Associating Joint Histological Changes to Gait Abnormalities and Mechanical Sensitivity in a Rat Model of Post-traumatic Knee Osteoarthritis

Heidi E. Kloefkorn, Brittany Y. Jacobs, Kyle D. Allen, Ph.D..
University of Florida, Gainesville, FL, USA.

Disclosures:

Introduction: Osteoarthritis (OA) ultimately leads to pain and disability, which consumes billions of dollars in healthcare-associated costs and severely reduces the quality of life for millions of OA patients [Lawrence 2008]. While radiographic evidence of joint degradation and patient reports of OA symptoms are often concurrent, the severity of knee degeneration on radiographs is a relatively poor correlate to patient reports of OA symptoms [Dieppe 2005, Hannah 2000]. Since the primary reason OA patients seek medical treatment is pain, understanding the links between OA pathogenesis and symptoms is critical for the improved treatment and management of knee OA. The objective of this study is to investigate associations between histological measures of joint destruction and behavioral analyses of OA pain and disability using a rodent model of post-traumatic knee OA.

Methods: Seventy-two male Lewis rats (250 g, 3-months old) were acquired for this IACUC-approved experimental design. In 64 rats, a midline skin incision was made and the medial collateral ligament was exposed and transected. The knee was then placed in a valgus orientation to expose the medial meniscus. In 32 of these rats, the medial meniscus was radially transected in its central portions (MMT surgery, Janusz 2002); the 32 other rats served as sham control. The remaining 8 rats did not receive any surgery (naïve controls). At 1, 2, 4, and 6 weeks after surgery, 8 MMT and 8 sham animals were tested for mechanical sensitivity using the up-down method for von Frey microfilaments (Chaplan 1994), spatiotemporal gait characteristics using high-speed videography (250 fps, Allen 2012), and dynamic gait characteristics using 3-component force links (Kistler ±2 kN in Fz, ±1 kN in Fy,Fx, Allen 2012) Animals were euthanized following behavioral testing and joints were sectioned and graded using the OARSI histopathology scheme for the rat (Gerwin 2010). Behavioral and histological data were also collected on naïve controls; these data were used to set baseline behavioral and joint characteristics from male Lewis rats. Significant behavioral measures were identified using analysis of variance or a generalized linear model to account for a velocity covariate. Best subset linear regression modeling with minimization of Mallow’s Cp was used to identify histological features that had a significant correlation to changes in behavior.

Results: MMT animals had significant changes in peak vertical force and vertical impulse relative to contralateral limbs and sham operated limbs. Minimization of Mallow’s Cp identified cartilage loss in the hypertrophic zone, depth of cartilage damage in the central regions of the medial condyle, total width of cartilage surface damage, osteophyte size, and calcified cartilage damage score as correlates of changes in peak vertical force. These same histological measures, with the exception of osteophyte size, were correlates of changes in vertical impulse. Despite being a statistically significant non-zero correlates, none of the associations identified were found to be strong correlates of peak vertical force or vertical impulse changes (Pearson Correlation Coefficients ≤ 0.3). Minimization of Mallow’s Cp identified medial joint capsule repair and depth of cartilage damage in medial aspects of the medial condyle as correlates of limb withdrawal threshold (mechanical sensitivity). Depth of cartilage damage in medial aspects of the medial condyle was a moderately strong correlate of limb withdrawal threshold (Pearson’s Correlation Coefficient = 0.4195). Medial joint capsule repair was a relatively poor correlate of limb withdrawal thresholds, with the exception of the 1 Week time point where medial joint capsule repair associated with changes in limb withdrawal threshold. This may help to explain some sources of hind limb sensitivity following surgical simulation of knee OA in the MMT model, with capsular healing relating to early changes in limb sensitivity and cartilage damage relating to late stage sensitivity changes.

Discussion: The behavioral and histological data collected in our rat model of post-traumatic knee OA parallel clinic data, in that, measures of joint damage are relatively poor correlates of OA pain and disability. While joint damage and pain and disability coincide in our rat model of post-traumatic knee OA, the severity of damage explained only a small amount of the variance measured in rodent limb sensitivity or rodent gait compensations. These results could certainly be due to high variance in the measures. While gait testing in rodents has recently become more precise, continued improvement in the behavioral testing methods is possible. Similarly, recommendations for histological measures of OA have recently shifted from semi-quantitative scores to more quantitative assessment of joint structures (Gerwin 2010). Continued advances in both measures may help discern stronger relationships between cartilage/bone damage and pain/disability in the future. In addition, our results in combination with clinical reports motivate the need to look at extra-articular tissues in the development of OA-associated pain and disability. A similar statistical approach could be used to investigate the importance of muscular changes, nervous system remodeling, and changes in pro-inflammatory mediators to the development of OA-associated pain and disability.

Significance: While OA-driven joint destruction and symptoms coincide, the severity of symptoms does not necessarily correlate
to the scale of joint destruction. Histologic features of knee OA, as assessed by the OARSI histopathology scheme for the rat, are only weak to moderate correlates of behavioral measures of knee OA subsequent to MMT surgery in the rat.

**Acknowledgments:** This work was supported by the National Institutes of Health / National Institute of Arthritis and Musculoskeletal and Skin Diseases (Grant #K99/R00AR057426).
