

Gait compensations and pathologic changes in subchondral bone microarchitecture are similar following medial collateral ligament and meniscal injury in the rat.

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INTRODUCTION: Pathologic subchondral bone modeling and/or remodeling are likely connected to abnormal movement patterns in osteoarthritis (OA). In the healthy and OA joint, the subchondral bone plays a critical role in joint function, working together with the articular cartilage to dissipate loads. Changes in movement patterns, likely adapted to avoid or reduce OA pain, may shift the magnitude and location of loads on the subchondral bone. In response, pathologic subchondral bone modeling and/or remodeling may occur, where cancellous and cortical bone undergo structural changes to meet the new demands of the skeleton. Despite the possible connections between altered movement and subchondral bone changes, few studies evaluate the relationship between pathologic changes in bone microstructure and the function consequences of OA. Understanding this relationship may inform the discordance between symptoms and joint damage during disease progression. In this study, we explored the relationship between subchondral bone remodeling and altered gait patterns across the development of rat OA. We hypothesized that changes in subchondral bone microarchitecture, related to subchondral bone remodeling and/or remodeling, would be associated with shifts in gait patterns in OA rats.

METHODS: Forty Lewis rats (n=20/sex, 300g, three months of age) were acclimated to their housing and gait testing rooms for one month. Baseline gait testing and in vivo μ CT scans were performed. Animals were then randomly split into three groups. One group received a medial collateral ligament transection + medial meniscus transection (MMT, fast progressing OA) and another received the medial collateral ligament transection (MCLT, slow progressing OA). All surgeries were performed on the right hindlimb. Naïve animals did not undergo any operations. Gait testing and in vivo μ CT scans were performed on all rats at 2-, 4-, 8-, and 12-weeks after the week of surgeries. For gait testing, animals were placed in an arena enclosed by Plexiglass and allowed to explore freely. Rat spatial and temporal gait patterns were recorded using ultra-high-speed videography. As rats walked, dynamic loads were recorded via paw-floor contact with Kistler force plates in the instrumented arena floor. For in vivo μ CT scanning, rats were anesthetized and placed in the μ CT machine (Bruker Skyscan 1176 μ CT). Images were acquired using 80kVP, 311 μ A, 45 μ m copper + 0.5mm aluminum filter, 2000 x 1336-pixel resolution. resolution, 18 μ m voxel, 0.5° rotation step, and 180° tomographic rotation. At 12 weeks post-op, all animals were sacrificed. Gait data and μ CT data were analyzed using linear mixed-effect models.

RESULTS: Both groups of OA rats developed similar compensatory gait patterns throughout disease progression. Across naïve, MCLT and MMT rats, stance times increased as OA developed. An increased stance time indicated rats had increased periods of time where their hind limbs were in contact with ground during movement (p<0.003). Interestingly, at week 4, MCLT males spent more time on both hindlimbs compared to MMT males at the same time point. Nevertheless, both MMT and MCLT rats had spatially and temporally symmetric gait patterns, indicating that the operated limbs landed directly between two separate foot strikes of the contralateral limb (spatial symmetry) and the operated limb struck the ground halfway in time between two separate foot strikes of the contralateral limb (temporal symmetry). Pathologic changes in the subchondral bone plate and subchondral trabecular bone were also similar across MCLT and MMT rats. In both OA groups, bone volume increased in the operated limbs (p<0.018, females). Trabecular thickness and trabecular number were also larger in the operated limbs of MCLT and MMT rats compared to the contralateral limbs (p<0.0038, females). Further, the subchondral bone plate thickness increased in OA rats compared to naïve animals. Together, these data indicated subchondral bone sclerosis in OA, with structural changes in trabeculae indicative or worsening OA over time. Interestingly, osteophytes were only formed in MMT rats, and did not appear in MCLT or naïve rats despite similar structural changes in the subchondral bone plate and subchondral trabecular bone across OA groups. Here, osteophyte growth may likely be due to both bone remodeling and/or modeling activity throughout disease progression.

DISCUSSION: Similar compensatory gaits and pathologic changes in subchondral bone microarchitecture in MMT and MCLT rats highlight a potential relationship between altered movement and OA subchondral bone. Evaluating this relationship is increasingly important given the current gap in knowledge between OA symptoms and OA pathology. In this work, we utilized the MMT and MCLT models to evaluate OA progression. Historically, the MCLT model has been used as a SHAM control. Nevertheless, we show here that OA-related shifts in gait patterns and pathologic changes in bone structure develop in MCLT animals and progressively worsen. Furthermore, the changes in gait pattern and bone structure in MCLT rats were like those seen in MMT animals, strengthening the potential relationship between compensatory movement and subchondral bone pathology. In this case, increased bone plate thickness, bone volume, trabecular thickness, and trabecular number in MCLT and MMT rats emphasizes the role subchondral bone in OA development. Additionally, the lack of cartilage damage in MCLT animals further highlights that the subchondral bone changes (and not cartilage damage) are likely connected to the compensatory gaits seen in OA rats. Surprisingly, despite similarities in gait patterns and bone structure in OA rats, osteophytes formed in all MMT rats but did not appear in MCLT rats. This finding was unexpected as osteophytes have been hypothesized to function as stabilizers in the OA joint, implying they are likely to form in OA cases with similar compensatory movements. However, regardless of their purpose in the joint, the osteophyte formations seen here are likely a result of bone modeling and/or remodeling processes that may more closely connected the joint-level kinetic and kinematic shifts not assessed here.

SIGNIFICANCE/CLINICAL RELEVANCE: The characterization of subchondral bone remodeling within the context of behavior can impact our understanding of how OA pathomechanics is connected to disease symptoms and joint destruction. Since there is no cure for OA, and treatments seek to reduce symptoms, the relationship between subchondral bone structure and compensatory movements can inform the discordance between joint damage and OA symptoms.

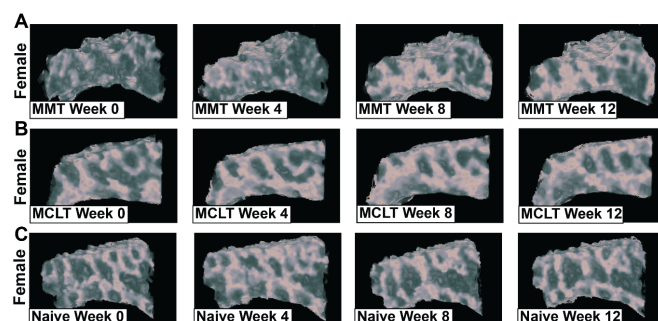


Figure. 1 Changes in female subchondral trabecular bone over time.

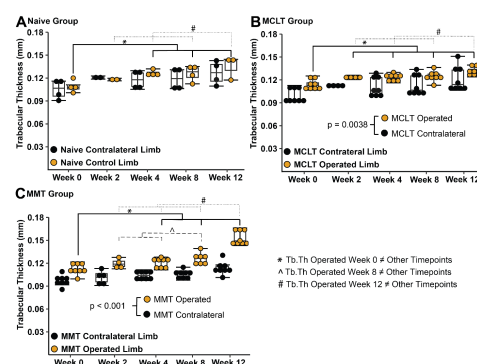


Figure. 2 Increased trabecular thickness in OA females over time.