

Research Retreat IV: ACL Injuries—The Gender Bias, April 3–5, 2008, Greensboro, NC

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In April 2008, more than 80 attendees from across the United States and Canada participated in the fourth research retreat focused on the gender bias in anterior cruciate ligament (ACL) injury. The retreat was cofounded by Irene Davis, PhD, PT, and Mary Lloyd Ireland, MD, who hosted the 3 previous research retreats in Lexington, Kentucky, in April of 2001, 2003, and 2006. In the first year (2001), a consensus document of what we know, don't know, and still need to know related to this problem was developed.¹ Each subsequent retreat has revisited and updated the previous consensus statement as new evidence has emerged.^{2,3} Over the past 6 years, the number of attendees has grown, and the retreats have attracted some of the foremost nationally and internationally known clinicians and scientists with a common interest in ACL injury. We were pleased to continue this important work by hosting Research Retreat IV in Greensboro, North Carolina.

The meeting featured an opening presentation from ACL Retreat cofounder Mary Lloyd Ireland, MD; invited keynote presentations by Scott McLean, PhD, and Bruce Beynon, PhD — expert scientists well known for their research into factors associated with the gender bias in ACL injury; and 31 fifteen-minute podium presentations of recently completed research relating to the gender bias in ACL injuries. The opening presentation set the stage for the meeting by providing a historical perspective of what research has taught us about the ACL injury gender bias over the past 20 years, and the keynote presentations focused on the current knowledge and theories associated with neuromuscular, biomechanical, anatomical, and hormonal risk factors. The podium presentations were organized into thematic sessions centered on sagittal-plane landing mechanics, sex comparisons in landing and cutting, fatigue and perturbation studies in landing and cutting, anatomical and hormonal factors, and risk factor screening and prevention. Significant time was provided for group discussion after each keynote and each group of podium presentations. At the conclusion of the meeting, participants revisited and updated the consensus statement from the 2006 retreat.² Following are the consensus statement, keynote presentation summaries, and abstracts organized by topic and presentation order.

CONSENSUS STATEMENT

As in past retreats, the consensus statement was developed with the input of all participants at the end of

the meeting. Participants were divided into groups focusing on neuromuscular, biomechanical, anatomical, and hormonal factors and risk factor screening and prevention factors, as in previous meetings. Within each group, the relevant section of the previous consensus document was updated as to (1) what we know based on new evidence that has emerged from the literature and the research presented at the retreat, (2) what remains unknown about these factors related to ACL injury, and (3) the important directions for future research to address these unknowns. The individual groups then presented their working drafts to the entire group of participants for further discussion. After further refinement, final drafts were circulated to consensus leaders and attendees for final comment after the meeting.

From these discussions, some general themes emerged that deserve special note. First, when understanding the risk factors associated with injury, a working definition of the injury is critical: in this case, a noncontact ACL injury. The participants at this meeting support the definitions presented by Marshall et al⁴ that distinguish among direct contact, indirect contact and noncontact, where noncontact is defined as “forces applied to the knee at the time of injury resulted from the athlete's own movements and did not involve contact with another athlete or object.” It may very well be that the risk factors associated with noncontact injury (eg, landing and change direction with no opponent nearby) are different from the risk factors for injury resulting from indirect contact (eg, perturbation from another player before the landing), and these distinctions should be carefully considered and documented in future retrospective and prospective injury risk studies.

A second important theme was the need to move beyond the purely descriptive sex comparison studies that continue to dominate the literature. Although much has been learned about characteristic sex differences in neuromuscular and biomechanical function over the past 12 years, we still know very little about the underlying causes (eg, anatomical, hormonal, other) of these differences or whether many of the observed differences truly reflect an increased injury risk for the physically active female. Also, more integration across risk factor categories is needed, rather than the continued examination of isolated risk factors. It is well accepted that ACL injury is likely a multifactorial problem in which the effects of one risk factor may be difficult to identify without accounting for other relevant risk factors. This approach appears to be

particularly important in our understanding of anatomical factors, as the effect of one alignment factor on knee loading patterns is difficult to quantify without accounting for the collective alignment of the entire lower extremity. It is also possible that risk factors for noncontact ACL injury might even differ among sport populations: for example, between elite and recreational athletes or between men and women. These differences may stem from the varied incidences of key risk factors—such as anatomy, hormones, and movement—across populations.

A similar integrative approach is needed when reporting neuromuscular and biomechanical outcomes associated with the examination of these risk factors. Oftentimes, neuromuscular (eg, muscle strength, muscle activation) and biomechanical (eg, kinematic and kinetic) outcomes are reported in separate studies; seldom are neuromuscular, kinematic, and kinetic variables collected on the same group of participants and reported together. Although the collective findings of neuromuscular and biomechanical studies have led to assumptions of their relationship to one another (eg, quadriceps-dominant activation patterns leading to reduced knee flexion and greater shear forces), these relationships have rarely been tested empirically. In order for scientists and clinicians to gain a more comprehensive and accurate understanding of the effect of relevant risk factors on weight-bearing knee joint function, future authors are encouraged to take a more comprehensive approach to risk factor assessment and make every effort to integrate and relate the neuromuscular and biomechanical outcomes of interest. As a step toward that end, the consensus statements related to neuromuscular and biomechanical factors have been integrated into a single section of this document.

