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Cross-relaxation imaging of human patellar cartilage *in vivo* at 3.0T

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SUMMARY

Objective: To compare quantitative magnetization transfer (qMT) parameters of patellar cartilage measured using cross-relaxation imaging (CRI) in asymptomatic volunteers and patients with osteoarthritis.

Design: The study was performed with Institutional Review Board approval and with all subjects signing informed consent. CRI of the knee joint was performed at 3.0T on 20 asymptomatic volunteers and 11 patients with osteoarthritis. The fraction of macromolecular bound protons (f), the exchange rate constant between macromolecular bound protons and free water protons (k), and the T_2 relaxation time of macromolecular bound protons (T_2^B) of patellar cartilage were measured. Mann–Whitney–Wilcoxon rank-sum tests were used to compare qMT parameters between asymptomatic volunteers and patients with osteoarthritis.

Results: Average f, k, and T_2^B of patellar cartilage was 12.46%, 7.22 s^{-1}, and 6.49 μs respectively for asymptomatic volunteers and 12.80%, 6.13 s^{-1}, and 6.80 μs respectively for patients with osteoarthritis. There were statistically significant differences between groups of subjects for k ($P < 0.01$) and T_2^B ($P < 0.0001$) but not f ($P = 0.38$) of patellar cartilage.

Conclusion: Patients with osteoarthritis had significantly lower k and significantly higher T_2^B of patellar cartilage than asymptomatic volunteers which suggests that qMT parameters can detect changes in the macromolecular matrix of degenerative cartilage.

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Introduction

Osteoarthritis is one of the most prevalent chronic diseases in the United States and worldwide[1]. Characteristic changes in the macromolecular matrix of articular cartilage occur during osteoarthritis including a decrease in proteoglycan content and disruption of the highly organized collagen fiber network[2–4]. Techniques to non-invasively assess the cartilage macromolecular matrix would be beneficial in osteoarthritis research studies to monitor disease-related and treatment-related changes in the composition and ultra-structure of cartilage[5]. Sensitive methods to detect early cartilage degeneration would also be useful in clinical practice to identify the cause of joint pain in symptomatic patients[6] and to allow early initiation of interventions such as weight loss, aerobic activity, and range of motion and strengthening exercises which may alleviate symptoms and potentially slow the rate of joint degeneration[7].

Various quantitative magnetic resonance (MR) imaging techniques have been used to evaluate articular cartilage. Multiple techniques including gadolinium enhanced spin-lattice relaxation time (T_1) imaging[8,9], sodium imaging[10,11], spin-lattice relaxation time in the rotating frame (T_{1rho}) imaging[12,13], and chemical exchange-dependent saturation transfer (CEST) imaging[14,15] have been shown to be sensitive for detecting changes in the proteoglycan content of cartilage. However, only a few MR techniques including spin–spin relaxation time (T_2) imaging[16–18] and diffusion tensor imaging[19–22] have been used to identify alterations in cartilage ultra-structure, and all currently used methods have limitations. T2 relaxation time is a nonspecific parameter which is influenced by multiple factors including organization of the

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collagen fiber network[16–18], water and macromolecular content[23–26], and orientation of cartilage relative to the main magnetic field[27]. While diffusion tensor imaging may provide sensitive and specific information regarding cartilage ultra-structure, it is technically challenging and typically requires the use of high field strength scanners and custom made coils which has limited its use for evaluating human articular cartilage *in-vivo*[19–22].

Quantitative magnetization transfer (qMT) imaging is MR technique which utilizes a two-pool model of magnetization exchange to acquire information regarding the cartilage macromolecular matrix[28–30]. qMT imaging techniques typically require multiple MT-contrast images with different magnetization preparatory pulses resulting in long scan times which have limited cartilage assessment to *ex-vivo* specimens[31–33]. Cross-relaxation imaging (CRI) is a qMT method which can create three-dimensional parametric maps of articular cartilage measuring the fraction of macromolecular bound protons (f), the exchange rate constant between macromolecular bound protons and free water protons (k), and the T_2 relaxation time of macromolecular bound protons (T_2^B) with high resolution and relatively short scan time based upon a limited number of MT-contrast images[34–36]. The parameter f provides an indirect measure of macromolecular content, while the parameters k, and T_2^B reflect the efficiency of magnetization exchange between macromolecular bound protons and free water protons and the spin diffusion between proton sites in macromolecules respectively which may be influenced by macromolecular organization and ultra-structure[30,37,38]. We have developed a CRI protocol for evaluating human patellar cartilage *in vivo* at 3.0T which can provide robust measurements of f, k, and T_2^B in a 19 min scan time. This study was performed to compare qMT parameters of patellar cartilage measured using CRI in asymptomatic volunteers and patients with osteoarthritis to determine whether the MR technique can detect changes in the macromolecular matrix of degenerative cartilage.

