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Noninvasive Assessment of Osteoarthritis Severity in Human Explants by Multicontrast MRI

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Abstract

Purpose—Medical imaging has the potential to noninvasively diagnose early disease onset and monitor the success of repair therapies. Unfortunately, few reliable imaging biomarkers exist to detect cartilage diseases prior to advanced degeneration in the tissue.

Method—In this study, we quantified the ability to detect osteoarthritis (OA) severity in human cartilage explants using a multicontrast magnetic resonance imaging (MRI) approach, inclusive of novel displacements under applied loading by MRI (dualMRI), relaxivity measures, and standard MRI.

Results—dualMRI measures, which characterized the spatial micromechanical environment by 2D finite and Von Mises strains, were strong predictors of histologically-assessed OA severity, both prior to and after controlling for factors e.g. patient, joint region, and morphology. Relaxivity measures, sensitive to local macromolecular weight and composition, including $T_{1\rho}$, but not T_1 or T_2 , were strong predictors of OA severity. A combined multicontrast approach that exploited spatial variations in tissue biomechanics and extracellular matrix structure yielded the strongest relationships to OA severity.

Conclusion—Our results indicate that combining multiple MRI-based biomarkers has high potential for the noninvasive measurement of OA severity and the evaluation of potential therapeutic agents used in the treatment of early OA in animal and human trials.

Keywords

osteoarthritis; human articular cartilage; displacements under applied loading with MRI (dualMRI); deformation and strain; quantitative MRI

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INTRODUCTION

Medical imaging modalities offer the possibility to noninvasively diagnose and monitor the progression of disease in tissues and organs. Multiple modalities, including radiography, ultrasound, and magnetic resonance imaging, are capable of directly and indirectly visualizing the morphology of articular cartilage, a thin tissue that transmits mechanical force and provides lubricated contact in joints. Unfortunately, these modalities are largely insensitive to subtle morphologic changes, and reliably detect only advanced osteoarthritis (OA), a condition in which articular cartilage progressively degenerates, causing pain and disability for which there is no known cure and for which joint replacement surgery is currently the most effective treatment. It is estimated that 27 million people in the U.S. are affected by this disease (1) with treatment costs estimated over \$80 billion annually (2). The pathogenesis of the disease involves a complex interplay of biomechanical, biochemical, metabolic, and genetic factors, that contribute to the break down the structure of articular cartilage over time. As a result, the mechanical properties and function of cartilage declines, including softening of the tissue (3) and increased friction and wear (4). The etiology of OA, with precise enzymatic and degradative cascades preceding gross tissue structural changes, suggest that imaging modalities offering functional information beyond morphology alone may be required to detect early disease stages.

Considerable emphasis in recent years has been placed on the early detection of OA, in order to develop and provide disease-modifying treatments for afflicted individuals, and minimizing the need for costly and invasive total joint replacement surgery. Modern noninvasive magnetic resonance imaging (MRI) techniques provide valuable information that shows promise for early OA detection (5). Some recent success has been achieved using MRI relaxivity, such as T_2 or $T_{1\rho}$ (6), (7), (8). Relaxivity is sensitive to changes in the structure and concentration of primary cartilage components, such as collagen, proteoglycan, and water (9), (10) and have been shown to increase in mid-to-late stage OA when compared to healthy tissue (6), (11). Unfortunately, relaxivity does not correlate highly with (gold standard) histological semi-quantitative scoring systems (11). Recently, displacements under applied loading by MRI (dualMRI) technology has been developed (12), (13), involving the close synchronization of exogenous mechanical loading with rapid MR acquisitions, to exploit the changes in cartilage structure and mechanical function (e.g. stiffness) known to occur as OA advances (3). The ability of dualMRI to visualize mechanical deformation has previously been demonstrated in bovine articular cartilage explants (12), a whole tibiofemoral joint (14), tissue engineered constructs (15), and an intervertebral disc degeneration model (16). It is yet unknown if dualMRI is capable of differentiating levels of OA severity in human articular cartilage, especially in the early stages of the disease.

