ACL Research Retreat VII: An Update on Anterior Cruciate Ligament Injury Risk Factor Identification, Screening, and Prevention March 19–21, 2015; Greensboro, NC

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The seventh ACL Research Retreat was held March 19–21, 2015, in Greensboro, North Carolina. The retreat brought together clinicians and researchers to present and discuss the most recent advances in anterior cruciate ligament (ACL) injury epidemiology, risk factor identification, and injury risk screening and prevention strategies. Subsequently, our goal was to identify important unknowns and future research directions.

The ACL Research Retreat VII was attended by 64 clinicians and researchers from Australia, Canada, India, Ireland, the Netherlands, South Africa, the United States, and the United Kingdom. The meeting featured 3 keynote and 29 podium presentations highlighting recent research. Keynotes were delivered by Bruce Beynnon, PhD (University of Vermont), Charles "Buz" Swanik, PhD, ATC (University of Delaware), and Mark Paterno, PhD, PT, ATC, SCS (Cincinnati Children's Hospital Medical Center), addressing their ongoing work related to sex-specific multivariate risk factor models for ACL injury,[1] the role of the brain in noncontact ACL injury,[2] and the incidence and predictors of a second ACL injury after primary ACL reconstruction and return to sport,[3] respectively. Podium and poster presentations were organized into thematic sessions of prospective and case-control risk factor studies, anatomical and hormonal risk factors, neuromuscular and biomechanical risk factors, injury risk assessment after ACL injury, and injury-prevention strategies. Time was provided for group discussion throughout the conference. At the end of the meeting, attendees participated in 1 of 3 breakout sessions on the topics of genetic, hormonal, and anatomical risk factors; neuromechanical contributions to ACL injury; and risk factor screening and prevention. From these discussions, we updated the 2012 consensus statement4 to reflect the most recent advances in the field and to revise the important unknowns and future directions necessary to enhance our understanding of

ACL injury. Following are the updated consensus statement, keynote presentation summaries, and free communication abstracts organized by topic and presentation order.

CONSENSUS STATEMENT

As our understanding of ACL injury risk and prevention grows, it is becoming increasingly apparent that ACL injury mechanism(s) is (are) multifactorial, resulting from the interplay of neuromuscular, biomechanical, anatomical, genetic, hormonal, and other factors. Although we have learned much in recent years about sex differences in neuromechanical movement patterns and the external loading factors that strain the ACL, far less is known about the factors that contribute to a structurally weaker ligament. This is important because the effect of external loading factors on injury risk potential (ie, the potential to cause ligament failure) likely depends on the intrinsic properties (ie, structural integrity and load-bearing capabilities) of the ligament. From this perspective, new evidence continues to emerge regarding the potential for one's genetic makeup and hormonal profile to substantially alter the structural properties of the ACL, making it more or less vulnerable to failure with external loading. This interplay between intrinsic ligament properties and external loading may explain why screening movement patterns alone has yet to yield consistent and reliable risk factor prediction models. Additionally, consensus is building that the risk factors may not be the same for males and females. As such, examining this interplay would help us to further elucidate whether females are at greater risk of noncontact ACL injury due to female-specific injury mechanisms or the same external-loading injury mechanisms apply to both sexes, but the underlying intrinsic risk factors are merely more prevalent in females.

Despite the likely multifactorial nature of this injury, studies of isolated risk factors (eg, anatomic, hormonal, genetic, kinematic, or kinetic) continue to dominate the literature. Further, because of the relatively low incidence of ACL injury, lower extremity biomechanics are often studied as outcome measures to represent ACL injury potential based on what we have learned from cadaveric ligament-loading studies. If we are to fully understand the movement behavior that results in elevated ACL loading, researchers need to study ACL injury as the outcome and move toward a more comprehensive assessment of both the nonmodifiable (ie, anatomy, genetics, and hormones) and modifiable (ie, neuromechanics) factors that influence risk. Conducting such multifactorial studies with injury as the outcome will allow us to determine important interactions and interdependencies among the various risk factors and identify the unique combination of factors that can most reliably predict future injury risk potential in the simplest way possible. Although tremendous challenges remain in performing such large-scale multivariate risk factor studies (eg, funding, personnel, and geographic restrictions), results from these types of studies are beginning to emerge and published findings have been incorporated into the current statement where available. Additional and important insights are also being gained from the studies of the incidence and predictors of a second ACL injury after primary ACL reconstruction and full return to sport participation; this information has also been added to the statement (see also Paterno[3]).

Because of the trends noted earlier, this consensus statement differs somewhat in format compared with previous statements. The first section focuses primarily on risk factor assessment as determined by ACL injury as the outcome variable. However, we have also included

biomechanical studies that describe how the ACL is stressed or strained in order to better understand mechanistically how global movements (and the intrinsic and extrinsic factors that affect them) may lead to ACL failure. Although this section is still divided into the traditional risk factor categories, we have made every effort to integrate the published findings from multivariate studies as they became available. Also new to this section is information on the risk of second-time ACL injury. The second and third sections focus on risk factor screening and prevention efforts, respectively.

Once again, we find that in the 3 years since the last ACL Research Retreat, many advances in our knowledge have shaped what we know about ACL injury risk and prevention and the important directions for future research that are needed to move the field forward. We hope that these proceedings will continue to stimulate quality research to more effectively identify those at risk before an injury occurs and to promote high-quality clinical interventions.