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REFERENCES

1. McClay Davis I, Ireland ML. ACL research retreat: the gender bias. Meeting report and abstracts. April 6–7, 2001. *Clin Biomech (Bristol, Avon)*. 2001;16(10):937–959.
2. Davis IM, Ireland ML, Hanaki S. ACL injuries: the gender bias. Research retreat III. *J Orthop Sports Phys Ther*. 2007;37(2):A1–A32.
3. McClay-Davis I, Ireland ML. ACL injuries: the gender bias. Proceedings and abstracts from Research Retreat II: April 4–5, 2003, Lexington, KY. *J Orthop Sports Phys Ther*. 2003;33(8):A2–A8.
4. Marshall SW, Padua DA, McGrath M. The incidence of ACL injury. In: Hewett TE, Shultz SJ, Griffin LY, eds. *Understanding and Preventing Non-Contact ACL Injuries*. Champaign, IL: Human Kinetics, 2007:5–29.

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NEUROMUSCULAR AND BIOMECHANICAL FACTORS

What We Know

1. The ACL is loaded by a variety of combined sagittal and nonsagittal mechanisms during dynamic sport postures considered to be high risk.¹⁻⁶
2. In vivo strain of the ACL is related to maximal load and timing of ground reaction forces.^{7,8}
3. Females typically display a more erect (upright) posture when contacting the ground during the early stages of deceleration tasks.⁹⁻¹²
4. Maturation influences biomechanical and neuromuscular factors.¹³⁻²⁰
5. Fatigue alters lower limb biomechanical and neuromuscular factors suggested to increase ACL injury risk.^{2,21-23} The effect of fatigue is most pronounced when combined with unanticipated landings, causing substantial central processing and central control compromise.²⁴

6. Trunk and upper body mechanics influence lower extremity biomechanical and neuromuscular factors.^{12,25,26}
7. Hip position and stiffness influence lower extremity biomechanical factors.^{2,10,27}

What We Don't Know

1. We still do not know the biomechanical and neuromuscular profiles that cause noncontact ACL rupture. An understanding of the causes is central to identifying how to prescreen at-risk individuals.
2. We do not yet understand the role of neuromuscular and biomechanical variability in the risk of indirect or noncontact ACL injury. Are there optimal levels of variability, and do deviations from these optimal levels increase the risk of injury?
3. Is noncontact ACL injury an unpreventable accident stemming from some form of cognitive dissociation

that drives central factors and the resulting neuromuscular and biomechanical patterns?

4. Is gross failure of the ACL caused by a single episode or multiple episodes?
5. Is noncontact ACL injury governed by single or potentially multiple high-risk biomechanical and neuromuscular profiles?

Where We Go From Here

1. To best understand movement patterns linked to noncontact ACL injury, authors should include comprehensive kinetic, kinematic, and neuromuscular (strength, postural stability, activation, and timing) profiles (henceforth referred to as *neuromechanics*).
2. We need to improve our understanding of neuromechanical variability within and between individuals as it relates to injury risk and injury mechanisms.
3. To fully appreciate joint loading profiles, we must better understand the interaction of anatomical structure, laxity, and neuromechanics.
4. Neuromechanical assessments of different tasks that mimic the mechanical demands commonly associated with sport-specific injury mechanisms should be performed with the testing methods and interpretations particular to the task demands.
5. Neuromechanical factors predicting ACL injuries need to be identified from prospective data.
6. We must develop tasks designed to stress the joint systems that mimic injury mechanisms and are realistic to the mechanistic purpose of the study. Further, musculoskeletal models describing cause-and-effect relationships need to be studied explicitly within a realistic injury scenario.
7. We should determine if a critical threshold of structural or functional weakness exists at which compensatory strategies become evident.
8. We need to continue to expand research models and analyses to include assessments of central processes (automaticity, reaction time, etc), cognitive processes (decision making, focus and attention, prior experience [expert versus novice, etc]), and metacognitive processes (monitoring psychomotor processes, etc).
9. Further understanding of the influence of the head, arms, and trunk segment on lower extremity neuromechanics is important.
10. Further understanding of the influence of the maturational process on lower extremity neuromechanics is necessary.
11. Work that translates laboratory measures to the field and field measures to the laboratory needs to be performed to help with the interpretation of field and laboratory findings. Validating commonly performed field assessment (eg, squatting, landing, etc) to known neuromechanics profiles is essential.
12. Technology must continue to advance and evolve to help us better understand in vivo mechanics, allow more precise transverse-plane measurements, and

improve the accuracy and ease of use of measurement techniques in general.