In this study, we employed a multicontrast MRI approach utilizing multiple MRI acquisitions to exploit function biomechanical and extracellular matrix content information for the assessment of OA severity in human osteochondral tissues (Figure 1). We combined dualMRI to map spatial patterns of mechanical strain, and magnetic relaxation rates and cartilage morphology using explanted osteochondral tissues exhibiting a wide range of structural integrity from patients with diagnosed osteoarthritis undergoing elective total knee

replacement surgery (Figure 2). The goals of this study were to 1) determine the ability of dualMRI detect early OA as defined by histological assays, 2) compare the potential of dualMRI to that of relaxivity for OA detection, and 3) determine if a multicontrast approach better predicts OA severity compared to any single-contrast approach alone. We hypothesized that individual MRI measures alone would be improved through a combined analysis employing multiple imaging contrasts to assess cartilage disease.

METHODS

Multicontrast MRI

To detect early stage OA, we employed multiple MRI acquisitions (multicontrast MRI; Figure 1) in osteochondral explants (61 total; diameter = 6.0 mm, height = 3.5 mm) obtained from volunteers (8 male, 2 female, 4 unknown, aged 68.1 ± 9.6 years) undergoing total knee replacement surgery following institutional approval (Figure 1). Osteochondral specimens were obtained from standardized regions within the joint, representing a distribution of wear and OA severity (Figure 2). Explants bathed in PBS were scanned using a 14.1 Tesla (T) MRI system (Bruker Medical GmbH) with a 30 mm RF coil. Cartilage morphology was studied using standard rapid acquisition with relaxation enhancement (RARE) and true fast imaging with steady-state precession (TrueFISP, noted here simply as FISP) imaging sequences. MRI relaxivity measures included standard T_1 , T_2 , and $T_{1\rho}$ acquisitions. A novel displacements under applied loading by MRI (dualMRI) technique was employed to assess strain behavior during cyclic loading of the cartilage. Histological assessment followed MR imaging.

Standard MRI

RARE was used to visualize 3D (2D multislice) morphology. RARE parameters were: TR/TE = 3000/8.92 ms; in-plane spatial resolution = $100 \times 100 \mu\text{m}^2$; image matrix size = 256×256 pixels²; number of averages = 1; slice thickness = 1.0 mm, number of slices = 15; flip angle = 180° ; RARE factor = 16. FISP was used to determine tissue morphology in an imaging plane through the center of the explant (Figure 2). FISP parameters were: TR/TE = 3.7/1.85 ms; in-plane spatial resolution = $100 \times 100 \mu\text{m}^2$; image matrix size = 256×256 pixels²; number of averages = 4; slice thickness = 1.0 mm; flip angle = 25° .

Pertinent morphologic features, including thickness, surface angle, and bone angle, were obtained from FISP images using ImageJ (NIH). Because cartilage thickness affects the aspect ratio (height/diameter) of the explants, it was recorded as the distance between the cartilage surface and the bone layer through the depth at the center of the sample. Variability was observed in the surface angle (SA) and bone angle (BA), measured with respect to the horizontal axis of images (Figure 3), due to the harvest procedure and inherent anatomical differences among samples.

MRI Relaxivity

Spatial (pixel-by-pixel) maps of T_1 , T_2 , and $T_{1\rho}$ relaxation time measurements were taken in succession. T_1 imaging parameters were: TE = 8.84 ms, TR = [100, 250, 500, 1000, 2000, 4000] ms, FOV = $2.56 \times 2.56 \text{ cm}^2$, slice thickness = 1 mm, matrix size = 256×256 . T_2 -

weighted images were taken using the same parameters except TE = [10, 30, 50, 70, 90] ms and TR = 1000 ms. $T_{1\rho}$ imaging parameters were: TE/TR = 8.92/2000 ms, spin-lock frequency of 500 Hz, and spin-lock durations of [10, 30, 50, 70, 90] ms. Relaxation times were determined using a monoexponential curve-fitting algorithm in ImageJ (Figure 1). We noted that $T_{1\rho}$ values had poor fits when calculated at individual pixels; consequently all parameters were also evaluated by curve-fitting the averages of the entire region of interest (ROI).

Displacements Under Applied Loading by MRI

The explants were cyclically and intermittently loaded in unconfined compression with a flat platen at 235 kPa and 0.33 Hz until they reached a quasi-steady state load-deformation behavior (12). Displacement-encoded data was noninvasively acquired in the same plane used for morphology and relaxivity measures. A DENSE-FISP imaging sequence (13) was used with a displacement encoding gradient area of $2.13 \pi/\text{mm}$. FISP parameters were identical to those described previously. To account for banding observed due to the pulse sequence and high field strength, data was acquired using repeated experiments and three different phase advance angles (60° , 180° , and 300°). For a complete 2D data set (i.e. with reference and x and y displacement encoding), the total acquisition time was approximately 14.4 min.

