Title

Longitudinal Evaluation of Osteoarthritic and Control Human Knee Articular Cartilage Morphology and MR Relaxation

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Longitudinal Evaluation of Osteoarthritic and Control Human Knee Articular Cartilage Morphology and MR Relaxation.

by

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THESIS

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Dedication and Acknowledgements

To begin, I would like to unreservedly thank my family and friends, whose steadfast love and support made not only this work, but my professional journey to date possible. I would furthermore like to thank my colleagues in the Musculoskeletal Quantitative Imaging Research group at the University of California San Francisco, many of whom have considerably contributed to my growth and maturation as a Scientist. Finally, I would like to thank Dr. Sharmila Majumdar for her unwavering guidance and perennial foresight in making this research possible.

Longitudinal Evaluation of Osteoarthritic and Control Human Knee Articular Cartilage Morphology and MR Relaxation

Joseph A. Schooler

Abstract

Knee osteoarthritis (OA) is a multifaceted diseases affecting many older adults. A main physiological characteristic of OA is the progressive loss of articular hyaline cartilage. Recently, there have been many proposed techniques that attempt to quantify early hyaline cartilage breakdown associated with OA. Preliminary stages of OA are marked by a reduction in PG and GAG followed by the degradation of the collagen network. Many techniques utilizing magnetic resonance imaging (MRI) have been proposed to noninvasively probe biochemical changes in human osteoarthritic cartilage. T1ρ and T2 relaxation time mapping may be useful as a noninvasive quantification of cartilage degradation. Moreover, osteoarthritic cartilage has displayed elevated voxel spatial heterogeneity of cartilage T1ρ and T2 relaxation time, as calculated by the grey-level co-occurrence (GLCM).

In this study we monitored cross-sectional and longitudinal evaluation of T1ρ and T2 relaxation times, GLCM spatial heterogeneity (texture analysis) of T1ρ and T2 relaxation, and cartilage volume and thickness in OA subjects versus healthy controls. Our results display significant increases over time in GLCM entropy in the medial tibia for both T1ρ and T2 relaxation and in the medial femoral condyle for T1ρ relaxation. A significant decrease in volume and thickness was observed in the medial tibia was also noted. These results indicate medial knee OA cartilage experiences a heightened level of spatial heterogeneity, possibly suggesting a predicative utility of T1ρ and T2 relaxation time texture analysis in the development of medial knee OA.

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Introduction

Osteoarthritis (OA) is a complex, metabolically active disease that affects nearly half of the population over 65 years of age (1). Although there are many motivating factors for studying OA, the increasing prevalence of this disease continues to place a tremendous economic burden on the US healthcare system (2). While this disease affects a multitude of diarthodial joints, it is commonly diagnosed in the knee (3). Factors predisposing one to the development of OA include age, gender, BMI, and environmental considerations (4)(5). A main pathological characteristic of OA is the progressive degeneration of articular (hyaline) cartilage.

Some of the main functions of hyaline cartilage are to provide protective support and truncate friction in synovial joints. Hyaline cartilage contains a relatively low concentration of rounded chondrocytes housed within an extracellular matrix (ECM) (6) . Within this ECM lies a mixture of water, collagen, and proteoglycan (PG) aggregates. Approximately 90-95% of collagen in hyaline cartilage is comprised of type II collagen with these fibrils essentially forming the backbone upon which PG aggregates will attach. Collagen fibrils are characterized by a triple helical tertiary structure, providing tensile force to counteract the PGs natural expansive tendencies. Within the ECM, PGs are composed of a central protein upon which many negatively charged glycosaminoglycans (GAG) motifs are attached (6) . Keratin sulfate (KS) and chondroitin sulfate (CS) are the prevalent GAG motifs present in hyaline cartilage. PG is dynamically synthesized and arranged by chondrocytes. The presence of high amounts of sulfates and carboxyl groups

are responsible for the GAG overall negative charge. The inclusion of these negatively charged PG molecules comprise the overall negative fixed charge density of hyaline cartilage. This gross negative charge subsequently attracts positively charged free ions along with water molecules to provide the appropriate electrostatic repulsive forces that give hyaline cartilage its characteristic swollen elasticity (6).

The arrangement collagen fibrils within hyaline cartilage display a characteristic laminar appearance. Proximal to the cortical bone collagen fibrils are arranged perpendicular to the cartilage-bone interface, giving rise to what is contemporarily known as the radial zone. As one travels superficially, a more random orientation is observed with the most superficial layer organized more parallel to the articular surface of the cartilage. This differing orientation places collagen fibrils in different spatial environments and has given rise to the so-called ‘magic angle’ effect (7), an orientation dependent MR signal phenomenon.

Within the context of magnetic resonance imaging (MRI), there have been many proposed techniques that attempt to quantify early hyaline cartilage breakdown associated with OA (8). Etiologically, the earlier stages of OA are marked by a reduction in PG and GAG while the disarrangement of the

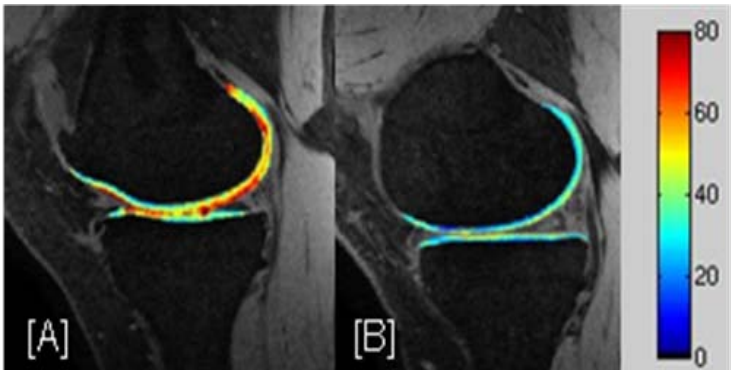


Figure 1 – Representative sagittal SPGR images with T1ρ relaxation times superimposed on articular cartilage as a color overlay of [A] OA patient, medial femoral condyle and medial tibia WORMS = 2 [B] control patient , WORMS = 0. Color intensity scale (far right) spans from 0-80 ms.

collagen network is observed later (9). Spin-lattice relaxation in the rotating frame, or T1ρ relaxation, examines the interaction between low frequency, motion-restricted water protons and their encapsulating PG matrix. T1ρ relaxation time has proven useful in the noninvasive quantification of biochemical changes within osteoarthritic cartilage, more specifically reductions in GAG concentration along with hydration (8-9). Significant correlations between elevated T1ρ relaxation time and the clinical diagnosis of OA have been well established in the literature (10). According to Akella et al (7), T1ρ relaxation time has displayed an inverse relationship with PG and GAG concentrations in hyaline cartilage. Quantitative T2 relaxation time is another MR technique that probes the relationship between spins contained within neighboring ECM water protons (11). Early collagen damage brought on by mechanisms associated with osteoarthritis causes an increase in the mobility of ECM water molecules and may perturb proton spin-spin interaction. This alteration is represented by an increase in T2 relaxation time (11) (12) (13). Both T1ρ and T2 relaxation represent non-invasive modalities from which early changes in the microarchitecture of cartilage may be classified and surveyed.