RISK FACTOR ASSESSMENT

Neuromechanical Risk Factors

Neuromechanical (ie, neuromuscular and biomechanical) factors, whether ascertained in vivo or in vitro, are generally derived from instrumented analyses of function that typically include kinematics, kinetics, and the timing and magnitude of muscular activation and force production. Our understanding of the role of neuromechanical factors in ACL injury has been advanced through cadaveric modeling, movement biomechanics, and neuromuscular insufficiency.

Important Knowns and Recent Advances. **Biomechanics Influencing ACL Strain.** Advances in our understanding of how the ACL is loaded and how it fails have arisen from cadaveric and computer models of simulated knee loads. These studies are foundational if we are to better understand and interpret "high-risk" movement biomechanics studies that do not estimate ACL loads or use ACL injury as an outcome. The ACL is loaded in vitro through a variety of isolated and combined mechanisms that are assumed to be present during dynamic sport postures considered to be high risk. Collectively, this work demonstrates that ACL strain increases with anterior tibial forces, tibiofemoral compression, and combined knee-abduction and knee–internal-rotation moments.[5–13] Mechanical couplings of external moments about the knee that include combined internal rotation and abduction are reported to increase ACL strains to near levels at which tissue ruptures.[8]

Recent cadaveric studies have applied loads to the knee that simulate activities representing high-risk ACL injury events. The timing of peak ACL strain appears to depend more on anteriorly directed tibial forces and knee-abduction moments, with peak internal tibial rotation occurring much later in the simulated landing.[10] In addition, knee abduction combined with internal knee rotation, anterior tibial translation, and increased tibial compression produces ACL injuries that appear consistent with clinical observations of ACL injuries.[14] During simulated single-legged landing, peak ACL strain increases with a combination of larger ground reaction forces and decreased hip angles.[15] Collectively, these cadaveric studies have clarified how the ACL is loaded and injured and formed the basis for assessing biomechanical variables thought to represent "high-risk" movement biomechanics.

***Movement Biomechanics*.** Noncontact ACL injuries are most commonly reported to arise from a sudden deceleration while changing direction when running or landing from a jump.[16] Quantitative analyses of actual injury events demonstrate that rapid knee abduction and internal rotation during the early weight-bearing phase occur at the time of injury.[17,18] Additionally, video observations of ACL injury occurrences demonstrate a relatively extended knee,[19] greater knee-abduction motion,[20–22] increased amounts of lateral trunk motion,[23] and a more posteriorly positioned center of mass.[24] These observational findings are largely supported by cadaveric model work and lend credence to the use of high-risk biomechanical measures as outcome variables.

To date, 2 groups have demonstrated landing biomechanics to be prospective risk factors of ACL injury. When researchers used full 3-dimensional biomechanical methods, larger peak knee-abduction moment and peak knee-abduction angle at initial contact during a drop jump were prospective risk factors in adolescent female athletes.[25] Use of a more clinically friendly video observation of a jump landing (Landing Error Scoring System [LESS]) in youth soccer athletes showed that participants who went on to sustain ACL tears had lower LESS scores.[26] However, LESS scores did not predict ACL injury in high school and college-aged athletes.[27]

A more erect or upright posture is commonly associated with increased vertical ground reaction forces.[28,29] This is important to understand as in vivo and in vitro strain of the ACL is related to maximal load and timing of ground reaction forces.[30,31] Similarly, anterior tibial translation increases as demands on the quadriceps increase.[32,33] Thus, this upright or extended posture when contacting the ground during the early stages of deceleration tasks has been suggested to be associated with the ACL injury mechanism.[34–38] Although short-term exhaustive exercise has resulted in changes in non–sagittal-plane variables associated with ACL injury risk,[39–43] exertional protocols that aim to simulate entire game or match duration and intensity have demonstrated subtle changes only in the sagittal plane, indicative of an at-risk upright posture.[44,45]

Females are known to be at greater risk of ACL injury than males,[46,47] so investigations have focused predominantly on sex differences. Several recent reviews[48,49] have indicated that females demonstrated greater knee-abduction postures during landing. Given the prospective findings of Hewett et al,[25] knee abduction may be a potential key biomechanical factor in defining female-specific ACL injury mechanisms.[49]

***Neuromuscular and Neurocognitive Insufficiency*.** Trunk neuromuscular control has been implicated as a risk factor for ACL injury. In a prospective study[50] of trunk displacement after sudden force release, greater trunk displacement was a prospective predictor of ACL injury in college-aged females but not males. Compared with an erect or preferred trunk posture, landing with the trunk relatively more flexed increased hip-flexion and hip-extensor moments while decreasing ground reaction forces, knee moments, and quadriceps activation amplitudes.[28,51] During various running and cutting tasks, trunk and hip movements (in all 3 planes of motion) were commonly associated, at different magnitudes, with knee-abduction angles and external knee-abduction moments.[52–55] Although trunk and hip associations with “high-risk” knee biomechanics are clearly supported by these latter studies, the correlational results do not suggest

cause and effect and could instead reflect task-dependent associations. Collectively, positions and movements of segments proximal to the knee could place the knee joint in a position of high risk for ACL injury.

