Quantification of Knee Cartilage In Vivo In the MMT Model of Osteoarthritis in Rats Using MRI

S. Dhamija[1], Z. Xie[1], S. Bove[2], P. Chiao[1], and S. M. Liachenko[1]

[1]Bioimaging, Pfizer, Inc., Ann Arbor, MI, United States, [2]Inflammation, Pfizer, Inc., Ann Arbor, MI, United States

Introduction

Preclinical drug development in the area of osteoarthritis (OA) requires robust and reliable assessment of disease progression. The morphology of the articular cartilage is considered to be the primary marker of OA progression. However, the challenges of small animal in-vivo imaging and image analysis have limited the use of MRI in preclinical OA research. We present an approach for the quantification of rat knee cartilage volume and surface area in the medial meniscal tear (MMT) model of OA [1].

Methods

The procedures used in this study were approved by local IACUC. Eleven male Sprague Dawley rats (SD; 415 ± 22 g) were subjected to the surgery (MMT N = 5, and sham N = 6) under isoflurane anesthesia as described previously [1]. For sham surgery, the medial collateral ligament was exposed, but not transected. MRI was performed three weeks after the surgery on a 7T Bruker Biospec scanner equipped with 12 cm ID gradient insert (up to 20 G/cm). Animals were anesthetized using isoflurane (3% induction and 1.2-1.5% maintenance). Rats were place supine on an electrically heated cradle and their right knees were flexed to an angle of 105°, and secured to the animal holder to prevent motion. An actively decoupled, curved quadrature receive-only surface coil (Bruker BioSpin) was placed on the knee and the cradle placed inside the magnet. RF excitation for imaging was delivered through a 72mm ID birdcage volume resonator. An i.v. bolus of Magnevist® (0.4ml/kg), followed by a constant infusion (0.44 ml/kg/hr) was delivered to improve synovial fluid-cartilage delineation. Optimal slice planning was performed using information obtained from quick orthogonal images in the coronal, axial and sagittal aspects. High resolution 3D FLASH anatomical images were acquired in the sagittal aspect with the following acquisition parameters: TE = 3.596ms, TR = 25 ms, FA = 30º, NA = 6, MTX = 512 × 170 × 64, resolution of 29 × 116 ×231 µm. Final images were randomized, and both the tibia and medial tibial cartilage were segmented. To segment the tibia, we employed a deformable model to fit the tibial surface extracted from an atlas to all individual images [2]. The results were reviewed by an expert and any (minimal) errors were corrected manually. Cartilage segmentation was performed by edge detection using a Canny filter, followed by classification of detected edge voxels as 'cartilage' and 'non-cartilage'. Then, a level set approach was used to allow cartilage edge voxels to 'attract' a curve. This curve was a segmented cartilage. The results of cartilage segmentation were also reviewed and errors were manually corrected. The area, volume, and average thickness of cartilage were computed. To determine the ROI we performed a point-wise statistical analysis of cartilage thickness to obtain the regions with statistically significant difference between the two groups [3]. This ROI was then mapped back to all individual data sets, and cartilage volume, thickness and surface area over ROI were measured.

Results

The cartilage was segmented successfully in all images. Figure 1A shows the P-value of unpaired comparison between the two groups. This statistical change map was used to guide the selection of the ROI for further analysis. The ROI chosen is shown in figure 1B. Table 1 shows the results of the analysis. The cartilage volume and average thickness in MMT rats decreased significantly by 24% and 33% respectively compared to Sham controls.

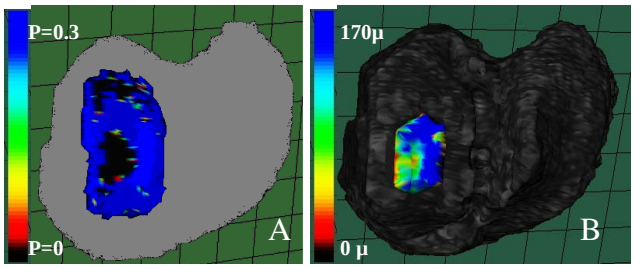

Figure 1. Rats-averaged statistical difference map-based selection of cartilage ROI (colored) over the tibial plateau (grayscale).
A – P-value of point-wise comparison of cartilage thickness between MMT and Sham rats. Black regions on blue cartilage map represents areas with P<0.005. B – ROI selected based on P-value map (A), which includes the area with point-wise P<0.05.

Table 1. Morphological markers of tibial medial cartilage (M ± SEM)

	Volume, mm^3	Average Thickness, mm
Sham	0.419±0.012	0.263±0.013
MMT	0.317±0.019	0.175±0.019
P	0.0031	0.0049

Discussion

The presented method of rat knee cartilage MRI and semi-automatic quantification provides a powerful tool for the assessment of therapeutic efficacy in animal models of OA. Proper cartilage delineation in small animal imaging imposes a significant challenge due to diminutive feature size and poor contrast even at a high magnetic field strength. The successful solution of this problem in our case required complex approach including the right choice of RF coil and pulse sequence together with artificial contrast enhancement and application of vigorous image analysis algorithms. Since both measured markers of cartilage morphology (volume and average thickness) are global metrics they are not too sensitive to local changes characteristic to OA development. We presented a statistical method of conversion them into sensitive local metrics by the choice of an appropriate ROI. This allowed us to enhance significantly the dynamic range of OA-related changes, which may increase the sensitivity of detection of drug efficacy in preclinical research. Further elucidation of the sensitivity and specificity of such approach with scan-rescan studies is warranted.

References

[1] Bove et al. (2006). *Osteoarthritis Cartilage* **14;**1041–48.
[2] Xie et al(2006) *Proc. SPIE* Vol. **6144**.