Published in final edited form as:

Magn Reson Imaging. 2011 April ; 29(3): 335–341. doi:10.1016/j.mri.2010.10.006.

Quantitative assessment of mobile protein levels in human knee synovial fluid: feasibility of chemical exchange saturation transfer (proteinCEST) MRI of osteoarthritis

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Abstract

Purpose—To establish the feasibility of chemical exchange saturation transfer (proteinCEST) MRI in the differentiation of OA knee joints from non-OA joints by detecting mobile protein and peptide levels in synovial fluid by determining their relative distribution.

Materials and Methods—25 knees in 11 men and 12 women with knee injuries were imaged using whole knee joint proteinCEST MRI sequence at 3 Tesla. The joint synovial fluid was segmented and the asymmetric magnetization transfer ratio at 3.5 ppm $MTR_{asym}(3.5ppm)$ was calculated to assess protein content in the synovial fluid. The 85th percentile of synovial fluid $MTR_{asym}(3.5ppm)$ distribution profile were compared using the independent Student t-test. The diagnostic performance of the 85th percentile of synovial fluid $MTR_{asym}(3.5ppm)$ in differentiating OA and non-OA knee joints was evaluated.

Results—The 85th percentile of synovial fluid $MTR_{asym}(3.5ppm)$ in knee joints with OA was $8.6\% \pm 3.4\%$ and significantly higher than that in the knee joints without OA ($6.3\% \pm 1.4\%$, $P < 0.05$). A knee joint with an 85th percentile of synovial fluid $MTR_{asym}(3.5ppm)$ greater than 7.7% was considered to be an OA knee joint. With the threshold, the sensitivity, specificity, and overall accuracy for differentiating knee joints with OA from the joints without OA were 54% (7/13), 92% (11/12), and 72% (18/25), respectively.

Conclusion—proteinCEST MRI appears feasible as a quantitative methodology to determine mobile protein levels in synovial fluid and identify patterns characteristic for OA disease.

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^{*}The abstract of the study won RSNA Research Trainee Award in December 2008 in Chicago, IL.

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Keywords

Human knee; Osteoarthritis; Synovial fluid; MRI; Chemical exchange saturation transfer; Amide proton transfer

1. Introduction

Osteoarthritis (OA) is a chronic condition characterized by the breakdown and eventual loss of articular cartilage of the joint [1]. It is estimated that nearly 27 million people in the United States are affected by OA and suffer stiffness, pain, and disability of this degenerative disease [2–4]. Efforts to identify disease-modifying OA interventions are important and require reliable imaging markers. The total protein concentration of synovial fluid in patients with OA was found to be slightly elevated compared to normal [5] and the endogenous peptides in synovial fluid was found to be associated with OA [6]. Non-immunoglobulin proteins, such as haptoglobin, α 2-macroglobulin, orosomucoid, transferrin, and ceruloplasmin, exhibit a higher concentration in OA joints compared to normal joints, which was found to correlate with increased capillary permeability in the synovial membrane due to capillary dilation and stasis [7]. The OA-induced accumulation of total protein was found to be alleviated by treatments such as combined hyaluronan and ultrasound treatment [8] and calycosin-7-O- β -D-glucopyranoside injection [9] in a rabbit model.

Protein level is generally measured by collecting synovial fluid via nonsurgical penetration and joint aspiration, which is an invasive procedure with inherent risks and therefore the evaluation of normal synovial fluid is limited [10]. The fluid sample is likely mixed with blood due to traumatic aspiration, which causes difficulty in assessing protein content in the synovial fluid. The non-invasive capabilities of protein content measurement may be achieved by chemical exchange saturation transfer (CEST) MRI. CEST MRI has recently emerged as a new quantitative molecular-MRI technique, in which the magnetization transfer ratio between the chemical exchangeable solute protons and the bulk water protons is determined [11–13]. The CEST MRI technique was first applied to biological tissues by Balaban and his colleagues [14]. They reported exchange between labile protons in low-concentration solute and water protons provides a sensitivity enhancement scheme useful as a new MRI contrast mechanism [15]. CEST MRI has been shown to detect the over-expressed proteins and peptides in brain tumors [16] as well as to detect cartilage glycosaminoglycan concentration [17, 18].