Neurocognitive insufficiency as a risk factor for ACL injury is supported by findings of worse baseline reaction times, processing speed, and visual-spatial awareness in athletes who went on to sustain an ACL injury compared with controls.[2,56] Evidence for a connection between central processing and neuromuscular insufficiency was provided by the finding that slower cognitive processing speed was associated with decreased trunk stability in males.[57]

Unknowns and Directions for Future Research.

1. External- and internal-loading profiles that cause noncontact ACL ruptures in the field, data that are central to optimal injury-prevention strategies, are unknown.[58] Video from actual injury situations (and control videos from these athletes before injury) must be accumulated[17,18,24] to allow us to better understand the mechanisms of in vivo ACL rupture. Additionally, cadaveric, mathematical, in vivo kinematic, and imaging research approaches should be combined to help us understand the postures, loads, and neuromuscular profiles that increase ACL strain or cause noncontact ACL rupture.[31,59]

2. Optimal ways to assess movement in the laboratory environment are still being debated with regard to single-legged and double-legged tasks.[60,61] To better understand how movement patterns and other structures in the kinetic chain affect ACL loads, we must continue to develop, improve, and validate quality laboratory-based models (eg, computational, cadaveric) that noninvasively estimate in vivo ACL forces and strain. Care should be taken to not overgeneralize results from 1 specific task to other tasks.

3. The influence of the kinetic chain (ie, ankle, hip, lumbopelvic, and trunk biomechanics) on modeled ACL strain or forces has been studied in controlled movements commonly performed in rehabilitation.62,63 However, the specific relationship of these kinetic chain concepts with ACL injury risk is unclear. Laboratory, cadaver, and simulation-based studies designed to evaluate cause and effect (ie, highly controlled human movement studies with 1 variable manipulated) are warranted to ascertain whether these kinetic chain factors are a cause of or compensation for poor knee biomechanics.

4. Typical biomechanical experiments rely on extracting singular measures to characterize complex human biomechanics. To better understand the richness of these data, we should consider alternative approaches to analyzing traditional biomechanical data: for example, nonlinear dynamics[64] and emerging data-analysis techniques, including statistical parametric mapping.[65–67]

5. To better understand the role of the central nervous system in ACL injury, research models should include assessments of central processes (eg, automaticity, reaction time), cognitive processes68 (eg, decision making, focus and attention, prior experience [expert versus novice]), and metacognitive processes (eg, monitoring psychomotor processes). The reader is referred to

Swanik,[2] who briefly reviewed anecdotal, theoretical, and recent clinical research evidence attempting to unravel the brain's role in maintaining joint stability.

6. Although investigation of an initial cadaveric model showed that the ACL is susceptible to fatigue failure during repetitive simulated pivot landings and a smaller cross-sectional area of the ACL is at greater risk for such failure,[69] we do not know if it is a single episode or multiple episodes (or both) that causes gross failure of the ACL.

7. To various degrees, the amount of maximal strength is related to movement mechanics, but how this is related to injury risk is unclear.[70–75] Further work on how neuromuscular properties beyond absolute strength (eg, muscle and joint stiffness, muscle mass, rate of force production) relate to ACL function and injury risk is warranted.

8. The general consensus is that maturation influences biomechanical and neuromuscular factors affecting ACL strain.[76–87] However, evidence for how maturation affects knee biomechanics is inconsistent.[88] Examining the influence of the maturational process on knee biomechanics and specifically on ACL loads may provide unique insights into the observed difference in injury rates by sex that emerges during the early stages of physical maturation. In this regard, multiyear, longitudinal studies are needed.

9. Methodologic concerns regarding data collection, processing, and analysis continue to confound the interpretation of biomechanical variables thought to be risk factors for ACL injury. Concerns related to validity[31] and reliability[89–91] need further study before we can trust the quality and consistency of the data. Data processing should be carefully considered for its potential effect on identifying high-risk individuals and associations with ACL injury risk.[92,93] The research community would also benefit from operational definitions of terms (eg, stiffness, stability) so that scientists and clinicians can more transparently interpret the results and conclusions.

Anatomical and structural risk factors

The primary anatomical and structural factors examined with regard to ACL injury risk include knee-joint geometry, knee-joint laxity, body composition, and lower extremity structural alignments. Most of the variables that account for these anatomical characteristics differ by sex, which suggests that the risk factors may not be the same for males and females. Although static alignment measurements have yet to emerge as strong predictors of ACL injury, evidence associating knee-joint geometry, knee-joint laxity, and body mass index with injury risk continues to build.

Important Knowns and Recent Advances. **Knee-Joint Geometry.** The majority of prospective and retrospective case-control studies comparing ACL-injured patients with uninjured controls indicate that ACL-injured patients have smaller ACLs (in area and volume),[94,95] greater lateral posterior-inferior tibial plateau slopes (but not necessarily medial tibial slopes),[96–100] and smaller femoral notch widths and notch width indexes.[95,98,101–108] The presence of a more prominent or thicker bony ridge on the anteromedial outlet of the femoral intercondylar notch has also been reported in ACL-injured patients versus controls.[95–98] In addition,

reduced condylar depth of the medial tibial plateau may be characteristic of ACL injury.[96,97,100] Coronal slope has not been associated with ACL injury risk.[97,100]

Multivariate analyses suggest that smaller ACL volume and femoral notch width at the inlet and outlet and greater anteromedial bony ridge thickness and posterior-inferior directed slope of the lateral tibial compartment may independently contribute to injury risk and together provide more information on injury risk potential.[95,98,109,110] However, because the geometric variables examined have differed, there is no clear consensus as to the unique combination of these variables that most strongly predicts ACL injury risk in males and females.

