Does Osteoarthritis Pain Severity Correspond More to Inflammation or Joint Damage?

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Osteoarthritis

- **Osteoarthritis (OA)** is a degenerative joint disease characterized by loss of cartilage and decreased joint function.

Risk Factors

Aging

Obesity

Gender

Injury

Whole Joint Disease

No Cure

240 Million

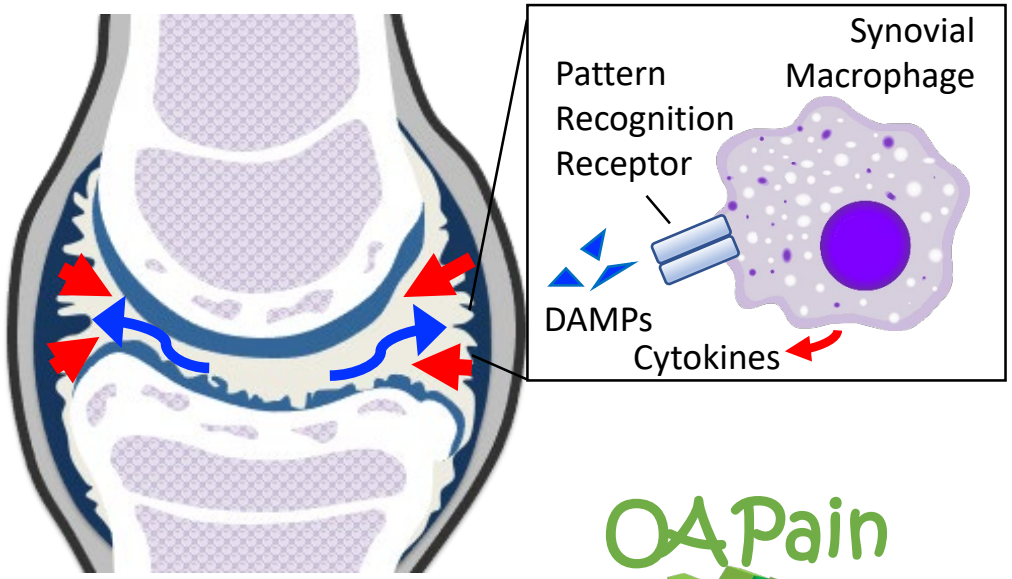
People Worldwide

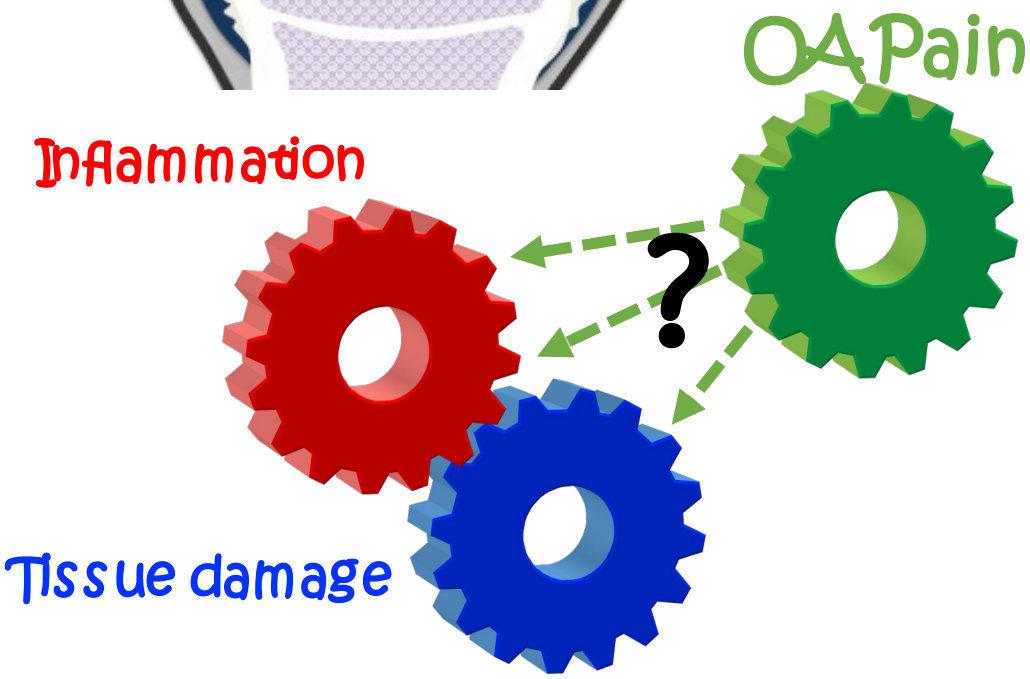
80%

Have Limited Motion

Hunter DJ. N Engl J Med 2015;372:1040-1047.

OA: Cycle of Damage & Inflammation



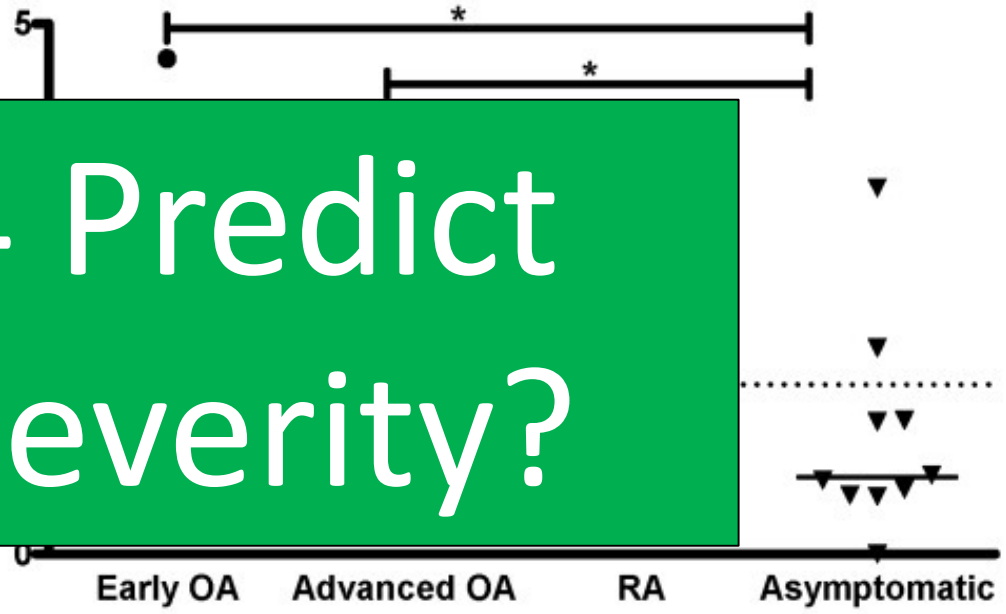


- Injury initiates a slow **chronic cycle** of joint tissue degeneration and unresolved activation of pro-inflammatory innate immune pathways.
- Clinically, the severity of OA joint damage (measured on x-rays) poorly predicts the severity of OA pain or loss of joint function.
- **Is inflammation a better biomarker of OA pain severity?**

OA and Inflammation

- CD14 is a monocyte/macrophage pattern recognition receptor that increases DAMP-mediated inflammation.
- **Macrop**
  from th
  which
- Serum
  early a
- Serum and synovial fluid sCD14 levels are associated with OA symptoms and disease progression (Daghestani et al. 2015).

