Classification of OARSI Scored Human Articular Cartilage Explants Through Multiparametric MRI Analysis at 3T

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Introduction: The development of noninvasive MRI approaches for early detection of osteoarthritis (OA) and monitoring response to therapeutic interventions has been the subject of intense activity. An important limitation in quantitative MRI studies of osteoarthritis is that individual MRI parameters exhibit substantial overlap between different degrees of cartilage degradation. This has been previously demonstrated in bovine nasal cartilage (BNC)—a model system for articular cartilage—where pathomimetic enzymatic degradation resulted in MRI parameters, which overlapped with those of control samples, resulting in limited classification accuracy[1]. Substantial improvements in accuracy were achieved through multiparametric analysis of MRI parameters[2,3]. However, these previous studies were of BNC, which is non-articular cartilage, and were conducted at 4°C sample temperature and high magnetic field strength (9.4T). The current work extends this multiparametric classification approach to study human articular cartilage explants at body temperature (37 °C) and clinical field strength (3T). Both univariate and multiparametric analyses based on MRI parameters T_1, T_2, T_2*, and ADC were used to discriminate between normal and OA cartilage as determined by OARSI histological scores[4].

Methods: *Sample Preparation.* Human tissue was obtained from knee joints in a protocol approved by the applicable Institutional Review Board from subjects undergoing elective arthroplasty. Two adjacent osteochonral plugs (6 mm dia) were harvested from each standardized femur locations (n=72), flash froze and stored at -80°C until analyzed; one of the plugs was histologically scored by two independent observers for OA severity using the OARSI scoring system[4] while its paired plug was imaged. Upon thawing, imaged plugs were inserted into a susceptibility-matched four-well polyetherimide (ULTEM) sample holder containing Fluorinert® FC-77 (Sigma-Aldrich, St. Louis, MO). *MRI Measurements.* Imaging was performed using a 3T Philips Achieva equipped with an 8 channel SENSE knee coil at a sample temperature of 37.0 ± 0.1 ºC. *T_1 measurements:* A 2D Look-Locker sequence with EPI readout (TE = 5 ms, TR = 6s, td = 50 ms, FA = 14°, ETL = 80, EPI factor = 3) was used to acquire two 4 mm thick slices with BW = 17.5 kHz, FOV = 75 × 44.5 mm (vertical × horizontal), MTX = 120 × 66 pixels and NSA = 2. *T_2 measurements:* A 3D multi-echo spin echo sequence (TE = 12 ms, TR = 767 ms, ETL = 30) was used with BW = 28.2 kHz, FOV = 75 × 45 × 23 mm, MTX = 188 × 78 × 7 pixels and NSA = 1. *T_2* measurements:* A 2D gradient echo sequence (TE1 = 1.5 ms, ΔTE = 4.2 ms, TR = 2 s, FA = 25°, ETL = 30) was used to acquire two 3.5 mm thick slices with BW = 98.9 kHz , FOV =75 x 45 mm, MTX = 152 × 73 and NSA = 2. *ADC measurements:* A 2D spin echo sequence with EPI readout (TE = 62 ms, TR = 2 s, EPI factor = 3) was used to acquire two 4 mm thick slices with b-values of 0, 333, 666, 1000, 1333, 1666, and 2000 s/mm^2, Δ = 25.3 ms, δ= 12.4 ms, BW = 12 kHz, FOV = 75 × 43.75 mm, MTX = 96 × 43 and NSA = 1. *Data Analysis*: Average signal intensity over all pixels in a region of interest (ROI) covering the entire cross-section of articular cartilage and excluding subchondral bone was fit to three-parameter monoexponential functions to yield T_1, T_2, T_2*, and ADC. *Classification Analysis.* Classification models based on mean parameter values (univariate) and Gaussian mixture models (multiparametric) were constructed using a random selection of training samples (n=24) and validated using the remaining samples (n=12). OARSI histological grades of OA severity (ranging from 0 to 6) were used to define normal and degraded cartilage, with scores greater than or equal to 2.5 representing the degraded group and scores less than 2.5 representing the normal group. Classification results were determined using the average over 100 independent selections of training and validation datasets and reported as sensitivity (rate of true positives), specificity (rate of true negatives), and accuracy (average of sensitivity and specificity). Univariate analysis was implemented using a custom code in MATLAB while model-based multiparametric analysis was implemented using the MCLUST package in R[5].

