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

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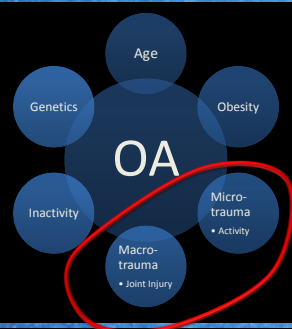
Disclosures

- Cattano NM, Driban JB, Barbe MF, Tierney R, Amin M, & Sitler MR
  - *No authors have professional or financial affiliations that would bias this work.*

Knee Osteoarthritis Risk Factors

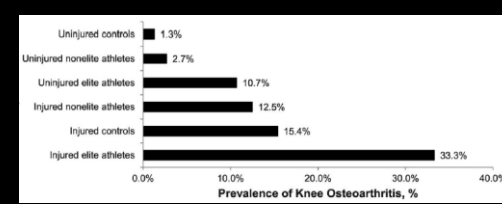
- Increased knee osteoarthritis (OA) prevalence rates



- 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

Prevalence Rates

- Sports Participation
- Knee Injury History



Driban et al., 2014; Roos et al., 2004;

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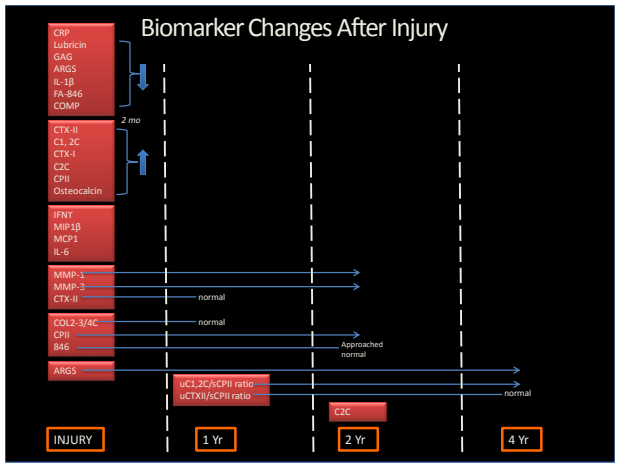


COMP and Walking

- 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

Abramson & Krasnokutsky, 2006; Kersting et al., 2005; Mundermann et al., 2009; Subburaj et al., 2010; Erhart-Hledik et al., 2012;

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

Niehoff et al. 2010; Niehoff et al. 2011; Kersting et al. 2005; Neidhart et al. 2000

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

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)*

***Potential covariates**; concurrent injury, time since injury, time since surgery, time since return to activity, gender, smoking, medication/supplement use.*

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

-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

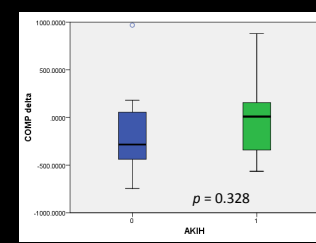
Data Analyses

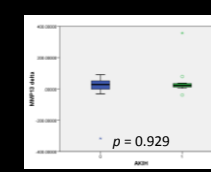
- Multiple Wilcoxon Signed Rank Tests
  - Serum biomarker changes pre to post exercise
  - Serum biomarker concentrations pre exercise
  - Pre-exercise functional outcome measures
- Multiple Spearman's Correlations
  - Pre-exercise functional outcome measures and serum biomarker concentration changes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

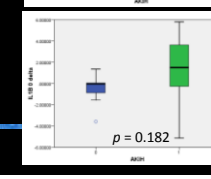
Results: Descriptive Statistics

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

Biomarker Changes Pre to Post Exercise







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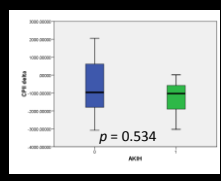
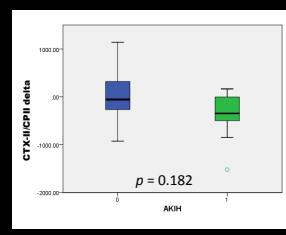
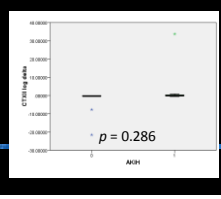
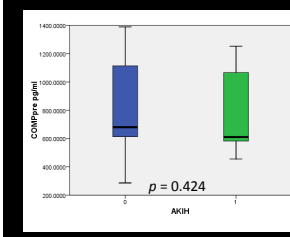
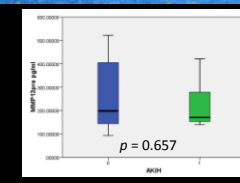


