Quantitative cartilage degeneration associated with spontaneous osteoarthritis in a guinea pig model

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Introduction: Osteoarthritis (OA) is a common and painful condition with a multi-factorial etiology of the musculoskeletal system affecting more than 50% of the U.S. population over 65 (1) (2). Degeneration of the articular cartilage tissue, which is believed to be a primary factor in the development of OA, is a slow process and typically takes decades to have full thickness loss, but can be significantly accelerated due to trauma or surgical procedures (3). Dunkin-Hartley guinea pigs have been shown to develop OA with the earliest stage of detection manifesting as early as three to four months of age. Therefore, the Dunkin-Hartley guinea pig model provides a practical system for the longitudinal studies of the progression of OA (3) (4) (5). $T_{1\rho}$ MRI is sensitive to the slow-motion interactions on glycosaminoglycan chains of PG with bulk water protons (6) and has been shown to correlate with cartilage proteoglycan content (6) (7). The $T_{1\rho}$ relaxation rate has been shown to increase linearly with PG loss in controlled degradation experiments performed on *ex vivo* bovine patellae samples (6) (8), in the porcine model of IL-1β induced cartilage degeneration (9), and in humans with chondromalacia (10). However, there have been no $T_{1\rho}$ MRI studies in the Dunkin-Hartley guinea pig model with naturally occurring joint disease that closely mimics human OA. Therefore, the aim of this study is to quantify age-dependent cartilage degeneration via $T_{1\rho}$ MRI with verification by histopathology measurements.

Methods: Duncan-Hartley guinea pigs were obtained at various ages and maintained under an IACUC approved protocol. The left hind stifle joint was imaged using $T_{1\rho}$ MRI on a 9.4 Tesla Varian horizontal 20 cm bore scanner. Reproducibility of $T_{1\rho}$ MRI with specified imaging parameters was described previously. Three age cohorts; 3 month old (N=8), 5 month old (N=6), and 9 month old (N=5), were used to determine the age-dependent osteoarthritic changes as measured by $T_{1\rho}$ MRI. Validation of age-dependent cartilage degeneration was confirmed by histology and Safranin-O staining. Cartilage thickness measurements were calculated through high resolution histological sections.

Results:

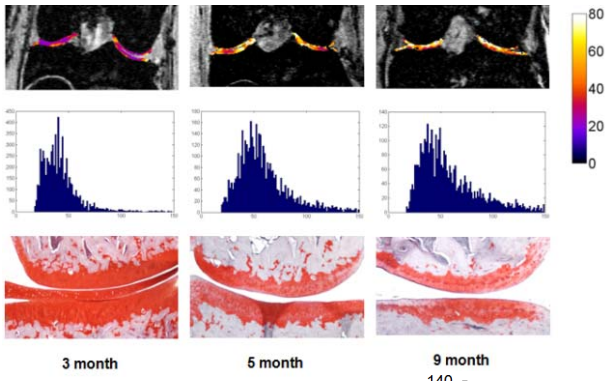

Figure 1: Representative $T_{1\rho}$ maps in color (top row) are overlaid on $T_{1\rho}$ MR images from representative 3, 5, and 9 month old animals. Color bar on the right represents $T_{1\rho}$ value in milliseconds. Histograms of $T_{1\rho}$ values and representative Safranin-O stained histological sections are shown below each image (middle and bottom rows, respectively). Both 5- and 9-month old animals displayed higher $T_{1\rho}$ values than the 3 month old, and age-related loss of PG loss was confirmed with subsequent histology images stained for PG content.

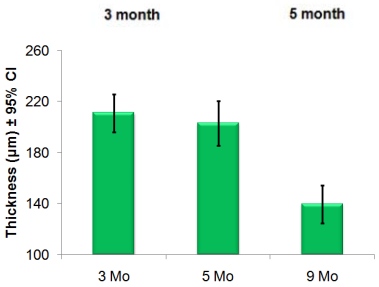

Figure 2: Mean cartilage thickness measurements are plotted with 95% confidence intervals (CI). Values are recorded using high-resolution histology. There are significant differences (‡=p<0.01) between both the 3- and 5-month old animals compared to the 9-month cohorts but not between 3- and 5-month old cohorts.

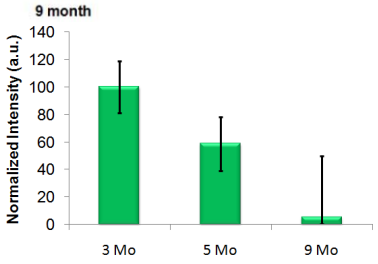

Figure 3: Mean cartilage thickness measurements are plotted with 95% confidence intervals (CI). Values are recorded using high-resolution histology. There are significant differences (‡=p<0.01) between both the 3- and 5-month old animals compared to the 9-month cohorts but not between 3- and 5-month old cohorts.

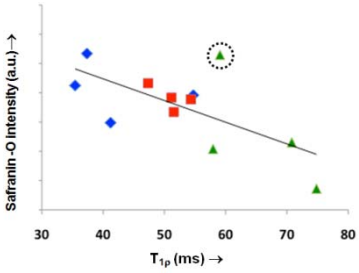

Figure 4: Mean signal intensities from Safranin-O stained histology sections of each animal vs. their average $T_{1\rho}$. Where ◆=3-month, ■=5-month, and ▲=9=month data. A moderate correlation (R^2=0.44, p<0.01) exists but is improved (R^2=0.67, p<0.01) if the outlier with abnormal and statistically significantly (z=-2.2) high stain intensity (indicated by dotted circle) is removed before analysis.

Conclusions: The data presented demonstrate that $T_{1\rho}$ can serve as a quantitative noninvasive tool to characterize joint cartilage degeneration during OA. Age-dependent changes, a characteristic of this well-defined animal model and verified with histological measurements of proteoglycan loss, strongly correlated with $T_{1\rho}$ across different age groups. $T_{1\rho}$ has adequate dynamic range to detect and track the progression of cartilage degeneration in the guinea pig model before gross anatomical changes such as cartilage thinning has occurred and is a surrogate to invasive analytical techniques. This study presents a technological advancement that would permit longitudinal studies of evaluating disease-modifying therapies useful for treating OA.

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