Recently, pixel spatial heterogeneity, often referred to as texture analysis, of biomedical images has been applied to characterize tissues across a vast array of anatomical systems (14) (15). Haralick *et al.* (16) developed a method of texture analysis based on the grey-level co-occurrence matrix (GLCM) that can be used to evaluate spatial distribution of pixel intensities in an image along a corresponding directionality. This method involves 14 different calculations that are partitioned mathematically into a contrast, orderliness, and statistics groups. In the more recent study of T1ρ and T2 relaxation time in knee OA, GLCM texture analysis has proved valuable. Past

experimentation has exhibited visual discrepancies in spatial T2 distribution with no significant difference in mean value (17) while Blumenkratz *et. al.* displayed elevated GLCM entropy of T2 values between osteoarthritic and healthy cartilage (18). Li *et. al.* (19) noticed significantly elevated T1ρ relaxation time GLCM contrast and entropy in OA subjects versus controls, further establishing the possible benefit of voxel heterogeneity in quantitative cartilage MR.

Human knee articular cartilage is a naturally curved and undulated tissue, adhering to the surfaces of the proximal tibia and fibula, distal femur, and patella. Since the bones upon which cartilage is attached are rounded in shape, the directionality of GLCM calculations will be parallel to the bone-cartilage interface at some points and perpendicular in others (figure 2). Techniques to flatten tissue in the hopes of more robust spatial variation analysis along tissues with well defined layers have been performed in tissues other than cartilage (20). Carballido-Gamio *et. al.* have shown a coefficient of variation decrease for non-flattened cartilage T1ρ GLCM parameters with increases for various pixel offsets (21). Flattening of T1ρ and T2 cartilage maps will allow for calculation of spatial heterogeneity of the natural lamina present in articular cartilage.

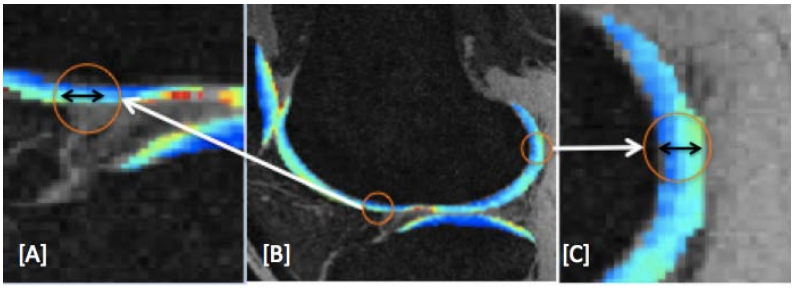


Figure 2 – Schematic illustrating GLCM analysis in the 0° direction. Notice the direction of analysis is parallel to the cartilage-bone interface near in image [A] and perpendicular in image [C].

Osteoarthritic degradation of the cartilage matrix is a complex process involving biochemical and mechanical influences (6). The destruction of proteoglycan and collagen

motifs associated with OA can lead to one of the hallmarks of the disease; articular cartilage lesions, fibrillation, thinning, and eventually full thickness cartilage loss (22). Many biomedical imaging modalities have been implemented in the morphological measurement of articular cartilage. The current gold standard in the evaluation of morphological cartilage changes is joint space width measurements, often performed on bilateral anteroposterior standing knee radiographs. Among the many semi-quantitative techniques performed to classify joint space narrowing is the Kellgren-Lawrence scale. This method attempts to analyze other common osteoarthritic changes to the knee along with joint space narrowing, including boney abnormalities such as the formation of osteophytes (23). Although this measurement is used indirectly to measure cartilage loss, the inherent insensitivity of radiographs to soft tissue contrast results in reduced specificity in knee cartilage classification (24) (25).

In more recent years, the development of cartilage MRI pulse sequences specific to the study of cartilage morphology has become substantially more sophisticated. Koo et al (26) have outlined critical MR data acquisition parameters to optimize sequences for cartilage morphometry measurements. Striking an appropriate balance between signal-to-noise (and contrast-to-noise), 3D image

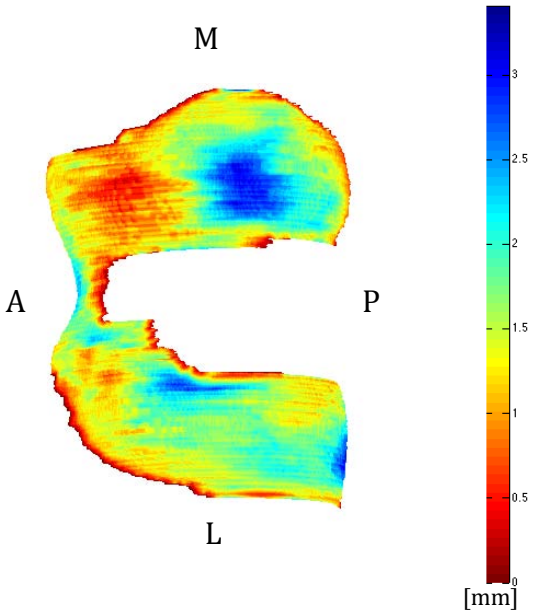


Figure 3 - An axial 3D representation of femoral cartilage thickness. Color scale represented in millimeters.

resolution, and acquisition time were all highlighted as crucial acquisition parameters. Eckstein et. al. (27) report that T1-weighted spoiled gradient-recalled echo sequences with fat suppression are contemporarily accepted as the most commonly used sequence for quantifying cartilage shape. The most common MR cartilage morphology metrics continue to be whole region of interest volume (mm^3) and mean thickness (mm) (source). Numerous studies have displayed a reduction in cartilage volume and mean thickness in osteoarthritic subjects, especially in the medial compartments.