REFERENCES

1. Markolf KL, Burchfield DM, Shapiro MM, Shepard MF, Finerman GA, Slauterbeck JL. Combined knee loading states that generate high anterior cruciate ligament forces. *J Orthop Res*. 1995;13(6):930–935.
2. McLean SG, Huang X, Su A, Van Den Bogert AJ. Sagittal plane biomechanics cannot injure the ACL during sidestep cutting. *Clin Biomech (Bristol, Avon)*. 2004;19(8):828–838.
3. Shimokochi Y, Shultz SJ. Mechanisms of noncontact anterior cruciate ligament injury. *J Athl Train*. 2008;43(3):396–408.
4. Withrow TJ, Huston LJ, Wojtys EM, Ashton-Miller JA. The effect of an impulsive knee valgus moment on in vitro relative ACL strain during a simulated jump landing. *Clin Biomech (Bristol, Avon)*. 2006;21(9):977–983.
5. Yu B, Garrett WE. Mechanisms of non-contact ACL injuries. *Br J Sports Med*. Aug 2007;41(suppl 1):i47–i51.
6. Shin CS, Chaudhari AM, Andriacchi TP. The influence of deceleration forces on ACL strain during single-leg landing: a simulation study. *J Biomech*. 2007;40(5):1145–1152.
7. Cerulli G, Benoit DL, Lamontagne M, Caraffa A, Liti A. In vivo anterior cruciate ligament strain behaviour during a rapid deceleration movement: case report. *Knee Surg Sports Traumatol Arthrosc*. 2003;11(5):307–311.
8. Withrow TJ, Huston LJ, Wojtys EM, Ashton-Miller JA. The relationship between quadriceps muscle force, knee flexion, and anterior cruciate ligament strain in an in vitro simulated jump landing. *Am J Sports Med*. 2006;34(2):269–274.
9. Schmitz RJ, Kulas AS, Perrin DH, Riemann BL, Shultz SJ. Sex differences in lower extremity biomechanics during single leg landings. *Clin Biomech (Bristol, Avon)*. 2007;22(6):681–688.
10. Pollard CD, Sigward SM, Powers CM. Gender differences in hip joint kinematics and kinetics during side-step cutting maneuver. *Clin J Sport Med*. 2007;17(1):38–42.
11. Decker MJ, Torry MR, Wyland DJ, Sterett WI, Steadman RJ. Gender differences in lower extremity kinematics, kinetics and energy absorption during landing. *Clin Biomech (Bristol, Avon)*. 2003;18(7):662–669.
12. Houck JR, Duncan A, De Haven KE. Comparison of frontal plane trunk kinematics and hip and knee moments during anticipated and unanticipated walking and side step cutting tasks. *Gait Posture*. 2006;24(3):314–322.
13. Barber-Westin SD, Galloway M, Noyes FR, Corbett G, Walsh C. Assessment of lower limb neuromuscular control in prepubescent athletes. *Am J Sports Med*. 2005;33(12):1853–1860.
14. Barber-Westin SD, Noyes FR, Galloway M. Jump-land characteristics and muscle strength development in young athletes: a gender comparison of 1140 athletes 9 to 17 years of age. *Am J Sports Med*. 2006;34(3):375–384.
15. Hewett TE, Myer GD, Ford KR. Decrease in neuromuscular control about the knee with maturation in female athletes. *J Bone Joint Surg Am*. 2004;86(8):1601–1608.
16. Noyes FR, Barber-Westin SD, Fleckenstein C, Walsh C, West J. The drop-jump screening test: difference in lower limb control by gender and effect of neuromuscular training in female athletes. *Am J Sports Med*. 2005;33(2):197–207.
17. Quatman CE, Ford KR, Myer GD, Hewett TE. Maturation leads to gender differences in landing force and vertical jump performance: a longitudinal study. *Am J Sports Med*. 2006;34(5):806–813.
18. Hass CJ, Schick EA, Tillman MD, Chow JW, Brunt D, Cauraugh JH. Knee biomechanics during landings: comparison of pre- and postpubescent females. *Med Sci Sports Exerc*. 2005;37(1):100–107.
19. Russell PJ, Croce RV, Swartz EE, Decoster LC. Knee-muscle activation during landings: developmental and gender comparisons. *Med Sci Sports Exerc*. 2007;39(1):159–170.
20. Swartz EE, Decoster LC, Russell PJ, Croce RV. Effects of developmental stage and sex on lower extremity kinematics and vertical ground reaction forces during landing. *J Athl Train*. 2005;40(1):9–14.

21. Chappell JD, Herman DC, Knight BS, Kirkendall DT, Garrett WE, Yu B. Effect of fatigue on knee kinetics and kinematics in stop-jump tasks. *Am J Sports Med.* 2005;33(7):1022–1029.
22. Kernozek TW, Torry MR, Iwasaki M. Gender differences in lower extremity landing mechanics caused by neuromuscular fatigue. *Am J Sports Med.* 2008;36(3):554–565.
23. Orishimo KF, Kremenik IJ. Effect of fatigue on single-leg hop landing biomechanics. *J Appl Biomech.* 2006;22(4):245–254.
24. Blackburn JT, Padua DA. Influence of trunk flexion on hip and knee joint kinematics during a controlled drop landing. *Clin Biomech (Bristol, Avon).* 2008;23(3):313–319.
25. Kulas A, Zalewski P, Hortobagyi T, DeVita P. Effects of added trunk load and corresponding trunk position adaptations on lower extremity biomechanics during drop-landings. *J Biomech.* 2008;41(1):180–185.
26. Chaudhari AM, Hearn BK, Andriacchi TP. Sport-dependent variations in arm position during single-limb landing influence knee loading: implications for anterior cruciate ligament injury. *Am J Sports Med.* 2005;33(6):824–830.
27. Chaudhari AM, Andriacchi TP. The mechanical consequences of dynamic frontal plane limb alignment for non-contact ACL injury. *J Biomech.* 2006;39(2):330–338.