When compared with males, females have smaller ACLs as assessed by length, cross-sectional area, and volume, even after adjusting for body size.[111] After adjusting for age and anthropometric factors, the female ACL has less collagen fiber density (area of collagen fibers/total area of the micrograph)[112] and decreased mechanical properties, including strain at failure, stress at failure, and modulus of elasticity.[113] Females are also reported to have greater lateral and medial posterior-inferior tibial slopes,[114,115] reduced coronal tibial slopes,[114] taller femoral notch heights, and smaller femoral notch widths than males.[111] Femoral notch width and angle are reported to be good predictors of ACL size (area and volume) in males but not in females[111]; multivariate analyses suggest that the individual characteristics may provide unique information[110] and collectively influence femoral notch impingement theory.[111] Sex differences in knee structural anatomy may also explain why associations of these variables with ACL injury history are somewhat different between males and females.[95,98,110]

Biomechanically, good evidence indicates that knee-joint geometry is related to higher-risk biomechanics. Greater posterior-inferior lateral tibial slopes are associated with greater anterior joint reaction forces,[116] anterior translation of the tibia relative to the femur,[117,118] and peak anterior tibial acceleration[119]; when combined with a smaller ACL cross-sectional area, these factors are associated with greater peak ACL strains.[120] Greater relative posterior-inferior slope of the lateral versus the medial tibial plateau has been associated with greater peak knee-abduction and internal-rotation angles,[116,121] whereas a reduced coronal slope has been associated with greater hip adduction and knee valgus upon landing in females.[121]

Knee-Joint Laxity. Greater magnitudes of anterior knee laxity,[122,123] genu recurvatum,[122,124–127] general joint laxity,[84,122,124,127] and internal-rotation knee laxity[128] have been reported in the contralateral knees of ACL-injured patients compared with controls.

Knee-joint laxity varies considerably among individuals, likely because of a combination of genetic,[129] hormonal,[130–135] and anatomical[136–138] factors. On average, females have greater sagittal (anterior knee laxity, genu recurvatum)-,[104,122,139–143] frontal (varus-valgus rotation)-, and transverse (internal-external rotation)-plane[135,144–146] and generalized joint laxity compared with males.[104,122] Sex differences in frontal-plane and transverse-plane knee laxity persist, even in males and females with similar sagittal-plane knee laxity.[135,144,146] Females are also more likely to experience acute increases in knee laxity during exercise[147] and across the menstrual cycle.[130–135]

Greater magnitudes of knee laxity may have both biological and biomechanical consequences. Evidence from animal studies[148–150] suggests that greater knee laxity is associated with ligament biomarkers indicative of greater collagen turnover, more immature cross-links, and lower failure loads. Biomechanically, greater magnitudes of knee laxity and general joint laxity have been associated with higher-risk landing strategies more often observed in females (eg, greater knee-extensor loading and stiffening, greater dynamic knee valgus), particularly in the planes of motion where greater knee laxity is observed.[139,151–157] The acute changes in knee laxity observed during exercise and across the menstrual cycle are of sufficient magnitude to push an individual toward higher-risk movement strategies.[155,156,158–160]

Lower Extremity Alignment. Although the results of 2 large prospective studies are not yet available[161] (see also Beynnon et al[1]), no clear consensus in the literature consistently links any 1 lower extremity alignment factor to ACL injury. Lower extremity alignment differs among maturational groups and also develops at different rates in males and females within those groups.[162] Once fully matured, females have greater anterior pelvic tilt, hip anteversion, tibiofemoral angle, and quadriceps angle.[142,163] No sex differences have been observed in measures of tibial torsion,[142] navicular drop,[142,143,163] or rearfoot angle.[142,164]

Body Composition. Increasing evidence from 2 large, prospective, multivariate risk factor studies showed that an elevated body mass index predicts future ACL injury in females but not in males.[104] (See also Beynnon et al.[1]) Higher body mass index in females is more likely to reflect a higher proportion of fat mass versus lean mass relative to body weight[165,166]; less relative lean mass has been associated with greater knee-joint laxity[137] and dangerous biomechanical strategies.[51,167] This may explain why the combination of greater joint laxity and greater body mass index is a stronger predictor of ACL injury risk in females than either variable alone.[104] (See also Beynnon et al.[1])

Unknowns and Directions for Future Research.

1. Anatomical and structural factors have often been examined independently or in small subsets of variables. Even among 3 larger, prospective multivariate risk factor studies[104,161] (see also Beynnon et al[1]), the anatomical variables examined are quite disparate, making it difficult to build a clear consensus on the best prediction model of ACL injury risk for screening purposes. Further large-scale risk factor studies that account for all relevant lower extremity anatomical and structural factors are needed to reach this consensus. Prospective confirmatory analyses of currently identified risk factor models across different races and ages are also needed.