This study aims to track the baseline and longitudinal changes in full-thickness T1ρ and T2 mean relaxation time, GLCM spatial homogeneity of T1ρ and T2 relaxation time, and morphological variations between healthy and osteoarthritic cartilage. The multitude of T1ρ and T2 relaxation time analysis parameters presented in this report may allow us determine which parameters show the most progression in osteoarthritic cartilage by monitoring quantitative cartilage MR metrics. Another central goal is to determine if a specific morphological or GLCM quantitative MR metric might be more sensitive than full-thickness T1ρ and T2 mean values alone. This sensitivity is defined as the greatest longitudinal statistical significance of a GLCM parameter between OA and controls compared to their respective baseline relationships

Methods

Cohort:

93 subjects were recruited and scanned in accordance with UCSF Committee on Human Research guidelines. Upon recruitment, patents underwent a bilateral anteroposterior standing knee radiographs for stratification based Kellgren-Lawrence score. Subjects were monitored over 3 years (4 total time points). Subjects had a mean age of 50 years (± 14.3), mean BMI of 26.1 kg/m2 (± 5.4) and 54% of the subjects were female. Table 1 (right) shows the distribution of OA and control subjects (based on knee compartment Whole Organ Magnetic Resonance Imaging scoring). Notice subject attrition, which was most commonly due to subject dropout or end stage OA surgical intervention precluding them from further participation.

LFC		
Time Point	Control	OA
B	64	29
1yr	44	14
2yr	29	7
3yr	23	2
MFC		
Time Point	Control	OA
B	58	35
1yr	38	20
2yr	29	7
3yr	18	8
LT		
Time Point	Control	OA
B	68	23
1yr	48	9
2yr	29	6
3yr	24	1
MT		
Time Point	Control	OA
B	63	27
1yr	44	13
2yr	30	6
3yr	21	5
Patella		
Time Point	Control	OA
B	31	58
1yr	21	38
2yr	14	22
3yr	12	13

Table 1 – Sample size of osteoarthritic and healthy control subjects at each time point.

Clinical Grading:

Morphological assessment of knee articular cartilage was performed by 2 UCSF experienced Radiologists using a sagittal fat-saturated FSE T2-weighted clinical imaging sequence (matrix 512x256, FOV=16cm, slice thickness=2mm) and graded using modified semi-quantitative Whole Organ Magnetic Resonance Imaging scoring (WORMS) (28). The T2-weighted FSE images propensity to display good cartilage tissue contrast, along with strong signal from fluid allow complete clinical analysis of a multitude of knee structures. Subjects were classified as osteoarthritic by the appearance

of a partial thickness focal defect; A WORMS score of two or greater. Cartilage lesions on a sagittal T2-weighted FSE images are visible (figure 4) below.

Magnetic Resonance Imaging:

MR data was acquired on a 3T Signa HDx MR (GE Healthcare, Piscataway, NJ) scanner with a dedicated 8-channel phased array knee coil. Cartilage T1ρ and T2 maps were generated using 3D T1ρ mapping techniques (29) based on a gradient echo sequence (TR/TE=9.3/3.7 ms; FOV=6–8 cm, matrix=256 × 128, slice thickness=2 mm, BW=31.25 kHz, views per segment=64, Trec=1.5 s, TSL=0, 10, 40, 80 ms, FSL=500 Hz)(Li 2011). T2 weighted images were acquired using sagittal 3D T2 mapping (TR=3700 ms, TE=4.1, 14.5, 25, 45.9 ms, FOV=6–8 cm, matrix=256 × 128, slice thickness=2 mm, BW=31.25 kHz, views per segment=64, Trec=1.5 s). WORMS scoring was based on a clinical sagittal T2 fast-spin echo sequence (TR/TE=4300/51 ms, FOV=6–8 cm, matrix=512×256, slice thickness=1 mm, echo train length=9, bandwidth=31.25 kHz, NEX=2). A fat-saturated 3D SPGR sequence (TR/TE=15/6.7 ms, flip angle=12, FOV=6–8 cm, matrix=512 × 512, slice thickness=1 mm, bandwidth=31.25 kHz, NEX=1) was acquired for the purposes of cartilage segmentation. Parallel imaging was used on all imaging sequences utilizing ASSET with an acceleration factor at 2.

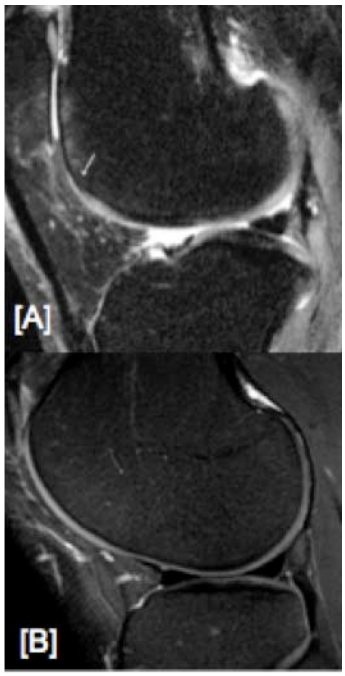


Figure 4 - Sagittal T2-weighted FSE images displaying [A] an OA patient (WORMS = 4) and [B] a healthy control (WORMS=0).

Image Processing:

Five knee compartments (lateral femoral condyle (LFC), medial femoral condyle (MFC), lateral tibia (LT), medial tibia (MT), and Patella (PAT)) were segmented on T1-weighted SPGR images using a Bezier spline based semi-automatic segmenting algorithm. Post-processing and analytical software related to segmentation and quantification of T1ρ and T2 images were executed in a MATLAB (MathWorks, Natick MA) based in-house software package. The first echo of the T1ρ and T2 weighted sequences were registered to the SPGR images prior to segmentation using a rigid based algorithm developed at UCSF. T1ρ and T2 maps were fit using the equations listed in figure 5. Transformation matrices associated with T1ρ and T2 first echo to SPGR registration were then applied to their corresponding maps. Cartilage segmentations were then superimposed upon T1ρ and T2 maps to extract relaxation time compartmental mean values, superficial and deep laminar values, and all GLCM metrics. Deep and superficial laminar analysis for the six compartments was defined using Euclidian distances, utilizing the bone spline as a reference with the same in-house MATLAB developed software package. Segmentations were then superimposed upon T1ρ and T2 maps to extract relaxation time mean values per compartment. Cartilage flattening was performed using the same in-house software based on the compartmental region of interest GLCM contrast, entropy, and variance for

$$S(TSL) \alpha\ S_0 \exp\left(-\frac{TSL}{T_{1\rho}}\right)$$

$$S(TE) \alpha\ S_0 \exp\left(-\frac{TE}{T_2}\right)$$

Figure 5 - Map signal fitting equations for both T1ρ (top) and T2 (bottom).

the five compartments were calculated using the same in-house MATLAB developed software.