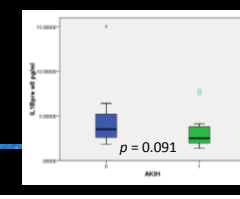




Baseline Biomarker Comparisons







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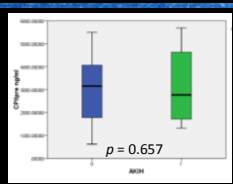
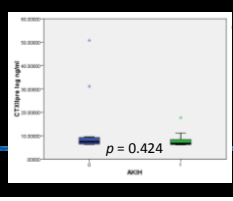
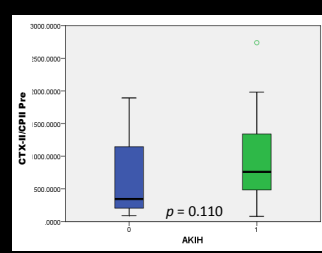
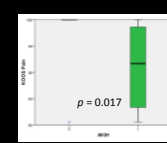


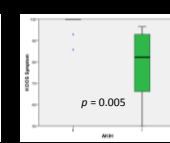


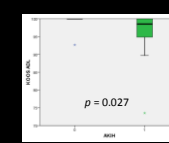


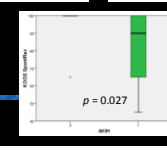
Results: Symptomatic & Functional Differences

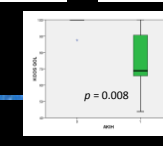
- Injured participants had significantly lower KOOS scores in all subscales than healthy controls.











Results: Patient Reported Outcomes Correlated with Biomarker Changes

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

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

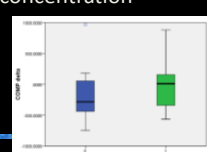
- COMP changes not significantly different
  - AKIH group (median increase 9.6 pg/mL)
  - Control group (median decrease 283.92 pg/mL)

Insignificant Trend:
Erhart-Hledik et al. 2012 ✓

No Group Differences:
Mundermann et al. 2008 ✓

Significant COMP:
Mundermann et al. 2009
Subburaj et al. 2012 ✗

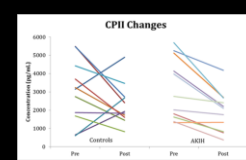
- Unable to distinguish biomarker concentration differences between groups
  - High biomarker variability
  - Exercise intensity



Exploratory Biomarker Responses

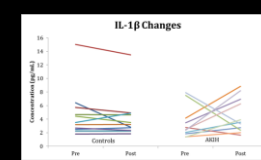
CPII

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



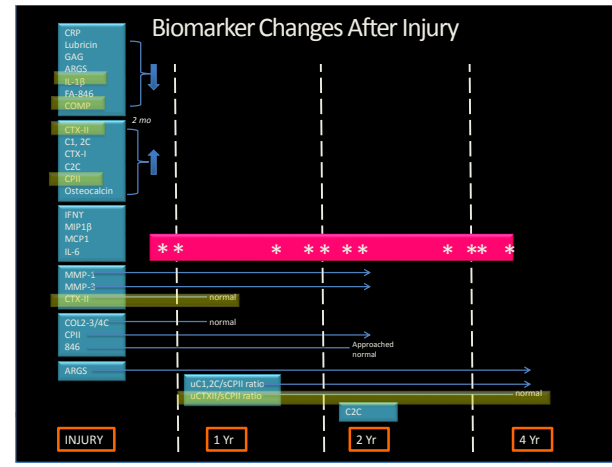
IL-1β

- 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., 2005; 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

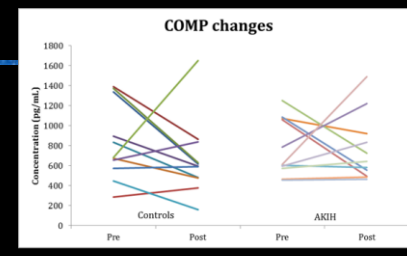
- Participants with a knee injury history respond similar to matched healthy controls after a run.
- Participants with a knee injury history have overall lower outcome scores.
- Pre-exercise outcome scores relate to biomarker responses.

