with histomorphometric parameters such as bone volume fraction \((r = -0.89, p < 0.0001; r = -0.5, p < 0.007; \text{ respectively})\) and trabecular number \((r = -0.71, p < 0.0001; r = -0.38, p < 0.037; \text{ respectively})\).

Fig. 1. Coronal section of medial tibial plateau of saline injected knee (A). The MIA-injected knee (B–D) shows loss of proteoglycan, chondrocyte proliferation (B, arrow), chondrocyte cluster (B, arrow head), fibrillation (C, arrow), delamination, subchondral bone sclerosis, and fibrotic bone marrow (D, arrow).

Conclusions: These findings demonstrate that the low-dose MIA rat model closely mimics the pathological features of progressive human OA such as cartilage degradation, subchondral bone sclerosis, cyst and osteophyte formation. Moreover, this model demonstrates measurable changes in both the cartilage and the subchondral bone. Monitoring of low-dose MIA induced OA in rats using in vivo micro-CT enables tracking of structural changes in the tibial subchondral bone for the individual animal over time, and could be used to track changes in bone in preclinical drug intervention studies for treatment of OA.

Fig. 2. Coronal micro-CT images show osteophytes (A, arrow) and cysts (C, asterisk) in the medial tibia of MIA-injected knee. Histology sections confirmed osteophyte (B, arrow) and cyst (D, asterisk) formation. Note the presence of osteoblasts lining the areas of bone resorption (D, arrow).

Conclusions: These findings demonstrate that the low-dose MIA rat model closely mimics the pathological features of progressive human OA such as cartilage degradation, subchondral bone sclerosis, cyst and osteophyte formation. Moreover, this model demonstrates measurable changes in both the cartilage and the subchondral bone. Monitoring of low-dose MIA induced OA in rats using in vivo micro-CT enables tracking of structural changes in the tibial subchondral bone for the individual animal over time, and could be used to track changes in bone in preclinical drug intervention studies for treatment of OA.

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PREMATURE OSTEOARTHRITIS IN THE TEMPOROMANDIBULAR AND KNEE JOINTS OF BARDET-BIEDLE SYNDROME MICE
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Purpose: A homozygous recessive disorder in humans called Bardet-Biedl Syndrome (BBS) results in primary cilia defects. BBS mutant mice similarly exhibit ciliopathy related disorders. Chondrocytes are known to contain primary cilia. Primary cilia have been shown to play fundamental cellular roles. In the present study we analyzed the temporomandibular (TM) and knee joints of BBS mutant mice as a normal collagen chondrocyte specific animal model of osteoarthritis (OA) in humans.

Methods: BBS mutant mice, and age-matched controls, were compared histologically at 3, 6 and 12 months of age. Tissues were fixed in 4% paraformaldehyde, processed to paraffin sections, stained with Hemotoxylin, Safranin O and Fast Green, and analyzed using light microscopy. Joint morphology was characterized and compared using ImageJ (NIH; Bethesda, MD). Sections were stained for HtrA1 and DDR2.

Results: BBS mutant mice demonstrated evidence of OA including articular cartilage (AC) fissuring, thinning, decrease in proteoglycan saturation with a concomitant increase in HtrA1 and DDR2. Chondrocytes exhibited a propensity for clustering within the matrix. The exacerbation of OA related abnormalities was more pronounced in TM versus knee joints.

Conclusions: These results suggest a mechanism of early onset OA in TMJ and knees of BBS mutant mice. The degradation pattern of the articular cartilage, including up regulation of HtrA1 and DDR2, in the TMJ and knees of BBS mutant mice follows the same recognized process that has been observed in mutant collagen OA mouse models. The exacerbated condition of the TMJ compared to knee might indicate that TMJ AC is unique. The present study shows the relevance of the BBS homozygous mouse as a viable alternative model for the human condition of OA.

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CARTILAGE AND BONE DISEASE IN RATS WITH MUCOPOLYSACCHARIDOSES TYPE VI (MAROTEAUX-LAMY DISEASE): A NEW, NATURALLY OCCURRING ANIMAL MODEL OF ARTHRITIS
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Background & Purpose: The mucopolysaccharidoses (MPS) are a group of 11 distinct inherited disorders due to mutations in the genes encoding enzymes of glycosaminoglycan (GAG) degradation. Progressive and severe bone and cartilage pathology are characteristic of these disorders. Naturally occurring animal models have been described for several MPS, with similarly severe cartilage and bone disease. The goal of this study was to determine the inflammatory and cartilage/bone changes in the rat model of MPS type VI (Maroteaux-Lamy disease), and to study of the effects of anti-TNF-alpha drugs on the disease progression.

Methods: The age-progressive cartilage and bone disease in MPS VI rats were studied by a variety of standard biochemical, histological and clinical methods. MPS VI rats also were treated with the anti-TNF-alpha drug, CTNO1081, and the effects on cartilage and bone disease evaluated.

Results: The pathological and biochemical changes in the MPS VI rats were very similar to those reported previously in patients with arthritis and induced animal models of the disease. These included elevation of various inflammatory markers, including TNF-alpha, enhanced chondrocyte apoptosis, synovial hyperplasia, and proteoglycan degradation. We therefore treated these animals with the experimental anti-TNF-alpha drug, CTNO181. When initiated at 1 month of age, intravenous treatment with CTNO1081 prevented the elevation of TNF-alpha, RANKL and other inflammatory molecules, not only in the blood, but also in articular chondrocytes and fibroblast-like synoviocytes (FLS). Treatment of 6 month-old animals also reduced the levels of these molecules to normal. The number of apoptotic articular chondrocytes in MPS VI rats was similarly reduced, with less infiltration of synovial tissue into the underlying bone.