Statistics:

Baseline linear regressions between the OA and control group, treating the patient as a random effect, were performed for each variable in using JMP software version 8 (SAS Institute, Cary NC) adjusting for age, gender, and BMI. For longitudinal analysis a generalized estimating equation was executed with an exchangeable correlation structure, interactions between time point, OA versus control, gender, age, and BMI regressed. All longitudinal statistics were performed in SAS 9.3 (SAS Institute, Cary NC).

GLCM Metrics:

Three main GLCM texture parameters including Contrast, Entropy, and Variance (30) were calculated along two angles (0°, 90°) and at a one pixel offset. The directions parallel and perpendicular to the bone-cartilage interface provide texture information along differing lamina. The horizontal (0°) direction corresponds to the A/P axis and the vertical (90°) direction corresponds to the I/S axis. In theory, these metrics will all increase as the

Contrast

$$\sum_{i,j=0}^{N-1} P_{i,j}\left(i-j\right)^2$$

Entropy

$$\sum_{i,j=0}^{N-1} P_{i,j}\left(-\ln P_{i,j}\right)$$

Variance

$$\sigma_i^{\,2} = \sum_{i,j=0}^{N-1} P_{i,j}\left(i-\mu_i\right)^2 \quad \sigma_j^{\,2} = \sum_{i,j=0}^{N-1} P_{i,j}\left(j-\mu_j\right)^2$$

Figure 6 – GLCM contrast, entropy and variance equations. Co-occurrence matrix P with pixels i,j and μ_i and μ_j being the number of co-occurrences of pixels i,j

voxels within a region of interest become more heterogeneous.

Results

Baseline Data Analysis

Morphology

Compartment	Group	Mean Volume (mm^3)	Mean Thickness (mm)
LFC	Control	3994.26 ± 1255.68	1.5 ± 0.27
	OA	3770.38 ± 1121.24	1.56 ± 0.36
LT	Control	1885.61 ± 608.84	1.93 ± 0.39
	OA	1302.17 ± 522.78	1.33 ± 0.48
MFC	Control	2722.13 ± 937.22	1.43 ± 0.29
	OA	2367.94 ± 994.29	1.31 ± 0.38
MT	Control	1209.73 ± 414.22	1.24 ± 0.25
	OA	1087.55 ± 465.26	1.09 ± 0.32
Patella	Control	3053.31 ± 1082.86	2.23 ± 0.39
	OA	2179.05 ± 927.03	1.68 ± 0.5

Table 2 – Baseline mean cartilage volume and thickness calculations with standard deviations. Shaded measurements indicate a statistical significance of $p \leq 0.05$.

A significant decrease was observed in osteoarthritic cartilage volume for every compartment measured at baseline (table 2). Significant decreases in mean thickness of subjects with OA were observed in both the medial and lateral tibia along with the patella. While the MFC displayed a reduction in osteoarthritic cartilage mean thickness, this was only approaching statistical significance ($p = 0.07$). The LFC showed no difference in mean thickness between OA and control cartilage.

T1ρ Relaxation Time

Comparment	Group	Full-Thickness T1ρ (ms)	Bone Layer T1ρ (ms)	Articular Layer T1ρ (ms)
LFC	Control	39.78 ± 4.5	34.19 ± 3.93	45.12 ± 5.59
	OA	42.76 ± 4	37.14 ± 4.63	48.11 ± 4.28
LT	Control	33.35 ± 4.42	26.1 ± 5.11	40.27 ± 5.17
	OA	37.76 ± 7.6	32.84 ± 9.7	42.43 ± 7.24
MFC	Control	41.17 ± 5.13	36.2 ± 5.22	45.92 ± 5.88
	OA	45.47 ± 5.36	40.06 ± 5.99	50.83 ± 5.56
MT	Control	34.85 ± 4.45	28.49 ± 5.88	41.12 ± 5.44
	OA	38.51 ± 6.06	32.36 ± 7.65	44.89 ± 7.57
Patella	Control	42.12 ± 6.6	35.66 ± 8.17	48.86 ± 7.81
	OA	43.73 ± 4.97	38.85 ± 7.84	48.71 ± 7.4

Comparment	Group	T1ρ GLCM Contrast 0°	T1ρ GLCM Entropy 0°	T1ρ GLCM Variance 0°
LFC	Control	22.18 ± 29.28	5.38 ± 0.3	114.1 ± 45.42
	OA	38.9 ± 70.28	5.41 ± 0.49	156.87 ± 123.68
LT	Control	34.85 ± 45.93	5.42 ± 0.33	129.74 ± 58.23
	OA	35.72 ± 38.71	5.42 ± 0.38	147.05 ± 61.66
MFC	Control	17.19 ± 28.69	5.33 ± 0.32	99.83 ± 34.65
	OA	38.6 ± 46.11	5.24 ± 0.33	182.77 ± 112.64
MT	Control	49.88 ± 72.22	5.21 ± 0.32	123.31 ± 81.77
	OA	90.5 ± 84.48	5.12 ± 0.43	189.51 ± 105.71
Patella	Control	44.27 ± 54.55	5.33 ± 0.37	100.07 ± 56.22
	OA	53.31 ± 66.98	5.37 ± 0.41	139.69 ± 67.4

Comparment	Group	T1ρ GLCM Contrast 90°	T1ρ GLCM Entropy 90°	T1ρ GLCM Variance 90°
LFC	Control	86.95 ± 50.38	5.66 ± 0.39	104.35 ± 45.42
	OA	101.13 ± 52.26	5.63 ± 0.53	150.83 ± 123.68
LT	Control	93.53 ± 80.34	5.62 ± 0.43	121.05 ± 58.23
	OA	100.42 ± 87.86	5.49 ± 0.68	136.09 ± 61.66
MFC	Control	90.48 ± 36.4	5.65 ± 0.41	89.21 ± 34.65
	OA	168.27 ± 159.23	5.35 ± 0.46	159.84 ± 112.64
MT	Control	80.27 ± 68.05	5.32 ± 0.32	126.49 ± 81.77
	OA	108.02 ± 134.21	5.15 ± 0.45	169.97 ± 105.71
Patella	Control	56.92 ± 36.93	5.49 ± 0.56	100.96 ± 56.22
	OA	75.27 ± 55.36	5.56 ± 0.53	134.3 ± 67.4

Table 3 – Baseline mean full-thickness, laminar, and GLCM calculations of T1ρ relaxation time with standard deviations. Shaded measurements indicate a statistical significance of $p \leq 0.05$.