The approach using a CEST sensitivity enhancement scheme for amide protons, called amide proton transfer or proteinCEST imaging, can estimate the concentration of the amide protons in endogenous mobile proteins and peptides via water signal [19–22]. Amide protons in peptide bonds have a resonant frequency of 3.5 ppm offset from water protons, i.e. 448 Hz at 3 Tesla MRI. Amide protons cannot be directly imaged due to low concentration and short T2 relaxation time [23]. In proteinCEST MRI a saturation pre-pulse with different frequency offsets is applied to obtain the magnetization transfer-spectrum, which exhibits both amide-proton-induced water signal decrease (at the offset of 3.5 ppm;

namely the proteinCEST effect) and direct water signal saturation (normally assigned as 0 ppm). Because there is no proteinCEST effect at -3.5 ppm, the asymmetric saturation at ± 3.5 ppm can be used to measure the chemical exchange of amide protons by suppressing other saturation effects concurrent with proteinCEST measurements [22].

The purpose of this study was to establish the capability of proteinCEST MRI to quantitatively measuring mobile protein levels in synovial fluid for differentiating human knees with OA from those without OA.

2. Methods

2.1.1. Patients

Institutional review board approval was granted for this HIPPA-compliant study, and informed consent was waived. 28 patients with knee injury were recruited from the sports medicine clinic of the Ohio State University Medical Center. All patients complained of pain in the study knee. Patients with hemarthrosis were excluded from this study due to the possible effect on protein level of the synovial fluid. Five patients were excluded for the following reasons: a large knee that would not fit into the knee coil in one patient, inadequate image quality caused by motion artifacts or low image resolution in three, incomplete magnet field shimming in one. proteinCEST MR imaging of the knee was performed successfully in 23 patients (11 [48%] men and 12 [52%] women; 31 ± 8 years; range, 17–49 years), in which 12 had a history of previous knee trauma, knee surgery or arthroscopy. Classification on disease state (OA or non-OA knee) was performed by a radiologist based on clinical imaging (MRI and radiographs) and whole knee joint evaluation of the knee independent of this study [24].

2.1.2. MR Imaging Examinations

All patients were imaged in a 3 Tesla MR system (Achieva, Philips) using an 8-channel receiver knee coil. Whole knee joint proteinCEST MRI was acquired using a sagittal turbo spin echo (TSE) sequence with the following parameters: TR/TE = 5625/26 ms; TSE factor = 15; Field of view = 165×165 mm²; Matrix = 224×124 ; Slice thickness = 3 mm; Slice gap = 0 mm; Number of slices = 28–35; Number of signal averages = 1. In this study TSE images were acquired without and with saturation pre-pulses at two frequency offsets (3.5 and -3.5 ppm), composed of a train of sixteen 1400° block pulses with pulse length of 30 ms and saturation amplitude of 130Hz (~ 3.0 μ T). The scan time was 15 min without parallel imaging in first 7 subjects and 5 min with sensitivity encoding (SENSE) factor of 3 in the rest 16 subjects for shorter acquisition since no effect on protein level evaluation was found by compare the acquisitions with and without SENSE on phantom scans. A whole magnetization transfer (MT) spectrum was acquired on one subject using sagittal single-slice single-shot TSE with the following parameters: TR/TE = 5250/84 ms; TSE factor = 56; Field of view = 165×165 mm²; Matrix = 96×77 ; Slice thickness = 4 mm; Number of signal average = 1. MT spectrum was composed of 33 different frequency offsets (-8 to 8 ppm, interval 0.5 ppm) with the acquisition of 3 minutes without parallel imaging. Both proteinCEST-MRI methods were implemented within FDA-regulated SAR limit.