2. Most investigations of tibial plateau geometry are based on measures of the subchondral bone, and recent research[110] suggests that accounting for the overlying cartilage and meniscal geometry when characterizing plateau slope and depth may improve prediction. However, because these measures are complex and costly, it will be important to determine the extent to which they provide additional information on ACL injury risk once more clinically accessible risk factors are taken into account. (See also Beynnon et al.[1])

3. Studies examining the combined effects of joint laxity, tibial geometry (lateral tibial slope, medial : lateral tibial slope ratio, coronal slope, medial condylar depth) and ACL morphology, as

well as interactions among these variables, on tibiofemoral joint biomechanics and ACL strain and failure are encouraged.

4. Although anatomical and structural factors are often thought to be nonmodifiable, we have limited knowledge of how these structural factors change during maturation or whether physical activity (or other chronic external loads) can influence this development over time, particularly during the critical growth periods. Prospective longitudinal studies are needed to help us understand the underlying factors that result in at-risk anatomical and structural profiles during maturation while also considering relevant modifiable factors such as body composition, neuromuscular properties, and physical activity.

5. Recent evidence[168] suggests that individuals with specific laxity profiles may perceive functional deficits during activities of daily living and sport. We do not yet know the multiplanar laxity profiles that pose the greatest risk for ACL injury or the threshold at which the magnitude of knee laxity becomes problematic.

6. Because body mass index is not a true measure of body composition or body mass distribution, future studies using a more detailed analysis of body composition are needed to fully understand how body composition contributes to faulty lower extremity biomechanics and injury risk.

Genetic Risk Factors

Rupture of the ACL is a multifactorial condition. Increasing evidence from both familial and case-control genetic association studies indicates that genetic sequence variants play an important role in its occurrence.

Important Knowns and Recent Advances. Since the previous ACL retreat, a growing number of common DNA sequence variants within genes involved in various biological processes have been associated with susceptibility to ACL rupture. These include variants within several genes that encode collagens[169–175] and proteoglycans[176] involved in the formation of the collagen fibril, the basic building block of ligaments. A subset of these variants has been specifically associated with ACL ruptures in females but not in males.[171,173,174,177] The ACL's collagen fibril and the rest of its extracellular matrix continuously undergo remodeling after mechanical loading to maintain tissue homeostasis. In support of this, variants within genes that encode proteins involved in cell-signaling pathways, such as angiogenesis-associated signaling[178] and the apoptosis-signaling cascade,[179] as well as remodeling (specifically matrix metalloproteinases[180,181]), have also been associated with ACL ruptures. Many of the anatomical, structural, and other risk factors are themselves multifactorial phenotypes determined by, to a lesser or greater extent, both genetic and environmental factors.[182] Based on the current evidence, it is therefore unlikely that the identified genetic variants are independent risk factors and more likely that they modulate risk through their effects on structural differences and other biological variations.

Genetic association studies in humans have recently been strengthened by a publication reporting the association of variants within genes, including collagen and other genes proposed to have a

detrimental effect on ligament structure and strength, with canine cranial cruciate ligament rupture.[183] Using a genome-wide association study design, the same investigators[184] have also identified 3 main chromosomal regions, which include variants within neurologic pathway genes, associated with canine cranial cruciate ligament rupture.

Unknowns and Directions for Future Research.

1. Most of the genetic risk factors for ACL rupture to date have been identified in white populations, and the reported associations cannot necessarily be extrapolated to other population groups. For example, the functional Sp1-binding site polymorphism (rs1800012, G/T) within the COL1A1 gene is associated with ACL rupture in white populations.[169,170,172,175] However, the frequency of the minor T allele of this variant is much lower in many other population groups (www.ensembl.org) and therefore unlikely to be informative within all populations.[185] Hence, investigators should identify appropriate informative genetic markers for other population groups.

2. Although establishment of an international consortium or registry was recommended at the last ACL retreat,[171] most of the published case-control genetic association studies have involved relatively small sample sizes, especially with respect to the sex-specific genetic effects. The establishment of an international consortium or registry will allow us to test the hypothesis of a stronger genetic contribution in individuals who tear their contralateral ACL rather than retear the same ACL or incur no further ACL injury. The establishment of an international consortium will also make it possible to recruit large sample sizes for whole-genome screening methods, enabling us to identify all the potentially important biological pathways involved in ACL ruptures and how these might differ by population.

3. None of the associated variants alone cause ACL ruptures. Rather, the injury is the result, at least in part, of a poorly understood, complex interaction of external loading and other factors, as well as intrinsic stimuli, with the genetic background of the individual. Further research is needed to ascertain the extent to which the associated variants may result in interindividual variations in the structure and, by implication, the mechanical properties of the ACL and surrounding tissues, as well as its responses to mechanical loading and other stimuli, thereby affecting the risk of injury.

4. Although scientists are only starting to understand the contribution of genetics to ACL injury, numerous companies are marketing direct-to-consumer genetic tests for common injuries, including ACL ruptures. However, these tests are premature because the genetic data are incomplete and have not been considered together with clinical indicators and lifestyle factors, which may allow an appropriately qualified health care professional to identify an altered risk for injury.

