The Role of Knee Laxity in ACL Injury Risk: Implications for Clinical Practice

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Despite extensive research, we still don’t know the biological mechanisms that underlie a female’s increased risk for ACL injury (ACL Retreat ‘15).

- Sex differences in NM control often implicated.
- Addressing only NM control has not made a major dent in our injury rates
  - NNT = 109
- Biomechanical screening has really not bee effective in identifying those at risk
- Recognized as multifactorial problem.
Understanding the Etiology

**Extrinsic**
- sport specific factors
- exercise environment

**Anatomical**
- tibial geometry
- body composition

**Hormonal**
- sex hormones
- collagen metabolism

**Biomechanical**
- neuromuscular control
- movement strategies

**Genetic Polymorphisms**
- (variants)

**Joint Laxity**
Objectives

- Evidence regarding knee laxity as an ACL injury risk factor
- Through what mechanisms/pathways does knee laxity contribute to injury risk?
  - Biological evidence
  - Biomechanical evidence
- Clinical Implications
  - Injury Risk Screening
  - Risk Modification
Knee Joint Laxity

- Passive joint mobility (looseness) of the knee joint
- Typically measured as the total magnitude of joint displacement at a predetermined / standardized load
  - e.g. anterior knee laxity (AKL) = anterior displacement of tibia relative to femur with 130N anterior applied load
- Can / has been measured in multiple ways
Knee Jt Laxity

- Sagittal Plane
  - Anterior knee laxity (AKL)
  - Genu recurvatum (GR)
  - General joint laxity (GJL)
- Frontal Plane ($VV_{LAX}$) *
  - Varus-valgus rotation laxity
- Transverse Plane ($IER_{LAX}$) *
  - Internal-external rotation laxity

Some more clinically friendly than others...
Between Subject Variations

- Considerable variability between individuals (Shultz data from multiple studies from 2009-2013; not published in combined fashion)

- Greater and more variable in females than males

* 25-30% greater in females than males
Multi-planar Knee Laxity

- Magnitude of knee joint laxity not uniform across planes of motion (Shultz et al, J Athl Train ‘12)

<table>
<thead>
<tr>
<th>Table 1. Laxity Values Stratified by Cluster (N=140) (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster (Women/Men/% of Participants in Cluster)</td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Anterior knee laxity, mm</td>
</tr>
<tr>
<td>Genu recurvatum, °</td>
</tr>
<tr>
<td>Varus-valgus rotation laxity, °</td>
</tr>
<tr>
<td>Internal-external rotation laxity, °</td>
</tr>
</tbody>
</table>

- Sex difference not uniform
  - Females have 25-30% greater $V{V_{LAX}}$ and $I{E{R_{LAX}}}$ than males, even when matched on $A{P_{LAX}}$
ACL Injury Risk Factor

- Both prospective and retrospective studies have consistently associated greater magnitudes of knee joint laxity with a greater risk of ACL injury
  - Anterior knee laxity (AKL) $^0,5,7-9$
  - Genu recurvatum (GR) $^0,3-7$
  - General joint laxity (GJL, which includes GR) $^0,2,3,6-8$
  - Internal rotation knee laxity $^1$

Prospective, Multi-variate Studies

- Uhorchak et al 2003
  - 1200 Military Cadets
  - 24 injured
    - Height*
    - Weight*
    - Notch Width*
    - Eminence Width*
    - GJL*
    - AP Laxity
    - Thigh Strength
    - BMI
    - Sit and Reach

- Beynnon et al 2016
  - HS & College Athletes
  - 109 injured; 227 matched controls
    - Demographics (16)*
    - Joint Laxity (3)*
      - AP Laxity, GJL
    - Lower Extremity Align (11) *
      - GR
    - Strength (4 joints)*
    - Personality

*Male; ‡ Female risk factor
Uhorchak et al, 2013

- Most Predictive Model
  - Males ($R^2 = .152$)
    - Narrow femoral notch width + GJL
  - Females ($R^2 = .625$)
    - Combination of narrow femoral notch width, AKL, and BMI greater than 1 SD above mean
      - $AKL + BMI = 37.7x$ relative risk
      - BMI alone = $3.5x$ relative risk
      - AKL alone = $2.7x$ relative risk
      - BMI + GJL = $13.2x$ relative risk
      - Notch width + BMI = $26.3x$ relative risk
Beynnon et al, 2016

Most Predictive Model

Males
- ↑AP Laxity*
- ↑Posterior knee stiffness
- ↑navicular drop
- ↓standing Q-angle