Does sCD14 Predict PTOA Pain Severity?



Nair, et al. 2012

Objective

- To investigate the relative contribution of damaging joint calcification and structural pathology versus a serum macrophage-related inflammatory biomarker as mediators of OA pain.

Hypothesis:

- OA pain is more strongly correlated with circulating sCD14 levels compared to joint calcification/damage.

Study design

C57BL/6 Male & Female Mice

Acclimatized

Control Fat Diet 10% fat

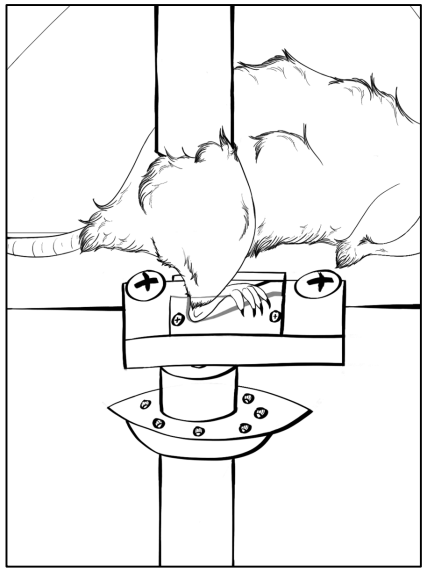
OR

High Fat Diet 45% fat

16 weeks old mice

Diet 20 weeks

Pain Analysis Pre-Injury



Compression Injury or Sham at 36 weeks Old

Pain Analysis 2 & 4 Weeks Post Injury

4 weeks

Tissue Collection at 40 weeks old

End Point

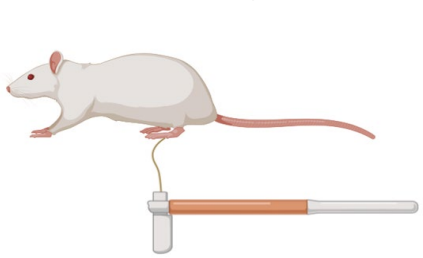
Pain analysis
Joint Morphology
(micro-CT & Histology)
Inflammation

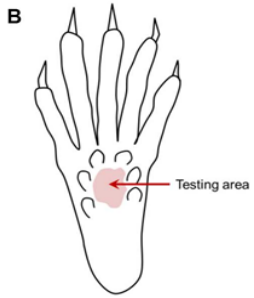
N=10 per group: 80 Total
40 Males and 40 Females

Methods

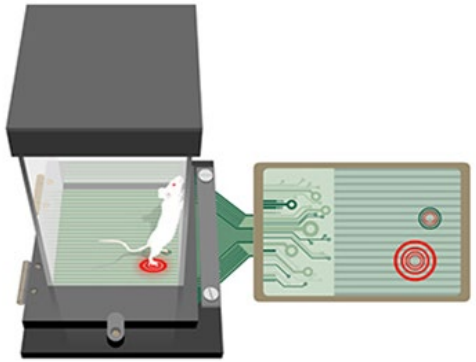
Pain Analysis (Completed)

- Evoked Pain (Von Frey Filament)



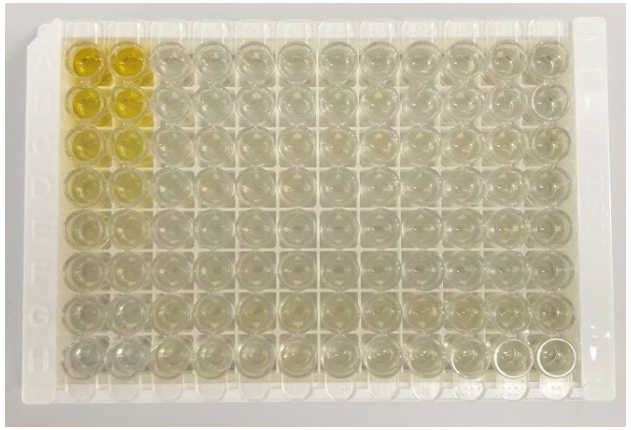


- Spontaneous Pain (Dynamic Weight Bearing)



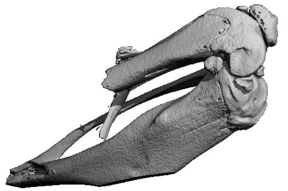
Inflammation Analysis (Completed)

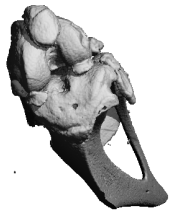
- Serum CD14 (ELISA)

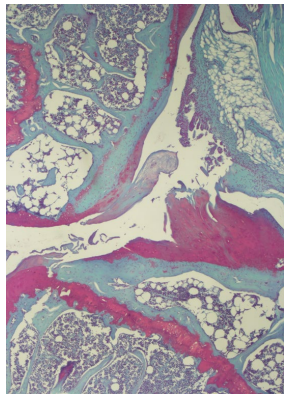


Knee Joint Pathology (Ongoing)

- Bone Structure Changes (MicroCT)
- Cartilage Damage (Histology)



