Conclusions: HFD-induced OA in mice is due to low grade inflammation and not the consequence of mechanical overload, since no relation between body weight and OA grade was observed. Moreover, the OA process was inhibited to a great extent by treatment with two drugs with anti-inflammatory properties. The inflammatory response to a metabolic high fat challenge may predict the individual susceptibility to develop OA later in life. The use of statins or PPAR-γ-agonists (such as rosiglitazone) could be a strategy to interfere in the progression of OA.

112 EFFECT OF THE SELECTIVE CATHEPSIN K INHIBITOR, MIV-711, ON MARKERS OF CARTILAGE DEGRADATION AND ON GROSS AND HISTOPATHOLOGY SCORES IN DOGS SUBJECTED TO PARTIAL MEDIAL MENISCECTOMY, AN EXPERIMENTAL MODEL OF OSTEOARTHRITIS

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Purpose: Cathepsin K is a cysteine protease capable of degrading several bone and cartilage matrix components. Previously, a pan-cathepsin inhibitor provided cartilage-protective effects in dogs subjected to partial medial meniscectomy, an experimental model of osteoarthritis (OA). In the current study we evaluated MIV-711, a potent (Ki: 0.98 nM) and highly selective cathepsin K inhibitor (>1,000-fold selectivity vs. related cathepsin enzymes) in the same model.

Methods: Female beagle dogs were subjected to partial medial meniscectomy of the left knee and were treated with either vehicle (n = 15) or MIV-711 (n = 15) at 30 μmol/kg (17 mg/kg) once daily starting the day before surgery. Treatment continued for 28 days after surgery followed by necropsy on day 29. Plasma, synovial fluid and urinary samples were collected at various time points during the experiment and at necropsy. Biomarkers of collagen degradation were measured using commercially available ELISA kits. Gross and microscopic changes of the femorotibial joints were assessed.

Results: MIV-711 significantly reduced CTX-II levels (marker of cartilage degradation) in urine (by 80%, p < 0.001) compared to baseline and by 61% (p < 0.001) compared to vehicle. Synovial fluid levels of CTX-II in both knees were also significantly reduced by 55–57% (p < 0.001) compared to baseline and by 31–36% (p < 0.01) compared to vehicle. Synovial levels of MIV-711 were significantly higher in the operated left knee than in the right knee. Subjective and calculated gross pathology scores were reduced by 25–37% in the femur and in the tibia by 13–37% in MIV-711-treated animals compared to vehicle. Total lesion area in the tibia was 26% lower in MIV-711-treated animals and the most severe lesion area was reduced by 75%. Various scores of tibia cartilage histopathology were 9–17% lower in the tibia of MIV-treated dogs.

Conclusions: We have previously shown that once daily oral dosing with MIV-711 affects markers of cartilage degeneration in a dog OA model. Taken together, these data suggest MIV-711 may be beneficial not only for treatment of osteoporosis but also for OA.

113 ESTABLISHING THE HOMOZYGOUS SPONDYLOEPIPHESEAL DYSPLASIA CONGENITA MUTATION AS A MODEL FOR OSTEOARTHRITIS

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Purpose: Osteoarthritis (OA) is one of the leading causes of joint pain and disability in the United States. There is a lack of effective treatments for the disease because of a poor understanding of its pathogenesis. Murine models, such as spondyloepiphysial dysplasia congenita (sedc), are important in further understanding OA. The purposes of the present study are to (1) establish the homozygous sedc mutation (s/s) as a model of osteoarthritis; (2) characterize the articular cartilage in sedc mice by identifying cellular changes over time and localizing the major structural proteins present in the extracellular matrix; (3) to identify a possible mechanism involved in the pathogenesis of OA.

Methods: Knee and temporomandibular joints of homozygous wild-type (+/+ ) and homozygous sedc (s/s) mice were compared histologically at 2, 6 and 9 months. The mice were euthanized and their tissues were prepared and stained using Fast Green and Safranin O to show the presence and localization of proteoglycans and collagen. Immunohistochemical staining (IHC) for Ddr2 and Mmp-13 was also performed to detect changes in the presence of both of these degradative proteins. In addition, toluidine blue stained sections were analyzed to determine the matrix vs. chondron area in both the mutant and the wild-type mice. TEM photomicrographs were taken for comparison of cell diameter, pericellular matrix and fibril diameter.

Results: Histological analysis of the mutant showed increased pericellular space and disorganization of the chondrocytes. Rather than superficial fissuring as seen in the sedc heterozygous model, the sedc homozygous mice displayed increased fissuring only along the tidemark that separates calcified from non-calcified cartilage. Homozygous mutant mice displayed increased cartilage separation, increased pericellular diameter, increased proteoglycan staining, and cell clustering as early as 2 months. IHC staining showed a lack of upregulated Ddr2 and Mmp-13 in mutant mice. TEM of the mutant showed atypical cell morphology including cytoplasmic membrane extensions, amorphous material in the pericellular matrix and smaller diameter collagen fibrils in the interterritorial matrix.

Conclusions: Homozygous sedc mice develop premature OA in comparison with wild-type controls. Therefore, the homozygous mutant presents itself a valuable murine model of the study of OA. However, the s/s mouse is unlike other OA models in that the tissue degeneration does not appear to be typical of other models that involve the enzymatic degradation pathway involving Ddr2, HtrA1 and Mmp-13.

114 OSTEOARTHRITIS-LIKE CHANGES IN THE MURINE KNEE JOINT BY MEANS OF FORCED RUNNING

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Purpose: Various murine knee osteoarthritis (OA) models are known. However, few non-invasive model has been developed. In this study, we developed murine kneeOA model with forced running on the treadmill and evaluate the OA-like changes by X-ray and histology.

Methods: To 9-week old CB57/BL6 mice, forced running were applied 3 times a week (15minutes a once; running distance=165m). At 2, 4, 6, 8 weeks, the knee joints were excised and analyzed with magnified X-ray. Further, they were subjected to histological analysis (HE, Safranin-O, Toluidine blue). OARSI score was used to semi-quantitative evaluation. And they were immunostained by type II, X collagen.