Females
- Parent with ACL injury hx
- ↑ AP Laxity
- ↑ BMI

Odds Ratios (per unit change)
- 1.56
- 1.34
- 1.26
- 0.76
- 3.84
- 1.24
- 1.22

* family Hx, no longer significant in males once AP laxity accounted for
Take Home

- Both univariate and multi-variate studies consistently identify ↑AP laxity as a significant independent predictor of ACL injury
  - Once AP Laxity accounted for, GR and GJL do not add additional information
  - However, the combination of ↑AP laxity + ↑BMI associated with substantially greater risk in females
- Risk factor models are sex specific
  - Suggest mechanisms, thus approach to screening and prevention, are different for males and females
Two Likely Scenarios

- A lax knee represents a structurally weaker ligament that is more prone to failure at a given load?
  - Factors that affect ACL structure and biology
  - What causes greater knee laxity to begin with?
- A lax knee is more unstable and less protected against mechanical loading during sport?
  - Indirect biomechanical consequence of a lax knee

Greater Knee Laxity?
Female Susceptibility

- Understanding these mechanisms particularly relevant to females
  - Greater risk of ACL injury
  - Greater knee joint laxity than males, particularly in the frontal and transverse plane
    - Beynnon '05, Hsu '06, Markolf '78, Nguyen '07, Rozzi '99, Scerpella '05, Sharma ‘00, Shultz ’05 & ‘11, Trimble ’02, Uhorchak ’03
  - More likely to experience acute changes in their knee laxity across the menstrual cycle and during exercise
    - Beynnon ‘05, Deie ’02, Shultz ’05, ’10, & ‘13
Scenario #1

Does greater knee laxity in females represent a structurally weaker ligament that is more prone / susceptible to failure at a given load....
ACL Structure & Biology

- Female ligaments are less stiff (more lax) and structurally weaker than male ligaments, even once accounting for age, ACL size, and body size
  - Less collagen fiber density (fibers per area) and lower mechanical properties (e.g. less strain / stress at failure)
  - Thought to result from metabolic / remodeling processes that regulate ligament properties
    - Genetics and hormones likely play a role

Chandrashekar ‘06, Hashemi ‘08, Comerford ‘05
Genetics

- Responsible for much of the variation in our physical characteristics
- Familial predisposition for ACL injury risk known for some time (Flynn ‘05, Harner ‘94)
- Only recently have specific variants within the genes coding for types I, V & XII collagen (COL1A1, COL5A1, and COL12A1) been associated with ACL injury (Khoschnau ‘08, Posthumus ‘09–’10)
  - Main structural components of ligaments
  - Associations often limited to females!

Collagen Gene Variants → Mechanism?
Genetics and Joint Laxity

- Identified variants have the potential to alter relative content and structure of Type I, V and XII collagen, thus biomechanical properties (load tolerance) of the ligaments

- May manifest as differences in joint laxity
  - Also heritable
  - ↑ laxity consistently associated with ↑ risk
  - ↑ laxity associated with ligament biomarkers indicative of greater collagen turnover, more immature cross links, and lower failure loads (Comerford ‘05, Quasnichka ‘05, Wang ‘06)
Genotypes that were under / over represented in those with a history of ACL injury were also under / over represented in those with greater joint laxity

- Sex-specific associations were the same as those observed for ACL injury
- Genetic variants not associated with ACL injury were also not associated with joint laxity
Clinical Implications

- Suggests joint laxity may represent one physical trait (phenotype) or mechanism through which genetic variation determines a female’s predisposition for ACL injury.

- However... not everyone with the implicated genotype(s) had greater joint laxity or a history of injury.
Sex Hormones

- May explain the female specific associations
- Underlie many of the sex-specific characteristics that emerge during puberty
- Consensus in the literature that the risk of ACL injury is not uniform across the menstrual cycle
  - Greater risk pre-ovulatory vs post ovulatory (Arendt ‘02, Wojtys ‘02, Slauterbeck ’02, Myklebust ‘03, Beynnon ‘06)
- Profound influence on ACL biology and joint laxity
  - Hormone receptors on ACL capable of regulating gene expression and collagen metabolism (Lu ‘96 & ’97)
  - Normal physiological variations in sex hormones across a females menstrual cycle can have a profound effect on ligament behavior and markers of collagen metabolism (Heitz ‘99, Deie ‘02, Park ‘09, Shultz ‘04, Shultz ‘12)
Table 6: Summary of menstrual cycle phase classification methodology for previous studies examining the relationship between phase of the menstrual cycle and risk of suffering ACL injury.

