Biomarker Changes After a Running Bout Among Individuals with a History of Acute Knee Injury

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Disclosures
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No authors have professional or financial affiliations that would bias this work.

Knee Osteoarthritis Risk Factors
- Increased knee osteoarthritis (OA) prevalence rates
- Muthuri et al., 2011; Frobell et al., 2013; Lohmander et al., 2004; Buckland-Wright et al., 2000; Harris et al, 2013; Driban et al., 2014

Knee Osteoarthritis Risk Factors

OA

Sports Participation
- Prevalence Rates

Prevalence Rates

Sports Participation
Knee Injury History

Prevalence of Knee Osteoarthritis, %

Driban et al., 2014; Roos et al., 2004; Frobell et al., 2013; Lohmander et al., 2004; Harris et al, 2013; Buckland-Wright et al., 2000; Driban et al., 2014
**Problem Statement**

- Biochemical response has been studied in a healthy and OA population, but not in a younger physically active population including a possible knee injury history motivated to return to activity.

- The relationships between patient reported outcomes and biochemical response to activity is unknown.

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**COMP and Walking**

- **Cartilage Oligomeric Matrix Protein (COMP)**
  - Significantly increased post exercise
  - 30 min walking in OA and healthy populations
  - Not significant increase post exercise
  - 30 min walking in OA population
  - Change pre to 3.5 h post walk
  - Predictive of cartilage loss

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**Cartilage Oligomeric Matrix Protein (COMP) Response to Activity**

- **Walking**
- **Running → Dose dependent response**
  - 30 min running at self-selected pace
  - 30 min running at 2.2 m/s pace
  - 1 hr running at self-selected pace
  - Marathon running

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**Biomarker Changes After Injury**

- **Injury**
- **2 mo**
- **1 Yr**
- **2 Yr**
- **4 Yr**

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Abramson & Kroon-Neulen, 2006; Kersting et al., 2005; Mundermann et al., 2009; Subburaj et al., 2010; Erhart-Hledik et al., 2012; Niehoff et al. 2010; Niehoff et al. 2011; Kersting et al. 2005; Neidhart et al. 2000
**Purpose Statement**

- Determine biomarker concentrations pre exercise and change pre to post exercise in AKIH participants in comparison to healthy control participants.
- Determine if self-perceived pre exercise functional differences existed between groups, and whether these measures correlated with biomarker concentration changes.

**Participants / Design**

- 2 group pre-test/post-test (n = 22)
  - Independent variable
    - Group
      - Injured (n = 11)
      - Control (n = 11)
  - Matched by gender (same), age (± 2 y), mass (± 6 kg), height (± 5 cm), sport/physical activity impact level (same)

**Primary Outcomes**

- Dependent Variables
  - Biomarker concentrations
    - COMP
    - CTX-II, CPII, MMP-13, IL-1β, CTX-II/CPII ratios
  - Tegner Activity Score
  - Knee Osteoarthritis Outcome Score (KOOS)
    - 5 subscales

**Procedures**

- Study Forms, Questionnaires & 30 min rest
- Treadmill Run 2.2 m/s (Niehoff, 2011)
- 7 mL Blood Draw
- Centrifuged at 1000 rpm for 20 min at 4°C
- Serum pipetted into 2 mL cryovials
- Stored at -80°C until analysis
Biomarker Analyses

- All samples stored at -80°C until data collection completed.
- Samples were transported to Temple University for ELISA analyses:
  - COMP, CTX-II: MyBioSource
  - IL-1β, MMP-13: Abcam Inc.
  - CPII: IBEX Pharmaceuticals

Data Analyses

- Multiple Wilcoxon Signed Rank Tests:
  - Serum biomarker changes pre to post exercise
  - Serum biomarker concentrations pre exercise
  - Pre-exercise functional outcome measures
- Multiple Spearman’s Correlations:
  - Pre-exercise functional outcome measures and serum biomarker concentration changes
- Statistical significance defined as \( p \leq 0.05 \)

Results: Descriptive Statistics

<table>
<thead>
<tr>
<th>Variable</th>
<th>AKIH (n = 11)</th>
<th>Control (n = 11)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>5F/6M</td>
<td>5F/6M</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.09 ± 1.04</td>
<td>19.91 ± 1.64</td>
<td>-0.310</td>
<td>0.760</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.74 ± 0.13</td>
<td>1.73 ± 0.11</td>
<td>-0.094</td>
<td>0.926</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>74.38 ± 13.98</td>
<td>73.35 ± 14.42</td>
<td>-0.171</td>
<td>0.866</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.45 ± 2.83</td>
<td>24.19 ± 2.83</td>
<td>-0.214</td>
<td>0.833</td>
</tr>
<tr>
<td>Tegner</td>
<td>6.91 ± 1.51</td>
<td>6.91 ± 1.76</td>
<td>0.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Biomarker Changes Pre to Post Exercise