Table 1. Validation set sensitivity, specificity, and accuracy from univariate classification.

MR Parameter	Sensitivity	Specificity	Accuracy
T_1	0.59	0.61	0.60
T_2	**0.46**	**0.77**	**0.62**
T_2*	0.44	0.56	0.50
ADC	0.22	0.63	0.43

Table 2. Validation set sensitivity, specificity, and accuracy from multivariate Gaussian classification MCLUST.

MR Parameter	Sensitivity	Specificity	Accuracy
T_1, T_2	0.86	0.71	0.79
T_1, T_2*	0.78	0.77	0.78
T_1, ADC	0.77	0.74	0.76
T_2, T_2*	0.78	0.67	0.73
T_2, ADC	**0.70**	**0.92**	**0.81**
T_2*, ADC	0.71	0.59	0.65
T_1, T_2, T_2*	**0.73**	**0.96**	**0.85**
T_1, T_2, ADC	0.63	0.77	0.70
T_1, T_2*, ADC	0.70	0.63	0.67
T_2, T_2*, ADC	0.80	0.69	0.75
T_1, T_2, T_2*, ADC	0.57	0.88	0.73

Results and Discussion: Table 1 shows the validation set classification results for T_1, T_2, T_2*, and ADC of which T_1 and T_2 were the best univariate classifiers with accuracies above 0.60. It is interesting to note, in contrast to pathomimetically degraded BNC results at high field where T_1 showed substantially better classification accuracy as compared with T_2, in the current analysis the accuracy of classification according to T_2 was comparable to that of classification by T_1. This could be due to T_2's sensitivity to disruption in collagen and the lamellar structure of articular cartilage with degradation—both of these sample attributes influence the histological score, as well to the evidently increased dynamic range of T_1 measurements at high field. Table 2 shows the validation set classification results for all multiparametric model combinations. Bi-variate combinations showed substantial improvement in classification accuracy over univariate. For example, (T_2*, ADC)—containing the two poorest performing univariate parameters with accuracies of 0.50 and 0.43, respectively, shows substantially improved classification accuracy of 0.65. Overall, the best classifier was (T_1, T_2, T_2*) with an accuracy of 0.85. Interestingly, the combination of only two parameters, (T_2, ADC) showed comparable classification accuracy with an accuracy of 0.81. This parameter combination is of particular interest due to recent advances in rapid acquisition of high resolution 3D T_2 and ADC maps of the entire knee[6]. We note that these preliminary results analyze aggregate parameters that are averaged over the entire depth of the tissue and do not take into account depth-wise changes which are known to occur with the progression of OA. We expect that more detailed regional analysis which uses MRI parameter values at different tissue depths will improve classification accuracy, particularly due to the depth dependence of tissue degradation on the OARSI score.

Conclusions: Multiparametric statistical analysis of basic MRI parameters at clinical field strength under in vivo conditions yields substantially improved accuracy in discriminating between normal and OA human articular cartilage explants, as determined by OARSI histological scores, as compared to conventional univariate analysis. These initial results represent a promising step towards clinical detection of cartilage matrix degradation during early stages of OA using acquisition schemes that are readily available on clinical MRI systems.

References: 1) Lin PC, et al. Magn Reson Med 2009; 62(5):1311–1318. 2) Lin PC, et al. J Magn Reson 2009; 201(1):61-71. 3) Lin PC, et al. Magn Reson Med 2012; 67(6):1815-1826. 4) Pritzker KP, et al. Osteoarthritis Cartilage 2006; 14(1):13-29. 5) Fraley C and Raftery AE J. Classif. 2003; 20:263-286. 6) Staroswiecki E, et al. Magn Reson Med 2012; 67(4):1086-96.