<table>
<thead>
<tr>
<th>Study (sample size, year)</th>
<th>Menstrual Cycle Phase Assignment Method*</th>
<th>Findings (% of ACL injuries occurring during Pre- or Post-Ovulatory phases of the menstrual cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-Ovulatory Phase†</td>
</tr>
<tr>
<td><strong>Myklebust</strong>&lt;sup&gt;7&lt;/sup&gt; (n=17; 1998)</td>
<td>Calendar Counting</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Wojtys</strong>&lt;sup&gt;36&lt;/sup&gt; (n=28; 1998)</td>
<td>Calendar Counting</td>
<td>42%</td>
</tr>
<tr>
<td><strong>Arendt</strong>&lt;sup&gt;37&lt;/sup&gt; (n=83 total, 58 not taking oral contraceptives; 2002)</td>
<td>Calendar Counting</td>
<td>Higher Risk‡</td>
</tr>
<tr>
<td><strong>Wojtys</strong>&lt;sup&gt;38&lt;/sup&gt; (n=51; 2002)</td>
<td>Calendar Counting and Hormone assessment</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Slauterbeck</strong>&lt;sup&gt;10&lt;/sup&gt; (n=37; 2002)</td>
<td>Calendar Counting and Hormone assessment</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Myklebust</strong>&lt;sup&gt;8&lt;/sup&gt; (n=46; 2003)</td>
<td>Calendar Counting</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Beynnon</strong>&lt;sup&gt;5&lt;/sup&gt; (n=46; 2006)</td>
<td>Calendar Counting and Hormone assessment</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Adachi</strong>&lt;sup&gt;3&lt;/sup&gt; (n=18; 2008)</td>
<td>Calendar Counting</td>
<td>83%</td>
</tr>
</tbody>
</table>

*Calendar Counting classification method implies menstrual cycle questionnaire-based assessments.
†Pre-Ovulatory Phase defined as days 1-14 in a normal 28-day menstrual cycle. Post-Ovulatory Phase defined as days 15-28 in a normal menstrual cycle.
‡ No specific percent ACL injury breakdown provided.
• 22 Females
  • measured daily over 1 menstrual cycle
• 20 Males
  • measured 1 / wk for 4 weeks
Primary Findings

- On average
  - Sex difference greater in early luteal phase
  - Laxity changed 3-4 days post hormone changes
  - Strong correlations between hormone & laxity changes once accounting for delay
  - More than estrogen

<table>
<thead>
<tr>
<th>Hormone Predictors</th>
<th>% Variance Explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen (E2)</td>
<td>5.4%</td>
</tr>
<tr>
<td>E2 + P4 + Testosterone</td>
<td>25.9%</td>
</tr>
<tr>
<td>E2 + P4 + T + Time Delay (3-4d)</td>
<td>63.3%</td>
</tr>
</tbody>
</table>
Normal physiological variations in sex hormones also associated with changes in markers of collagen metabolism

Shultz et al J Orthop Res ‘12

Biological Consequence...

Greater laxity associated with ligament biomarkers indicative of greater collagen turnover, more immature cross links, and lower failure loads

Comerford ‘05, Quasnichka ‘05, Wang ’06
Relaxin

- Mounting evidence the hormone relaxin may have a profound effect on the structural integrity of the ACL
  - Relaxin receptors identified on the ACL
  - Exposure not limited to pregnancy
  - Shown in cell culture and animal studies to ↑tissue remodeling, leading to a more lax and structurally weaker ligament over time (BASELAX)
  - May also interrupt interfibrillar bonds and allow collagen fibril sliding within hours (CYCLAX)

Dragoo ‘03, ‘09; Faryniarz ‘06; Galey ‘03; Kang ‘14; Naqvi ‘05; Takano ‘09, Unemori ‘90; Wood, ‘03
Females with higher relaxin levels (>6.0 pg/mL) had 4.4x greater risk of ACL injury (Dragoo et al, AJSM 2011)

- Theorized ↑ risk due to altered ligament laxity and strength
  - Did not examine laxity
- Single Relaxin Sample on day 6 or 8 post ovulation (Bryant-greenwood ‘93, Stewart ‘90)
  - Undetectable relaxin levels in 64% of females
Summary – Biological Consequence

- Compelling evidence that lax ligaments may be more susceptible to failure at a given load
  - Still need more direct evidence *in-vivo*
- Genetics may in part dictate this susceptibility, but relationship likely moderated by other factors (e.g. sex hormones, relaxin)
- Identifying the resultant physical trait (e.g. joint laxity), maybe ultimately be more telling and clinically useful for screening purposes

*Hormones
Anatomy
Exercise, etc*

*Genetic Variants*

*Knee Laxity Phenotypes*

*ACL Injury Susceptibility*
Scenario #2

Is a lax knee more unstable and less protected against mechanical loading during sport?
Higher Mechanical Loads?

