Sex and the ACL: Does It Really Matter?

- Mechanism of Injury
- Core
- Research
- Prevention
- MLI

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25 Years After Appreciating Non-contact ACL higher rates in basketball, what progress have we made?

25 Years of Observation has led to many research ideas

- 80 males, 64 females
  - Knee injuries: Number (% of gender)
    - Males, 11 (13%); Females 34 (53%) p<.0001
  - 20 (18%) underwent surgery
    - Males 6 (7.5%); Females 20 (31%) – 21 surgeries
      p=.0007
  - ACL reconstructions: 2 males, 8 females

  M. L. Ireland, C. Wall, “Epidemiology and Comparison of Knee Injuries in Elite Male and Female United States Basketball Athletes” MSSE 1989. Presented at ACSM Annual Meeting Salt Lake City, Utah
Injury Mechanisms – Body Positions

Basketball

VROOM . . .
- Valgus
- Rotation
- Out
- Of control
- Movement

It takes 70 milliseconds to tear the ACL
Knee: Cone of Stability

Basketball: non-contact, unexpected, not thinking

Position of No Return

- Is it really knee valgus?
  - Seen from frontal plane, YES, but NOT from sagittal plane
  - Injury – Landing Pivot Shift
  - Knee: Anterior subluxation of tibia
  - Hip: Internal Rotation and Adduction
  - Femoral rotation
    - first internal, then external
  - Anterior tibial translation = “valgus collapse”
Observation of ACL Injury Patterns

- Allow us to develop hypotheses in the lab for computer modeling
- Bring lab studies back out to the training room
- Joint position and muscle activation is critical to knee stability
- Strength is not as important as timing of activation
  - Best: hamstrings firing on flexed knee-hip
  - Worst: quadriceps dominance in extended hip-knee
“Core” Definition
• (Latin) cor HEART
• Central or innermost part of anything
• The most important part
• Essence; pith
• The hard central part of an apple, pear, etc., that contains seeds

“Core Stability”
• Defined as the lumbopelvic-hip complex where a person’s center of gravity is located and all movement begins
• Provides a stable base to allow optimal kinetic chain function
• Weak core does not allow for production of efficient movements leading to possible injury

Lateral Core Muscles
• Stabilize the hip laterally
• Transfer force
Trunk muscles and movements

- Flexion & Extension
- Rotation
- Lateral Flexion


RESULTS & CONCLUSIONS:

- Hip external rotation strength was the only useful predictor of injury status
- Males produced greater hip ABD, ER, and lumbar spine stability measures
- Uninjured athletes were significantly stronger in hip ABD and ER


Single leg squat test

This subject is demonstrating excessive movement of the right femur into adduction and internal rotation, both of which are positive signs of decreased core muscle capacity.

Isometric femoral abduction strength test and isometric femoral external rotation strength test

Timed isometric flexor endurance and side bridge tests


Single-Leg Squat is the best assessment of altered core stability and neuromuscular activity


Multiple Factors Resulting in ACL Injuries

• NOT modifiable:
  • Anatomic/Structural
  • Hormonal
• Modifiable:
  • Neuromuscular/biomechanical
• Expert think tanks agree that modifiable factors are most important
• Emphasize modifiable factors for return-to-play and prevention programs

Simple Single-Leg Squat
- Give clinicians information on neuromuscular control

Plank Test
- Measures lumbar and pelvic control in side or sagittal plane
- Can see excessive lumbar lordosis

Observe in Fatigue and Non-fatigue states


Alignment
Proximal control / Core stability

POSITION OF SAFETY
HEAD Neutral, Neck neutral, LUMBAR SPINE neutral, PELVIS anterior, FEMUR neutral, KNEE neutral

POSITION OF NO RETURN
HEAD Forward, NECK hyperextended, LUMBAR SPINE anteriorly rotated, PELVIS neutral, FEMUR anteriorly rotated, KNEE neutral

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Ongoing ACL Research at the University of Kentucky

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ACL Research Current:

- ACL outcomes study: track pre-op, 3, 6, 9 months after surgery, assess new outcomes tests, gait, and jumping performance

- Currently the study tracks:
  - Functional tests: Trunk control test and endurance, knee frontal and sagittal plane control, quadriceps strength
  - Gait, Drop vertical jump 6 and 9 months
  - 9 months assess sport readiness, put through fatigue protocol reassess functional tests
  - Provide, patients, MD’s feedback at 6 months of progress, hope it has immediate (for patients) and long-term benefits (practice)
Gait Analysis, Balance, and Strength

- Current Studies
- Normal subjects
- Post ACL recon vs normal
- Trunk measurements
- Relationships of hip, trunk, balance, gait to injuries
- What do the functional tests we do really tell us?