Hormonal Risk Factors

Sex hormones likely underlie many of the sex-specific characteristics that emerge during puberty. In particular, the large magnitudes of and monthly variations in estrogen and progesterone concentrations that females experience continue to be active areas of ACL injury

risk factor research. The hormone relaxin has also gained attention in recent years for its potential to influence ACL structural integrity and injury risk.

Important Knowns and Recent Advances. Hormone receptors (eg, estrogen, testosterone, and relaxin) have been localized on the human ACL,[186–190] suggesting they are capable of regulating gene expression and collagen metabolism in a way that may influence the biology of the ACL and other soft tissue structures. This idea is supported by studies that have demonstrated associations of normal physiologic variations in sex hormone concentrations across the menstrual cycle with substantial changes in markers of collagen metabolism and production,[191] knee-joint laxity,[130–135] muscle stiffness,[131] and the muscle-stretch reflex.[192] These biological changes may also have secondary neuromechanical consequences, as previously noted.[155,156,158–160]

Although results from prior epidemiologic studies have suggested that the risk of an ACL injury appears to be greater during the preovulatory phase of the menstrual cycle compared with the postovulatory phase,[193–197] our understanding of the underlying mechanism for this increased likelihood has not advanced. Understanding these processes is difficult given the substantial variability in the timing and magnitude of hormone changes among individuals,[134] the time-dependent effect for sex hormones and other remodeling agents to influence a change in ACL tissue characteristics,[134,190] and the potential interactions among several sex hormones, secondary messengers, remodeling proteins, mechanical stresses, and genetic influences.* For example, interactions among hormones, mechanical stress, and altered ACL structure and metabolism have been observed in some animal models.[148,205,206]

In recent years, the hormone relaxin has gained attention as a potential ACL injury risk factor based on a prospective study of National Collegiate Athletic Association Division I female athletes that showed elevated concentrations in those with ACL injuries compared with uninjured controls.[207] Even though studies examining the effect of relaxin on collagen metabolism in human knee ligaments in situ are lacking, in vivo and in vitro animal studies and human cell culture studies suggest that relaxin administered at physiologic levels can have a profound effect on soft tissue remodeling.[204,208–211] In turn, this may lead to a less organized[212] and less dense (both in fiber diameter and density) collagen structure,[204,212] which may manifest as a weaker and more lax ACL.[186] This concept is supported by an animal model in which guinea pig ACLs treated with relaxin at pregnancy levels were 13% more lax and 36% to 49% weaker.[213]

Unknowns and Directions for Future Research.

1. Our understanding of the biological consequences of sex hormones on collagen metabolism and the structural integrity of the ACL in the human knee in situ remains limited. The underlying sex-specific molecular and genetic mechanisms of sex hormones on ACL structure, metabolism, and mechanical properties and how mechanical stress on the ACL alters these relationships and injury risk potential remain important areas of study.

2. Good evidence demonstrates that some (but not all) females experience substantial cyclic changes in their laxity and knee-joint biomechanics across the menstrual cycle,[155,158,160] but

it is not yet possible to clinically screen for these potentially high-risk individuals. Understanding the underlying processes that regulate ligament biology and resultant ligament behavior may allow us to better screen for these individuals and prospectively examine how these factors influence injury risk potential.

3. Given the time-dependent effect of sex hormones on soft tissue structures, we need to determine how the time of injury occurrence aligns with acute changes in ACL structure and metabolism or knee-laxity changes and how the rate of increase or the time durations of amplitude peaks in hormone fluctuations across the menstrual cycle play roles in the magnitude or timing of soft tissue changes.

4. When examining hormone influences in physically active females, it is important to match the complexity of interparticipant differences in timing, magnitude, and interactive changes in sex hormone concentrations across the cycle with our study designs. Investigations should (1) verify the phases of the cycle (or desired hormone environment) with actual hormone measurements (considering relevant hormones to include estrogen, progesterone, and possibly others) rather than relying on calendar day of the cycle[214] and (2) obtain multiple hormone samples over repeated days to better characterize hormone profiles within a given female.[215,216] This may be particularly important when documenting relaxin exposure. Because relaxin rises and peaks during a relatively short window (6–10 days) after ovulation based on other hormonal events,[217–220] we do not know if the high proportion of undetectable levels within a single sample (as high as 64%–80%)[221–224] is due to timing or suggests that only a subset of females are exposed to appreciable relaxin levels due to mediating factors.[219,221,225]

5. Because cyclic hormone concentrations affect soft tissues and knee-joint function, studies comparing females with males should be made during the early follicular phase in females, when hormone levels are at their nadirs (preferably 3–7 days postmenses).

6. Menstrual dysfunction in exercising females may be more prevalent than originally thought (up to 50% in exercising females).[216,226,227] Thus, the effects of menstrual disturbances on injury risk potential are poorly understood.

7. Although the authors of epidemiologic studies have reported no protective effect of oral contraceptives on ACL injury risk,[72,73] these medications are known to vary substantially in the potency and androgenicity of the progestin compound delivered, which ultimately determines the extent to which they counteract the estrogenic effects.[228] We need to better understand how the different progestins influence soft tissue structures, knee function, and ACL injury risk. Furthermore, the exogenous hormones delivered in different types of contraceptives (eg, vaginal ring, transdermal patch, oral pills) are metabolized differently and may have different effects on musculoskeletal tissues.[229] Relevant comparisons should then be made among users of hormonal contraceptives (of all 3 types) and eumenorrheic, amenorrheic, and oligomenorrheic females to determine if ACL injury risk or observed soft tissue changes vary.