- High-risk knee biomechanics during sport activity have long been considered a primary cause for a female’s greater susceptibility for ACL trauma, and are the primary target of injury prevention programs

  Renstrom ‘08, Alentorn-Geli ‘09, Hewett ‘06, Yoo ‘09
Begs the Question Why?

- Why do females develop higher risk biomechanics?
  - Not all women do! -- Not all women get injured!
- Need to understand underlying cause to know who to target and where / when best to intervene

**Sex-Dimorphic Risk Factors**
- Genetics
- Sex Hormones
- Body Composition
- Muscular Strength
- Lower Extremity Alignment
- Knee Joint Geometry
- Knee Joint Laxity

**↑ High-Risk Knee Joint Biomech**
- Hip adduction
- Hip internal rotation
- Shallow knee flexion
- Knee valgus
- Knee internal/external rotation

**↑ Risk of Suffering Non-Contact ACL Injury in Females**
Neuromechanical Consequences of Knee Laxity

NIH RO1 AR053172

Does the magnitude of one’s baseline and any acute increases in knee laxity influence a females lower extremity neuromechanics during weight bearing tasks?
Methods

- Recreationally active females (N=71; eumenorrheic) and males (N=48) were tested at two time points:
  - Females tracked over two consecutive cycles to capture days of minimum (T1) and maximum (T2) AKL
  - Males matched in time (T1 and T2) & baseline AKL (±0.5mm)
  - Measured biomechanics
    - Baseline (T1)
    - Change from T1 to T2 (T2 – T1)
Baseline Knee Laxity
Baseline Knee Laxity

- **Sagittal Plane** (*Shultz ‘06 and ‘11*)
  - Individuals (M & F) with ↑ AKL experienced greater anterior translation of the tibia relative to femur during the transition of the knee to weight bearing.
  - Likely exacerbated by ↑ lateral A→P tibial slope
  - Known anatomical risk factor for ACL injury
Neuromechanical Consequences

Sagittal Plane -- During the initial landing of a drop jump

- **Females:** Greater AKL and GJL and lower GR associated with greater loads transferred to the knee joint:
  - ↑ knee work absorption ($R^2 = .210$)
  - ↑ knee joint stiffness ($R^2 = .127$)
  - ↓ ankle joint stiffness ($R^2 = .115$)

- **Males:** Greater GJL predicted:
  - ↓ ankle joint stiffness ($R^2 = .209$)
    - ↓ ankle moment ($R^2 = .099$)
    - ↑ peak ankle flexion ($R^2 = .147$)

*Shultz et al MSSE ‘10*
Neuromechanical Consequences

- Sagittal Plane
  - Implicated AKL, GR, and GJL as distinct laxity characteristics
    - Together explained more of the variance in knee energetics than when each laxity variable was examined separately.

**TABLE 2. Bivariate (Pearson’s R) correlations for AKL, GR, and GJL by sex.**

<table>
<thead>
<tr>
<th>Pearson Correlation</th>
<th>Females (n = 68)</th>
<th>Males (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AKL</td>
<td>GR</td>
</tr>
<tr>
<td>AKL (mm)</td>
<td>1.000</td>
<td>0.533*</td>
</tr>
<tr>
<td>GR (°)</td>
<td>1.000</td>
<td>0.360*</td>
</tr>
<tr>
<td>GJL (score)</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*P < 0.05.
Neuromechanical Consequences

- Frontal and Transverse Plane (AJSM ‘09)
- Compared males and females with above average vs. below average LAX_{VV} and LAX_{IER} on transverse and frontal plane hip and knee motions during drop jump landings