What we test:

- **Trunk control**: through side plank, plank test
- **Knee control**: Repeated step downs - assess frontal and Sagittal plane control
- **Knee strength**: Isometric quadriceps strength test

Through these functional tests we aim to better quantify, qualitative assessments of neuromuscular control that we feel may predispose someone to a subsequent injury.

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- 40 females (20 ACL reconstructions, 20 controlled) underwent instrumented gait analysis.
  - Between group and limb comparisons made for vertical impact force, loading rate, sagittal plane knee and hip angles.

- **We are not doing as well as we think we are!**

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- **Results**:
  - Significantly greater initial vertical impact force and loading rates.
  - Smaller knee extensor moment and hip angle during walking.
  - Significant gait deviations in elevated impact loading and loading rates that did not resolve long term after the individual resumed full activities. This may contribute to early risk of degenerative joint disease.
A Comparison of Knee Kinetics between Male and Female Recreational Athletes in Stop-Jump Tasks.


Women had greater knee extension valgus moment ACL stress greatest backward stop jump

The Three Stop-Jump Tasks

Functional Assessment Tests

- Basic vs. Advanced
  - Strength – leg press
  - Balance
  - Timed agilities
  - Sport-specific dry-land testing to show athlete level of readiness to return to field of competition

Tim Hewett
Valgus collapse
Functional Assessment

Functional Tests: Triple Jump

Prevention Program Websites

- Cincinnati Children’s Hospital
  www.cincinnatichildrens.org/svc/alpha/a/sports-med/acl.htm
- PEP Program
  - ACL Prevent
    www.aclprevent.com
  - Soccer program
  - Santa Monica, California
Injury Prevention-ACL Tear

Simple as: ABC’s

• Agility
• Balance
• Core
• Strength

Developing an ACL Prehab Program

Core stabilization starts at a young age
ACL Reconstructions

- Most common age ACL reconstructions in US: 15 for females, 18 for males
  — American Board of Orthopaedic Surgeons
- Females are younger than males by 5 years

15 YO Female Soccer Athlete is the most non-compliant and difficult to treat after ACL reconstruction

Player perception:
- 43% were able to play at the same level.
- 27% felt they did not perform at the level before their ACL tear
- 30% were unable to return to play.
- Player position did not statistically affect the ability to return to play.
- Fear of reinjury or further damage was cited by 50% of players who did return to play.

We are not doing as well as we thought!

Does age, level of play increase ACL Risk?

Soccer athletes <16 who move up are more likely to be injured than seniors
“The Uneven Playing Field”

By Michael Sokolov

• Janelle Pierson
  • High school soccer player
  • Multiple ACL injuries, both knees
  • Mindset: after surgeries, multiple knee injuries
    • Rehab hard
    • Get back on the field
    • Compete fiercely
    • Hope not to be injured

Dr. Ruth Jackson

“Do the best you can for those who need you . . .
. . . you know that.”

Dr. Jacquelin Perry
The “Grande Dame” of Orthopaedics

• The country’s foremost expert on gait analysis
  • May 31, 1918 — March 11, 2013
Osteoarthritis
Sex Differences and Are We Preventing OA by ACLR?

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Disclosures (PI)

• EARLY DIAGNOSIS
  – NIH R01 AR052784
  – NIH BIRT AR052784-04S1
• EARLY TREATMENT
  – NIH R21 046995
  – NIH R01 AR051963NIH
  – NIH RC2AR058929
  – NIH P60 AR054731
• PREVENT OR DELAY OA
  – NIH R13 AR056563
  – NIH U13 AR060692
Who is At Risk for Osteoarthritis?

**Obesity (5X greater risk)**
- Prevalent in US, developed world.

**Aging (50% > age 65)**
- Prevalent in US, developed world.

**Joint Injury (50% in 10 years)**
- Young and active → EARLY DISABILITY

Women and Knee Osteoarthritis

- Higher Incidence
- More Pain
- Less Function
- Greater Disability
  - Physical
  - Psychological
Effects of Age and Gender

• Overall, 4X the risk. Sangha 2000

• Prior to Age 50, women’s risk of OA is similar to men. Arden and Nevitt 2006
  – ?Menopause
  – ?Estrogen/HRT
  – ?Anatomy

Pre-Title 9 Cohorts!