- [Graph showing changes in biomarkers pre to post exercise with statistical significance marked as \( p = 0.328 \) and \( p = 0.328 \).]
**Results: Symptomatic & Functional Differences**

- Injured participants had significantly lower KOOS scores in all subscales than healthy controls.

\[ p = 0.017 \]
\[ p = 0.005 \]
\[ p = 0.027 \]
Results: Patient Reported Outcomes Correlated with Biomarker Changes

<table>
<thead>
<tr>
<th>Measures</th>
<th>COMP</th>
<th>CPII</th>
<th>MMP-13</th>
<th>CTX-II</th>
<th>IL-1β</th>
<th>CTX-II/CPII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tegner</td>
<td>-0.20</td>
<td>0.36</td>
<td>0.01</td>
<td>-0.11</td>
<td>-0.13</td>
<td>-0.45*</td>
</tr>
<tr>
<td>KOOS Pain</td>
<td>-0.03</td>
<td>0.19</td>
<td>0.06</td>
<td>-0.19</td>
<td>-0.36</td>
<td>-0.03</td>
</tr>
<tr>
<td>KOOS Symptoms</td>
<td>0.01</td>
<td>0.13</td>
<td>0.05</td>
<td>-0.23</td>
<td>-0.34</td>
<td>-0.07</td>
</tr>
<tr>
<td>KOOS Activities of Daily Living</td>
<td>0.07</td>
<td>0.15</td>
<td>-0.03</td>
<td>-0.15</td>
<td>-0.39</td>
<td>-0.01</td>
</tr>
<tr>
<td>KOOS Sport &amp; Recreation</td>
<td>0.07</td>
<td>0.24</td>
<td>0.10</td>
<td>-0.26</td>
<td>-0.24</td>
<td>-0.08</td>
</tr>
<tr>
<td>KOOS Quality of Life</td>
<td>-0.07</td>
<td>0.22</td>
<td>-0.10</td>
<td>-0.21</td>
<td>-0.50*</td>
<td>-0.12</td>
</tr>
</tbody>
</table>

Key Findings

- Biochemical response was similar between groups
- Significant functional and symptomatic differences between groups
- Current activity level related to changes in collagen degradation:synthesis ratios
- Decreased quality of life related to increases in IL-1β after running

Primary : COMP Response

- COMP changes not significantly different
  - AKIH group (median increase 9.6 pg/mL)
  - Control group (median decrease 283.92 pg/mL)
  - No Group Differences: Mundermann et al. 2009
  - Significant COMP: Mundermann et al. 2009
  - Unable to distinguish biomarker concentration differences between groups
    - High biomarker variability
    - Exercise intensity

Exploratory Biomarker Responses

CPII
- Two times greater CPII decreases in injured participants than in control participants

IL-1β
- Increased in injured participants
- Decreased in control participants
Baseline Biomarker Comparison

- No statistically significant differences between groups despite previous findings.
- AKIH participants
  - Average = 2 years (range of 4 to 44 months) after injury
- Large variability

Injury History = Poorer Outcomes

- Injury history participants are still trying to participate in similar activities despite reporting pain and symptoms that affect their function and quality of life
- Functional differences may be precursors
  - Activity modifications
  - Underlying biomarker abnormalities
  - Disease onset/progression

Biomarker Changes & Functional Correlations

- IL-1β & KOOS Quality of Life
  - Lower KOOS quality of life scores had greater increases in IL-1β
  - Evidence of association between negative emotional states and increased systemic inflammation
- Potential targets for intervention efforts

Johnston & Webster, 2009; Al-Shatti et al., 2009; Elliott et al., 2008
Biomarker Changes & Functional Correlations

- Lower activity levels had greater increases in collagen turnover ratios
  - Shift towards more degradation than synthesis
- Reinforces dose-dependent response

Limitations

- Standardized exercise intensity level
- Restricted biomarker panel
- Sample size

Conclusions

- Participants with a knee injury history respond similar to matched healthy controls after a run.
- Participants with a knee injury history have overall lower outcome scores.
- Pre-exercise outcome scores relate to biomarker responses.

Acknowledgements

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Questions?

Thank you
OA Pathomechanisms in Knee Injury

Cattano et al., 2013; Harris et al, 2013

<table>
<thead>
<tr>
<th>Level 10</th>
<th>Competitive sports- soccer, football, rugby (national elite)</th>
</tr>
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<tbody>
<tr>
<td>Level 9</td>
<td>Competitive sports- soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball</td>
</tr>
<tr>
<td>Level 8</td>
<td>Competitive sports- lacrosse or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing</td>
</tr>
<tr>
<td>Level 7</td>
<td>Competitive sports- tennis, running, motorcars speedway, handball Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running</td>
</tr>
<tr>
<td>Level 6</td>
<td>Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week</td>
</tr>
<tr>
<td>Level 5</td>
<td>Work- heavy labor (construction, etc.) Competitive sports- cycling, cross-country skiing, Recreational sports- jogging on mown ground at least twice weekly</td>
</tr>
</tbody>
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