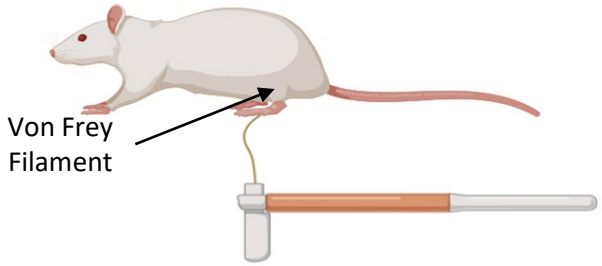


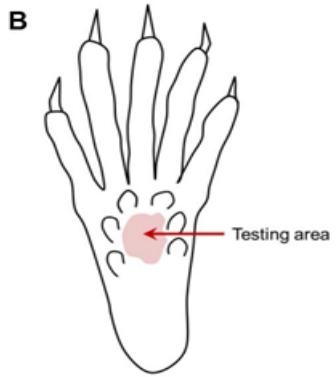


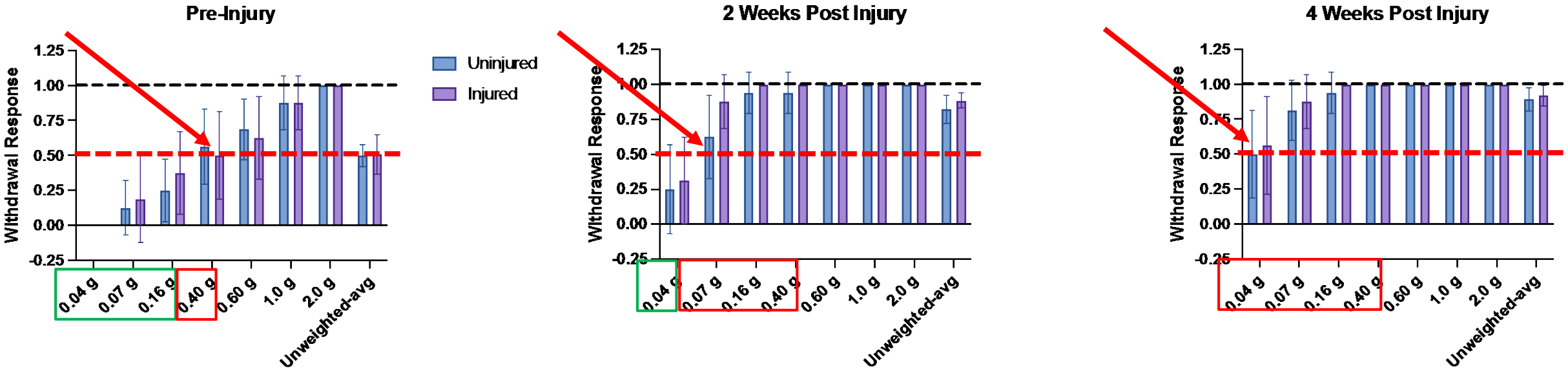
Results

How do injury and diet affect OA pain behavior responses?

