chondral plate thickness and trabecular bone parameters of the tibial epiphysis were calculated. At the end of the 12-week period, histological analysis was performed on the proximal tibias. Cartilage damage was scored and GAG loss was evaluated using safranin-O staining.

Results: The thickness of the medial and lateral subchondral plate already decreased from 3 weeks post-surgery in the OVX+IA group. At 12 weeks post-surgery, both medial and lateral subchondral plate thickness was significantly lower in the OVX+IA group than in the Sham+Saline, Sham+IA, and OVX+Saline groups. The trabecular bone parameters in the tibial epiphysis did not change in all groups. Overall, the cartilage damage was very mild. In the OVX+IA group, the damage at the medial tibia plateau was mildly higher than in the other groups. The GAG depletion was higher in both Sham+IA and OVX+IA groups at the medial tibia plateau, but OVX did not strengthen the IA effect. Osteophytes were found in both Sham+IA and OVX+IA groups, mainly at the medial tibia plateau.

Conclusions: In both the medial and lateral subchondral plate, the combination of IA and OVX lead to a decrease in thickness, whereas IA alone or OVX alone did not. This indicates that hormone depletion makes the subchondral bone plate more susceptible for thinning in a situation where cartilage damage is triggered by IA. The cartilage damage was very mild in all groups and occurred mainly at the medial tibia plateau. The bone changes did not seem to influence the cartilage damage.

86
T1RHO RELAXATION EVALUATION OF KNEE OSTEOARTHRITIS IN A GUINEA PIG MODEL
C. Wang, M. Fenty, W.T. Witschey III, A. Borthakur, R. Reddy
University of Pennsylvania, Philadelphia, PA

Purpose: T1rho-weighted imaging has shown promise as a diagnostic measure of early osteoarthritis. The T1rho relaxation time during a spin-locking pulse has enhanced sensitivity to the interaction between bulk water molecules and extracellular matrix macromolecules such as the proteoglycans in the articular cartilage. In this study, we evaluated the efficacy of T1rho MRI in determining the osteoarthritis changes in an animal model (Dunkin-Hartley guinea pig) of spontaneous osteoarthritis. Guinea pigs of young and old age groups (2.5 month and 9 month-old accordingly) are imaged with a T1rho MRI pulse sequence, and their cartilage T1rho values were measured at the femoral-tibial joint.

Methods: All animal-related experiments were reviewed and approved by our institute's animal use committee (IACUC). MRI was performed on the left knee joint of three 2.5-month-old and three 9-month-old guinea pigs on a Varian 9.4T horizontal-bore MRI scanner with a custom-built 2.5 cm diameter knee coil. Following localization of the joint with a standard gradient-echo protocol, a series of T1rho images were obtained in the coronal plane using a spin-lock prepared gradient-echo pulse sequence with the following parameters: TE/TR=8.04/1500ms, TSL (duration of spin-lock pulse)= 1, 10, 20, 30 and 40 ms, spin-lock frequency=1500Hz, slice thickness=1mm, FOV=3x3cm, Matrix=512x256. This protocol yields an in-plane resolution of 59x117 microns, with the highest resolution across the femoral-tibial cartilage. Cartilage was manually segmented from each image by simple thresholding of pixel intensities, and the cartilage signal was fitted to an exponentially decaying function in order to obtain T1rho values on a pixel-by-pixel basis.

Results: Figure 1 shows that the femoral-tibial cartilage from the old animal is thinner than that of the young animal and has elevated T1rho values. Indeed, the average T1rho is significantly greater (p<0.025) in the cartilage in all three 9-month animals compared to the three younger animals (Figure 2), suggesting that T1rho is directly related to the degree of cartilage degeneration in this model of spontaneous osteoarthritis.

Conclusions: T1rho is shown to be sensitive to knee osteoarthritis in this animal model. The protocol is sensitive to osteoarthritis cartilage degeneration. In the future, we will use a 3D T1rho imaging protocol to image animals of multiple age groups. Although this result is preliminary, it nevertheless shows the feasibility of using T1rho MRI in conjunction with guinea pig model in evaluating potential therapies in longitudinal studies.

87
DYNAMIC BONE HISTOMORPHOMETRIC ANALYSIS OF SUBCHONDRAL BONE CHANGES IN THE RAT MENISCAL TEAR MODEL OF OSTEOARTHRITIS
GlaxoSmithKline, Collegeville, PA

Purpose: Osteoarthritis (OA) is a joint disease characterized by cartilage degradation, osteophyte formation, and changes to the subchondral bone. While rodent models of OA mimic the cartilage changes noted in the human condition, changes to the subchondral bone in these models have yet to be fully characterized. The purpose of the present study therefore was to characterize the subchondral bone changes using dynamic bone histomorphometry in the rat medial meniscectomy model of OA.
Methods: Osteoarthritis was surgically induced in female Sprague-Dawley rats (13 months of age) by transection of the medial collateral ligament and medial meniscus of the femorotibial joint. An additional group of animals (control) did not receive surgery. Dynamic bone histomorphometry was conducted on the subchondral bone of 5 meniscal tear rats and 4 naïve rats that were labeled with fluorochrome on days 5 and 12 post-meniscal tear. The rats were sacrificed after 14 days. Five micron, undecalified sections were stained with Villaneuva bone stain, embedded in methyl methacrylate, and analyzed using fluorescent microscopy. For static bone histologic assessment, joints were processed using routine light microscopy. A rectangular region of interest (0.75 mm in width) was defined and measurements obtained using Osteomeasure software v3.02.

