INTRODUCTION
Potential treatments of osteoarthritis may be best studied in an animal model where disease progression can be non-invasively monitored. Several models have been demonstrated to result in osteoarthritis as diagnosed by histological analysis of disease severity (3, 4). Studying progression with histology requires a cross-sectional study design with numerous animals. The use of magnetic resonance (MR) imaging to monitor osteoarthritis in animal models has been limited to large animals, late stage osteoarthritis, or non-clinical research scanners (1, 3). The ability to monitor early osteoarthritis changes will be crucial in the assessment of effective drug treatments. The goal of this study is to evaluate the sensitivity of high-resolution magnetic resonance imaging to identify early arthritic changes such as surface fibrillation, loss of proteoglycan and disorganization in a rabbit model.

MATERIALS AND METHODS
Five adult New Zealand White rabbits were used (3 female, 2 male, avg. weight 4.0 kg). All were retired breeders with radiographically confirmed physical closure. Osteoarthritis was surgically induced in the right knees by ACL transection and medial meniscectomy following procedures approved by our University Committee on Animal Resources. The left knees underwent sham operations and served as controls. After 2 to 5 weeks, MR images were obtained of each knee in vivo under mild sedation. A specifically designed two-array phased array surface coil was used as a receiver in a 1.5 T clinical MRI scanner (GE Horizon, Milwaukee, WI). Images were acquired in the sagittal plane with six different imaging sequences including: T1-weighted spin echo, double echo fat suppressed spin echo, 3D GRE, and fat suppressed 3D SPGR pulse sequences, and T1-weighted fat suppressed spin echo images obtained before and after IV gadolinium administration. A 3 cm field of view with a 256 x 256 pixel matrix yielded a resolution of 120 µm per pixel. Typical slice thickness was 0.9 mm. During all image sequences, the knee was rigidly fixed with an external fixator system to allow accurate comparison of MR images to histological slides. Animals were then sacrificed and legs were fixed in 10% formalin. With the external fixator still in place, 3 mm slabs were cut on a low speed diamond saw, maintaining the orientation and locations of the MR images. Tissues were then decalcified in EDTA and a step sectioning procedure used to obtain 3 µm histologic slides corresponding to the centers of the MRI sections. Sections at each MR image position were stained with Hematoxylin and Eosin, and with Safranin O/Alcian blue.

Femoral and tibial articular cartilage osteoarthritis were independently scored using the grading system described by Colombo (1). A score of 0 to 4 is assigned for each of eleven parameters. Digital images were acquired of representative sections to measure articular cartilage thickness for the tibia and femur surfaces. A grading system was developed to score articular cartilage changes visualized on MR images. Scores graded signal abnormality, cartilage thickness change, and surface irregularity for each imaging sequence. Possible scores range from 0 to 54. Correlations were evaluated using the non-parametric Spearman Rank Correlation test. Between group comparisons were made with Mann-Whitney U tests.

RESULTS
Correspondence of MR images and histological sections was confirmed, and a representative pair from an unoperated knee is shown in Figure 1. A total of 69 MR images were compared to histological sections. The medial compartments of the operative right knees showed evidence of early osteoarthritis. The disease severity was worse in the femur (avg. 17.17/44) than tibia (avg. 10.93/44) and the changes on the two surfaces were strongly correlated (ρ 0.812, p = 0.0003). While MRI grade correlated to histological grade (ρ 0.582, p = 0.0002), the correlation was strongest when only cartilage thicker than 600 µm was included (ρ 0.642, p = 0.003). Rabbit tibial cartilage averaged 730 µm in thickness, compared to 410 µm in the femur (p < 0.0001). MRI to histological grade correlation was best for the tibial surface (ρ 0.64, p = 0.002). Early degenerative changes in the tibia (defined as a score of 5) were identified by our MRI grading system with a sensitivity of 74% and specificity of 95%.

DISCUSSION
Our high resolution MR imaging improves upon previous reports of knee osteoarthritis imaging (1, 3) by using a clinical scanner to detect earlier evidence of osteoarthritis in a common animal model. The animals in our study exhibited tibial changes graded 10.93 compared to an estimated grade of 27.1 at 6 wks. in previous work (1). Previously, MRI imaging did not detect arthritic changes until 14 wks following surgery. While our imaging techniques were still unable to detect some changes in the thinner femoral cartilage, strong correlations were found between femoral and tibial grades. Image resolution is clearly an important factor in defining the success of MR images to detect subtle changes, however the resolution obtained in this study compares reasonably to clinical scans in humans with respect to typical cartilage thickness. Given our ability to discern even early degenerative disease in the rabbit knee, it appears practical to use this model to non-invasively examine the effectiveness of future osteoarthritis treatments in longitudinal studies.

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REFERENCES

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