Evoked Pain Response

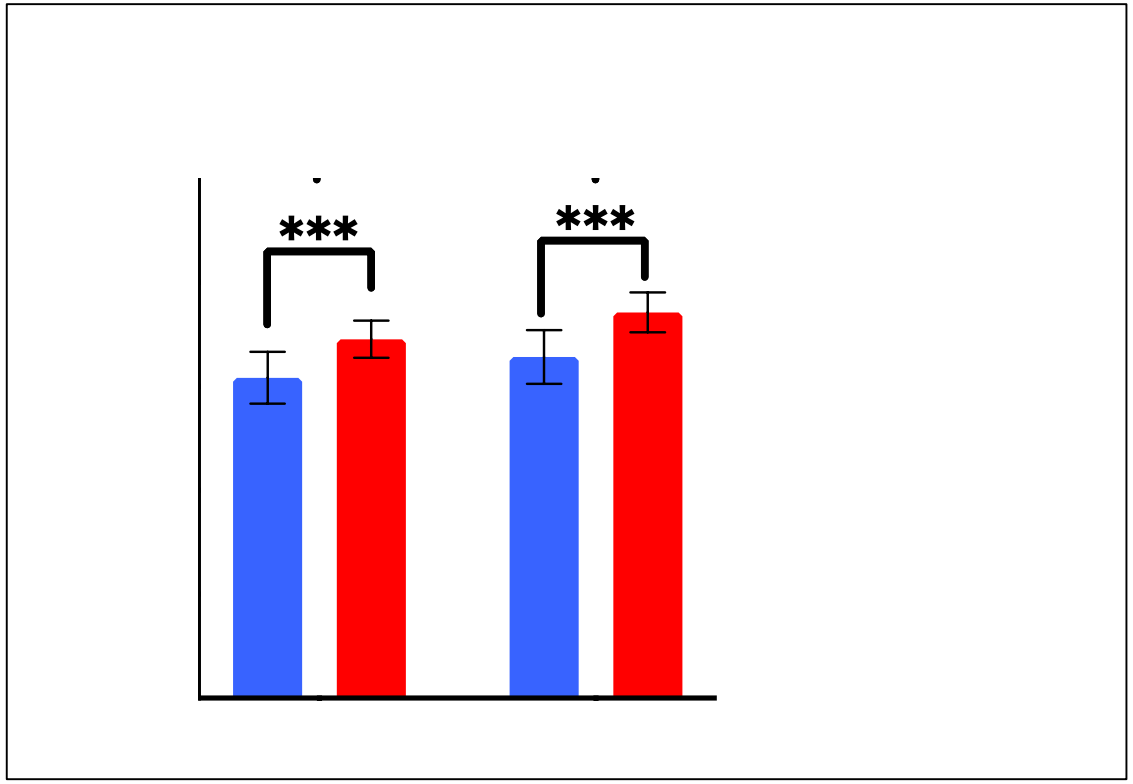




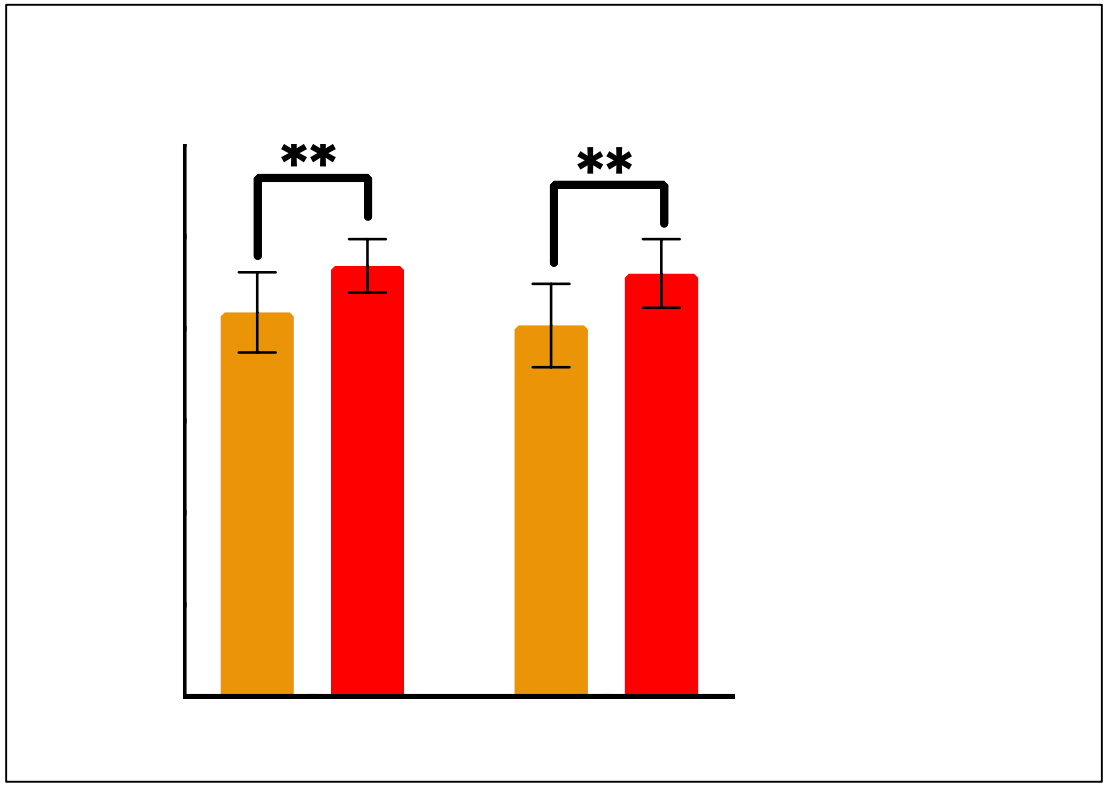


Von Frey Filament Test Results

4 Weeks Post Injury



Injured limb-specific and HFD sensitive mechanical allodynia

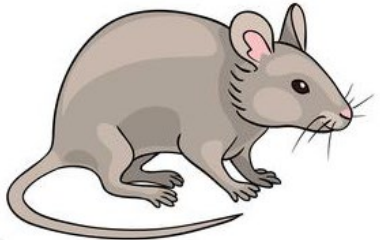


Whole-body injury-dependent mechanical allodynia

Spontaneous Pain Response Using Dynamic Weight Bearing Test

How do injury and diet affect spontaneous pain behaviors?

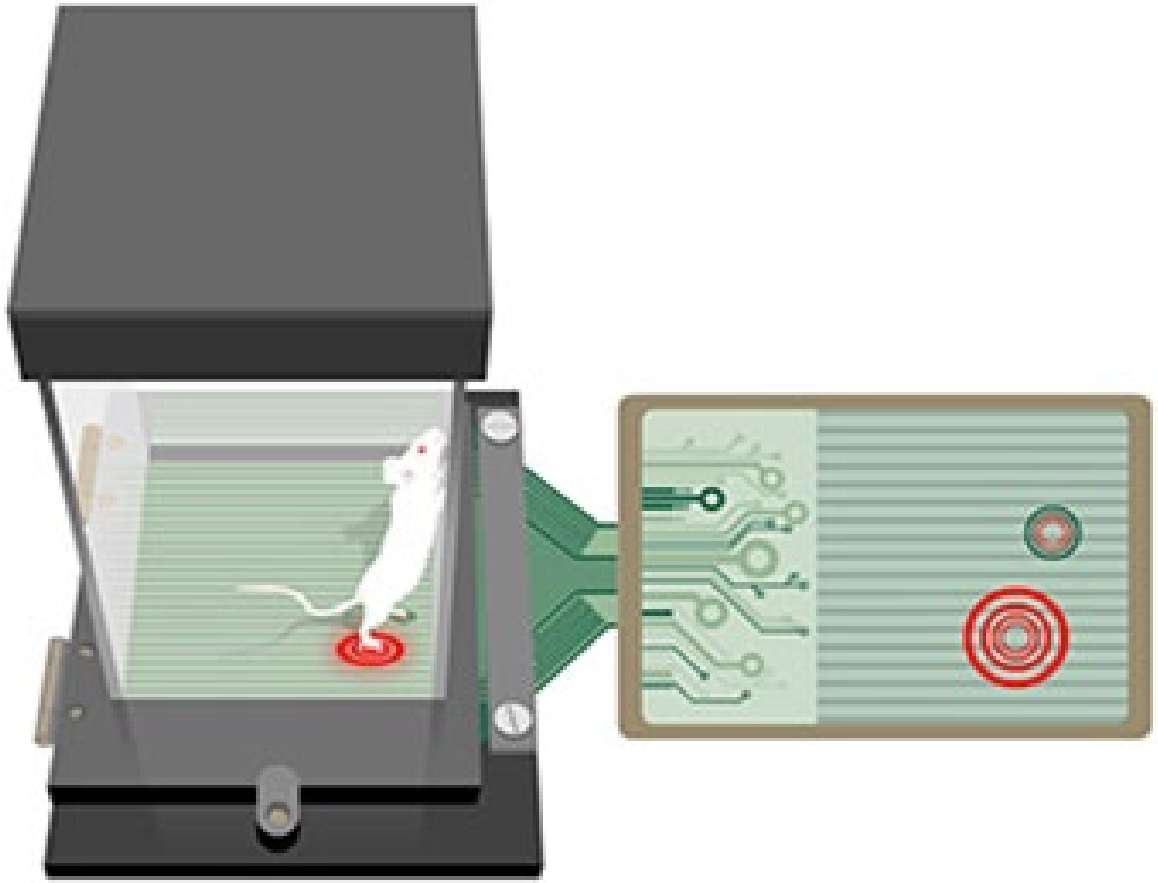
Rearing



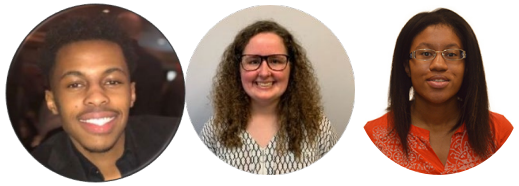
Mice walking around

1 = Equal distribution of weight

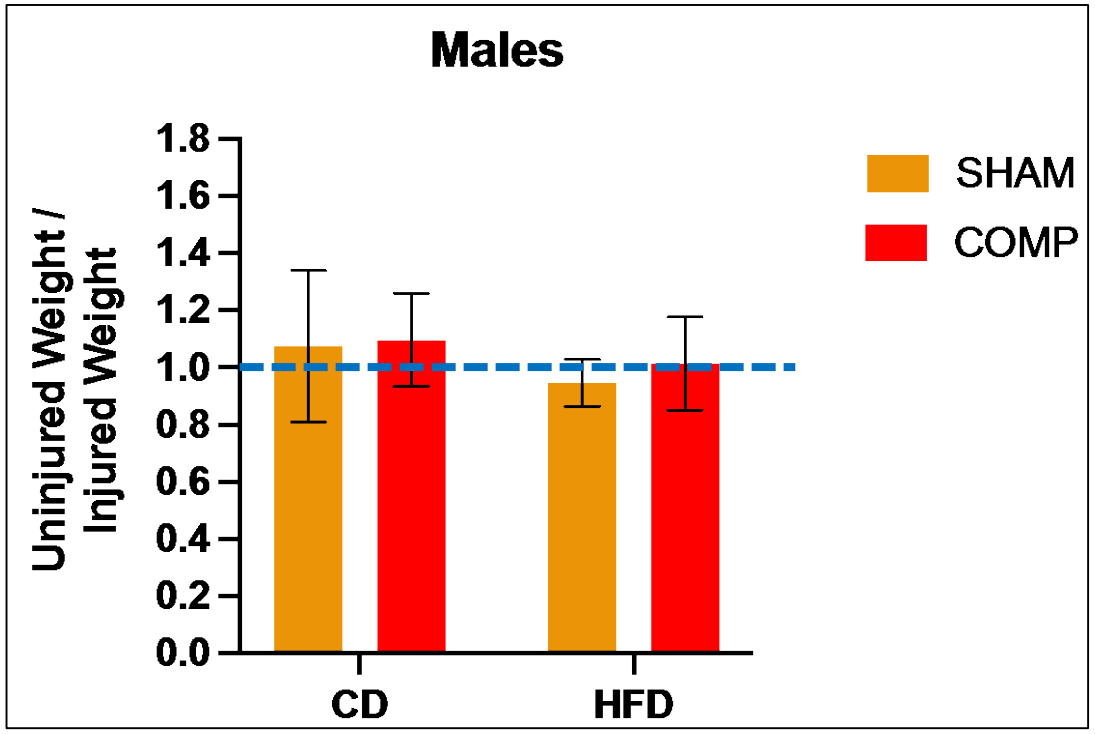
>1 = Less weight supported on injured limb

