ACL Tear: Osseous Impact, inflammation, Early Posttraumatic Osteoarthritis
“The Die is Cast”

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I do have financial disclosures to make

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Frequent injuries among the young
Rising Incidence
Associated injuries to meniscus and articular cartilage are frequent and determine outcome!!
Pre-collegiate surgery is a predictor for intra-collegiate surgery
• 50% of patients undergoing ACL reconstruction have radiographic OA at 10 years (Lohmander et al. AJSM, 2009)

• 46% of those are clinically symptomatic (Øiestad et al. AJSM 11/2010)

• Inflammatory and chondral breakdown markers are elevated in serum at 2 and 5 years after ACL injury indicating chronic inflammation that is continuing after injury and ACL reconstruction (Lohmander et al., Arthritis Rheumatol. 2015)

ASSOCIATED INJURIES

• Meniscus lesions: 30-60%

• Bone Bruises: 85-100%

• Chondral lesions: 40-100%

But are these associated injuries relevant?

ACL + Meniscus:

• ~ 50% of patients undergoing ACL reconstruction have radiographic OA at 10 years (Lohmander et al. AJSM, 2009)

• 80% of combined ACL and meniscus and 62% of isolated ACL patients had radiographic OA at 10-15 years

ACL and Focal chondral defects (FCD):

• Patients with chondral defects had significantly lower KOOS scores 2-5 years after ACL reconstruction
Bone bruises lead to chondral damage long-term.

Do Bone bruises predict outcome at 2 or 6 years after ACL surgery?

- Presence of bone bruise not associated with pain at time of injury or outcome at 12 years (Dunn W. et al, AJSM 2012, Hanypsiak et al, AJSM 2008)

- Multiple reviews did not associate outcome with presence of bone bruises (Illingworth KD et al, KSSTA 2014; Bisson LJ et al, AJSM 2013; Patel SA et al, Sports Med 2014)

- There is an association of bone bruise volume and presence (LTP and MTP) with meniscus tears (Bisson LJ et al, AJSM 2013)

MOON Onsite cohort n=100

- **Presence Location** of bone bruise no predictor of outcome at 2 and 6 years after ACL reconstruction

- **Severity** of bone bruises is not a predictor of outcome at 2 and 6 years

- **Volume** of bone bruises is not a predictor of outcome at 2 and 6 years

Presence of bone bruise and additional chondral damage at time of injury is a predictor of worse outcome
So do bone bruises not matter?

• They are a measure of energy transmitted at the time of injury.

• The actual bone bruise may not matter, the associated injuries to meniscus and cartilage are predictors of worse outcome.

• Bone bruises alone are just an incomplete and inaccurate picture of the actual injury mechanism and therefore may not reliably serve as an outcome predictor.

Schematic Diagram of healing response after wounding:

What about the hemarthros?

• Chondrocytes cultured in blood undergo proteoglycan loss.

• 2 joint bleeds lead to irreversible chondral damage in canine articular cartilage.

• A single joint bleed will lead to an increase of CTX-II within 4-5 days after bleed.

Blood in the joint initiates chondral breakdown.
How about inflammation

- Inflammation does not subside after joint injury
- It is mitigated by the initial hemarthros
- Inflammation seems to occur in phases that can be clinically differentiated
  - Early
  - Transitional
  - Chronic / Late

Inflammatory markers immediately after ACL injury

Lattermann C, Kraus VB, Spindler KP et al., CORR 2016 (accepted for publication)

True Progression of inflammatory markers after ACL injury (schematic)
Inflammatory markers after ACL injury: Kanon study

121 Adult ACL injured patients underwent imaging, blood and synovial fluid draws. Comparison with an uninjured cohort.

~ 3 months after injury:
• TNF-α: 6x
• IL-6: > 1000x
• ARG5: 1.4 x
• CTX-II: 8x

~ 6 years after injury:
• IL-1, IL-6, TNF-α, ARG5-aggrecan and CTX-II elevated up to 5 years after injury

Lohmander et al., Arthritis Rheumatol. 2015

Inflammation

• inflammation may play a significant role in outcomes and symptomatology

• lack of longitudinal data regarding synovial or serum markers of inflammation in a well controlled ACL injury cohort

Hypothesis:

• early intervention with triamcinolone acetonide (Kenalog) will lead to a reduction in post-injury pain.
• will lead to a reduction of inflammatory and collagen breakdown markers as measured in synovial fluid
Study design:

- GCP-RCT (ClinTrials.gov: NCT01692756)
- 68 patients (17/group)
- multicenter (UK, Vanderbilt)
- triple blinded
- i.a.

MOON-AAA Trial

I:
- age: 14-32 (closed growth plates)
- no previous knee injury
- no contralateral knee injury
- no additional ligament injury > Grade 1 MCL
- injury happened during sporting activity

E:
- injury occurred more than 8 days before enrolment
- previous ipsi or contralateral knee surgery
- known allergy to Triamcinolone acetonide
- i.a TA injection into the injured knee within 3 months prior to participation

Results:

- enrolled 49 patients after 2 years (41 UK, 8 Vandy)
- 45 patients with complete data sets at 6 months