ANATOMICAL AND STRUCTURAL FACTORS

What We Know

1. The female ACL is smaller in length, cross-sectional area, and volume compared with the male ACL, even after adjusting for body anthropometry.¹
2. The female's femoral notch height is larger, but the femoral notch angle is smaller than in males, which may influence femoral notch impingement theory. Femoral notch width is a good predictor of ACL size (area and volume) in males but not in females. Femoral notch angle is a good predictor of ACL size in females but not in males.¹
3. The female ACL is less stiff (has a lower modulus of elasticity) and fails at a lower load level (lower failure strength), even after adjusting for age, body anthropometrics, and ACL size.²
4. The ultrastructural analysis of the ACL shows that the percentage of area occupied by collagen fiber (area of collagen fibers/total area of the micrograph) is lower in females than in males when adjusted for age and body anthropometrics.³
5. Adult females have greater anterior pelvic tilt,^{4,5} hip anteversion,⁵ tibiofemoral angle⁵, quadriceps angle,^{4,5} genu recurvatum,^{5,6} anterior knee laxity,⁷⁻¹¹ and general joint laxity¹²⁻¹⁴ than adult males.
6. In adults, no sex differences have been observed in measures of tibial torsion,⁵ navicular drop,⁴⁻⁶ or rearfoot angle.^{5,15}
7. Lower extremity alignments are different among maturational groups and also develop at different rates in males and females.¹⁶

What We Don't Know

1. Do variations in tibial slope (anterior-posterior and medial-lateral), ACL volume, ultrastructure, and laxity and femoral notch geometry, condylar geometry, and lower extremity alignment or the interaction among these variables increase the likelihood of ACL strain and failure?
2. Can physical activity influence these anatomical and structural factors and, if so, when, how, and for how long do the changes occur as a result of physical activity?

3. What effect does meniscal geometry have on ACL strain and failure during activity?
4. Do variations in anatomical and structural factors influence neuromuscular and biomechanical function?

Where We Go From Here

1. In a retrospective comparison of ACL-injured and healthy knees, smaller ACL volumes were noted in those with ACL injury (abstract 20). Further research is needed to examine whether decreased ACL volume predicts ACL injury.
2. Early evidence suggests an association between (1) posterior-inferior tibial slope and ACL insufficiency,¹⁷ and (2) elevated posterior-inferior tibial slope and increased ACL strain (abstract 23). More studies examining the influence of posterior tibial slope on ACL strain and failure are needed.
3. Early evidence suggests a difference between medial and lateral tibial slopes and that females have greater tibial slopes than males (abstract 23). Further research is needed to understand the relationship of these sex differences in tibial plateau geometry to ACL injury risk.
4. Early evidence (computational work) suggests that individual tibiofemoral joint geometry (including articular morphology and ligament insertions) influences ACL strain (abstract 22). Further work is needed to identify participant-specific tissue properties via laxity testing and to validate the computational models.
5. Future authors should also consider case-control study designs for examining structural factors because they are not acutely affected by ACL ruptures.
6. We should continue studying ACL injury mechanisms by simulating physiologic conditions in laboratory environments.
7. Interactions among tibial slope (anterior-posterior, medial-lateral), ACL volume, ultrastructure, and laxity and femoral notch geometry, condylar geometry, and lower extremity alignment should be examined for their potential to increase the likelihood of ACL strain and failure.
8. The influence of physical activity during maturation and across the life span on anatomical and structural factors should be addressed.

9. The role of meniscus geometry in ACL strain and failure during activity should be examined.
10. The influence of anatomical (eg, posture, structure, body composition) and structural (eg, tibial slope, condylar geometry) factors on neuromuscular and biomechanical function should be identified, both in adults and in maturing youth.