SCREENING

For effective injury prevention, prospective risk factors for ACL injury should be established before preventive measures are introduced.[230] Abnormal movement strategies may be modifiable and can be targeted in injury prevention.

Important Knowns and Recent Advances

Advances in clinic- or field-based screening tools may play an important role in identifying athletes who will benefit from injury-prevention programs.[26] Clinically oriented screening tools (eg, LESS, tuck jump) show good agreement with laboratory-based biomechanics (concurrent validity).[231–234] Screening tools are sensitive in detecting changes in movement quality over time.[235,236] Additionally, the ability of clinically oriented screening tools to identify individuals at risk for future ACL injury may be population specific (eg, sex, age, sport).[26,27,233] For example, the LESS effectively identified elite youth soccer athletes at higher risk of sustaining ACL injuries, with a score of 5 yielding a sensitivity of 86% and a specificity of 64%.[26] However, the LESS has not been found to predict future injury in adults.[237]

Data continue to show that athletes are at higher risk of ACL injury in game situations: increased game-play exposure increases ACL injury risk.[237,238] This suggests that screening in more of a real-life scenario may be of benefit in identifying those at greatest risk of injury.

Younger athletes with a previous ACL injury should be considered at higher risk for subsequent injury[239–244] and identified through preseason screening, especially in pivoting and cutting sports.[245] In his keynote summary, Paterno3 briefly reviewed the risk of subsequent injury.

Unknowns and Directions for Future Research

1. Which elements (eg, specific faulty movements, combination of faulty movements, strength assessment) of clinically oriented screening tools predict future ACL injury risk (predictive validity) is unknown. We need to develop other clinically oriented screening tools that have good sensitivity and specificity for predicting future ACL injury risk. Wearable sensors and advanced in-game monitoring may be helpful in assessing ACL injury risk and should be further explored.

2. We must understand how laboratory-based (eg, drop vertical jump) and clinically oriented screening tools (eg, tuck jump, 2-dimensional assessment, clinical nomogram) predict ACL and other lower extremity injuries.[25,26,246,247]

3. Although ongoing improvements to inexpensive and accurate screening methods to identify high-risk athletes remain of interest, enhancing existing training protocols and implementing neuromuscular training for all young athletes are warranted.[248] Future authors should identify the relative effectiveness of injury-prevention programs that are seamlessly integrated into universal training and, potentially, physical education programs.

4. The most common tests used by professional male soccer clubs to identify noncontact ACL injury risk are the functional movement screen, questionnaires to recognize risk factors such as

previous injury, and isokinetic assessments.[249] Because the predictive ability of these tests is uncertain, clinicians must become familiar with evidence-based ACL injury-screening tools.

5. It is important to consider that when screening for characteristics that predict ACL injuries, identified and validated ACL injury risk factors may not align with more traditional variables that have been shown to directly increase ACL loading in cadaver-based or simulation studies (ie, anterior tibial shear, knee valgus, and internal rotation torque). Continued investigations to recognize ACL injury risk factors through clinical screens are necessary.[50]

INJURY PREVENTION

Injury-prevention programs have been shown to reduce the incidence of ACL injuries. However, overall ACL injury rates and the associated sex disparity have not yet diminished. We still have much to learn in order to maximize the effectiveness of these programs, determine areas for improvement, and establish highly sensitive screening tools to target prevention efforts at those with the greatest risk for injury.

Important Knowns and Recent Advances

Various injury-prevention programs that incorporate elements of balance training, plyometric training, education, strengthening, and technique training or feedback have been shown to reduce ACL injury in females[195,250–257] or alter biomechanical and neuromuscular variables thought to contribute to ACL injury.[258–267] Injury-prevention programs with successful outcomes (eg, injury-rate reduction, improvement in neuromuscular control or performance) are performed 2 to 3 times per week and last for a minimum of 10 to 15 minutes.†

Most exercises implemented in male soccer players to prevent noncontact injuries involve eccentric exercise (in general), balance, and specific hamstrings eccentric training.[249] However, data regarding the effectiveness of prevention programs to reduce ACL injuries or modify risk factors for ACL injuries in male athletes are scarce and inconclusive as to recommendations for single-legged and multidirectional maneuvers.[269,270]

Improvements in movement quality after 12 weeks of training do not appear to be retained once the program ends. Thus, optimal results for retention and transfer require training principles that entail sufficient practice, variation, and frequency.[236] Recent researchers have focused on improving the delivery of injury-prevention programs. For example, feedback should emphasize successful performance and ignore less successful attempts; this benefits learning because of its positive motivational effects.[271] Programs that focus on correcting individualized techniques also appear to be successful.[272–274] Real-time feedback has been used to positively affect landing biomechanics.[275–278] However, expert modeling combined with self-modeling seems to be the most effective way to change landing biomechanics.[263,274,279–281] Additionally, motor skills can be learned with an internal focus of attention (ie, on the movements themselves, as in “flex your knees when landing”) or with an external focus of attention (ie, focus on the movement effect, as in “touch the target as you land”).[282] Age-appropriate injury-prevention training programs can effectively modify biomechanics in children.[235,283]