TABLE 1. Demographics for LAX_{LOW} and LAX_{HIGH} Females and Males

<table>
<thead>
<tr>
<th></th>
<th>LAX_{LOW}</th>
<th>LAX_{HIGH}</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAX_{VV} (°)</td>
<td>10.9±2.7</td>
<td>16.3±2.7†</td>
<td>13.4±3.0</td>
</tr>
<tr>
<td>LAX_{IER} (°)</td>
<td>19.9±4.3</td>
<td>34.5±4.8†</td>
<td>26.8±7.5*</td>
</tr>
<tr>
<td>AKL (mm)</td>
<td>5.5±1.5</td>
<td>7.9±2.2†</td>
<td>6.6±2.2</td>
</tr>
<tr>
<td>BMI</td>
<td>22.0±2.4</td>
<td>22.9±2.7</td>
<td>22.4±2.6*</td>
</tr>
<tr>
<td>MVIC (Nm/kg)</td>
<td>2.3±0.4</td>
<td>2.3±0.4</td>
<td>2.3±0.04*</td>
</tr>
<tr>
<td>Quad</td>
<td>1.8±0.3</td>
<td>1.7±0.2</td>
<td>1.7±0.3*</td>
</tr>
<tr>
<td>Ham</td>
<td></td>
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</tbody>
</table>

*F ≠ M (P<.05), † LAX_{HIGH} > LAX_{LOW}
Neuromechanical Consequences

- Both females and males with HIGH vs. LOW VV\textsubscript{LAX} and IER\textsubscript{LAX}:
  - landed in and remained in 6.3\degree and 5.3\degree greater hip adduction throughout the landing
  - Produced greater and more prolonged hip adduction and knee varus moments
Neuromechanical Consequences

- Females with HIGH vs. LOW $V_{V_{LAX}}$ and $I_{ER_{LAX}}$ also landed in more knee valgus ($3.8^\circ$) and moved toward greater hip adduction, hip internal rotation and knee valgus as the landing progressed (no difference observed in males).
Muscle Activation Amplitude (%MVIC)

Females

Males

(P=.020)

(P=.035) *

LAXLOW
LAXHIGH

LAXLOW
LAXHIGH

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

Pre-Landing Post-Landing

Pre-Landing Post-Landing
Baseline Knee Laxity

- Take home points
  - High risk knee joint biomechanics (e.g., ↑ dynamic knee valgus) observed in the same plane(s) of motion as greater magnitudes of knee laxity
    - Laxity effects on biomechanics appear to be more pronounced in females (likely because they have higher magnitudes of knee laxity to begin with)
  - Effect of knee laxity on knee joint biomechanics and ACL injury are likely more complex than a single laxity variable
Acute Laxity Changes
Across the Menstrual Cycle
During Exercise
Cyclic Changes in Knee Laxity

- Cyclic changes in AKL as large as 3-5mm observed in some women (Heitz ‘99, Deie ‘02, Eiling ‘07, Park ‘08, Shultz ‘04, ‘10)
- Not uniform in all women in magnitude or timing
  - Coincide with cyclic changes in sex hormones and markers of collagen metabolism (Shultz ‘04, ‘12)
  - Difficult to predict high laxity responders
- Can further increase sex differential in knee laxity
- Can further impact knee joint biomechanics
Cyclic changes in genu recurvatum, GJL, VV<sub>LAX</sub> and IER<sub>LAX</sub> subsequently documented (Shultz et al ’10 & ‘11)
**Cyclic Changes in Knee Laxity**

**Fig 1.** Females Clustered on Cyclic Knee Laxity

<table>
<thead>
<tr>
<th>Cluster</th>
<th>AKL</th>
<th>GR</th>
<th>VV</th>
<th>IER</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.2±1.0(1)*</td>
<td>0.0±0.7(1,2,4)</td>
<td>-2.5±1.7(1,2,4,5)</td>
<td>-2.1±6.4(4)</td>
</tr>
<tr>
<td>C2</td>
<td>0.0±0.5(1,4)</td>
<td>1.6±0.7(3,5)</td>
<td>0.7±0.9(3)</td>
<td>2.4±3.6(1,4)</td>
</tr>
<tr>
<td>C3</td>
<td>1.1±0.3(2,3,5)</td>
<td>1.6±0.8(3,5)</td>
<td>0.8±2.0(3)</td>
<td>-1.9±5.3(2,4)</td>
</tr>
<tr>
<td>C4</td>
<td>1.0±0.7(2,5)</td>
<td>1.6±0.5(3,5)</td>
<td>1.0±2.4(3)</td>
<td>19.1±3.8(1,2,3,5)</td>
</tr>
</tbody>
</table>