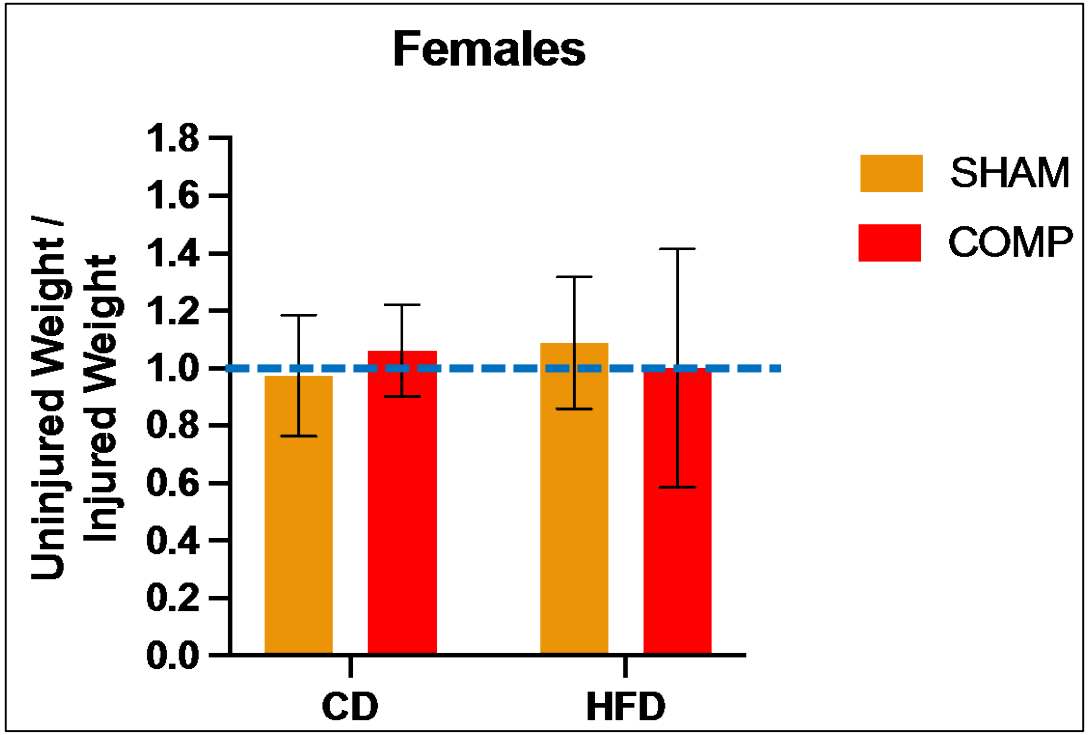


Stationary Rearing Hindlimb Weight Distribution Ratio

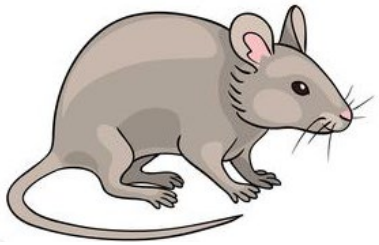


4 Weeks Post Injury





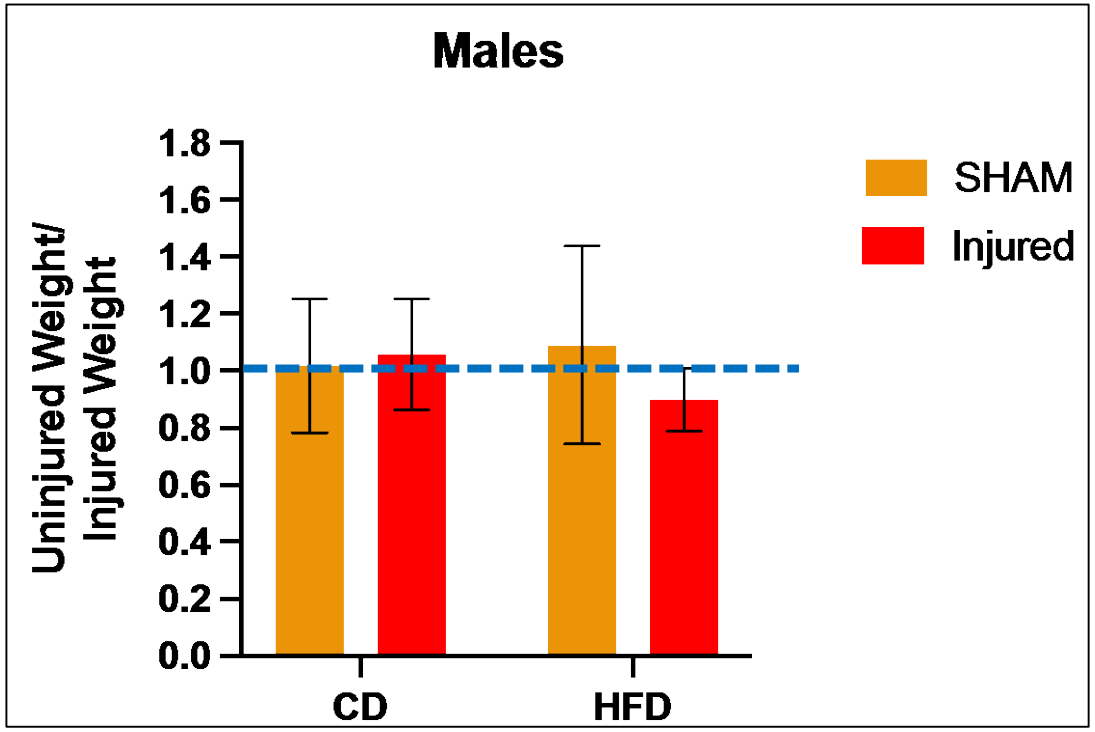
Neither injury or diet shifted bodyweight support during static rearing