2.1.3. MR Imaging Analysis

The proteinCEST MRI analysis was performed using in-house developed software based on the Interactive Data Language (IDL, ITT Visual Information Solutions, Boulder, CO) environment. When the saturation pre-pulse is applied to amide protons, it may saturate bulk water protons due to the small frequency difference between them (3.5 ppm). Therefore, the magnetization transfer from amide protons cannot be directly measured from the conventional magnetization transfer ratio (MTR) at 3.5 ppm. To reduce the interference of other saturation effects concurrent with proteinCEST measurements, the asymmetric magnetization transfer ratio (MTR_{asym}) at 3.5 ppm was calculated by subtracting MTR at -3.5 ppm from MTR at 3.5 ppm, which was used to detect mobile protein levels:

$$MTR_{\text{asym}}(3.5\text{ppm}) = \frac{S_{\text{sat}}(-3.5\text{ ppm})}{S_0} - \frac{S_{\text{sat}}(3.5\text{ ppm})}{S_0},$$

where S^{sat} and S^0 are the water signal intensities measured with and without the saturation pre-pulse, respectively [25]. $MTR^{\text{asym}}(3.5\text{ppm})$ has been shown to be highly sensitive to magnetic field B^0 inhomogeneity. Correction of inhomogeneity of the magnetic field B^0 was implemented by volume shimming or finding the minimum in a whole MT spectrum. For the case with a whole MT spectrum, a region of interest was drawn in the synovial fluid and the corresponding spectrum was fit using a least-square polynomial of order 20. Using the fit coefficients, the calculated magnetization transfer spectrum was interpolated into 1601 offsets with an offset resolution of 0.01 ppm. The frequency offset at the minimum of the interpolated magnetization transfer spectrum was defined as the water resonance frequency (B^0), from which the whole spectrum was shifted and $MTR^{\text{asym}}(3.5\text{ppm})$ was calculated.

The synovial fluid has much higher signal intensity than bone marrow and fat on the images with saturation pre-pulse at -3.5 ppm due to being close to fat resonance frequency. A threshold was manually adjusted until the separation between the synovial fluid and fat tissues was achieved by visual inspection. Furthermore, the non-synovial fluid tissues, such as small vessels or cysts, were manually removed from the images. The rest voxels with high signal intensity were categorized as synovial fluid, and the sum of voxel volumes defined to be the volume of the synovial fluid.

$MTR_{\text{asym}}(3.5\text{ppm})$ maps were visualized by three-dimensional reconstruction of the segmented synovial fluid voxels. $MTR_{\text{asym}}(3.5\text{ppm})$ values were then tabulated in a pixel histogram and the 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ was calculated. The reader was blinded to the patient diagnosis.

2.1.4. Statistical Analysis

$MTR_{\text{asym}}(3.5\text{ppm})$ showed spatial inhomogeneity in synovial fluid and the 85th percentile level in synovial fluid distribution was defined as the lower boundary of high synovial fluid protein and peptide concentration. The independent Student t-test was used to compare the 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ in patient knees with OA and those without OA. To evaluate the diagnostic performance of the 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ in differentiating knee joints with OA and knee joints without OA,

receiver-operating-characteristics (ROC) analysis was performed. Thereafter, the area-under-the-curve of the 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ was evaluated. From the ROC curve, the optimal cutoff value showing the best separation between joints with and without OA was extracted. The sensitivity, specificity, and overall accuracy corresponding to the cutoff value were calculated. P-values less than 0.05 were considered to indicate a significant difference. Statistical analyses were performed by using SPSS software (SPSS 16.0; SPSS Inc, Chicago, IL, USA).

3. Results

The overall characteristics of the 23 patients imaged with knee proteinCEST MRI are shown in Table 1. There was no significant difference in patient age or weight between patients with OA of the knee (n=11) and those without OA of the knee (n=12). A total of 25 whole knee joint proteinCEST MRI data sets were obtained with both injured knees imaged in two patients. The average synovial fluid volume segmented from knee proteinCEST MRI was 9.3 ± 10.5 mL with the range from 1.7 mL to 36.3 mL, as 3-dimensional volume visualized in Fig 1b and 2b. There was no significant difference in synovial fluid volume between knees with OA (8.1 ± 9.6 mL, range: 2.1–32.7 mL) and those without OA (10.7 ± 11.8 mL, range: 2.8–36.2 mL, $P = 0.55$).