**Table 1.** Means±Sd Delta (T2-T1) Laxity Values Stratified by Cluster

**Group** | **Label** | **AKL (mm)** | **GR (deg)** | **VV (deg)** | **IER (deg)** |
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>Δ⁻VV,IER</td>
<td>0.2±1.0(1)*</td>
<td>0.0±0.7(1,2,4)</td>
<td>-2.5±1.7(1,2,4,5)</td>
<td>-2.1±6.4(4)</td>
</tr>
<tr>
<td>C2</td>
<td>Δ⁺GR VV,IER</td>
<td>0.0±0.5(1,4)</td>
<td>1.6±0.7(3,5)</td>
<td>0.7±0.9(3)</td>
<td>2.4±3.6(1,4)</td>
</tr>
<tr>
<td>C3</td>
<td>Δ⁺AKL GR VV/⁻IER</td>
<td>1.1±0.3(2,3,5)</td>
<td>1.6±0.8(3,5)</td>
<td>0.8±2.0(3)</td>
<td>-1.9±5.3(2,4)</td>
</tr>
<tr>
<td>C4</td>
<td>Δ⁺ALL++,IER</td>
<td>1.0±0.7(2,5)</td>
<td>1.6±0.5(3,5)</td>
<td>1.0±2.4(3)</td>
<td>19.1±3.8(1,2,3,5)</td>
</tr>
<tr>
<td>Male</td>
<td>Male</td>
<td>0.1±0.5(1,4)</td>
<td>-0.1±0.7(1,2,4)</td>
<td>-0.3±1.7(3)</td>
<td>0.1±4.7(4)</td>
</tr>
</tbody>
</table>

C1 (N=35); C2 (N=17); C3 (N=14); C4 (N=5); Male (N=49)

*(Shultz et al MSSE '12)*
Cyclic Changes in Knee Laxity

- Cyclic increases were of sufficient magnitude to further alter LE biomechanics during landing (Shultz et al ‘12)
- ↑ in both $AP_{LAX}$ and $VV_{LAX}$ resulted in 4-5° greater net movement toward knee valgus
- ↑ overall cyclic knee laxity particularly vulnerable:
  - Initially landed in more valgus (1.6°) external rot (3.2°), and continued to move toward more knee valgus and ext rotation
Exercise May Further Exacerbate These Effects!

- **During Exercise:**
  - Knee laxity reported to increase as much as 20-30% above baseline within 20-30 minutes of exercise (*Nawata ‘99, Rowe ‘99, Sailors ‘95, Skinner ‘86, Steiner ‘86, Stoller ‘83, Weisman ‘80*)
  - Consistent with the time in a game or practice when injury rates begin to rise (*Dallalana ’07, Gabbett ‘00, Hawkins ‘99 & ‘01, Price ‘04*)
**Methods** *(Shultz et al MSSE '13; JAT ‘15)*

- 30 F & 30 M intercollegiate and club athletes completed a 90 intermittent exercise protocol

<table>
<thead>
<tr>
<th></th>
<th>Warm Up</th>
<th>First Half</th>
<th>Half Time</th>
<th>Second Half</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AP\text{_LAX} &amp; LE Biomech</strong></td>
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<td>PreWm</td>
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<td>PostWm</td>
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<td>Post30</td>
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**VV\text{\_LAX} and IER\text{\_LAX}**  

<table>
<thead>
<tr>
<th></th>
<th>Warm Up</th>
<th>First Half</th>
<th>Half Time</th>
<th>Second Half</th>
<th>Recovery</th>
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<tbody>
<tr>
<td>5 meters</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>10 meters</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>505 Agility Sprint</td>
<td></td>
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Exercise Related Laxity Changes (Shultz '13)

Inter-subject Variability

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AP_{LAX}$</td>
<td>$0.7 \pm 1.0 \text{ mm}$</td>
<td>$-0.10$ to $5.9 \text{ mm}$</td>
</tr>
<tr>
<td>$VV_{LAX}$</td>
<td>$0.5 \pm 1.7 \text{ o}$</td>
<td>$-1.7 \text{ o}$ to $5.7 \text{ o}$</td>
</tr>
<tr>
<td>$IER_{LAX}$</td>
<td>$1.7 \pm 4.9 \text{ o}$</td>
<td>$-4.1 \text{ o}$ to $13.3 \text{ o}$</td>
</tr>
</tbody>
</table>

33% (F) vs 10% (M)

- $\uparrow AP_{LAX} > 1.9 \text{ mm}$
- $\uparrow VV_{LAX} > 2.8 \text{ o}$
Primary Findings (Shultz et al ‘15)

- Fatigue tended to decrease knee extensor loads, stiffness and energy absorption....
- $\uparrow$ Baseline $AP_{LAX}$: more likely to increase knee loads w/ fatigued (M&F).
- $\uparrow$ Exercise-related $AP_{LAX}$: further increased KE loads & stiffness in males.
Primary Findings *(Shultz et al ‘15)*