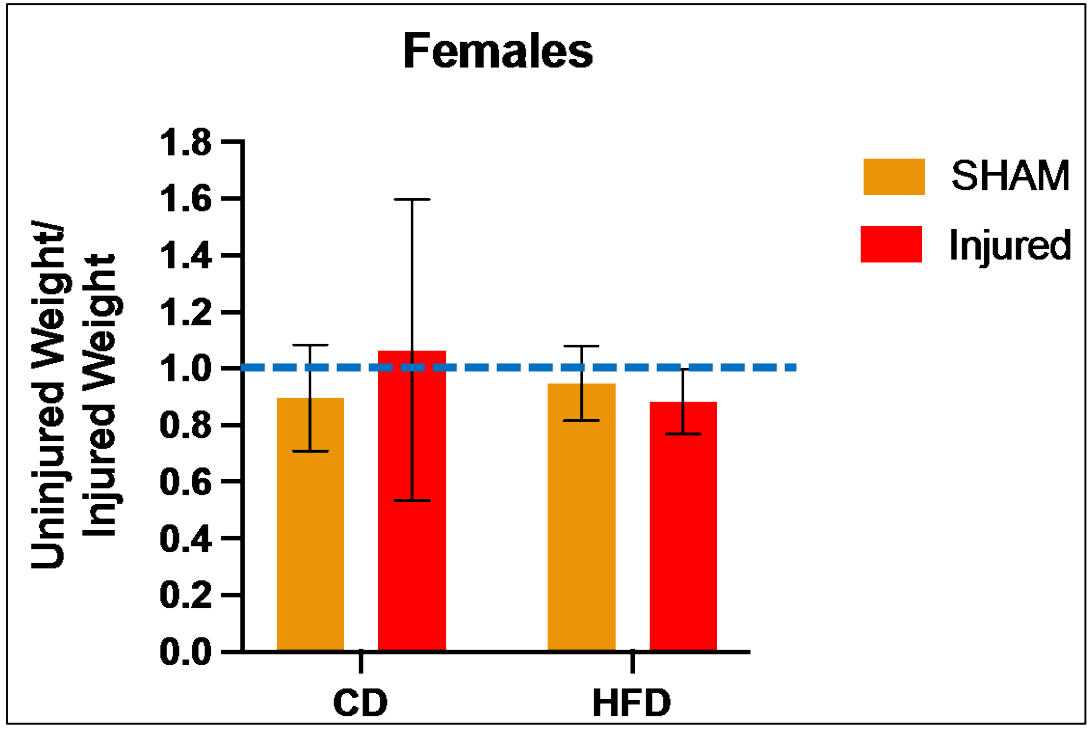


Weight Distribution Ratio While in Motion



4 Weeks Post Injury

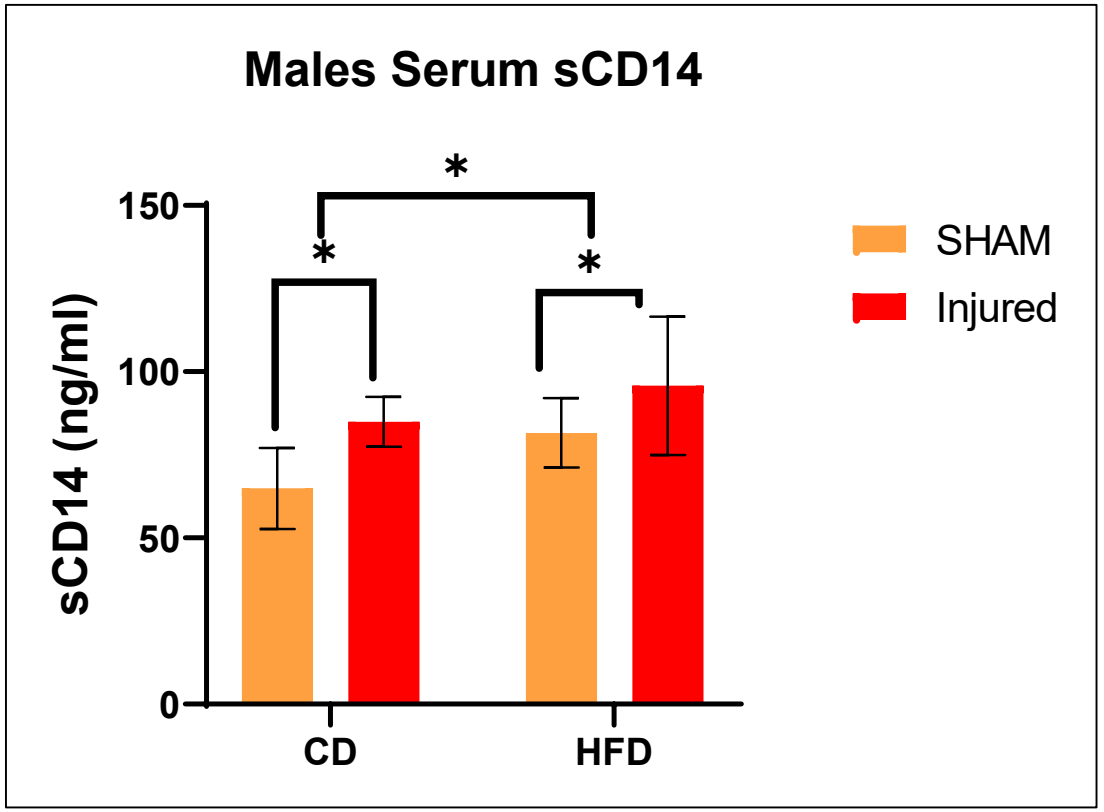


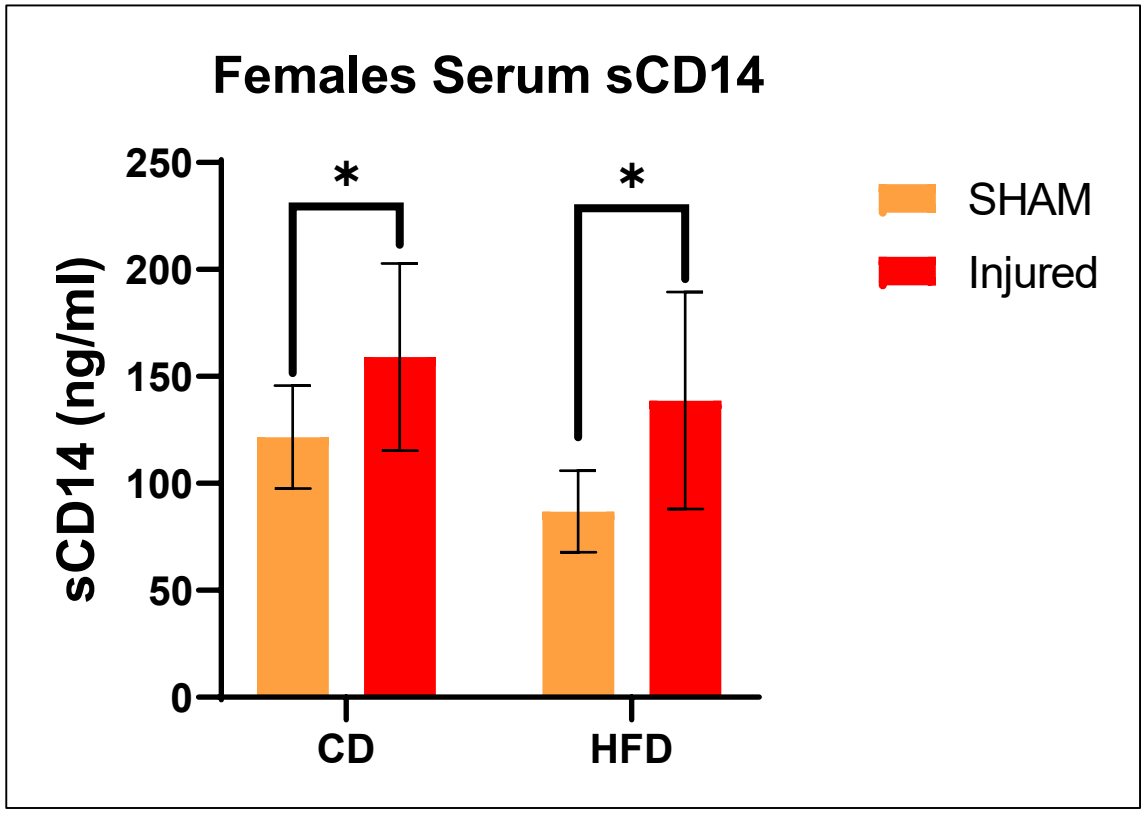


Neither injury or diet shifted hindlimb support during movement

Serum Levels of Macrophage Inflammatory Marker sCD14