REFERENCES

1. Chandrashekar N, Slauterbeck J, Hashemi J. Sex-based differences in the anthropometric characteristics of the anterior cruciate ligament and its relation to intercondylar notch geometry: a cadaveric study. *Am J Sports Med.* 2005;33(10):1492–1498.
2. Chandrashekar N, Mansouri H, Slauterbeck J, et al. Sex-based differences in the tensile properties of the human anterior cruciate ligament. *J Biomech.* 2006;39(16):2943–2950.
3. Hashemi J, Chandrashekar N, Mansouri H, Slauterbeck JR, Hardy DM. The human anterior cruciate ligament: sex differences in ultrastructure and correlation with biomechanical properties. *J Orthop Res.* 2008;26(7):945–950.
4. Hertel J, Dorfman JH, Braham RA. Lower extremity malalignments and anterior cruciate ligament injury history. *J Sport Sci Med.* 2004;3(4):220–225.
5. Nguyen AD, Shultz SJ. Sex differences in clinical measures of lower extremity alignment. *J Orthop Sports Phys Ther.* 2007;37(7):389–398.
6. Trimble MH, Bishop MD, Buckley BD, Fields LC, Rozea GD. The relationship between clinical measurements of lower extremity posture and tibial translation. *Clin Biomech (Bristol, Avon).* 2002;17(4):286–290.
7. Beynon BD, Bernstein IM, Belisle A, et al. The effect of estradiol and progesterone on knee and ankle joint laxity. *Am J Sports Med.* 2005;33(9):1298–1304.
8. Rosene JM, Fogarty TD. Anterior tibial translation in collegiate athletes with normal anterior cruciate ligament integrity. *J Athl Train.* 1999;34(2):93–98.
9. Scerpella TA, Stayer TJ, Makhuli BZ. Ligamentous laxity and non-contact anterior cruciate ligament tears: a gender-based comparison. *Orthopedics.* 2005;28(7):656–660.
10. Shultz SJ, Sander TC, Kirk SE, Perrin DH. Sex differences in knee joint laxity change across the female menstrual cycle. *J Sports Med Phys Fitness.* 2005;45(4):594–603.
11. Uhorchak JM, Scoville CR, Williams GN, Arciero RA, St Pierre P, Taylor DC. Risk factors associated with non-contact injury of the anterior cruciate ligament: a prospective four-year evaluation of 859 West Point cadets. *Am J Sports Med.* 2003;31(6):831–842.
12. Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. *Ann Rheum Dis.* 1973;32(5):413–418.
13. Jansson A, Saartok T, Werner S, Renstrom P. General joint laxity in 1845 Swedish school children of different ages: age- and gender-specific distributions. *Acta Paediatr.* 2004;93(9):1202–1206.
14. Rikken-Bultman DG, Wellink L, van Dongen PW. Hypermobility in two Dutch school populations. *Eur J Obstet Gynecol Reprod Biol.* 1997;73(2):189–192.
15. Astrom M, Arvidson T. Alignment and joint motion in the normal foot. *J Orthop Sports Phys Ther.* 1995;22(5):216–222.
16. Shultz SJ, Nguyen AD, Schmitz RJ. Differences in lower extremity anatomical and postural characteristics in males and females between maturation groups. *J Orthop Sports Phys Ther.* 2008;38(3):137–149.
17. Brandon ML, Haynes PT, Bonamo JR, Flynn MI, Barrett GR, Sherman MF. The association between posterior-inferior tibial slope and anterior cruciate ligament insufficiency. *Arthroscopy.* 2006;22(8):894–899.

HORMONAL FACTORS

What We Know

1. A consensus is emerging from the literature that the likelihood of suffering an ACL injury is not evenly distributed across the menstrual cycle; instead, the risk of suffering an ACL disruption is greater during the preovulatory phase of the menstrual cycle than in the postovulatory phase.¹⁻⁵ During the preovulatory phase, hormone levels are changing dramatically, falling to their nadirs with the onset of menses and once again rising rapidly near ovulation.
2. Evidence exists for sex hormone receptors (estrogen, testosterone, and relaxin) on the human ACL.⁶⁻¹⁰
3. Evidence exists for sex hormone receptors (estrogen, testosterone) on skeletal muscle.¹¹⁻¹³
4. Large individual variations in female hormone profiles should be appreciated in study designs.¹⁴
5. Consistent with individual variability in hormone profiles, the magnitude of change in laxity (ie, anterior knee laxity, genu recurvatum) that females experience across the menstrual cycle varies substantially¹⁵ (abstract 19).
6. Because of the individual variability in hormone profiles across the menstrual cycle, a single measurement within a single phase (even with hormonal

confirmation) is not adequate to accurately characterize the same hormone profile or time point in a particular phase of the menstrual cycle for all females.

7. The mechanical and molecular properties of the ACL are likely influenced not only by estrogen but by the interaction of several sex hormones, secondary messengers, remodeling proteins, and mechanical stresses.^{7,10,14,16-18}
8. A time-dependent effect exists for sex hormones and other remodeling agents to influence a change in ACL tissue characteristics.^{10,14}
9. Some evidence in animal models suggests interactions among mechanical stress, hormones, and altered ACL structure and metabolism.¹⁹⁻²¹

What We Don't Know

1. What is the underlying mechanism for the increased likelihood of ACL injury in the preovulatory phase?
2. How do ACL injury rates vary in females who are eumenorrheic or oligomenorrheic or using oral contraceptives?
3. What are the effects of sex hormones on ACL structure, metabolism, and mechanical properties? The influence of hormones on ACL biology has been examined in a variety of animal models²¹⁻³⁰ and

relatively few human studies,^{18,31} but a consensus is lacking due to variations in study designs and the varieties of species examined.