ACLT Accelerates OA Development

• ACLT risk is higher in females

• Young female soccer players:
  – Mean: Age 31 years, BMI of 23
  – 82% radiographic changes
  – 75% with knee symptoms
  – 51% radiographic knee OA

Lohmander et al, Arthritis Rheum 2004
**Sex and Age in ACLT**

- **Females**
  - 51.4% overall
  - 78% ages 14-18
  - 44% ages 18-30
  - 35% ages 31-40


**Articular Cartilage After ACLT**

- Cartilage Appears “Normal”
- Subsurface Abnormalities
  - Optical Coherence Tomography
  - MRI T2 Map
  - **Ultrashort Echo Time (UTE) Enhanced T2* Map**

Enhanced Clinical Diagnosis of Early Osteoarthritis
NIH R01 AR052784
Female Cartilage at Risk!

- Females have thinner cartilage than males. (Faber)
- Thinner cartilage has greater cell death and fracture risk after impact injury. (Szczodry / Chu 2009)

Recovery After Anatomic ACLR

- MRI UTE T2* to the MFC deep subsurface cartilage is elevated after ACLT
- In some, deep UTE T2* return to levels of uninjured controls at 2 years after aACLR suggestive of healing.
Scott Dye “Envelope of Function”

- After ACLT
  - Zone of Homeostasis
    - Nonweightbearing – brief period
    - 2 Hours of Walking
  - Zone of Supraphysiological Overload
    - 2 Hours of Soccer
  - Zone of Structural Failure
    - 6 Hours of Soccer
  - Zone of Subphysiological UnderLoad
    - Nonweightbearing

Dye, Clin Orthop, 1996

Joint/Cartilage Recovery Takes Time

- Symptoms
- Neuromuscular
- Bone Scan
- Synovitis/Effusions
- % recovery of Cartilage UTE-T2*
  - 6 months ≈ 50%
  - 1 year ≈ 70%
  - 2 years ≈ 70%
The Effects of ACLR

- Successful at stabilizing the knee Cutting Sports
  - High Level, High Intensity Activities
- Joint/Cartilage Homeostasis may lag behind symptomatic and neuromuscular recovery

In some individuals, ACLR may “give the patient enough stability to go back to strenuous sports and then ruin the knee” * Jan Gillquist


Conclusions

- Women suffer more from OA than men.
- Young females with ACLT are at increased risk for premature knee OA.
- Neuromuscular recovery may precede recovery of joint and cartilage homeostasis.
- Return to sports/activities need to be also tailored to biological recovery.
- Biological markers and personalized treatment strategies are needed.
Sex and the ACL

Epidemiology and Risk Factors

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Disclosures

• Sports Medicine Fellowship Support
  • Smith & Nephew
• Medical Student Educational Support
  • Synthes

Epidemiology

• 100,000-200,000 ACL injuries a year in U.S.
• At least 50% in young athletes
• Female participation has dramatically increased
• Females at increased risk
  • Overall
  • Sport specific
  • Sports that require pivoting, landing from a jump or deceleration (soccer, basketball, handball)
Risk Factors for ACL Injury

**INTRINSIC**

**EXTRINSIC**

**UCLA Health**

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**Risk Factors for ACL Injury**

- **ENVIRONMENTAL**
- **NEUROMUSCULAR**
- **HORMONAL**
- **ANATOMIC**
- **OTHER**
  - Previous injury
  - Genetic
  - Cognitive function

**UCLA Health**

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**Environmental Risk Factors**

- **Surface**
  - Norwegian handball: Female > risk on synthetic floors (Olson et al)
  - Grass types (Bermuda vs. Rye)
  - Artificial surfaces
- **Footwear**
  - Cleat characteristics (high torsional resistance)
- **Weather**
  - Hot weather in open stadiums
  - High evaporation rates and low rainfall (Orchard, et al)
- **Bracing**
  - Prophylactic brace decreased risk of knee injury (Sider et al)
  - Remains controversial