T2 Relaxation Time

Comparment	Group	Full-Thickness T2 (ms)	Bone Layer T2 (ms)	Articular Layer T2 (ms)
LFC	Control	32.39 ± 4.38	29.9 ± 4.34	34.76 ± 5.09
	OA	34.72 ± 4.69	32.1 ± 5.17	37.13 ± 4.73
LT	Control	26.26 ± 4.35	22.73 ± 5.16	29.61 ± 5.03
	OA	33.27 ± 7.56	30.44 ± 8.28	35.92 ± 7.38
MFC	Control	31.97 ± 4.06	30.22 ± 4.18	33.63 ± 4.62
	OA	34.24 ± 4.69	32.06 ± 5.48	36.31 ± 4.5
MT	Control	27.81 ± 4.68	25.02 ± 6.7	30.56 ± 4.6
	OA	33.1 ± 5.46	30.67 ± 7.89	35.58 ± 5.5
Patella	Control	35.27 ± 4.87	31.15 ± 5.64	39.47 ± 5.72
	OA	37.04 ± 5.65	34.94 ± 7.31	39.13 ± 5.6

Comparment	Group	T2 GLCM Contrast 0°	T2 GLCM Entropy 0°	T2 GLCM Variance 0°
LFC	Control	20.58 ± 30.68	5.21 ± 0.35	124.06 ± 119.17
	OA	36.18 ± 64.66	5.18 ± 0.41	158.98 ± 145.38
LT	Control	27.56 ± 46.77	5.19 ± 0.27	123.49 ± 82.32
	OA	29.57 ± 32.32	5.3 ± 0.37	138.4 ± 55.35
MFC	Control	8.96 ± 11.04	5.09 ± 0.37	82.44 ± 51.85
	OA	26.24 ± 28.31	5.14 ± 0.29	164 ± 124.01
MT	Control	32.19 ± 59.96	5.06 ± 0.29	131.88 ± 94.29
	OA	53.56 ± 43.32	5.06 ± 0.4	205.04 ± 193.76
Patella	Control	34.94 ± 41.92	5.07 ± 0.31	76.7 ± 40.08
	OA	41.1 ± 51.56	5.05 ± 0.43	108.25 ± 69.32

Comparment	Group	T2 GLCM Contrast 90°	T2 GLCM Entropy 90°	T2 GLCM Variance 90°
LFC	Control	95.55 ± 96.95	5.54 ± 0.44	116.08 ± 118.92
	OA	96.93 ± 87.82	5.5 ± 0.46	149.99 ± 143.56
LT	Control	92.21 ± 99.33	5.48 ± 0.27	114.46 ± 83.14
	OA	83.34 ± 48.89	5.4 ± 0.7	122.17 ± 51.09
MFC	Control	67.35 ± 38.54	5.53 ± 0.44	73.87 ± 50.51
	OA	134.52 ± 129.87	5.35 ± 0.4	138.26 ± 88.11
MT	Control	126.43 ± 98.91	5.29 ± 0.33	121.31 ± 91.88
	OA	145.54 ± 208.91	5.07 ± 0.43	190.73 ± 172.05
Patella	Control	22.4 ± 18.22	5.16 ± 0.3	82.9 ± 47.97
	OA	48.49 ± 56.44	5.27 ± 0.48	105.84 ± 63.07

Table 4 – Baseline mean full-thickness, laminar, and GLCM calculations of T2 relaxation time with standard deviations. Shaded measurements indicate a statistical significance of $p \leq 0.05$.