Results: Bone histomorphometric analysis demonstrated an increase in both trabecular bone area and thickness (21% and 30%, respectively). No difference was noted in trabecular number or in the height of the epiphysis. However, greater than 2-fold increases were observed in the percentage of labeled perimeter and bone formation rate (BFR) per bone surface (BS) and total volume (TV) reference. Additionally, a near 2-fold increase in the percentage of eroded perimeter, a bone resorption parameter, was noted.

Conclusions: A thickening or sclerosis of the subchondral bone directly below the lesion is observed in rats as early as 14 days post-medial meniscectomy. Both bone formation and resorption parameters are increased at this time. However, further studies need to be performed to clarify the sequence of events. In any case, this indicates involvement of the subchondral bone in this rat model of OA.

88
THE CANINE BILateral GROOVE MODEL OF OsteoArthritis
F. Intema1, S.C. Mastbergen1, S.A. Vocum2, A. Zuurmond3, J. DeGroot3, F.P. Lafeber1
1Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands; 2Pfizer Inc PGRD, Ann Arbor, MI; 3TNO Quality of Life, Leiden, The Netherlands

Purpose: The canine Groove model of osteoarthritis (OA) is based on a combination of surgically applied mechanical damage of the articular cartilage followed by transient forced intermittent loading of the affected joint. Cartilage degeneration in this model is not just the expression of surgically applied damage but is the result of progressive development of experimental OA [1]. Furthermore, degenerative cartilage changes are very similar to those seen in the canine ACLT model [2] and slightly progressive over time [3] and mimic those of human OA (ms in preparation). In studies aiming at local treatment of experimental OA it is optimal to have an internal (untreated) osteoarthritic control. Such an approach is not hampered by inter-animal variation and allows paired statistical evaluation of treatment efficacy with an internal OA control. Therefore, we developed and characterized a bilateral version of the canine Groove model.

Methods: In 6 dogs, grooves were surgically made in the weight-bearing areas of the articular cartilage of the femoral condyles of both knee joints; the tibial plateau was left untouched. Six additional dogs underwent bilateral sham surgery. The degree of osteoarthritis was quantified 20 weeks after surgery and was compared in retrospect to 23 animals that underwent the identical procedure in a single knee joint with the contra-lateral knee serving as a non-osteoarthritic control (unilateral Groove model).

Results: Bilateral surgery according to the Groove model resulted in characteristics features of OA. This was based on the observed ineffective repair response in which an increase in proteoglycan synthesis (+41%, p < 0.05), a diminished retention of these newly formed proteoglycans (-171%, p < 0.05), and an enhanced release of proteoglycans (+193%, p < 0.05) resulted in decreased cartilage proteoglycan content (-51%, p < 0.05). These biochemical effects were corroborated by the histological features of osteoarthritis (modified Mankin grade Δ+4). The results were comparable to the originally developed unilateral Groove model. Interestingly, features of OA were slightly more severe in the bilateral model than in the unilateral variant (proteoglycan release 81%, proteoglycan content -15% and modified Mankin grade Δ+2.35; all p < 0.05).

Conclusions: The bilateral canine Groove model shows consistent and clear development of features of OA. As a bilateral model, it provides an internal animal osteoarthritic-control, enabling paired statistical evaluation of treatment efficacy in case of local treatment, excluding inter-animal variations. This makes the bilateral Groove model of additional value in evaluation of treatment modalities.

References

89
EXPERIMENTAL OSTEOSTHritis IN A STABLE KNEE JOINT USING A CRITICAL SIZE DEFECT IN AN OVINE MODEL
S. Nehrer1, M. Gruber2, M. Schiian2, R. Plasenzotti2, R. Dorortka2
1Danube University Krems, Krems, Austria; 2Medical University of Vienna, Orthopedic Department, Vienna, Austria

Purpose: Animal models simulating osteoarthritis are often associated with irreversible changes of the biomechanics- like ligament transection or meniscectomy. Although these models successfully induce osteoarthritis, the results of experimental repair procedures are impaired by the persistent biomechanical problem. The aim of this study is to define the critical size of a chondral lesion to induce osteoarthritis in a stable joint, allowing a more uninfluenced comparison of cartilage repair procedures.

Methods: 16 mature Austrian mountain sheep with a physiological joint status were divided randomly into four treatment groups. In each group a full thickness chondral cartilage defect was created in the weight bearing area of the right medial femoral condyle. The diameter of the defects was 7 or 14 millimetres. The sheep were fully weight bearing mobilized for six and twelve weeks. Osteoarthrosis was determined by gross assessment, India-ink staining, biomechanical testing, histology (Mankin and OARSI Score) and immunohistochemistry for collagen type I and II. COMP was chronologically monitored by ELISA.

Results: In the six weeks group only minor osteoarthrosis was detected in both defect sizes. After 12 weeks the seven millimetre defect created focal monocompartimental OA at the medial femoral condyle with minor degenerative changes at the corresponding tibia. The OARSI and Mankin Scores showed moderate to sever degenerated areas over the whole femoral condyle, and differed significantly from the other treatment regimes. The 14mm defect induced minor OA at the femoral condyle, but created major degenerative changes on the tibia.

Conclusions: A 7mm full thickness chondral defect with a weight bearing loading regime of 12 weeks can be considered as a suitable animal model to induce OA in otherwise stable joint. Therefore this model seems to be suitable to challenge cartilage repair procedures and therapies in experimental studies.