**UCLA Health**
Neuromuscular Risk Factors

- Patterns of Movement
  - Female vs. Male (Chappell et al, Decker et al)
    - Less knee and hip flexion
    - Increased knee valgus
    - Increased internal rotation of hip
    - Increased external rotation of tibia

- Patterns of Muscle Activation
  - Increased quadriceps activation in females (Huston et al, Wolys et al, Malinzak et al)
  - Decreased hamstring activity
  - Produces anterior displacement of the tibia

Neuromuscular Risk Factors

- Muscle Stiffness
  - Decreased knee stiffness in females (Granata et al)
  - Ability to resist anterior tibial translation

- Core Stability
  - Increase in size and weight at puberty (in absence of neuromuscular control) may put females at risk (Hewett et al)

Hormonal Risk Factors

- Interest in hormonal influences on ACL injury heightened with the discovery of receptors for sex hormones in ACL tissue.
- Sex hormones affect ligament loading properties
  - Animal Tissue Studies (sheep, goat, rabbit)
    - Conflicting results
      - Decreased load to failure (Slauterbeck et al)
      - No difference (Geneviratue et al., Strickland et al)
Hormonal Risk Factors

• Human Tissue Studies
  • Dose dependent decrease in fibroblast proliferation and type 1 procollagen synthesis (Yu et al.)
  • This may lead to increases in anterior knee laxity
• Menstrual Cycle and ACL Injury
  • Female sex hormone concentrations fluctuate during the menstrual cycle.
  • Determining the phase during injury is difficult.
  • Increased risk has been reported in most phases of the menstrual cycle.
    • Ovulatory phase (Wolys et al.)
    • Immediately before or after onset of menses (Slauterbeck et al)
    • Pre-ovulatory (Beynnon et al)
  • Time dependent effects of sex hormones need to be taken into account.

Hormonal Risk Factors

• Hormonal intervention to reduce the risk of ACL injury is not justified.
• No modifications in activity are recommended for females any time during their menstrual cycle.

Anatomic Risk Factors

• Notch width/Notch width index (NWI)
• Q-angle
• Knee valgus
• Posterior tibial slope/Tibial plateau depth
• ACL size and volume
• Knee laxity
• Subtalar joint pronation & navicular drop
• Articular cartilage surface geometry
• BMI
Anatomic Risk Factors

- Notch width/NWI
  - Different measurement techniques (MRI/x-ray)
  - Females < males
- Q-Angle
  - Females > males
  - May predict varus-valgus knee position
- Knee Valgus
  - Females > dynamic knee valgus on landing (Ford et al, Hewett et al)
  - Posterior Tibial Slope
    - Females > males
    - Combined increased posterolateral tibial plateau slope and shallow medial tibial plateau (Hashemi et al)

Anatomic Risk Factors

- ACL size, volume and properties
  - Females < males (Anderson et al, Uhorchak et al)
  - Possible different mechanical properties in females
- Subtalar joint pronation & navicular drop and BMI
  - Conflicting conclusions in the literature

Anatomic Risk Factors

The goal of identifying anatomic risk factors is essential to our understanding of ACL injury for both males and females, however, these risk factors, unlike others, may be difficult to alter.
Other Risk Factors

- Prior Injury
  - ACL reconstruction risk for injury to other knee or graft. (Orchard et al, Walden et al)
  - Ankle injury (Kramer et al)

- Genetic
  - Familial (Flynn et al, Harner et al)
  - Genotypes
    - COL5A1 gene associated with ACL tears in females (Posthumus et al)

- Cognitive Function
  - Slower reaction time/processing speed (Swanik et al)

Summary

- Females are at greater risk for sustaining an ACL injury.
- Reasons are highly complicated and multifactorial.
- Consensus is difficult given differences in study design and classification schemes.
- Future research will lead to better understanding of sex differences and provide a pathway to prevention.

Thank you.
ACL Tear Risk: Do Hormones Matter?