Longitudinal Data Analysis

Morphology

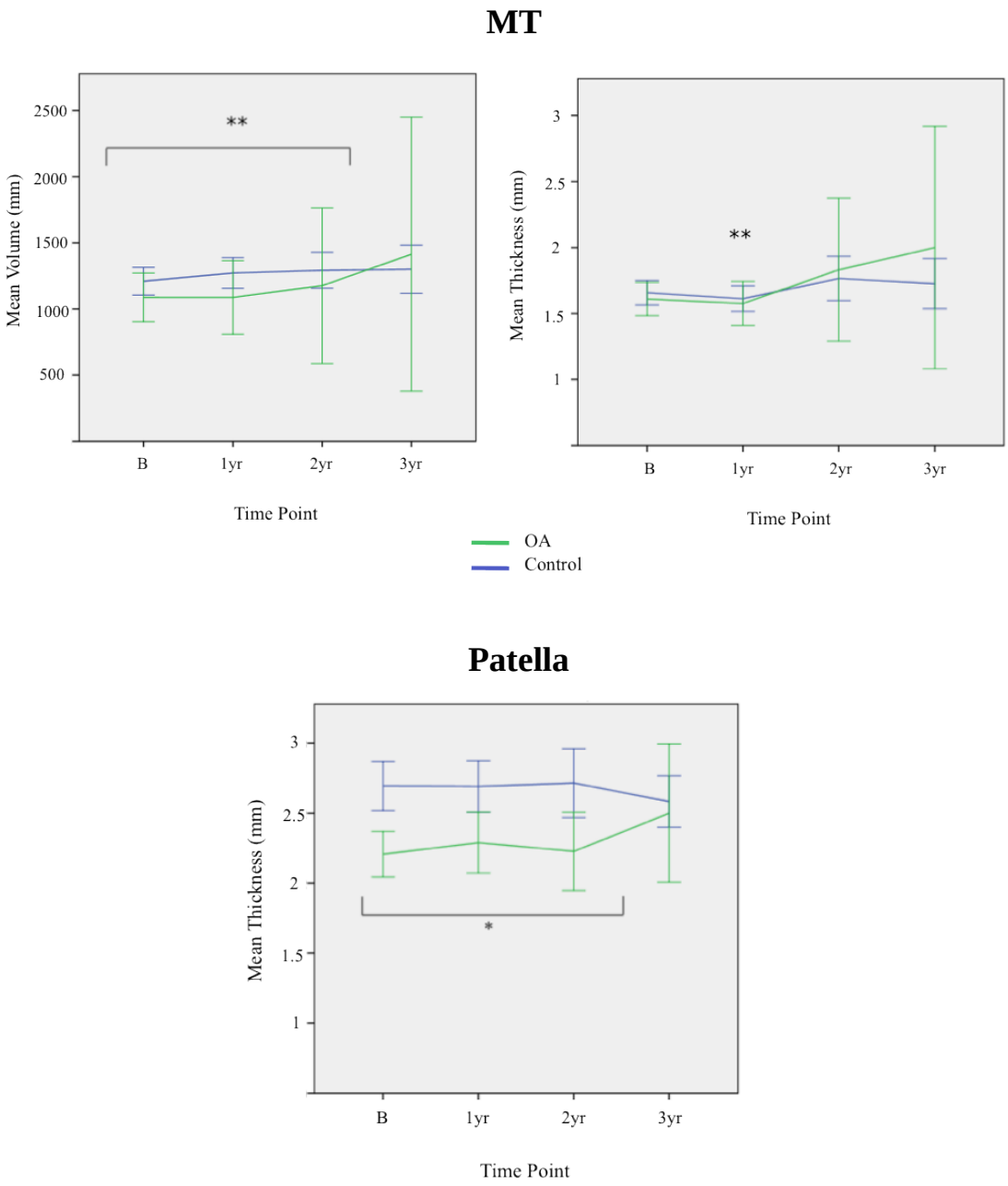
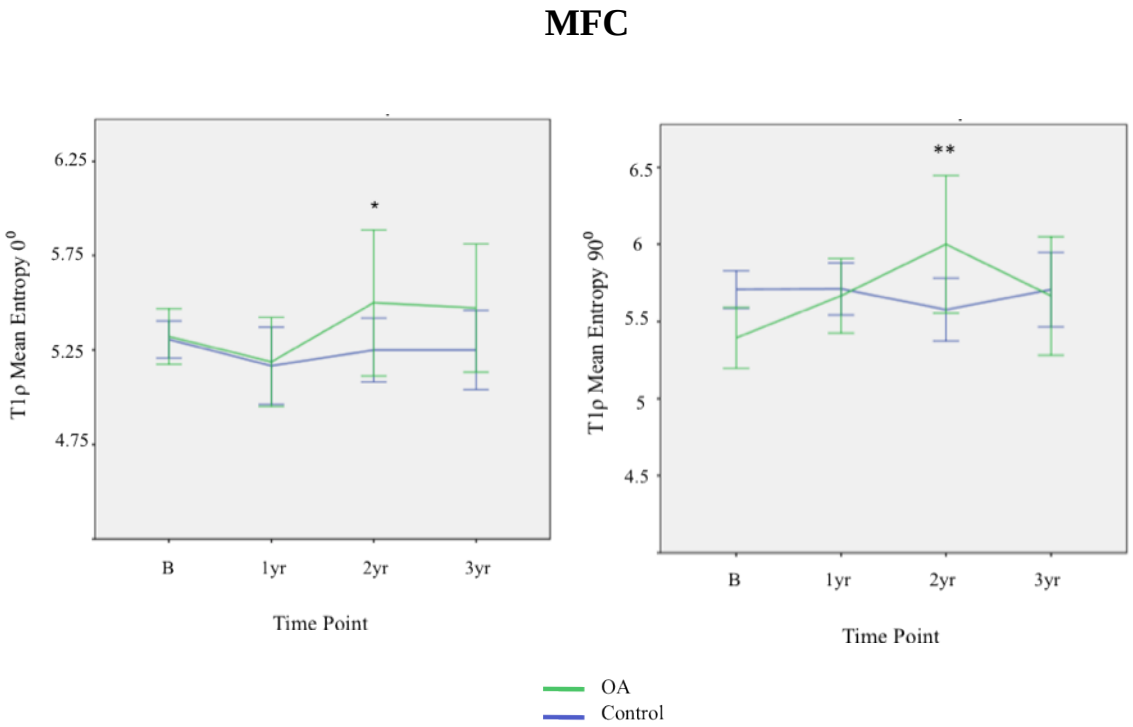


Figure 7 –Significant longitudinal morphology relationships Single asterisk indicates a p-value between 0.09 and 0.05 while a double asterisk indicates a p-value < 0.05. Error bars represent 95% confidence intervals.

T1ρ Relaxation Time



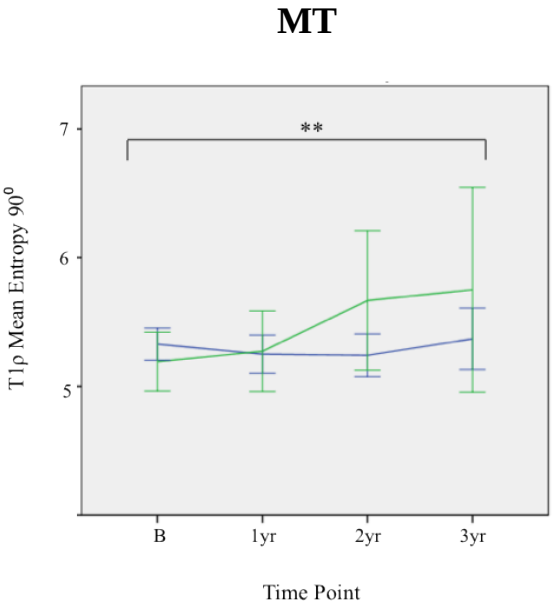


Figure 8 –Significant longitudinal T1P ρ relationships. Single asterisk indicates a p-value between 0.09 and 0.05 while a double asterisk indicates a p-value < 0.05. Error bars represent 95% confidence intervals.