In the case with a whole MT-spectrum, $MTR_{\text{asym}}(3.5\text{ppm})$ was 2.5% on synovial fluid ROI, indicating the presence of mobile proteins and peptides detectable by proteinCEST-MRI (Fig. 1). The spatially inhomogeneous distribution of $MTR_{\text{asym}}(3.5\text{ppm})$ in knee synovial fluid is shown in Fig. 2 and 3. The 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ in the knee joints with OA was $8.6\% \pm 3.4\%$ (range: 3.7% to 15.6%), which was significantly higher than that in the knee joints without OA ($6.3\% \pm 1.4\%$, range: 4.4% to 10.0%, $P < 0.05$), as shown in Fig. 4.

The area under the ROC curve for differentiating knee joints with OA from the joints without OA is 0.73 (standard error: 0.10; 95% Confidence Interval: 0.53–0.93; Fig. 5). From the ROC curve, an 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ of 7.7% was determined as a cutoff value for differentiating knee joints with OA from those without OA. Therefore a knee joint with an 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ greater than 7.7% was considered to be an OA knee joint.

With this threshold from the ROC curve, the sensitivity, specificity, and overall accuracy for differentiating knee joints with OA from the joints without OA were 54% (7/13), 92% (11/12), and 72% (18/25), respectively.

4. Discussion

This study investigated the feasibility of proteinCEST-MRI for non-invasively measuring protein and peptide levels in knee synovial fluid. The 85th percentile of synovial fluid $MTR_{\text{asym}}(3.5\text{ppm})$ of knee joints with OA was significantly higher than that of knee joints without OA. Our results are in agreement with previous lab reports, which showed the mean total protein in OA patients was 3.1 g/dL, higher than in normal patients with a mean value of 1.7 g/dL [5]. The ROC analysis showed high specificity of the 85th percentile of synovial

fluid $\text{MTR}_{\text{asym}}(3.5\text{ppm})$ cutoff level to differentiate between knee joints with and without OA. Based on these results, we suggest that the 85th percentile of synovial fluid $\text{MTR}_{\text{asym}}(3.5\text{ppm})$ is a feasible cutoff as non-invasive tool to identify OA in knee joints.

Our results shows the significant difference in the 85th percentile of synovial fluid $\text{MTR}_{\text{asym}}(3.5\text{ppm})$ between OA and non-OA knees. All other percentiles including the median did not exhibit any significant difference between OA and non-OA knees, except the 90th percentile showing a weak but significant difference. The 85th percentile of synovial fluid $\text{MTR}_{\text{asym}}(3.5\text{ppm})$ instead of the mean or median was selected as a criteria to differentiate OA. This does not have any clinical or research precedent for use since this study is the first evaluation of proteinCEST-MRI of synovial fluid. One of the reasons could be the spatial inhomogeneity of mobile protein and peptides in the synovial fluid, as illustrated in $\text{MTR}_{\text{asym}}(3.5\text{ppm})$ maps (Fig 2b and Fig 3b). Cellular components in the synovial fluid were found to be influenced by gravitational forces and settle into the more steep parts of the joint at rest [10]. Similarly, the protein and peptide concentration distribution in the synovial fluid may be affected by these factors. The criteria selection may be limited by the small population of this study. A larger population analysis needs to validate this threshold to ensure the proper assessment of the protein and peptide spatial distribution in the synovial fluid.

The MRI-detectable mobile protein and peptide concentration in synovial fluid was found to be significantly higher in a limited number of patient knee joints with OA. The patient population in this study was relatively young (35 ± 9 years) and may only show mild osteoarthritis and less elevated mobile protein and peptide concentration. In future studies, and older population and larger number of patients will be included for assessing the capability of proteinCEST MRI on OA management.