Demographics:

| Age (years) | 10.9 ± 0.8 |
| Gender | M/F (n) | 18/8 |
| BMI (kg/m²) | 26.1 ± 5.3 |
| Knee 1 MCL injury | 4/6 (67%) |
| Isolated Lateral Meniscus Tear | 15/4 (20%) |
| Combined Medial and Lateral Meniscus Tear | 19/5 (28%) |
| T2/Tr: High Signal Intensity Cartilage Defects | 3/16 (2%) |
| Median (IQR) | 0 |
| Range | 0-2 |

* In scoring, grade I lesions were 2 while lesions with I had a grade I lesion.
Results:

- no major complications
- no differences in outcomes regarding meniscal or cartilage injuries
- total of 2 ACL retears at 6 months (4%), both of them traumatic during sporting activities

Results: Biomarkers untreated

<table>
<thead>
<tr>
<th>Time 1</th>
<th>Time 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX I (pg/mg)</td>
<td>1.70 ± 0.12</td>
<td>2.47 ± 0.28</td>
</tr>
<tr>
<td>COMP (pg/mg)</td>
<td>811.4 ± 40.8</td>
<td>941.9 ± 49.6</td>
</tr>
<tr>
<td>GAG (pg/mg)</td>
<td>389.2 ± 102.6</td>
<td>219.3 ± 95.4</td>
</tr>
<tr>
<td>NTX (pg/mg)</td>
<td>22.4 ± 10.9</td>
<td>26.0 ± 11.0</td>
</tr>
<tr>
<td>T2D6 (ng/ml)</td>
<td>253.3 ± 148.6</td>
<td>236.6 ± 207.1</td>
</tr>
<tr>
<td>MIP-1 (pg/ml)</td>
<td>389.7 ± 45.1</td>
<td>388.0 ± 33.8</td>
</tr>
<tr>
<td>MIP-3 (pg/ml)</td>
<td>450.0 ± 345.6</td>
<td>450.2 ± 308.5</td>
</tr>
<tr>
<td>IL-1β (pg/ml)</td>
<td>37.1 ± 1.5</td>
<td>11.2 ± 2.1</td>
</tr>
<tr>
<td>IL-1α (pg/ml)</td>
<td>2.6 ± 0.54</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>TNFα (pg/ml)</td>
<td>2.37 ± 0.83</td>
<td>2.87 ± 0.84</td>
</tr>
</tbody>
</table>

* p < 0.05 compared to baseline

Inflammation

Chondrodegradation

Treatment Results: dramatic reduction

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Placebo</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX I (pg/mg)</td>
<td>0.23 ± 0.27</td>
<td>0.32 ± 0.27</td>
<td>0.59 ± 0.27</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>COMP (pg/mg)</td>
<td>37.1 ± 21.2</td>
<td>42.9 ± 13.9</td>
<td>17.5 ± 7.1</td>
<td>32.1 ± 5.7</td>
</tr>
<tr>
<td>GAG (pg/mg)</td>
<td>106.8 ± 124</td>
<td>77.3 ± 16.3</td>
<td>64.2 ± 29.5</td>
<td>70.4 ± 14.3</td>
</tr>
<tr>
<td>NTX (pg/mg)</td>
<td>0.6 ± 0.0</td>
<td>3.0 ± 0.7</td>
<td>2.8 ± 0.6</td>
<td>0.5 ± 0.0</td>
</tr>
<tr>
<td>T2D6 (ng/ml)</td>
<td>57.6 ± 24.8</td>
<td>98.0 ± 29.5</td>
<td>111.1 ± 18.6</td>
<td>89.5 ± 24.4</td>
</tr>
<tr>
<td>MIP-1 (pg/ml)</td>
<td>105.8 ± 206.8</td>
<td>248.9 ± 74.6</td>
<td>180.1 ± 180.6</td>
<td>69.6 ± 32.4</td>
</tr>
<tr>
<td>MIP-3 (pg/ml)</td>
<td>204.0 ± 215.0</td>
<td>270.0 ± 206.0</td>
<td>312.0 ± 217.0</td>
<td>128.0 ± 241.0</td>
</tr>
<tr>
<td>IL-1β (pg/ml)</td>
<td>28.0 ± 42.6</td>
<td>47.1 ± 16.8</td>
<td>17.5 ± 16.8</td>
<td>34.0 ± 24.9</td>
</tr>
<tr>
<td>IL-1α (pg/ml)</td>
<td>11.0 ± 1.7</td>
<td>4.3 ± 0.8</td>
<td>1.7 ± 0.3</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>TNFα (pg/ml)</td>
<td>1.9 ± 0.9</td>
<td>1.06 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>1.0 ± 0.3</td>
</tr>
</tbody>
</table>

* p < 0.05 compared to baseline

# *Significantly different between groups*
ACL injury is a joint injury rather than an injury to one ligament.
Non mechanical effects of this injury such as inflammation may play a significant role in the long term outcomes.
Early treatment after ACL injury may need to be initiated more aggressively, particularly with respect to the initial hemarthros.
Surgery treats the biomechanical instability at the expense of a second biological insult.

Conclusions:

- ACL injury is a joint injury rather than an injury to one ligament.
- Non mechanical effects of this injury such as inflammation may play a significant role in the long term outcomes.
- Early treatment after ACL injury may need to be initiated more aggressively, particularly with respect to the initial hemarthros.
- Surgery treats the biomechanical instability at the expense of a second biological insult.

Take home:

- The die may be cast but we can do better to treat early and recognize the ACL tear as a severe joint injury.
- That should have consequences for:
  - acuity of treatment
  - activity counseling
  - risk prediction
  - future treatment approaches
Thank you

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