T2 Relaxation Time

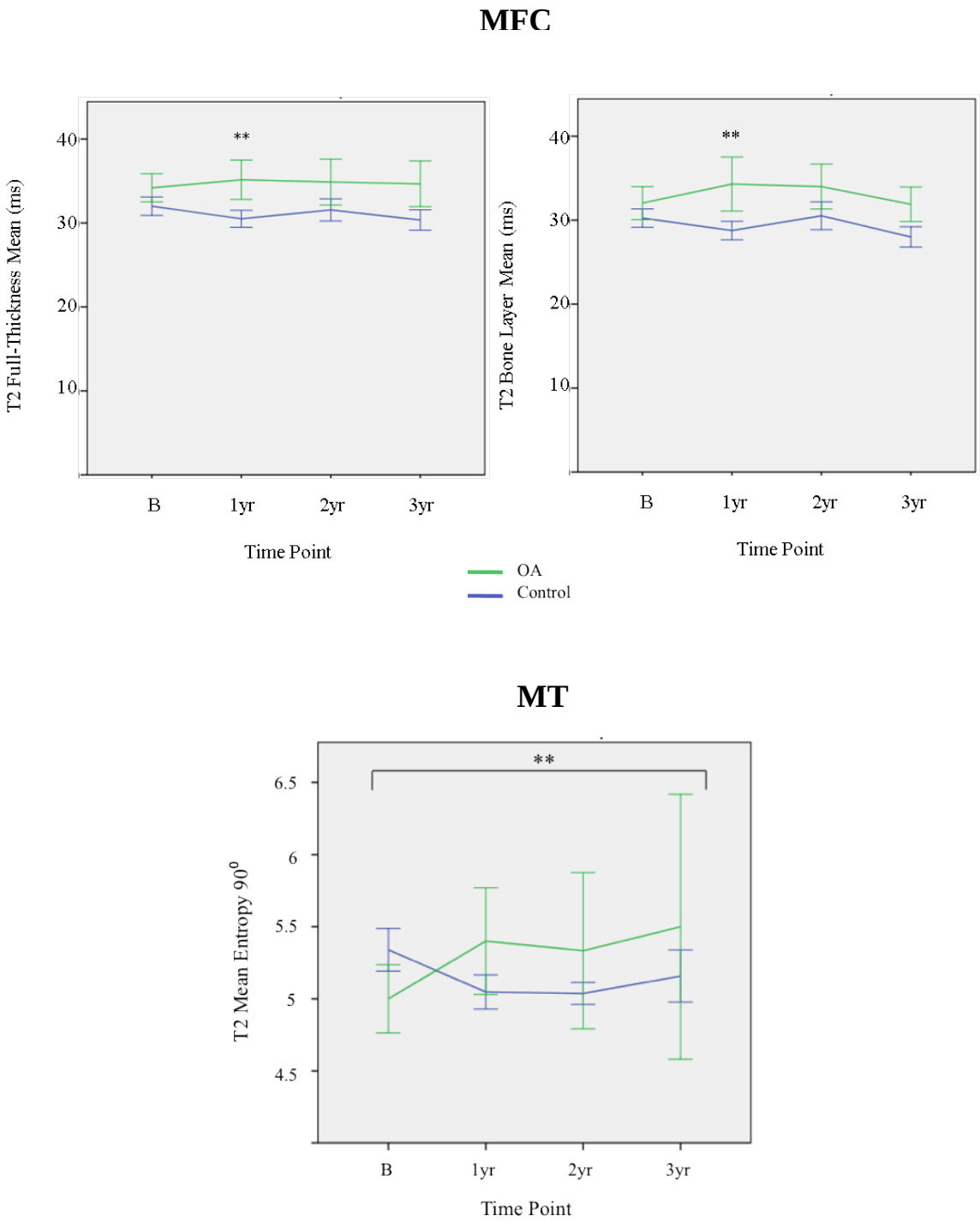


Figure 9 –Significant longitudinal T2 relationships. Single asterisk indicates a p-value between 0.09 and 0.05 while a double asterisk indicates a p-value < 0.05. Error bars represent 95% confidence intervals.

Results continued

Mean full-thickness T1ρ relaxation times were significantly elevated in osteoarthritic cartilage in every compartment with the exception of the patella. Bone layer T1ρ relaxation time were significantly increased in every compartment with the exception of the medial tibia, which showed a trend towards a significant increase ($p=0.08$). Articular layer T1ρ values were only significantly higher in the femoral cartilage (LFC, MFC).

T1ρ horizontal (0°) GLCM contrast was significantly elevated in medial compartments (MFC, MT) in osteoarthritic subjects. Baseline results indicate no significant differences in horizontal T1ρ GLCM entropy across the entire knee between healthy controls and osteoarthritic cartilage. Horizontal T1ρ GLCM variance was significantly elevated in every compartment excluding the patella. Vertical T1ρ contrast mimicked the trends displayed in the horizontal direction in that a significant elevation was detected on the medial side of the knee (MFC, MT) for the OA group. Vertical T1ρ entropy, similarly to its horizontal counterpart, displayed no significant trends between the two cohorts. Vertical T1ρ variance was significantly elevated in osteoarthritic subjects in both femoral compartments, as well as the lateral tibia.

Mean full thickness T2 relaxation times were significantly elevated in every compartment except for the LFC. Osteoarthritic bone layer T2 relaxation times were significantly elevated in the patella both tibial compartments as compared to healthy

controls, while elevated T2 articular layer relaxation time was significant in every compartment except the patella.

T2 horizontal (0°) GLCM contrast was significantly elevated in the medial compartments (MFC, MT) along with the LFC. Vertical T2 contrast was significantly elevated in only the MFC and patella. In analyzing both vertical and horizontal T2 GLCM entropy, the only significant increase was observed in the horizontal T2 entropy of the MFC in osteoarthritic subjects. Significantly elevated GLCM variance was observed in the MFC, MT, and patella for both the horizontal and vertical directions.

Longitudinal Data Analysis

Longitudinal analysis was performed for each of the abovementioned baseline variables. In observation of this cohort we were most interested in the interaction of time with cartilage metrics of OA subjects versus healthy controls and how those differences progress with respect to baseline associations.

The medial tibia and patella displayed the most predictive morphological changes between healthy controls and OA subjects. The interaction between OA versus control and time indicated that cartilage volume was significantly lower ($p=0.02$) for both 1-year and 2-year time points with respect to baseline OA versus control interactions. The same trend was observed for mean thickness of the medial tibia however a strong significance was only observed at the 1-year time point ($p<0.01$). Mean patellar thickness changes were shown to approach significance ($p=0.07$) for all time points with respect to baseline differences.