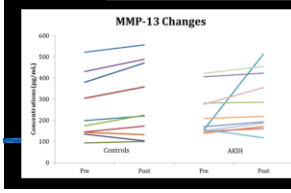
Acknowledgements

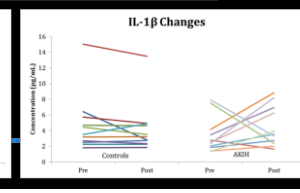
- Thank you to West Chester University's Provost Initiative Grant for supporting this research project.

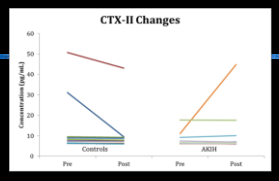
Questions?

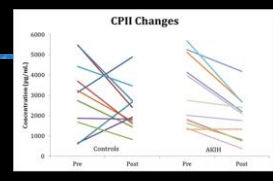
Thank you

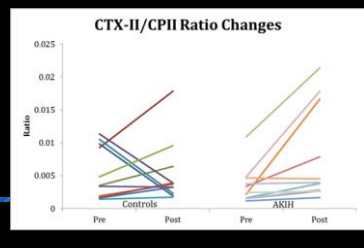


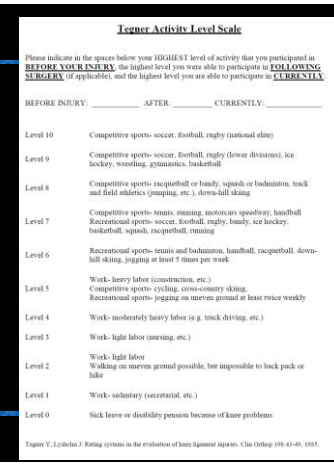












Tegner Activity Level Scale

Please indicate in the spaces below your HIGHEST level of activity that you participated in **BEFORE YOUR INJURY**, the highest level you were able to participate in **FOLLOWING SURGERY** (if applicable), and the highest level you are able to participate in **CURRENTLY**

BEFORE INJURY: _____ AFTER: _____ CURRENTLY: _____

Level 10	Competitive sports- soccer, football, rugby (national elite)
Level 9	Competitive sports- soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball
Level 8	Competitive sports- racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing
Level 7	Competitive sports- tennis, running, motorcars speedway, handball Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running
Level 6	Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week
Level 5	Work- heavy labor (construction, etc.) Competitive sports- cycling, cross-country skiing, Recreational sports- jogging on uneven ground at least twice weekly
Level 4	Work- moderately heavy labor (e.g. truck driving, etc.)
Level 3	Work- light labor (nursing, etc.)
Level 2	Work- light labor Walking on uneven ground possible, but impossible to back pack or hike
Level 1	Work- sedentary (secretarial, etc.)
Level 0	Sick leave or disability pension because of knee problems

Tegner Y, Lysholm J: Rating systems in the evaluation of knee ligament injuries. Clin Orthop 198:43-49, 1985.

Level 10	Competitive sports- soccer, football, rugby (national elite)
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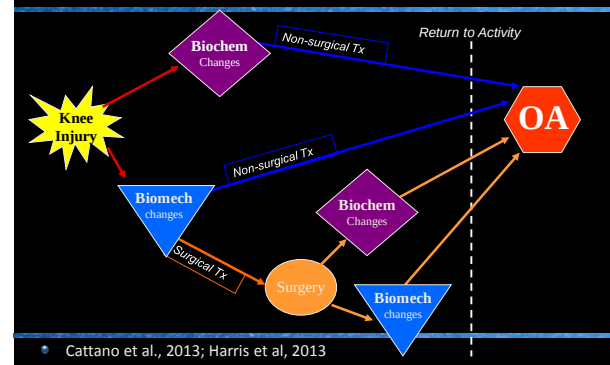
OA Pathomechanisms in Knee Injury



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