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- Beckman Dickenson

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  - Partnership for Clean Competition
The gender discrepancy

- Women 2-9 times more likely to tear than male counterparts
- 1 in 10 female athletes will injure ACL each year

Active areas of research

- Biomechanics
- Genetics
- Hormones
- Computerized Bracing
Gender Differences

- Training techniques (Griffin LY. J Am Acad Orthop Surg, 2000)
- Ligament size
- Hormones

Hormone Induced Ligament Laxity

- Estrogen
- Relaxin

Effects of Estrogen

- ACL contains receptors for estrogen (Liu et al.)
  - similar distribution as relaxin receptors
  - inhibition of fibroblast proliferation and collagen synthesis
- Rabbit ACLs treated with estrogen are biomechanically weaker (Slauterbeck et al.)
- Estrogen present in males
- 50% of studies show no effect
Relaxin

- Peptide hormone found in the sera of pregnant and non-pregnant females
- *Not in male serum* (controversial)
- Secreted by:
  - Luteal phase of menstrual cycle
  - Pregnancy corpus luteum

Relaxin = Potent *collagenolytic* hormone

Gene Expression

\[ \text{Relaxin} = \text{Interstitial collagenase} \]
**Clinical Effects of Relaxin**

- Responsible for connective tissue remodeling at the maternal-fetal interface during late pregnancy and parturition
- Women have significant pelvic joint laxity and separation of the pubic symphysis of up to 10 mm during parturition *(Goldsmith LT. Endocrinol Metab Clin North Am, 1995)*

**Clinical Effects of Relaxin**

- Pregnant women with pelvic pain and pubic diastasis have increased levels of circulating relaxin *(MacLennan AH. Lancet, 1986)*
- Ligamentous laxity of knee reported in pregnant women with high relaxin titers
Estrogen and Relaxin

- Expression of relaxin receptors appears to be under the control of estrogen
- Increases response of target organs to relaxin
- Increases release of endogenous relaxin
- Increases relaxin binding sites on human smooth muscle and rat myometrium

Relaxin + Estrogen

- Solid line - relaxin
- Dashed line - estrogen

Clinical Effects

- ACL injury rate during luteal phase of menstrual cycle? (Myklebust, et al) (controversial)

- Schauberger, Blecher et al., Dumas et al. reported transient laxity of the ACL in pregnant patients

- Laxity greatest during 2nd half pregnancy, decreases by 14 percent at four months postpartum
• Hypothesis: Human ACL tissue contains specific, saturable binding sites for relaxin

• ACL remnants harvested from 5 female and 5 male patients during routine ACL reconstruction

• Exclusion criteria:
  • Positive pregnancy test
  • History of pregnancy
  • Estrogen replacement therapy
  • Oral contraceptives

**Study Design**

• **Group 1** - biotinylated relaxin (localize relaxin receptors)
• **Group 2** - unmodified relaxin (negative control)
• **Group 3** - biotinylated relaxin + 2000x excess human insulin-structural homologue of relaxin (binding specificity)
• **Group 4** - biotinylated relaxin + 2000x excess unmodified relaxin (competitive inhibition)

**FITC Labeling**

[Images of FITC labeling for female and male](image)
Silver Intensified Colloidal Gold

ACL Synovium

Silver Intensified Colloidal Gold

Cells lining blood vessel walls

Results

- No binding after incubation with unmodified relaxin
- Specific binding confirmed in presence of 2000x excess of human insulin, the structural homologue of relaxin
- Competitive inhibition demonstrated in presence of 2000x excess of unlabeled relaxin
Conclusion

- Specific relaxin receptors are present within the **female** ACL
- No binding to **male** ACL
- Clinical correlation of these findings are necessary
ACL cells respond to Relaxin

Adult guinea pigs divided into three groups:
- 20 µg/hr relaxin x 3 wks
- 20 µg/hr relaxin + 5 µg/hr estradiol x 3 wks
- control before surgical transection of ACL and positive ACL tear control after transaction
Does relaxin correlate with female ACL injury?

NCAA Division I female athletes screened for levels of serum relaxin.

Blood drawn 7-10 days post-ovulation.

Relaxin-2 ELISA to quantify hormone levels.

Progesterone ELISA confirms cycle timing.

Results

Relaxin concentration significantly higher in participants with history of ACL injury.

Participants with serum relaxin concentration > 6.0 pg/ml had over four times increased risk of ACL tear.
Next steps: Medication development

Next steps: Identify relaxin in knee joint

- Collect synovial fluid samples from out-of-season female athletes with knee injuries
- Identify if relaxin exerts its effect via synovial fluid vs blood

Summary

- Prospective studies will need to monitor many parameters, due to multifactorial ACL tear risk factors:
  1. Biomechanical risk factors
  2. Genetics
  3. Hormone levels (in females)
  4. Imaging data (tibial plateau inclination)