- Once accounting for fatigue and $AP_{LAX}$ related effects:
  - $\uparrow VV_{LAX}$ and $IER_{LAX}$ during exercise consistently associated with greater dynamic knee valgus.
  - $\uparrow$ Hip adduction excursion
  - $\uparrow$ Knee valgus / $\downarrow$ knee varus excursion
  - Relationships tended to be stronger in those who had more $VV_{LAX}$ and $IER_{LAX}$ initially.
Summary of Biomechanical Consequences

- Greater knee joint laxity associated with the higher risk movement patterns more often observed in females
  - More pronounced in females compared to males, because they have more laxity to begin with
- Acute increases across the menstrual cycle and during exercise are large enough in some individuals (but not all) to further alter knee joint biomechanics

![Diagram showing the combination of genetics, hormones, and exercise affecting knee joint laxity.]

Greater Baseline Knee Laxity + Greater ↑ with Menst Cycle + Greater ↑ with Exercise = ???
Implications for Clinical Practice
Injury Risk Screening
Prevention
Screening and Prevention

- Critical to understand the biological mechanisms that underlie an individual’s predisposition for ACL injury.

- What to intervene on?......When to intervene?

  - Establish extent of injury problem
    - Incidence
    - Severity

  - Establish etiology and mechanism of injury

  - Introduce a preventative measure

  - Re-Assess injury problem (Step #1) to determine effectiveness

van Mechelen ’92
Screening

- Multiple factors likely combine to explain the higher risk of ACL injury in females
  - Ultimately need to know which factors to target in ACL screening and prevention efforts
- Knee laxity appears to be one important factor
  - Influenced by multiple factors also thought to influence ACL injury
    - genetics, hormones, anatomical, knee joint geometry
  - May represent deficiencies in ACL structural integrity and may also explain the “higher risk” knee biomechanics often observed in females.
Physiological Make-up

- Genetics
- Hormones
- Body Composition
- Knee Anatomy
- Physical Activity

Physical Trait of Knee Laxity

Result of combined physiological variations

ACL Injury

Predisposition to Injury

Difficult to measure clinically

Can be measured clinically

If knee laxity reflects the clinical outcome of these multi-factorial influences, we may be able to screen more accurately / reliably for a female’s predisposition before injury occurs, using simple, cost-effective test(s)

In turn, understanding the underlying biological mechanisms may ultimately lead to more targeted prevention strategies
Screening

• Screening for a combination of AKL, BMI and Family Hx increase sensitivity of identifying those at risk:
  • Females with a combination of AKL and BMI greater than 1 SD above mean were 37.7 times more likely to suffer an ACL injury (Uhorchak et al ‘03)
    • BMI alone = 3.5x greater risk
    • AKL alone = 2.7x greater risk
  • Females with combination of ↑AP laxity, ↑BMI, & family history of ACL injury (Beynnon, ’16)

• All clinically accessible measures
Limited evidence that a self-reported knee outcome survey may be beneficial as part of a pre-participation screening battery to identify those with perceived functional deficits associated with their knee laxity (Taylor, ‘15)

- 20F & 20M completed the KOS-ADL and KOS-SAS prior to laxity assessment (Irrgang ‘98)
  - No difference in scores between sexes.
  - Females with greater postero-lateral knee laxity reported lower scores during ADLs ($R^2 = .74$) and sport ($R^2 = .67$).
  - More likely to report weakness and giving way, difficulties with stopping, starting, jumping, cutting & pivoting
  - Relationships stronger in females (greater laxity than males)
  - Is there a critical threshold at which knee laxity becomes problematic?
ACL Injury Prevention Strategies

- Despite the modest success of ACL prevention programs (Hewett ‘06, Yoo ‘09, Taylor ‘13), we have yet to see a clear reduction in injury rates, or relative risk in females compared to males. (Hootman ‘07, Lyman ‘09)

- We have yet to address non-modifiable factors in our prevention strategies

  - Factors that influence ACL biology and integrity largely ignored (Scenario #1)
  - Underlying causes of high risk knee biomechanics in women (Scenario #2)
Modifiable vs. Non-modifiable

- Addressing “non-modifiable” risk factors (e.g. genetics, laxity, hormones) may alter our approach to injury prevention
  - 6-week neuromuscular training program may be effective to correct a modifiable problem – but a long-term intervention (over an athlete’s career?) may be necessary to counteract a non-modifiable structural weakness.
- If structural, is there a potential to positively modify stresses – thus structure – early in life?
- If not possible to correct or positively modify, can we “shore up” through intrinsic or extrinsic supportive measures?
Is knee laxity modifiable?