T1ρ GLCM entropy in osteoarthritic cartilage increased significantly from the OA versus control baseline relationship in the medial compartments (MFC, MT). In the MFC vertical (90°) T1ρ entropy was significantly elevated in OA subjects versus healthy controls compared to baseline values at 2 years (p=0.02). In the horizontal direction this same relationship approached significance (p=0.06) also at the 2-year time point. In the MT, vertical T1ρ GLCM entropy increased significantly in OA cartilage throughout all time points with respect to baseline relationships (p=0.05). No longitudinal relationships were significant for any full-thickness, bone, or articular layer mean T1ρ values.

T2 mean and bone layer relaxation time in the MFC were significantly elevated at the 1-year time point in OA subjects with respect to the baseline relationships. (p=0.04 and p=0.02, respectively). Similarly to T1ρ, vertical T2 GLCM entropy increased significantly across all time points in OA subjects when compared to baseline associations.

Discussion

Baseline morphologic data displayed a marked reduction in cartilage volume between OA and control subjects throughout the whole knee. Mean thickness was significantly lower in tibial and patellar cartilage while no statistical significance was observed in femoral cartilage. Our data is consistent with previous studies that have demonstrated a significant reduction in cartilage volume (31) and mean thickness (32) with similar clinical stratifications. Longitudinally we observed a progressive loss of cartilage volume in OA subjects in medial tibia up to the 2-year time point (p=0.02) and mean thickness decreases at 1-year. These findings implicate longitudinal morphological

changes in MT cartilage of symptomatic OA subjects. The longitudinal decrease in mean thickness of osteoarthritic patellar cartilage approached significance (p=0.08) until 2 years and then gained thickness. The thickness increases of OA cartilage at the 3-year time point in both the MT and Patella may be due to cartilage swelling or tapered sample size.

T1ρ full-thickness mean values were significantly elevated in OA subjects in each compartment except the patella. These findings are consistent with T1ρ relaxation time patterns based on multiple clinical definitions of OA (10) (19) (33), Significant increases in OA bone layer T1ρ at baseline were observed in every compartment except for the MT and articular layer increases were only significant in the femoral cartilage (LFC, MFC). Upon analyzing baseline T1ρ GLCM parameters contrast was significantly elevated in the medial compartments only in both the horizontal and vertical directions. Interestingly, baseline entropy calculations showed no significant increases in OA subjects in either direction In fact, osteoarthritic cartilage displayed lower (albeit insignificant) entropy than healthy controls in the medial compartments. However, upon analysis both the MFC and MT displayed strongly significant longitudinal interactions of T1ρ entropy between OA and control subjects when compared to baseline relationships. These interactions are indicative of diseased cartilage T1ρ relaxation time becoming more disordered than healthy cartilage over time. In the absence of T1ρ full-thickness or laminar mean values displaying a strong longitudinal relationship, it is apparent that T1ρ GLCM entropy, especially in the vertical direction) is a sensitive biometric in the longitudinal separation of symptomatic and healthy controls in the medial knee compartments.

In the survey of quantitative T2 relaxation we found significantly elevated T2 relaxation time in baseline full-thickness and laminar compartments of OA cartilage, consistent with previous studies (34). All three baseline horizontal T2 GLCM measurements were found to be significantly elevated in OA subjects in the MFC. Longitudinally, full-thickness mean and bone layer T2 relaxation times were increased in OA subjects at the 1-year time point. Similarly to T1ρ, the interaction between OA and control MT cartilage with time displayed a significant interaction (elevated vertical entropy in OA subjects) suggesting heightened disorder of T2 relaxation time of OA MT cartilage compared to baseline interactions.

The most significant limitation of this study is the lack of lateral knee OA subjects at the 3-year time points. The sample size for the LFC and LT was reduced to 2 and 1 respectively at the final time point in this study. Another limitation we faced is the scale of the time points. It would perhaps be more informative as to the relationship of these quantitative MR cartilage metrics to stratify time points in 6 month intervals rather than annually. Also increasing the study to longer than 3 follow-up data points could show some of the curious non-linear trends observed in some of these data, most notably the longitudinal thickness increases for the patella and MT near the latter time points.

Conclusion

Osteoarthritis is an etiological intricate disease. Magnetic resonance imaging provides some intriguing methods by which to quantify early biochemical changes associated with OA. In this study we observed the cross-sectional and longitudinal

behaviors of cartilage morphology, T1ρ, and T2 relaxation time metrics. A reduction in MT and patellar osteoarthritic cartilage volume over time indicates that these compartments are the most effected by the prevalence of cartilage lesions. In regards to T1ρ, and T2 relaxation, our longitudinal results indicate that medial compartment (MFC and MT for T1ρ and MT for T2) osteoarthritic cartilage becomes significantly heterogeneous with time while control cartilage does not. The longitudinal T1ρ entropy interactions could be indicative of a heterogeneous GAG breakdown within the matrix at the medial joint compartments while the T2 MT entropy increases suggests that the appearance of cartilage lesions creates higher voxel disorder.. The strong correlation of vertical GLCM entropy in both T1P and T2 indicate that this metric may be a viable predictor in the early detection of medial compartment osteoarthritic cartilage. GLCM calculations on flattened T1ρ and T2 maps can provide useful information about the trends of medial compartment OA.

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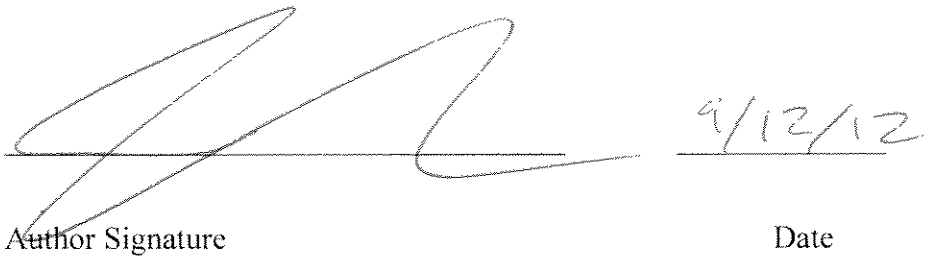

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