Injury and HFD increased sCD14

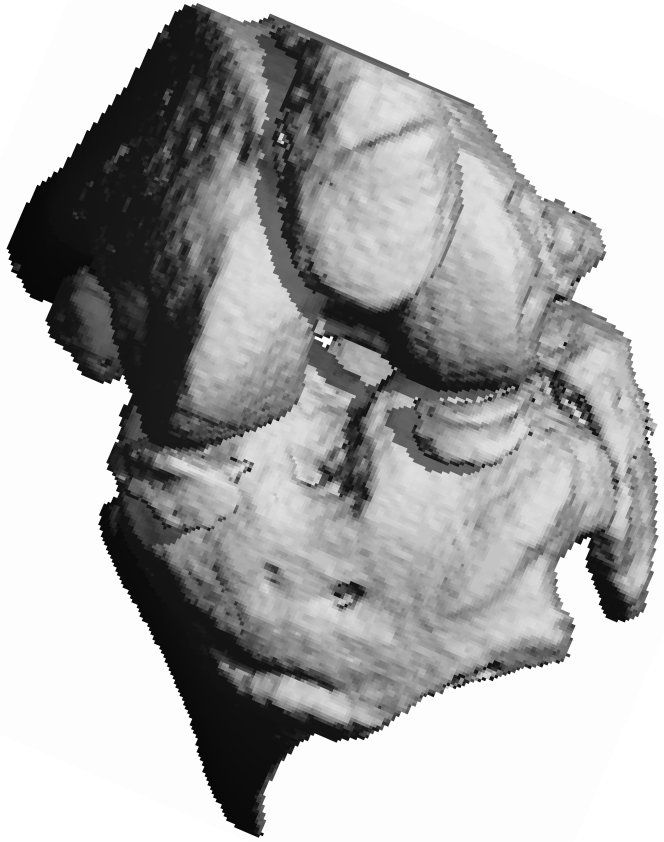
Injury (but not HFD) increased sCD14

Ongoing Joint Damage Analysis

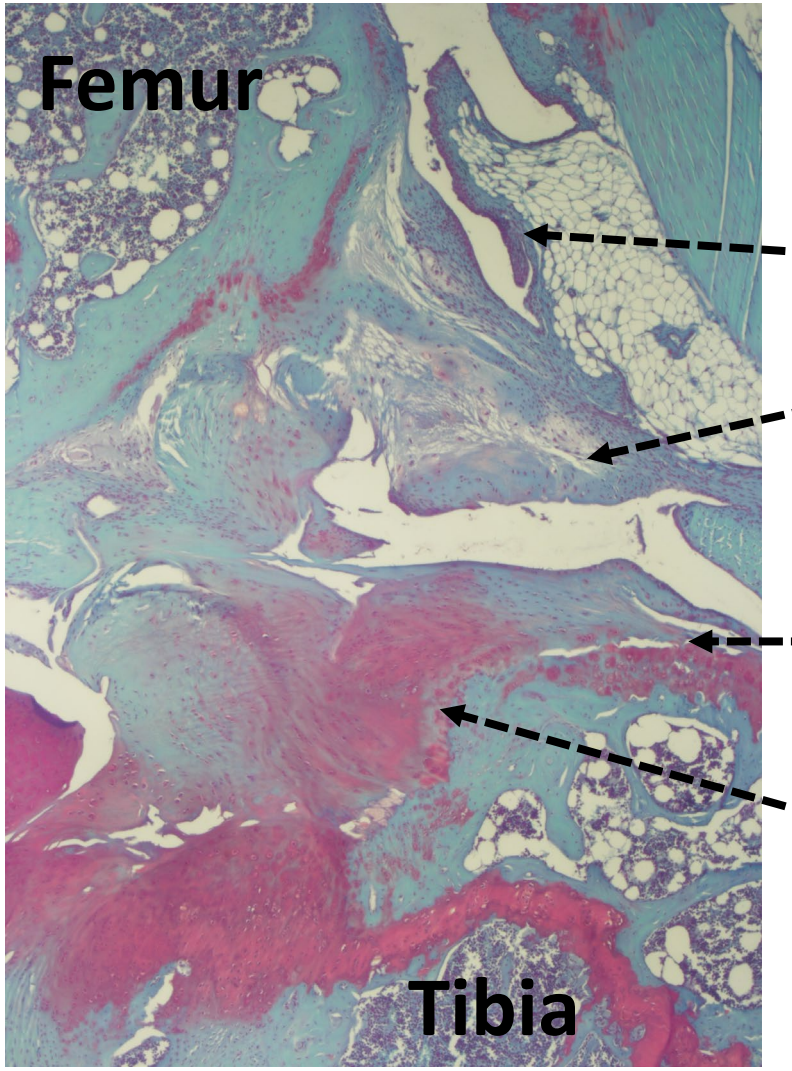


MicroCT Image

Quantify epiphysis bone volume (overall joint calcification)