Conclusions: Many of the inflammatory and cartilage/chondrocyte pathological changes that occurred in the MPS VI rats resembled those...
that occur in arthritis, and we therefore propose that the these animals may be an important, naturally occurring model of this disease. We also find that activation of the toll-like receptor 4 (TLR4) signaling pathway is a key factor contributing to the cartilage disease in MPS VI rats, and that anti-TNF-alpha drugs have a positive influence on the cartilage disease in these animals.

122 GENDER DIFFERENCES IN OSTEOARTHRITIS PAIN BEHAVIOR MEASURES IN MICE

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Purpose: To define gender differences in spontaneous and evoked osteoarthritis (OA) pain behaviors in C57Bl6 mice.

Methods: Mice: Eight week old C57Bl6 male and female. Chronic OA was produced by injection of 10 IU Type IV Collagenase into the left knee. The contralateral, non-arthritic knee was the non-painful control.

Pain behavior was measured four wks post-collagenase injection. Spontaneous pain behaviors were measured by video gait analysis (DigiGait™, Mouse Specifics, Inc, Quincy, MA) and voluntary wheel running (VitalView Data Acquisition System, Minimitter, Bend, OR). Evoked pain response (EPR) was measured by tallying fights + vocalizations/1 min with repeated firm palpation of the knees (tenderness) and by hind limb withdrawal responses to the application of von Frey filaments (hyperalgesia).

Analgesia: Morphine sulfate (0.7 mg/kg in 5μl) was injected into the arthritic knees.

Results: Wheel running was slightly reduced in males with arthritis pain and less so in females. Analgesia appeared to improve wheel running in both arthritic males and females. A limp was demonstrated in both arthritic male and female mice by a significantly decreased ratio of stance to stride time. IA morphine normalized this in males but not females. EPR (tenderness) increased significantly with arthritis and normalized with IA morphine in both male and female mice. Withdrawal threshold to von Frey filament testing decreased in male mice with arthritis and normalized with IA morphine treatment. Female mice did not show any change in withdrawal threshold with arthritis or analgesia.

Conclusions: These data demonstrate that collagenase induced arthritis pain is measurable in male and female C57Bl6 mice. Joint tenderness was increased in both males and females with arthritis and demonstrated an analgesic response with IA morphine in both sexes. Hyperalgesia (von Frey) was increased with OA in males and normalized with analgesia but did not change in females. Alterations in gait were seen in both males and females with OA and normalized with IA morphine, in males, but we were not able to demonstrate an analgesic response in females. Further studies to investigate the dose response of IA morphine in females and to evaluate other IA analgesics are needed. Male mice may be preferable when studying pain behaviors and analgesic responses in arthritic mice.

123 DIET-INDUCED DIABETES ACCELERATES PROGRESSION OF OSTEOARTHRITIS FOLLOWING MENISCAL/LIGAMENTOUS INJURY


Purpose: Increasing obesity and type 2 diabetes, in part due to the high fat (HF) Western diet, parallels an increased incidence of osteoarthritis (OA). This study was undertaken to establish a causal relationship between HF diet and accelerated OA progression in a mouse model and to determine the relative roles of weight gain and metabolic dysregulation in this progression.

Methods: Five week old C57BL/6 mice were placed on HF (60% kcal) or low fat (LF, 10% kcal) diets for 8 or 12 wk prior to a meniscal-ligamentous injury (MLI) of the knee to initiate OA. One group was switched from LF to HF diet at the time of MLI surgery.

Results: Body weight of mice on the HF diet peaked at 45.9±2.1g compared to 29.9±1.8g for LF diets, with only the HF group becoming diabetic. Severity of OA was greater in HF mice, evidenced by Chambers scoring and articular cartilage thickness and area. To assess the importance of weight gain, short and long term HF diets were compared to LF diet. Short and long term HF groups outweighed LF controls by 6.2g and 20.5g, respectively. Both HF groups became diabetic and OA progression, evidenced by increased Chambers score and decreased cartilage thickness was comparably accelerated relative to LF controls. In the HF group, increased osteophyte formation in both sham and MLI-treated joints was adjacent to thickened synovium that stained for MLI-treated joints was adjacent to thickened synovium that stained for cadherin 11 and TNFα.

Conclusions: These results demonstrate that HF diet-induction of type 2 diabetes in mice accelerates progression of OA in a type 2 diabetic mouse model independent of marked weight gain, suggesting that metabolic dysregulation is a co-morbid factor in OA-related cartilage degeneration.

124 LONGITUDINAL STUDY OF CARTILAGE AND SUBCHONDRAL BONE CHANGES IN A SPONTANEOUS ANIMAL MODEL OF KNEE OA

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Purpose: Osteoarthritis (OA) is a common degenerative disease characterized by cartilage loss and subchondral bone changes. Many studies have investigated the association between cartilage and bone changes in OA models but few documented the changes in these tissues in the medial and lateral compartments of the knee joint during early development of OA. The aim of this study was to determine the association and sequential changes in cartilage and subchondral bone during development of spontaneous OA in the medial and lateral compartment of Dunkin Hartley (DH) guinea pig knee joints.

Methods: Six male (DH) guinea pigs tibias were examined at 10, 16, 24 and 30 weeks of age. At each time point, macroscopic and microscopic changes to cartilage were evaluated by a modified Outerbridge classification and modified Mankin grading, respectively. Bone mineral density (BMD) of medial and lateral right tibia epiphysial region at all time points was determined by dual X-ray absorptiometry (DXA), while subchondral bone plate thickness (SbPTh) and subchondral trabecular bone morphometry were assessed using micro-computer tomography (micro CT).