Ankle Sprain to OA: Implications for Mitigating Cartilage Degeneration

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Associate Professor & Katherine Smith Gunter Fellow
The Rationale

• **What we know:**
  – LAS have long-term consequences including CAI and PTOA.
  – Interest in long-term health is driving research in PTOA across all joints.
  – Early detection will be vital because conservative treatments for severe PTOA are not effective.

• **What we think we know:**
  – The most promising approaches for slowing PTOA progression include early interventions to restore appropriate biomechanics and maximize cartilage health.

• **What I hope to share:**
Goals & Agenda

- Ankle Post-Traumatic OA
  - Epidemiology & Pathways

- Observed declines post-injury

- Identifying therapeutic targets
  - Biomechanics & Blood biomarkers
  - Patient-reported outcomes

- Clinical Implications

Dr. Kyeongtak (KT) Song
Post-Doctoral Fellow at U. Kentucky
Pathway to Ankle PTOA

- Rehabilitative literature suggests a linear progression

[Diagram showing the pathway from Acute Ankle Sprain through Chronic Ankle Instability to Ankle Post-Traumatic OA with 78% of CAI and 40% of LAS]
Pathway to Ankle PTOA


- **Acute Ankle Sprain**
  - Ligament Laxity
  - Joint Alignment
  - Proprioception
  - Muscle Function
  - Balance
  - Gait

- **Chronic Ankle Instability**
  - Ligament Laxity
  - Joint Alignment
  - Proprioception
  - Muscle Function
  - Balance
  - Gait

- **Ankle Osteoarthritis**
  - Arthrokinematics
  - Joint Alignment
  - Muscle Function
  - Balance
  - Gait
Pathway to Ankle PTOA

2. Focus on CAI.

• As many as 78% of CAI cases develop ankle PTOA

• >90% of CAI cases examined arthroscopically had degenerative changes and/or chondral lesions.
  – Taga et al 1993, Komenda and Ferkel 1999, others

Rungprai et al. The Open Orthopaedics Journal. 2017
Pathway to Ankle PTOA

Acute Ankle Sprain → Ankle Post-Traumatic OA

Chronic Ankle Instability
Pathway to Ankle PTOA

• 70-80% of ankle OA cases are post-traumatic.
  – Up to 80% of PTOA are due to ligamentous injury.

• 50% of ankle PTOA patients with a hx of ligamentous injury report only a single LAS.

• 13% of CAI and 9% of recent LAS had radiographic evidence of OA.
  – Lofvenberg et al. 1994
2016 consensus statement of the International Ankle Consortium: prevalence, impact and long-term consequences of lateral ankle sprains

Phillip A Gribble,¹ Chris M Bleakley,² Brian M Caulfield,³ Carrie L Docherty,⁴ François Fourchet,⁵ Daniel Tik-Pui Fong,⁶ Jay Hertel,⁷ Claire E Hiller,⁸ Thomas W Kaminski,⁹ Patrick O McKeon,¹⁰ Kathryn M Refshauge,⁸ Evert A Verhagen,¹¹ Bill T Vicenzino,¹² Erik A Wikstrom,¹³ Eamonn Delahunt¹⁴

Evidence review for the 2016 International Ankle Consortium consensus statement on the prevalence, impact and long-term consequences of lateral ankle sprains

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Pathway to Ankle PTOA

Ligamentous Ankle Injuries

Osteochondral Lesions

Structural Impairments

Neuromuscular/ Sensorimotor Impairments

Biomechanical Alterations

Chronic Ankle Instability

Exacerbate

Altered Joint Loading

Progression to Ankle PTOA

Song & Wikstrom
2019 Phys Sportsmed
Goals & Agenda

• Ankle Post-Traumatic OA
  – Epidemiology & Pathways

• Observed declines post-injury

• Identifying therapeutic targets
  – Biomechanics & Blood biomarkers
  – Patient-reported outcomes

• Clinical Implications
Visualized Declines

• 55% of CAI patients had cartilage lesions < 2 years post LAS.
  – Hintermann et al 1978

• 50% of CAI patients had degenerative changes.
  – Average age: 29 years; Median time from injury: 7 months.
  – Takao et al 1984

• 95% of CAI patients had intra-articular problems 2 years from time of injury.
  – Ferkel and Chams 1979
Imaged (Standard) Declines

• Traditional PTOA diagnosis:
  – Radiographs with joint space narrowing

• Conventional MR
  – 42% of CAI patients 6-12 months post injury have K&L grades of $\geq 1$
  – Good sensitivity for severe cartilage lesions but poor for minor lesions
    • Cha et al. 2012

Image from: The Bone School
PTOA Pathogenesis

- **Visualization:** can detect early declines but isn’t a good screening tool.
- **Standard Imaging:** can only detect severe declines in cartilage health.

**Compositional alterations without morphological changes**
- Reduced proteoglycan density & collagen disorganization.
  - Loss of viscoelastic properties.

**Altered response to mechanical loads**
- Composition governs response to load.

**Morphological changes**
- Altered loads leads to the breakdown of cartilage.

Visualization:
- Can detect early declines but isn’t a good screening tool.

