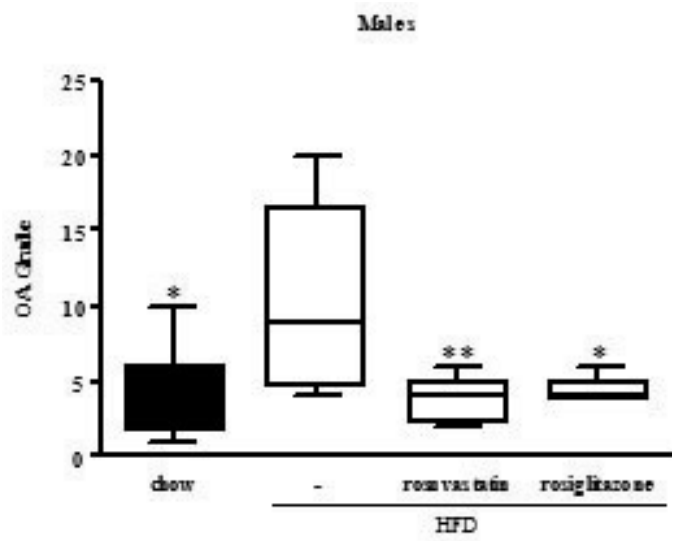
chow. Both treatments resulted in reduced huCRP levels, indicative for their anti-inflammatory action. Furthermore, a positive correlation was found between the relative individual induction of huCRP evoked by HFD at day 3 and end point OA grade. Leptin and resistin levels did not correlate with OA severity.



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 PPARγ-agonists (such as rosiglitazone) could be a strategy to interfere in the progression of OA.

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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 of MIV-711 in dogs subjected to partial medial meniscectomy had a positive effect on markers of bone resorption while maintaining markers of bone formation. The present results now show that selective cathepsin K inhibition achieved by 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.

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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 spondyloepiphyseal 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 contols. 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 invoke the enzymatic degredation pathway involving Ddr2, HtrA1 and Mmp-13.

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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 knee OA 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 morphologically 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 typeII, X collagen.

Results: Ossification of lateral meniscus were detected in radiograph. Histologically hypertrophic chondrocyte and chondroplasia or ossification of meniscus were observed. Those changes were observed dominantly in the lateral compartment rather than in the medial. Mean OARSI score in control, 2, 4, 6, and 8 weeks were 0±0, 1.06±0.42, 1.88±0.72, 2.19±0.99, 2.5±0.5 points, respectively..The immunoreactivity of type II collagen in the articular cartilage decreased with the indicated periods of the forced running in both medial and lateral cartilage.Although type X collagen expression was limited to the deep calcified zone below the tidemark in the control knee, it appeared and increased in the superficial and middle zones above the tidemark according to the index periods of the forced running.
Conclusions: This murine knee OA model will allow study of mechanical and genetic interactions in joint health and in OA initiation and progression.

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ATLAS OF MACROSCOPIC AND MICROSCOPIC LESIONS OF THE KNEE JOINT IN AN OSTEOARTHRITIS CRANIAL CRUCIATE LIGAMENT TRANSECTION DOG MODEL 90 DAYS AFTER SURGERY

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Purpose: The purpose of the study was to create an atlas of the macroscopic and microscopic osteoarthritis lesions in the CCLT (Cranial Cruciate Ligament Transection) dog model of osteoarthritis (OA).
Method: Twenty one skeletally mature young female beagle dogs with a mean body weight of 10kg were used for the study. Transection of the cranial cruciate ligament (CCL) of the right knee joint was performed. Three months after the surgery dogs were euthanized and tibial and femoral condyles, femoral trochlea, patella and menisci were examined immediately by three experienced observers. Gross examination of the osteophytes, articular cartilage, synovium and menisci was realized for each of these sites. Histology, histomorphometry and immunohistochemistry were performed.
Results: in all of the operated knees, fibrillation of the cartilage was noted; neither cartilage edema nor more severe lesions were macroscopically observed. Cartilage lesions were reported in decreasing order of frequency: in the medial and the lateral tibial condyle, in the lateral femoral condyle, the femoral trochlea, the medial femoral condyle and the patella. Osteophytes were classified as evident or large on the femoral trochlea, small on the lateral femoral and tibial condyles and on the patella. Medial meniscal damages were observed in 5 of the 21 operated knees. The superficial layer of the cartilage was fibrillated and discontinuous but this change did not extent in the transitional layer or deeper. Most of the cells were rounded and organized tangentially to the surface. In the transitional and deep layers of the cartilage, some chondrocytes were moderately hypertophic and in the deep layer clusters of chondocytes were observed. However this varied between dogs. The histological appearance of the cartilage from every control joint was normal. In 50% of the operated knees, collagen type III was present around the chondrocytes in the superficial and transitional layers. No collagen type I and II was seen. In the operated knees, histology revealed a high density of collagen in the synovial membrane. These collagen fibers were slightly wavy fibers and localized deeply in the synovial membrane. In the control knees, the density of the collagen fibers was lower and the fibers were highly undulated. Neither in the operated nor in the control knees were inflammatory cells observed. Histomorphometry showed fibers were 10 to 15 fold thicker than the mesothelium in the ACLT knees ninety days following the surgery while they were at least twice thinner in the control knees.
Conclusion This exhaustive atlas could be used as a template in preclinical and clinical studies and could allow future comparisons between studies.