Sample Uninjured Knee Joint



Semi-quantitative histopathology evaluation

Synovial lining thickening

Synovial hyperplasia

Cartilage Damage

Fibrocartilage Growth

Sample Injured Knee Joint

Summary of Results

Evoked Pain:

- Mechanical allodynia increased at 2 and 4 weeks post injury and sham
- Males: pain sensitivity linked to injured limb and high-fat diet.
- Females: injury caused a whole-body increase in pain sensitivity (both injured and uninjured limb) that was independent of diet

Spontaneous Pain:

- There was no difference in hindlimb weight support at 4 weeks post injury

Inflammation:

- Injury increased serum sCD14 in both male and female mice compared to sham mice, with a high-fat diet also increasing sCD14 in males.

Structural Analysis of Knee Joint:

- In progress, results pending.

Conclusion

- Pain behavior is complex and differs between male and female mice and their sensitivity to a high-fat diet.
- sCD14 is associated with knee injury in male and female mice, and like the pain results, it was increased by a HF diet only in males.
- Although our joint damage results are pending, these findings support a potential link between sCD14 and OA pain. Our collaborator (Dr. Carla Scanzello) is testing this mechanism using a CD14 monoclonal antibody.

Acknowledgements

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VA Collaborative Merit Award

OMRF

Langston Biomedical Research Scholars

References

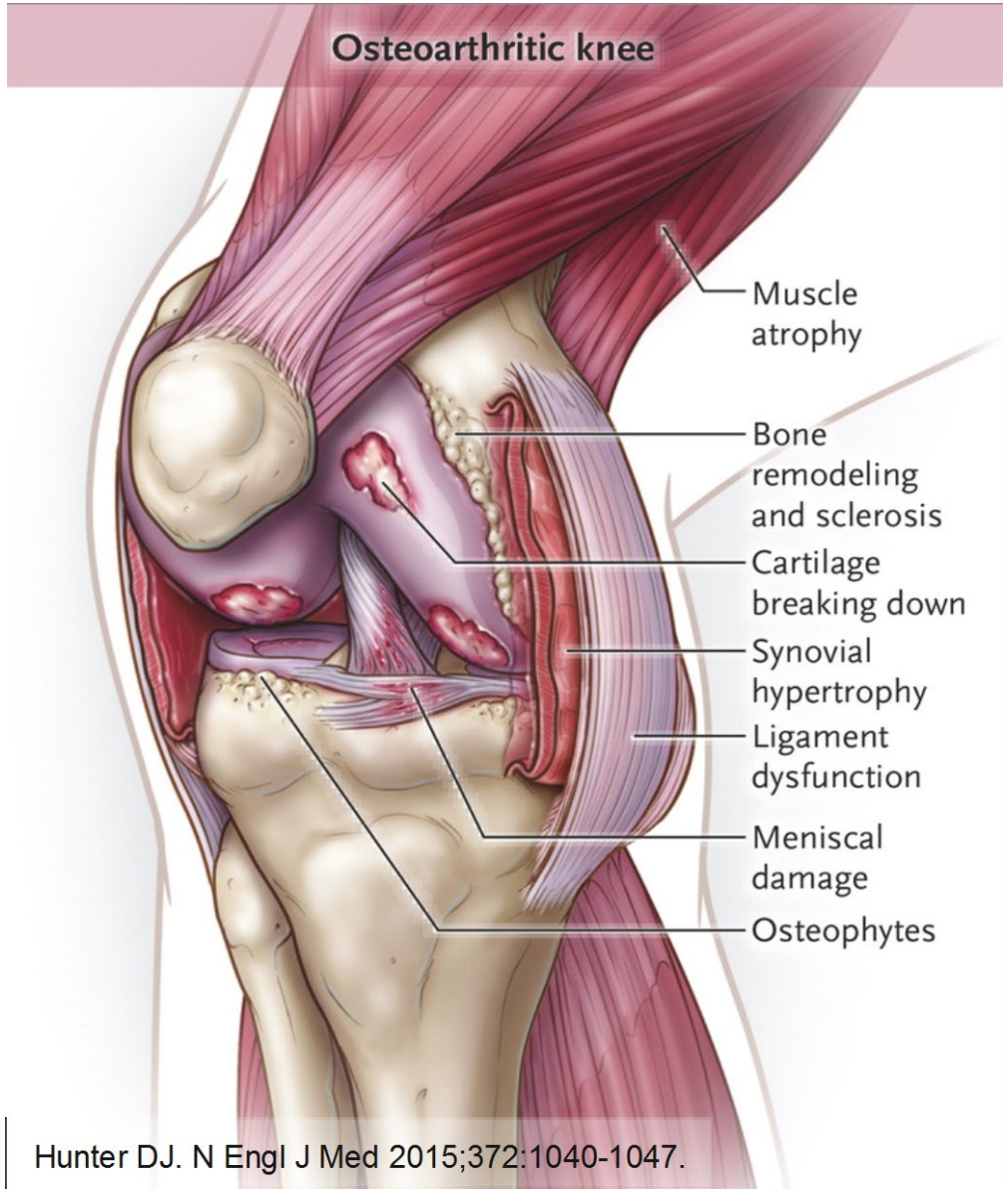
- Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 2007;35(10): 1756e69.
- Lohmander, et al.2007
- Scanzello, et al. 2012

Conclusion

- There is a direct correlation between pain and sCD14.
  - Based on my research OA pain will be strongly correlated with circulating CD14 levels compared to joint calcification.
- The effect of diet on pain was more evident in the male mice compared to the females.
- The female mice exhibited a more systemic effect that was not diet dependent.
- Structural analysis are still pending:
  - These results should show the effects of the compression injury compared to the sham and the effects of obesity on structural damage.
  - This will be compared to the pain and inflammation results to identify the correlation.

Osteoarthritis

- The knee joint undergoes many complex structural and inflammatory changes during the development of OA.
- This process involves progressive **joint damage** and chronic low-grade **inflammation** that leads to **OA pain**.
- In the clinical setting the severity of post-traumatic osteoarthritis (PTOA) joint damage is often measured using x-rays.
- However, these results do not show a strong correlation between OA pain and joint damage.



Hunter DJ. N Engl J Med 2015;372:1040-1047.