Standard Imaging:
- Can only detect severe declines in cartilage health.

Composition governs response to load.

Altered loads lead to the breakdown of cartilage.
Compositional Declines

• T1ρ: sensitive to macromolecular changes (i.e. proteoglycan density).
• T2 mapping: sensitive to water content and/or collagen fiber orientation.
  – Keenen et al 2011, Mlynarik et al 2004

• $\uparrow$ T2 mapping relaxation times of the tibiotalar cartilage (i.e. greater water content and/or fiber disorientation) in LAS and CAI patients.

• $\uparrow$ T2 mapping relaxation times of the subtalar cartilage in CAI patients.
  – Kim et al 2018
T1ρ Compositional Declines

• ↑ T1ρ tibiotalar relaxation times (i.e. ↓ proteoglycan density) in those with CAI relative to controls despite comparable cartilage volumes between the groups.
  – Wikstrom et al. 2019

• ↑ T1ρ subtalar relaxation times in those with CAI relative to controls despite comparable cartilage volumes between the groups.
  – Song et al. In Review

• T1ρ tibiotalar and subtalar relaxation times associate in controls but not in those with CAI.
  – Song et al. In Review
T1ρ Compositional Declines

• Patients were unloaded for 30 minutes prior to scan.
• Siemens Magnetom TIM Prisma 3T scanner and an 8-channel flex coil.

• A T1ρ prepared 3D FLASH sequence was used to estimate T1ρ.
  – Bandwidth= 350Hz/Px, spin lock power= 500Hz, and spin lock durations= 40, 30, 20, 10, 0 ms.
T1ρ Compositional Declines

Anatomical / PD Space Scan  T1ρ Scan
T1ρ Compositional Declines
T1ρ Compositional Declines

Chronic Ankle Instability

Uninjured Control
T₁ρ Compositional Declines

- Disrupted shank-rearfoot couple in those with CAI.

BUT STILL RELYING ON MR
Strain Alterations

• Composition governs how cartilage responds (i.e. deforms) and recovers (i.e. resiliency) from loading.
  – Eckstein et al 2015

• What tool do we have that can quantify response to loading and be a surrogate measure of cartilage composition?
Strain Alterations: Conventional MR

• In healthy controls, talar cartilage deformed 2% to 14.6% following a range of static and dynamic activities.
Van Gickel et al 2011
Strain Alterations: Dual-Fluoroscopy

- ↑ peak strain and an anteromedial shift in peak strain location in those with CAI.
  - Bischof et al. 2010

Wan et al 2008
Strain Alterations: Ultrasound
Strain Alterations: Ultrasound

Ankle PTOA Pathway

Post-Injury Declines

Identifying Therapeutic Targets

Clinical Implications
Strain Alterations: Ultrasound

- US morphology (i.e. thickness) appears to be a clinical surrogate of MR based talar morphology
  – Song et al. 2020

Association between the US normalized CSA and T1ρ MR-based volumes for (a) overall, (b) medial, and (c) lateral talar dome. (open squares: uninjured controls, closed circles: chronic ankle instability)
Strain Alterations: Ultrasound

- Talar cartilage in those with CAI responds differently to a static loading protocol (2-minute static stance) than controls after controlling for weight.
  - Song et al. MSSE In Press

<table>
<thead>
<tr>
<th>Overall Talar Dome</th>
<th>Raw change (mm)</th>
<th>MDC (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAI</td>
<td>-0.054±0.038</td>
<td>0.014</td>
</tr>
<tr>
<td>Control</td>
<td>-0.033±0.032</td>
<td>0.013</td>
</tr>
</tbody>
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Strain Alterations: Ultrasound

- Talar cartilage in those with CAI responds differently to a static loading protocol (2-minute static stance) than controls after controlling for weight.
  
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<th>MDC (mm)</th>
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<tr>
<td><strong>CAI</strong></td>
<td>-0.066±0.046</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>-0.031±0.043</td>
<td>0.029</td>
</tr>
</tbody>
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Strain Alterations: Ultrasound

- Talar cartilage in those with CAI respond differently to a dynamic loading protocol (60, 24” hops) than controls after controlling for weight.
  - Song et al. MSSE In Press

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<tr>
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<th>MDC (mm)</th>
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<tbody>
<tr>
<td>CAI</td>
<td>-0.050±0.054</td>
<td>0.025</td>
</tr>
<tr>
<td>Control</td>
<td>-0.018±0.021</td>
<td>0.017</td>
</tr>
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Strain Alterations: Ultrasound

- Talar cartilage in those with CAI respond differently to a dynamic loading protocol (60, 24” hops) than controls after controlling for weight.
  
  — Song et al. MSSE In Press

<table>
<thead>
<tr>
<th>Medial Talar Dome</th>
<th>Raw change (mm)</th>
<th>MDC (mm)</th>
</tr>
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<tbody>
<tr>
<td>CAI</td>
<td>-0.050±0.054</td>
<td>0.026</td>
</tr>
<tr>
<td>Control</td>
<td>-0.017±0.036</td>
<td>0.019</td>
</tr>
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</table>
Blood Biomarkers

- Degradation of cartilage (e.g. AGG-1) and inflammation (e.g. IL-6) associate with ankle KL scores and intra-articular severity.