Compliance has a strong influence on the success of ACL injury-prevention programs.[284,285] However, knowledge and beliefs may not affect program adherence,[284,286] so other motivational factors must be considered. Coaches may be hesitant to implement an ACL injury-prevention program because they may feel it is "too much," not their primary interest,[286–288] does not offer a relative advantage over their existing practices, does not align with their needs, or is too complex to implement in their setting.[289] Yet having support from coaches and senior administrators is extremely important.[290] Athletes are willing to perform a lower extremity injury-prevention program if data indicate the program could improve performance and lead to fewer injuries.[291] Athletic performance is a crucial part of injury prevention; coaches and others are more likely to adopt a program that does not conflict with performance.[292] Also, injury-prevention training can improve performance in vertical-jump height, strength, and running speed.[268,273,274,293,294] Established frameworks could greatly help in organizing future research endeavors for large-scale injury-prevention implementation efforts.[295,296] On average, the implementation of a universal training program would save $100 per player per season and would reduce the incidence of ACL injury from 3% to 1.1% per season.[248]

Unknowns and Directions for Future Research

1. Although ACL injury-prevention programs are successful in reducing the risk of ACL injury, the ideal combination of and emphasis on training components within these programs should be further identified.[285,297–299] Research is necessary to determine which specific program elements are effective and necessary to reduce injury risk or promote biomechanical changes. For example, the preventive role of strengthening should be further examined.[53,300–309]

2. We must ascertain if streamlining injury-prevention programs, thereby making them more palatable to the public, will improve compliance. We need to establish if virtual-reality, real-time–feedback, and portable technologies will improve the implementation of and compliance with screening and injury-prevention programs.[26] With new products that use video feedback, exergaming, and "gamified" scoring, commonly encountered barriers that prevent the training staff from implementing and adhering to ACL injury-prevention programs might be overcome. This innovative approach might also help us to reach the goal of making injury prevention in the future just another aspect of the sport.[310]

3. We should continue to investigate how a participant's sex, age, skill level, and type of sport factor into the type and variety of exercises prescribed and technique training and feedback provided. Specifically, the most important age or stage of growth and development to begin implementing injury-prevention training should be determined.

4. During injury-prevention training programs, technique training and feedback are frequently provided to improve movement patterns. An external focus seems to be advantageous over an internal focus; however, more research is needed to establish the most effective training protocols (eg, frequency, timing, combinations of focus of attention) for improving movement patterns and optimizing the transfer of these learned patterns to sport-specific movements performed during a game. For instance, consciously learning optimal movement patterns rehearsed during training sessions might result in suboptimal transfer to the field, where

complex, unanticipated automatic movements are required.[282] Learning movement patterns with an external focus might enhance automatic motor control.[311]

5. Rehabilitation after ACL reconstruction that combines internal and external focus may enhance automatic movement control and improve performance.[312–314] However, we need to investigate the effects of injury-prevention training on ACL injury rates in those with a history of ACL injury.

6. We must understand how injury-prevention programs influence lower extremity injuries other than ACL injury.

7. We need to continue to study the performance-enhancement benefits associated with regular injury-prevention training.

8. The modes and frequency of feedback and instruction should be further investigated. Self-controlled feedback enhances retention of movement patterns over time.[274] Additionally, giving the athlete some control over a practice session (ie, an active role in deciding when to receive feedback) may enhance motor-skill learning when compared with prescribed training schedules.[315,316] It is interesting that athletes often have a relatively strong sense of how well they perform.[317] This so-called self-controlled practice has generally been assumed to initiate a more active involvement of the athlete, enhancing motivation and increasing the effort invested in practice.[282] In addition, sex-specific feedback strategies should be considered when implementing ACL injury-prevention programs. Males respond well to visual feedback, whereas females may prefer different learning strategies (eg, combined visual and verbal feedback).[273,274]

9. Although well-controlled ACL injury-prevention programs reduce the incidence of ACL injuries, we have yet to effectively implement multifaceted programs in different settings that are sustainable over time (widespread implementation with high compliance and retention rates over the long term). Developing packaged preventive training programs that can be implemented broadly across different settings through appropriately educated and trained coaches or team leaders may facilitate compliance and efficacy. To that end, the following should be considered when developing large-scale injury-prevention programs in the future: (1) low-cost, brief-time, packaged interventions; (2) adaptation of the program based on contextual factors for that setting (eg, sport, age, sex, environment); (3) incorporation of lay people (eg, coaches instead of athletic trainers or strength and conditioning specialists) to implement the program for that setting and population; (4) educating and obtaining organizational “buy in” from all levels (eg, school, club, administrators, coaches, players, parents); (5) embedding programs within the existing system when possible (eg, part of the warm-up or conditioning program, team challenge); and (6) developing written policies and procedures (ie, specifics of program, when to perform, how often to perform).

10. Although investigators have elucidated the influence of anatomical and structural factors on weight-bearing knee-joint neuromechanics,[116,119,120,153,154,160] this information has yet to be incorporated in our ACL injury-prevention efforts.

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