual cycle phase at the time of injury (as a surrogate measure for sex-hormone levels in serum) as a potential risk factor for ACL injury.[23] Yet we were unable to establish and validate an approach to accurately estimate sex-hormone concentrations in the absence of serum samples.[23] Conditional logistic regression analyses were used to assess the associations between variables and the risk of sustaining an ACL injury. Sex-specific analyses were conducted because a majority of the potential risk factors differed between females and males. Results from univariate analyses were used to inform the subsequent multivariate analysis. Multivariate analysis provided insight into whether variables had a direct causal effect on the risk of injury or an indirect effect that was mediated by other variables. In addition, multivariate analysis had the capacity to identify risk factors that might not be evident in univariate analysis; if a variable's effect was moderated by other variables, its association with risk would be apparent only after adjustment for the other variables. Most importantly, multivariate analysis allowed for the identification of variable combinations that were more predictive of risk than were individual factors.[20] This work confirmed research by Flynn et al[24] (who found that family history of an ACL injury was a strong predictor of injury) as well as investigations[25,26] that described associations between knee laxity and the risk of ACL injury.

The second phase evaluated magnetic resonance imaging measures of knee-joint geometry in a subset of 176 participants (88 cases, 88 controls). Bilateral 3-T images were obtained on all case and control participants and used to measure 32 aspects of knee anatomy.[11,16,19,21] Multivariate analysis revealed differences between females and males for the specific aspects of knee-joint geometry that had the greatest association with ACL injury risk. When male athletes were considered as a group, decreases in the wedge angle of the posterior lateral meniscal horn and ACL volume had the highest associations with the risk of sustaining a noncontact ACL injury (odds ratio [OR] = 1.23 per 1° decrease in wedge angle and OR = 1.43 per 0.1-cm^3 decrease in ACL volume). Consequently, male athletes with reductions in the wedge angle of the posterior lateral meniscal horn and ACL volume (relative to average values) would have 1.76 times the risk of experiencing a noncontact ACL injury. Evaluation of females revealed that those with an increased posterior-inferior–directed slope of the lateral tibial articular surface (OR = 1.32 per 1° increase), combined with a decreased femoral intercondylar notch width (OR = 1.5 per 1-mm decrease), had the highest associations with the risk of incurring a noncontact ACL injury. Therefore, female athletes with these differences would have double the risk (OR = 1.98) of sustaining a noncontact ACL injury.

Our study established that the aspects of knee anatomy associated with the risk of ACL injury differed between females and males. Although the associated variables were different, it is important to note that both females and males had certain combinations of knee-joint geometry that were more strongly associated with the risk of injury than when the individual measurements were evaluated in isolation.[20] Differences between the female and male risk models may indicate that the mechanisms responsible for producing this injury are also different between the sexes. These findings suggest that sex-specific screening mechanisms should be developed to identify individuals at increased risk for ACL injury. Although the development of the anatomic form of the knee is not well understood, it is clear that knee geometry is a nonmodifiable risk factor. However, armed with this knowledge, we can target injury-prevention strategies at those who possess an increased risk for injury.

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