Influenced by both modifiable and non-modifiable factors

- **Extrinsic**
  - sport specific factors
  - exercise environment

- **Anatomical**
  - tibial geometry
  - body composition
  - LE alignment

- **Hormonal**
  - sex hormones
  - collagen metabolism

- **Genetic Polymorphisms**

- **Joint Laxity**
Body Composition *(Shultz ’12)*

- LE lean mass a strong predictor of knee laxity in frontal and transverse but not AP planes (63F, 30M)
  - Stronger predictor than overall mass or BMI
  - Likely explains proportionally greater magnitudes of $VV_{LAX}$ and $IER_{LAX}$ vs. AKL in females (sex not a predictor once LELM accounted for)

\[
y = -1.3145x + 20.844 \\
R^2 = 0.5695
\]

\[
y = -1.6616x + 40.173 \\
R^2 = 0.2131
\]
Body Composition + Laxity

- May explain the substantially higher risk associated with the combination of greater BMI and greater knee joint laxity in females (Uhorchak ‘03, Beynnon ‘16)

- Elevated BMI typically due to greater fat mass in females (i.e. less LELM:TBM) vs. muscle mass in males.
Work Ongoing

- Is VV and IER laxity also an important, independent predictor of ACL injury risk
  - Is there a unique combination that poses a greater risk for adverse knee joint loads and ACL strain?
  - Continue to refine the clinical laxity tests that are the most prognostic screening tools
- Is knee laxity modifiable or non-modifiable?
  - Can we reduce one’s knee laxity through NM training or otherwise counteract these adverse effects?
NM Training

- Particularly relevant for females with a family (or personal) hx of ACL injury, ↑ knee laxity and ↑ BMI
  - Improve neuromechanics to ↓ external loads and stress-shield ACL as much as possible
- Multiple and varied programs have emerged since 1995 in attempt to reduce incidence of ACL injury
  - Multiple reviews compare and describe program components (Hewett ‘05, Griffin ’06, Renstrom ‘08, Alentorn-Geli ’09)
- Meta analyses confirm effectiveness, particularly when started early in season (Grindstaff ’06, Hewett ’06, Yoo ’09; Sadoghi ’12, Taylor ’15)
  - Ideal combination / emphasis of training components remains unclear (Sadoghi ’12, Taylor ’15)
Common Program Components

Successful programs typically include the following to accomplish these goals:

- Flexibility
- Strengthening of lower extremity / core muscles
- Body awareness and positioning
  - Education and Verbal Feedback
- Agility and Plyometric exercises
- Dynamic balance with perturbation training
Common Prevention Goals

- Improve NM control of knee stability via ↑ muscular strength, preparatory activity and reactivity
- Promote ↑ hip and knee flexion angles and weight over toes to reduce anterior knee loads
- Produce softer landing styles to reduced vertical ground reaction forces
- Decrease frontal and transverse plane motion/moments (functional valgus collapse)
- Improve postural control / responses to sudden perturbations
- Improve performance (↑ program buy-in compliance)
**Additional Emphasis?**

- ↑ thigh mass, strength and stiffness (particularly hamstrings)
  - Foundational, comprehensive strength base often lacking in these programs
  - Greater LELM associated with greater energy absorption at the knee (*Schmitz ‘10, Montgomery ‘12*)
    - ↑ knee flexion, ↓ ground reaction forces
  - Decreased frontal & transverse plane knee laxity?
  - Control varus-valgus motion and moments
    (*Olmstead ’86, Lloyd ’01, Hewett ’96, Lim ’09*)
Thank You
Is OCP Therapy Appropriate??

- Although stabilizes endogenous concentrations, exogenous hormones also biologically active
  - E2 and P4 can be 3–5x and 1–2x higher, respectively, than endogenous levels (Burrows ‘07)
- No evidence protective against ACL injury (Agel ‘06)
- Impact on ligament integrity unclear
  - May stabilize laxity, but effect on magnitude equivocal (Martineau ‘04; Pokorny ’00; Shultz ‘12)
  - May actually suppress collagen synthesis, and promote smaller collagen fibrils (tendons), together suggesting an inferior collagen structure (Hansen ‘05 & ‘09; Wreje ’00; Shultz ‘12)
- Impact may depend the type (mono vs triphasic) and androgenicity of the progestin (Burrows ‘07, Shultz ‘12)