MRI-based displacement fields were used to compute finite strains (transverse (E_{xx}), axial (E_{yy}), and shear (E_{xy})) as described previously (12) at a precision of 0.1% strain (13) (Figure 3). In order to provide a single measure that incorporates all three finite strains, Von Mises strains (VMS) were calculated from principle strains (E_1 , E_2).

$$E_{1,2} = \frac{E_{xx} + E_{yy}}{2} \pm \sqrt{\left(\frac{E_{xx} - E_{yy}}{2}\right)^2 + E_{xy}^2} \quad (1)$$

$$\text{VMS} = \sqrt{\frac{1}{2}((E_1 - E_2)^2 + E_1^2 + E_2^2)} \quad (2)$$

To facilitate a statistical analysis, strains were averaged over a middle zone layer (of 30% thickness) where the largest strains were typically observed. Other depth-dependent averages, e.g. strains averaged over a superficial zone layer, produced similar results (data not shown), and were not included in the present analysis. In addition, pixel-wise relaxation parameters were averaged in this same manner.

Histological Assessment

Following multicontrast MRI, the explants were fixed with Bouin's solution (Sigma-Aldrich, St. Louis, MO), defatted using a 70% ethanol solution, decalcified using 10% formic acid in citrate, and embedded in paraffin (4). Full-thickness H&E stained sections were evaluated histologically for OA severity by two independent observers (AJG and CPN) using the OARSI scoring system (17), which assesses OA severity (grade) and horizontal extent (stage). These measures are multiplied to give an OARSI score.

Statistical Analysis

Simple linear regressions were used to identify correlations between multicontrast MRI measures and OA severity. To account for potentially confounding variables, mixed model ANCOVAs were used. dualMRI and MRI relaxivity measures were used as the response variables, with patient was treated as a random variable, and joint region, thickness, SA, BA were classified as fixed effects. For the relaxivity model, SA and BA were omitted, as they had no influence on the relaxivity measures. Residuals from this analysis were then regressed with OA severity to test for a significant relationship between OA severity and each variable after removing the correlating effects of the other variables.

A separate mixed-model ANCOVA was developed to provide a predictive model for OA severity from the multicontrast measures. OA severity served as the response variable and patient was treated as a random effect. The fixed effects included in the model were determined from a larger pool of potential effects using an AIC minimization (18). VMS, whole-mask averages of T_2 and $T_{1\rho}$, region, thickness, SA, and BA were ultimately selected to be included in the model. The predicted OA values based on the best-fit model were then regressed with actual OA scores.

RESULTS

Multicontrast MRI of human osteochondral tissues provided unique and independent measures of cartilage biomechanics and extracellular matrix content in the context of disease (Figure 3). We found that biomechanical parameters alone, i.e. strain measures, were strongly related to OA severity, with improved correlations observed after accounting for covariates (Figure 4). Raw VMS, E_{xx} , and E_{xy} strains were all significant ($p < 0.007$, $R^2 > 0.121$), but not E_{yy} ($p = 0.112$, $R^2 = 0.043$). After controlling for covariates, correlations improved greatly. VMS, E_{xx} , and E_{xy} provided for the strongest overall correlations ($p < 0.001$, $R^2 > 0.212$), with E_{yy} becoming significant ($p = 0.005$, $R^2 = 0.133$).

In general, MRI relaxivity related poorly to OA severity. The pixel-wise relaxation parameters did not significantly correlate with OA score ($p > 0.137$, $R^2 < 0.051$). When we analyzed relaxivity over the whole sample, however, $T_{1\rho}$ did significantly correlate with OA severity ($p = 0.02$, $R^2 = 0.11$) (Figure 5). Unlike the dualMRI values, controlling for potentially relevant factors did not improve MRI relaxivity. In fact, $T_{1\rho}$ was no longer significant after accounting for covariates ($p = 0.085$, $R^2 = 0.067$). Values for the whole-mask fits were: T_1 average = 1852 ms, range = 1406 – 2389 ms; T_2 average = 31.9 ms, range = 13.6 – 113 ms; $T_{1\rho}$ average = 57.4 ms, range = 11.8 – 166 ms.