- Preliminary data (n=14) suggest that blood biomarkers may be able to detect early cartilage degradation.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=6)</th>
<th>CAI (n=9)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2C</td>
<td>Collagen degradation</td>
<td>219.0±47.2</td>
<td>266.4±49.9</td>
</tr>
<tr>
<td>CS846</td>
<td>New proteoglycans</td>
<td>3498.5±686.1</td>
<td>6558.0±5356.9</td>
</tr>
</tbody>
</table>
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Hubbard-Turner et al 2018
T2 & T1ρ Composition Correlates

- **Sensorimotor**
  - ↑ (worse) lateral Talar T2 relaxation times associated w/ worse ML TTS (r =0.51 to 0.63)
    - Golditz et al 2016
  - Worse Talar T1ρ values associate w/ worse EO AP TTB mean  (r= -0.46)
  - Worse Subtalar T1ρ values associate w/ worse EC AP TTB SD (r= -0.38)
**T1ρ Composition Correlates**

- **Biomechanics**
  - ↑ (worse) Talar T1ρ values associated w/ aberrant sagittal ($r \geq 0.546$) and frontal plane ($r \geq 0.466$) knee positioning at initial contact during gait.
  
  - ↑ (worse) Subtalar T1ρ values associated w/ lower linear loading rates during walking ($r = -0.423$) and greater subtalar instability ($r = 0.487$).
T2 & T1ρ Composition Correlates

• Patient-Reported Outcomes
  – No significant associations among Talar T2 values.
    • Golditz et al 2016
  – No significant associations among Talar T1ρ values.

IdFAI, FAAM, PROMIS, SF-36, FABQ
T1ρ Composition Correlates

• Blood Biomarkers
  - ↑ CS846 associated with worse Talar T1ρ (r = 0.618)
  - ↑ C2C associated with worse subtalar T1ρ (r=0.464)
Static Strain Correlates

- ↑ inversion laxity associated with ↑ overall (r= -0.423) and medial (r=-0.460) talar deformation.
Static Strain Correlates

- ↓ balance (TTB scores) associated with ↑ cartilage deformation.
  - ML TTB mean with lateral ($r=.456$) and overall ($r=.435$) deformation.
  - ML TTB SD with medial ($r=.457$) and overall ($r=.570$) deformation.
Static Strain Correlates

- Static loading deformation: no associations with
  - Walking gait biomechanics
  - Hop biomechanics
  - PROs including the SF-36, FAAM, AOS, or FAOS scores
Dynamic Strain Correlates

- ↓ DFROM (WBLT) associated with ↑ medial talar deformation (r= .402).

- ↑ (worse) side hop test time associated with an ↑ overall (r=- .591) deformation.
Dynamic Strain Correlates

- ↓ peak DF during landing was associated with ↑ medial cartilage deformation ($r = -0.382$).
- ↑ plantar flexion at initial contact associated with ↑ overall ($r = 0.376$) and medial cartilage deformation ($r = 0.437$).
Dynamic Strain Correlates

• ↑ peak vGRF associated w/ ↑ medial cartilage deformation (r = -0.440).

• ↑ loading rate associated w/ ↑ overall (r = -0.425) cartilage deformation.
Dynamic Strain Correlates

• ↓ PROMIS physical function (20a) scores associated with ↑ medial (r=.467) and overall (r=.441) deformation.

• No associations with SF-36, FAAM, AOS, or FAOS scores
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Clinical Implications

• Those with CAI have compositional declines and altered cartilage behavior patterns without morphologic changes.
  – Suggestive of early PTOA pathogenesis.

• Mechanical, sensorimotor, and biomechanical variables associate with the observed declines in cartilage health.
  – Suggests that select interventions may be able to slow PTOA progression.

• PROs do not associate with compositional declines but may associate with some behavioral makers of cartilage health.
Potential Target
• Poor Balance
• Limited DFROM

Possible Treatments
• Balance Training
  – Cruz-Diaz et al 2019, Youseef et al 2018, others
• Ankle Joint Mobilizations
  – Hoch et al 2012, 2014; others
• Multimodal interventions
  – Bagherian et al 2019, Powden et al 2019
Clinical Implications

Potential Target
• Altered biomechanics

Possible Treatment Strategies
• To be determined

Movement Specific Training with or without External Feedback

— Donovan et al 2016, Torp et al 2019, Migel & Wikstrom In Review
Clinical Implications

Measurement infrastructure

Plausible Interventions

SLOW ANKLE PTOA

Need cartilage health evidence

Ankle PTOA Pathway  Post-Injury Declines  Identifying Therapeutic Targets  Clinical Implications
Clinical Implications

Ankle Sprain to OA:
Implications for Mitigating Cartilage Degeneration

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Our Mission is to Explore, Educate & Engage in Musculoskeletal Injury Prevention

Thank You

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