4. What is the role of hormones on skeletal muscle structure and function in controlling dynamic motion? What, if any, changes occur in neuromuscular and biomechanical risk factors across the menstrual cycle? Although previous authors have suggested that cyclical changes in neuromuscular and biomechanical control may be negligible,^{32–34} these results may be incomplete due to the individual variations in hormone profiles (see What We Know, items 3–5).
5. Does the rate of increase or time duration of amplitude peaks in hormone fluctuations play a role in soft tissue changes?
6. For those females who experience changes in knee laxity across the menstrual cycle, what are the clinical implications of these changes on weight-bearing knee joint stability and neuromechanics?
7. What are the interactions among mechanical stress on the ACL, hormone profiles, and altered ACL structure and metabolism in physically active females?

Where We Go From Here

1. We must continue to consider the interactive effect of all relevant hormones on soft tissue structures and ACL injury risk.
2. The mechanisms by which sex hormones may explain sex-specific differences in ACL structure, metabolism, and mechanical properties that have been observed (also see Anatomical and Structural Factors) should be defined.
3. More studies using research designs relevant to the healthy, physically active female are needed to examine hormonal effects on ACL structural, metabolic, and mechanical properties.
4. When examining hormonal influences on knee joint function and ACL injury risk, females using oral contraceptives and those with irregular menstrual cycles (amenorrhea and oligomenorrhea) should also be investigated. The type of contraceptive should be documented and both the endogenous and exogenous levels of sex hormones evaluated.
5. Future studies of hormone risk factors should focus more on individual results, rather than mean values, as much variability exists in individual menstrual cycle characteristics.
6. Improved methods of measuring individual hormone profiles to better assess the complex roles of hormones in soft tissue changes should be developed. We need to verify phases of the cycle with actual hormone measures and consider all relevant hormones, including estrogen, progesterone, and possibly others. To confirm that the desired time in the cycle or a particular phase is truly captured in future study designs, hormone samples should be taken over multiple days rather than measured at a single time point.

7. When making female-to-male comparisons, factors should be assessed during the early follicular phase, when hormone levels are at their nadirs (preferably 3–7 days postmenses) to decrease the potential for cyclic hormonal fluctuations to confound the anatomical, neuromuscular, and biomechanical outcomes of interest.
8. The interaction among hormones, mechanical loading, and ACL mechanical properties in the physically active female should be examined.

REFERENCES

1. Arendt EA, Bershadsky B, Agel J. Periodicity of noncontact anterior cruciate ligament injuries during the menstrual cycle. *J Genl Spec Med.* 2002;5(2):19–26.
2. Beynon BD, Johnson RJ, Braun S, et al. The relationship between menstrual cycle phase and anterior cruciate ligament injury: a case-control study of recreational alpine skiers. *Am J Sports Med.* 2006;34(5):757–764.
3. Myklebust G, Engebretsen L, Braekken IH, Skjoldberg A, Olsen OE, Bahr R. Prevention of anterior cruciate ligament injuries in female team handball players: a prospective intervention study over three seasons. *Clin J Sport Med.* 2003;13(2):71–78.
4. Slauterbeck JR, Fuzie SF, Smith MP, et al. The menstrual cycle, sex hormones, and anterior cruciate ligament injury. *J Athl Train.* 2002;37(3):275–280.
5. Wojtyś EM, Huston L, Boynton MD, Spindler KP, Lindenfeld TN. The effect of menstrual cycle on anterior cruciate ligament injuries in women as determined by hormone levels. *Am J Sports Med.* 2002;30(2):182–188.
6. Dragoo JL, Lee RS, Benhaim P, Finerman GA, Hame SL. Relaxin receptors in the human female anterior cruciate ligament. *Am J Sports Med.* 2003;31(4):577–584.
7. Faryniarz DA, Bhargava M, Lajam C, Attia ET, Hannafin JA. Quantitation of estrogen receptors and relaxin binding in human anterior cruciate ligament fibroblasts. *In Vitro Cell Dev Biol Anim.* 2006;42(7):176–181.
8. Hamlet WP, Liu SH, Panossian V, Finerman GA. Primary immunolocalization of androgen target cells in the human anterior cruciate ligament. *J Orthop Res.* 1997;15(5):657–663.
9. Liu SH, al-Shaikh RA, Panossian V, et al. Primary immunolocalization of estrogen and progesterone target cells in the human anterior cruciate ligament. *J Orthop Res.* 1996;14(4):526–533.
10. Lovering RM, Romani WA. Effect of testosterone on the female anterior cruciate ligament. *Am J Physiol Regul Integr Comp Physiol.* 2005;289(1):R15–R22.
11. Lemoine S, Granier P, Tiffocche C, Rannou-Bekono F, Thieulant ML, Delmarche P. Estrogen receptor alpha mRNA in human skeletal muscles. *Med Sci Sports Exerc.* 2003;35(3):439–443.
12. Sinha-Hikim I, Taylor WE, Gonzalez-Cadavid NF, Zheng W, Bhasin S. Androgen receptor in human skeletal muscle and cultured muscle satellite cells: up-regulation by androgen treatment. *J Clin Endocrinol Metab.* 2004;89(10):5245–5255.
13. Wiik A, Glenmark B, Ekman M, et al. Oestrogen receptor beta is expressed in adult human skeletal muscle both at the mRNA and protein level. *Acta Physiol Scand.* 2003;179(4):381–387.
14. Shultz SJ, Kirk SE, Johnson ML, Sander TC, Perrin DH. Relationship between sex hormones and anterior knee laxity across the menstrual cycle. *Med Sci Sports Exerc.* 2004;36(7):1165–1174.
15. Shultz SJ, Gansneder BG, Sander TC, Kirk SE, Perrin DH. Absolute hormone levels predict the magnitude of change in knee laxity across the menstrual cycle. *J Orthop Res.* 2006;24(2):124–131.
16. Romani W, Patrie J, Curl LA, Flaws JA. The correlations between estradiol, estrone, estriol, progesterone, and sex hormone-binding globulin and anterior cruciate ligament stiffness in healthy, active females. *J Womens Health (Larchmt).* 2003;12(3):287–298.