Morphologic features varied widely across the samples. Cartilage thickness was 2.26 ± 0.56 mm (mean $\pm$ standard deviation), ranging from 1.0 to 4.3 mm. SA ($3.60^\circ \pm 3.99^\circ$) and BA ($5.24^\circ \pm 3.81^\circ$) also varied. These parameters were not significantly related to OA severity ($R^2 = 0.0275$, $p = 0.179$).

Multicontrast MRI better predicted OA compared to any individual parameter alone. When we regressed the model-predicted OA scores with the measured OA scores, we attained an R^2 of 0.482 with high significance ($p < 0.001$) (Figure 6).

DISCUSSION

Medical imaging provides critical noninvasive methods to potentially assess diseased tissues in the early stages. MRI offers excellent soft tissue contrast, especially for cartilage that appears bright with high signal-to-noise ratios for a variety of pulse sequences and acquisitions schemes. However MRI suffers from relatively low spatial resolution (i.e. with pixel dimensions on the order of 200–300 μm in clinical systems) that precludes assessment of subtle structural changes in early OA based on morphology alone. Multicontrast acquisitions advance MRI beyond simple morphology measures, and include the noninvasive assessment of tissue biomechanics and extracellular matrix structure and content, potentially sensitive imaging biomarkers of disease stage. The three main findings of this study were: 1) dualMRI significantly correlated with OA severity, 2) $T_{1\rho}$, but not T_2 or T_1 , correlated with OA severity, but to a lesser extent than dualMRI, and 3) combined multicontrast MRI better predicted OA severity than any of the techniques individually.

dualMRI correlated highly with histologically-defined OA severity. Articular cartilage has been shown to soften with advancing OA (3), and we have successfully demonstrated that strains measured by dualMRI were sensitive to histological changes in OA severity. Von Mises strain provided an efficient method to combine the transverse, axial, and shear strains into a single measure; though the individual strains correlated well with OA on their own, especially after adjusting for covariates. In the cartilage specimens employed in these studies, cartilage thickness was found to influence dualMRI measures, especially for the compressive axial strains (data not shown). This is consistent with prior studies (19), and indicates that cartilage thickness should be accounted for in future clinical studies.

We demonstrated that dualMRI is more representative of OA severity than MRI relaxivity. To our knowledge, this is the first report of significant correlations between noninvasive MRI and histologically-based OA scoring, although several groups have shown significant differences between T_2 and $T_{1\rho}$ and when grouped into either early and late stage OA (11), or early, mid, and late stages (6). We were able to significantly correlate $T_{1\rho}$ with OA severity, though the goodness of fit is fairly low with much unaccounted remaining variability, and controlling for potential covariates causes the significance of the correlation to be lost. It is important to note that relaxation parameters in cartilage are not well documented at 14.1 T; it remains to be determined whether the results shown here will hold at lower (3.0 T) clinical field strengths. Additionally, translation of dualMRI to clinical (e.g. 3.0 T) MRI systems is needed for testing in subjects with OA. Interestingly, our group recently achieved *in vivo* measurement of cartilage strain by dualMRI in a healthy volunteer at 3.0 T (data not shown), overcoming many technical obstacles (e.g. repeated joint loading, spatial resolution limits) and opening up the possibility for animal and human studies of cartilage degeneration in the clinical setting.

Multicontrast MRI, inclusive of multiple imaging biomarkers, provided the best correlation with OA severity. We have shown that including the relaxivity parameters into a predictive model along with dualMRI allows for a greater explanation of the variability seen in the data. Furthermore, because poor exponential fitting precluded the calculation of $T_{1\rho}$ in some samples (which decreased the sample size from 61 to 43), it is possible that correlations

would have further improved (both for $T_{1\rho}$ and multicontrast MRI) with the inclusion of additional data. It should be noted that our current model over-predicts for lower and under-predicts for higher OA severity values. An ideal model would have a best fit line with a slope of one and intercept through the origin. While the current model provides a good estimate of OA severity based on measurable parameters, this remains an area of improvement for future work. Interestingly, our predictive model treated patient as a random effect. The development and application of patient-specific information (e.g. age, gender, BMI, activity level, limb alignment, family history) in future studies may improve the multicontrast MRI predictive ability for early OA.