Materials and methods

Study group

The study was performed in compliance with HIPAA regulations and with approval from our Institutional Review Board. All subjects signed informed consent prior to their participation in the study. The study group consisted of 20 asymptomatic volunteers (15 males and five females between 23 and 45 years of age with an average age of 32.3 years) and 11 patients with osteoarthritis of the knee joint (seven males and four females between 45 and 62 years of age with an average age of 52.6 years). All patients with osteoarthritis of the knee joint complained of chronic knee pain and stiffness for a minimum of 6 months and showed definitive grade 2 osteophytes with no associated joint space loss on standing anterior-posterior radiographs of the knee[39,40]. All patients had mild osteoarthritis within the patellofemoral compartment with six patients showing small grade 1 osteophytes and five patients showing definitive grade 2 osteophytes on the patella and femoral trochlea and no patients showing joint space narrowing on axial radiographs of the knee[39].

MR examination

An MR examination of the knee joint was performed on all subjects in the study group using a 3.0T scanner (Discovery MR750, GE Healthcare, Waukesha, WI) and an eight-channel phased-array extremity coil (In Vivo, Orlando, FL). Foam padding was used to firmly secure the knee within the coil to minimize subject motion during the MR examination. All MR examinations consisted of the following sequences performed in the axial plane through the patellofemoral compartment of the knee joint: (1) the CRI protocol, (2) a frequency-selective fat-suppressed T2-weighted fast spin-echo sequence acquired using a 4050 ms repetition time, 85 ms echo time, 90° excitation flip angle, 31 kHz bandwidth, 14 cm field of view, 256 × 256 matrix, 4 mm slice thickness, and four signal averages, and (3) an SPGR sequence with iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) fat-water separation[41] acquired using a 12.4 ms repetition time, 3.4 ms, 4.2 ms, and 5.0 ms echo times, 14° excitation flip angle, 31 kHz bandwidth, 14 cm field of view, 256 × 256 matrix, 4 mm slice thickness, and one signal average. A frequency-selective fat-suppressed three-dimensional intermediate-weighted fast spin-echo sequence was also performed in the sagittal plane through the knee joint using a 2217 ms repetition time, 23.6 ms echo time, 90° excitation flip angle, 31 kHz bandwidth, 15 cm field of view, 256 × 256 matrix, 1 mm slice thickness, and one signal average. Coronal and axial reformat images were created from the volumetric fast spin-echo source data.

The CRI protocol consisted of six MT-prepared SPGR scans and four non-MT-prepared SPGR scans. The MT-prepared SPGR scans were performed with different combinations of MT offset frequencies and flip angles (2.5 kHz/1550°, 5 kHz/1550°, 10 kHz/1550°, 20 kHz/1550°, 2.5 kHz/890°, and 5 kHz/890°) with an 18-ms Fermi MT pulse, 42 ms repetition time, 3.2 ms echo time, and 13° excitation flip angle. The non-MT-prepared SPGR scans were performed over a range of excitation flip angles (4°, 10°, 20°, and 30°) with a 24 ms repetition time and 3.2 ms echo time. Actual flip angle imaging (AFI) was also performed for flip angle mapping using an SPGR scan consisting of two identical radiofrequency pulses followed by repetition times of 30 ms and 150 ms acquired with a 2.2 ms echo time and 55° excitation flip angle[42]. All SPGR scans were performed using a 31 kHz bandwidth, 14 cm field of view, 256 × 256 matrix for the MT-prepared and non-MT-prepared scans and 128 × 128 matrix for the AFI scans, 4 mm slice thickness, 10 slices, and one signal average. Total scan time for the CRI protocol was 19 min. In order to measure MTR, one additional MT-prepared SPGR scan was performed using the same imaging parameters except for a 250 kHz offset frequency and 1550° flip angle to create negligible MT effect.

Cartilage qMT parameter map reconstruction

Quantitative MR parameter maps of patellar cartilage were reconstructed using in-house software developed in MATLAB (MATLAB 2011b, MathWorks Inc, Natick, MA). Image registration software (FLIRT, Functional Magnetic Resonance Imaging of the Brain Analysis Group, Oxford University, United Kingdom) was used to correct for any subject motion which may have occurred between the multiple scans. MT-prepared SPGR scans, non-MT-prepared SPGR scans, and AFI scans were co-registered using the IDEAL-SPGR scan as the reference. The MT-prepared and non-MT-prepared SPGR datasets were simultaneously fitted on a pixel-by-pixel basis using a non-linear least squares two-pool model to create cartilage f, k and T_2^B maps[35]. Both excitation flip angle and MT saturation power were corrected for each pixel using the flip angle maps acquired from the AFI scans. In addition, cartilage MTR maps were created using a pixel-by-pixel measurement of the difference in the signal of the SPGR scan with negligible MT effect (250 kHz/1550°) and the SPGR scan with strongest MT effect (2.5 kHz/1550°) divided by the signal of the SPGR scan with negligible MT effect[43,44].

Comparison of morphologic and quantitative MR parameters between groups of subjects

Morphologic joint analysis was performed by a fellowship-trained musculoskeletal radiologist with 12 years of clinical

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