17. Slauterbeck JR, Hickox MS, Beynon BD, Hardy DM. Anterior cruciate ligament biology and its relationship to injury forces. *Orthop Clin North Am.* 2006;37(4):585–591.
18. Yu WD, Panossian V, Hatch JD, Liu SH, Finerman GA. Combined effects of estrogen and progesterone on the anterior cruciate ligament. *Clin Orthop Rel Res.* 2001;383:268–281.
19. Comerford EJ, Tarlton JF, Avery NC, Bailey AJ, Innes JF. Distal femoral intercondylar notch dimensions and their relationship to composition and metabolism of the canine anterior cruciate ligament. *Osteoarthritis Cartilage.* 2006;14(3):273–278.
20. Comerford EJ, Tarlton JF, Innes JF, Johnson KA, Amis AA, Bailey AJ. Metabolism and composition of the canine anterior cruciate ligament relate to differences in knee joint mechanics and predisposition to ligament rupture. *J Orthop Res.* 2005;23(1):61–66.
21. Lee CY, Liu X, Smith CL, et al. The combined regulation of estrogen and cyclic tension on fibroblast biosynthesis derived from anterior cruciate ligament. *Matrix Biol.* 2004;23(5):323–329.
22. Komatsuda T, Sugita T, Sano H, et al. Does estrogen alter the mechanical properties of the anterior cruciate ligament? An experimental study in rabbits. *Acta Orthop Scand.* 2006;77(6):973–980.
23. Liu SH, al-Shaikh RA, Panossian V, Finerman GA, Lane JM. Estrogen affects the cellular metabolism of the anterior cruciate ligament: a potential explanation for female athletic injuries. *Am J Sports Med.* 1997;25(5):704–709.
24. Rau MD, Renouf D, Benfield D, et al. Examination of the failure properties of the anterior cruciate ligament during the estrous cycle. *Knee.* 2005;12(1):37–40.
25. Seneviratne A, Attia E, Williams RJ, Rodeo SA, Hannafin JA. The effect of estrogen on ovine anterior cruciate ligament fibroblasts: cell proliferation and collagen synthesis. *Am J Sports Med.* 2004;32(7):1613–1618.
26. Slauterbeck J, Clevenger C, Lundberg W, Burchfield DM. Estrogen level alters the failure load of the rabbit anterior cruciate ligament. *J Orthop Res.* 1999;17(3):405–408.
27. Strickland SM, Belknap TW, Turner SA, Wright TM, Hannafin JA. Lack of hormonal influences on mechanical properties of sheep knee ligaments. *Am J Sports Med.* 2003;31(2):210–215.
28. Warden SJ, Saxon LK, Castillo AB, Turner CH. Knee ligament mechanical properties are not influenced by estrogen or its receptors. *Am J Physiol Endocrinol Metab.* 2006;290(5):1034–1040.
29. Wentorf FA, Sudoh K, Moses C, Arendt EA, Carlson CS. The effects of estrogen on material and mechanical properties of the intra- and extra-articular knee structures. *Am J Sports Med.* 2006;34(12):1948–1952.
30. Woodhouse E, Schmale GA, Simonian P, Tencer A, Huber P, Seidel K. Reproductive hormone effects on strength of the rat anterior cruciate ligament. *Knee Surg Sports Traumatol Arthrosc.* 2007;15(4):453–460.
31. Yu WD, Liu SH, Hatch JD, Panossian V, Finerman GA. Effect of estrogen on cellular metabolism of the human anterior cruciate ligament. *Clin Orthop Rel Res.* 1999;366:229–238.
32. Abt JP, Sell TC, Laudner KG, et al. Neuromuscular and biomechanical characteristics do not vary across the menstrual cycle. *Knee Surg Sports Traumatol Arthrosc.* 2007;15(7):901–907.
33. Chaudhari AM, Lindenfeld TN, Andriacchi TP, et al. Knee and hip loading patterns at different phases in the menstrual cycle: implications for the gender difference in anterior cruciate ligament injury rates. *Am J Sports Med.* 2007;35(5):793–800.
34. Dedrick GS, Sizer PS, Merkle JN, et al. Effect of sex hormones on neuromuscular control patterns during landing. *J Electromyogr Kinesiol.* 2008;18(1):68–78.