One limitation of this study is that the correlation of the mobile protein and peptide concentration in synovial fluid with the grade of OA has not been evaluated. Such grading can be accomplished using quantitative and semiquantitative assessment measures [24, 26]. Another limitation of the study is that proteinCEST MRI results were not compared with ex vivo protein concentration evaluation because synovial fluid aspiration was not performed. Furthermore, while proteinCEST MRI determines overall mobile protein and peptide concentration in synovial fluid, it does not allow for sub-classification of proteins contributing to the $\text{MTR}_{\text{asym}}(3.5\text{ppm})$.

In conclusion, proteinCEST MRI is feasible as a quantitative methodology to assess mobile protein and peptide levels in synovial fluid of knee joints and differentiate OA disease. This methodology has the potential for validation as a quantitative imaging marker for diagnostic characterization and assessment of response to therapeutic interventions of OA.

Acknowledgments

Source of support:

Wright Center of Innovation in Biomedical Imaging and OSUMC Imaging Signature Program at the Ohio State University, Columbus, OH

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Figure 1.

MT-spectrum of synovial fluid from one subject. (A) Sagittal single-slice single-shot T2-weighted image was acquired with a research pre-pulse at 33 different frequency offsets. A region of interest was placed on the synovial fluid region. (B) MT-spectrum of the region of interest shows the saturation of the water resonance as a function of saturation frequency with respect to water. Signal attenuation is due mainly to direct water saturation close to the water frequency and the solid-like MT effect over the whole spectral range. The MT-spectrum is asymmetric, and when one compares the positive and negative offsets in the 2–3.5 ppm region, there are noticeable drops on the positive side. (C) MTR_{asym} spectrum shows the positive values in the 2–3.5 ppm offset range from water, corresponding to the MRI-detectable mobile protein and peptide concentration in synovial fluid.

Figure 2.

MTR_{asy}(3.5ppm) map in knee synovial fluid and pixel histogram of MTR_{asy}(3.5ppm) in a patient with OA of the knee. (A) Sagittal MR image overlaid with MTR_{asy}(3.5ppm) in color. (B) Three-dimensional visualization of MTR_{asy}(3.5ppm) values in synovial fluid. (C) Pixel histogram showing a wide range of pixel MTR_{asy}(3.5ppm) values. The 85th percentile MTR_{asy}(3.5ppm) was 10.7% showing high protein and peptide concentration in knee synovial fluid.

Figure 3.

MTR_{asym}(3.5ppm) map in knee synovial fluid and MTR_{asym}(3.5ppm) pixel histogram in a patient without OA of the knee. (A) Sagittal MR image overlaid with MTR_{asym}(3.5ppm) in color. (B) Three-dimensional visualization of MTR_{asym}(3.5ppm) values in synovial fluid. (C) Pixel histogram with a smaller 85th percentile MTR_{asym}(3.5ppm) than Figure 2 confirms lower protein and peptide concentration.

Figure 4.

The 85th percentile of synovial fluid MTR_{asym}(3.5ppm) was significantly different in patient knees without OA and those with OA while there was overlap.

Figure 5. Receiver-operating-characteristics (ROC) curve using the 85th percentile of synovial fluid MTR_{asym}(3.5ppm) for the differentiation of knee joints with OA from the joints without OA. The area under the ROC curve is 0.731 (standard error: 0.103; 95% Confidence Interval: 0.530–0.932).

Table 1

Characteristics in 23 Patients with proteinCEST MRI of the Knee

Characteristics	Without Knee OA (n=12)	With Knee OA (n=11)	P Value
Age (years)	28 ± 6 (17–39)	35 ± 9 (22–49)	.05
Weight (kg)	82 ± 22 (39–115)	85 ± 18 (64–113)	.73
Sex	5 male/7 female	6 male/5 female	.54 [*]

Note.---Values for age, weight and synovial fluid volume are average ± standard deviation and numbers in parentheses are ranges;

^{*} Chi-square test.