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A SIMPLIFIED METHOD TO DETERMINE JOINT LOADING AS A SURROGATE MARKER OF PAIN/DISABILITY IN A CANINE MODEL OF OSTEOARTHRITIS, VALIDATED USING FORCE PLATE ANALYSES AS A GOLD STANDARD

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Purpose: In humans, evaluation of tissue structure damage/modification in osteoarthritis (OA) is difficult and can only be performed indirectly by use of surrogate markers, such as imaging and/or biochemical makers. In contrast, pain and disability can be validated, easily and longitudinally by use of questionnaires like WOMAC and VAS.
A direct evaluation of tissue structure changes can be performed in detail in animal models of OA by e.g. histochemical en biochemical techniques. On the other hand evaluation of OA pain and disability in animals remains a challenge. For dogs a well described and validated technique used in veterinary clinic and in research settings, is force plate analyses (FPA). This technique provides detailed information of joint loading (forces in 3 degrees of freedom including; propulsion (Fy min), stance (Fz) and brake (Fy max) force) as surrogate markers of pain and (dis)ability. Unfortunately this technique is time consuming (at least 45 min/ dog/ time point) and needs prolonged training. Therefore, a simplified method of studying joint loading was developed. A mobile weighing platform with four individual scales for each leg with parallel digital computer registration was designed. In the present study, this novel method was validated. The loading of the hind legs stifle joints was evaluated during progression of experimentally induced OA and, primarily, compared to Fz by use of FPA.
Methods: In twelve mixed breed (mongrel) dogs experimental OA was induced in the right stifle joint according to the Groove model. The left stifle joint served as a control. Twice at baseline and at every 5 weeks FPA was performed. In the same weeks the animals were put on the 4-plates weighing platform. Five measurements of 10 seconds were performed and analysed (approximately 5 min/ dog/ time point). The average of these 5*10 sec measurements were compared to the Fz (as well as Fy max and Fy min) obtained by FPA. In this first analyses baseline values (before surgery) and 10 weeks values (after surgery) were analysed, because the 5 week condition might still include pain/disability due to surgery and not solely to OA.
Results: By use of the 4-plates balance a decrease in loading of the OA right hind leg was found from 2.8±0.2kg at baseline to 2.5±0.2kg at 10 weeks follow-up ($p < 0.05$). A similar pattern was seen for the FPA-Fz from 4.5±0.1N to 4.3±0.1N ($p < 0.01$). A positive linear correlation was found between the delta as well as percentage decrease in loading of the right OA hind leg (10 weeks compared to pre-treatment) for both methods (R=+0.27 and R=+0.33, respectively; both $p < 0.03$).
The change in loading between the left control and the right OA leg at baseline was 0.6±0.3kg (ns) and increased to 1.0±0.3kg at 10 weeks follow-up ($p < 0.003$). The same was found for FPA-Fz, from −0.1±0.1N at baseline (ns) to 0.3±0.1N at 10 weeks ($p < 0.01$). Also for this difference between the control and OA hind joints a positive linear correlation existed between the 4-plates balance and the FPA-Fz (R=+0.22, $p < 0.02$).
Similar, statistically significant relations were found for the 4-plates balance and FPA-Fy max, but not for FPA-Fy min.
Conclusions: Pain/disability, due to OA in the extremities is difficult to measure in animal models, including dogs. FPA (force plate analyses) is the gold standard to evaluate (un)loading/(dis)ability of the extremities in dogs. The present study clearly demonstrates that the use of this novel designed mobile weighing platform with four individual scales with parallel computer controlled registration is a perfect surrogate for FPA as a measure for pain disability due to development of OA. The technique is less expensive, less time-consuming and simpler to accomplish, because it can be performed at any location. Although, FPA is clearly a more elaborated technique and provides more information about gait and different forces and the 4-plates balance is a more static measurement, the latter may be of good value in studies evaluating pain/disability in canine models of OA.