RISK FACTOR SCREENING AND PREVENTION

What We Know

1. Various training programs that incorporate elements of balance training, plyometric training, education, strengthening, and feedback alter biomechanical and neuromuscular variables thought to contribute to ACL injury.¹⁻⁵
2. Various intervention programs reduce the incidence of ACL injuries.⁶⁻⁸
3. The protective effects of ACL injury prevention training programs appear to be transient.⁹⁻¹¹

What We Don't Know

1. What are the mechanisms underlying the success of various injury prevention programs? Specifically, which elements of an injury prevention program (strengthening, plyometrics, etc) produce the desired protective effect?
2. How much training stimulus (ie, duration and timing) is required to produce the desired protective effect, and how long does the effect last?
3. At what age should an injury prevention program be implemented to reduce potential neuromuscular and biomechanical risk factors?
4. Do intervention programs need to be tailored to specific sports, specific ages, or an individual athlete's needs?

5. Do intervention programs influence athletic performance?

Where Do We Go From Here?

1. We should continue conducting prospective, randomized controlled studies to evaluate the ability of prevention strategies to alter neuromuscular and biomechanical risk factors and prevent ACL injury.
2. Evidence is emerging that the efficacy of ACL injury prevention programs is not uniform across all individuals (abstracts 29 and 31). Further research is needed to establish the characteristics of "responders" and "nonresponders" to an ACL injury prevention program.
3. To determine the optimal approach to alter biomechanical and neuromuscular risk factors thought to contribute to ACL injury, we should evaluate various intervention modalities (individually or in combination).
4. We need to develop and standardize screening tools to identify at-risk individuals who will benefit most from intervention programs.
5. How athletes of different stages of maturation respond to injury prevention programs should be evaluated.
6. The optimal timing of an intervention with respect to the competitive season should be determined.

7. Programs that improve compliance should be developed, and we need to understand why people comply or do not comply with programs.
8. The dose-response relationship with intervention and prevention programs should be investigated.
9. Whether injury prevention programs affect athletic performance should be evaluated.
10. Registries for ACL injury should be established to enable monitoring of long-term trends in ACL injury incidence, including sex differences.
11. Standard definitions for ACL injury should be developed to facilitate cross-study comparisons (eg, direct contact, indirect contact, and noncontact injury).

REFERENCES

1. Hurd WJ, Chmielewski TL, Snyder-Mackler L. Perturbation-enhanced neuromuscular training alters muscle activity in female athletes. *Knee Surg Sports Traumatol Arthrosc.* 2006;14(1):60–69.
2. Myer GD, Ford KR, Brent JL, Hewett TE. The effects of plyometric vs. dynamic stabilization and balance training on power, balance, and landing force in female athletes. *J Strength Cond Res.* 2006;20(2):345–353.
3. Myer GD, Ford KR, McLean SG, Hewett TE. The effects of plyometric versus dynamic stabilization and balance training on lower extremity biomechanics. *Am J Sports Med.* 2006;34(3):445–455.
4. Onate JA, Guskiewicz KM, Marshall SW, Giuliani C, Yu B, Garrett WE. Instruction of jump-landing technique using videotape feedback: altering lower extremity motion patterns. *Am J Sports Med.* 2005;33(6):831–842.
5. Pollard CD, Sigward SM, Ota S, Langford K, Powers CM. The influence of in-season injury prevention training on lower-extremity kinematics during landing in female soccer players. *Clin J Sport Med.* 2006;16(3):223–227.
6. Hewett TE, Lindendorf TN, Riccobene JV, Noyes FR. The effect of neuromuscular training on the incidence of knee injury in female athletes: a prospective study. *Am J Sports Med.* 1999;27(6):699–706.
7. Mandelbaum BR, Silvers HJ, Watanabe DS, et al. Effectiveness of a neuromuscular and proprioceptive training program in preventing anterior cruciate ligament injuries in female athletes: 2-year follow-up. *Am J Sports Med.* 2005;33(7):1003–1010.
8. Petersen W, Braun C, Bock W, et al. A controlled prospective case control study of a prevention training program in female team handball players: the German experience. *Arch Orthop Trauma Surg.* 2005;125(9):614–621.
9. Graves JE, Martin AD, Miltenberger LA, Pollock ML. Physiological responses to walking with hand weights, wrist weights, and ankle weights. *Med Sci Sports Exerc.* 1988;20(3):265–271.
10. Häkkinen K, Alen M, Kraemer WJ, et al. Neuromuscular adaptations during concurrent strength and endurance training versus strength training. *Eur J Appl Physiol.* 2003;89(1):42–52.
11. Petibois C, Déléris G. Effects of short- and long-term detraining on the metabolic response to endurance exercise. *Int J Sports Med.* 2003;24(5):320–325.