This study has several limitations. The magnitude of applied stress used was an order of magnitude lower than commonly experienced physiologic levels (20). It is possible that with a physiologic stress, the observed effects would have been magnified. However, the low stress employed in these tests indicates that the imaging methods are highly sensitive to even mild changes in articular cartilage. The low applied stress also minimized potential testing-associated damage in the explants, minimizing artifactual changes in histological OA severity measures. This is supported by the finding that FISP images taken before and after loading displayed no macroscopic changes. An additional limitation is that we were not able to study the full spectrum of OA severity, especially the most advanced stages involving cartilage denudation and bone deformation, as the cartilage required for dualMRI was largely absent in these regions. We noted during histologic scoring using the OARSI method that explants with different morphological features would frequently receive the same score. For example, an explant with severe localized damage can receive the same score as one with more moderate, widespread damage. Differences in structural properties may not be captured by these semi-quantitative histological scoring methods. It is possible that some of the variability in strain correlations with OA severity may be due to such differences. Finally, our use of $TR=1000$ ms for T_2 measurements may lead to a T_1 contribution to these values, although we expect this possibility to contribute minimally to the overall finding of the manuscript.

There is a clinical need for a non-invasive imaging method that is capable of detecting and measuring articular cartilage changes before cartilage loss occurs. These data demonstrate the potential of dualMRI, particularly in conjunction with other imaging biomarkers, to fulfill that need. With further refinement, multicontrast MRI may prove useful in many applications, such as functionally evaluating tissue engineering methods or investigating other load-bearing tissues such as meniscus or ligament.

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Figure 1. Multicontrast MRI was implemented to predict OA severity in human cartilage explants

Multiple imaging techniques were sequentially employed with explants bathed in PBS to assess the utility of this multicontrast approach to predict OA severity. RARE images provided 2D and 3D assessments of morphology. Relaxivity measures (T_1 , T_2 , and $T_{1\rho}$) were determined by curve-fitting monoexponential functions (representative data shown), and provided information on the biochemical makeup of the cartilage. FISP images acquired during the undeformed and deformed states before and after dualMRI were employed to ensure steady-state loading was maintained. DENSE-FISP was used to acquire 2D displacement data during cyclic mechanical loading, revealing the internal mechanics of the cartilage.

Figure 2. Human osteochondral explants with variable OA severity were studied using a high-field 14.1 T MRI system

Tissue was harvested from volunteers undergoing total knee replacement surgery, with institutional approval. A wide range of OA severity was observed within each patient, enabling correlations with MRI measures. Regions of harvest included the anterior femoral (AF) condyles, the posterior femoral (PF) condyles, and the tibial plateau. Explants were bathed in PBS while standard MRI, relaxivity, and dualMRI measures were acquired.

Figure 3. Spatially-dependent multicontrast MRI measures were acquired in each sample and compared to histological assessment of OA severity

Histological assessment by the OARSI methodology (Pritzker et al., 2006) was used to determine OA severity in explants. Finite strains (E_{xx} , E_{yy} , E_{xy}) determined by dualMRI significantly increased with OA severity. While relaxivity measures T_1 and T_2 did not exhibit any significant trend, we demonstrated that $T_{1\rho}$ correlated mildly with OA severity. Here, parameter fields are overlaid on RARE images.

Figure 4. Strain measures significantly correlate with OA severity

Unadjusted VMS, Transverse, and Shear strains significantly correlate with OA score (left), while Axial strains are variable. After controlling for variability introduced by confounding factors such as thickness, patient, location, surface angle, and bone angle, the correlation improves greatly. Axial strain, shown to be highly dependent on thickness, becomes significant after accounting for this relation.

Figure 5. $T_{1\rho}$, but not T_1 or T_2 , significantly correlates with OA score

Relaxation parameters are shown against OA severity. Here, relaxation parameters are calculated by curve fitting ROI averages, rather than averaging curve-fit pixels. Prior to controlling for potential covariates of patient, location, thickness, T_1 and T_2 do not correlate, while $T_{1\rho}$ weakly correlates. After controlling for the potentially confounding variables, trends generally worsened, and $T_{1\rho}$ was no longer significant.

Figure 6. Multicontrast MRI parameters best predict OA

The predicted OA scores of a statistical model that contains VMS, T_2 , $T_{1\rho}$, joint region, thickness, SA, and BA are compared to the measured OA scores. This combined model matches the actual data better than dualMRI or relaxometry individually. In this study, the very latest stages of OA (grey area) were not examined, lending credence to the ability of our technique to detect changes in early OA.