CEST MRI of Human Knee Cartilage at 3T and 7T

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INTRODUCTION

Osteoarthritis (OA) is one of the debilitating joint diseases of the musculoskeletal system. It is generally believed that the initiating event of OA is predominantly due to loss of proteoglycans (PG) from the tissue (1). In order for appropriate therapeutic intervention in OA, there is a critical need for diagnostic methods that quantify the early molecular changes in cartilage before the manifestation of morphological changes. Recently, it has been shown that chemical exchange saturation transfer (CEST) of labile –OH protons on glycosaminoglycans (GAG) with bulk water leads to a significant reduction of bulk water magnetization (WM) creating "gagCEST" (2). It is well known that the B_0 inhomogeneity would significantly affect the accuracy of the computed CEST values (3-5). In the current study, the feasibility of performing gagCEST on human cartilage *in vivo* was evaluated at 3T and 7T field strengths before and after the correction of B_0 inhomogeneity. Saturation pulse parameters were optimized to obtain maximal gagCEST in human cartilage and numerical simulations were performed to examine the effects of direct saturation (6) of water as well GAG –OH protons on the observed gagCEST.

MATERIALS AND METHODS

In CEST experiments, the CEST effect of the solute spins is computed generally using following equation: $CEST_{asy}(\Delta\omega)=100*[M_{sat}(-\Delta\omega) - M_{sat}(+\Delta\omega)]/M_0$ *[1]*, where M_0 is the WM without saturation, M_{sat} ($\pm\Delta\omega$) are the WM obtained with saturation at a '+' or '–' $\Delta\omega$ offset of the water resonance. Since the CEST asymmetry is based on the subtraction of images, any asymmetry created with local B_0 variation will contaminate the observed CEST asymmetry. Hence, a very good estimate and correction of local B_0 inhomogeneity is imperative to get accurate CEST asymmetry. The pulse sequence used in current study consists of a frequency selective saturation pulse train (SPT) (user selected saturation offset frequency ($\Delta\omega$), saturation duration and B_{1rms}) followed by a chemical shift selective fat saturation pulse and a segmented RF spoiled GRE readout acquisition with centric phase encoding order. At the end of the acquisition, a variable delay has been added to provide T1 recovery. The SPT is composed of Hanning windowed rectangular pulses and delays between them. At 3T a 48 ms pulse with a 2 ms delay is used where as at 7T a 99.8 ms pulse with a 0.2 ms delay is used. The number of pulses in the train can be adjusted to provide variable saturation duration. The peak B_1 of the Hanning windowed pulse is set to provide the required B_{1rms} value.

***Human Studies*:** The study was conducted under an approved Institutional Review Board protocol of the University of Pennsylvania. Five subjects were taken from a normal population in the age range of 28-40 yrs. CEST imaging of the human knee were performed at 3T on a Siemens clinical scanner and at 7T on a Siemens research scanner. The actual study protocol consisted of the following steps: a localizer, WASSR (4), z-spectral or CEST acquisitions and B_1 data collection. For WASSR acquisitions, $\Delta\omega$ range of -1 to +1 ppm with step size of 0.05 ppm was used. For z-spectrum acquisitions, $\Delta\omega$ range of -5 to +5 ppm with step size of 0.1 ppm was used. For CEST acquisitions, a limited $\Delta\omega$ range required for B_0 correction was used. This range was based on a quick inspection of dark regions in raw WASSR images (on scanner) at different $\Delta\omega$. Typical $\Delta\omega$ ranges used for CEST acquisitions were -1.7 to -0.3 ppm and 0.3 to 1.7 ppm with 0.1 ppm steps. For WASSR acquisitions, a 0.2 s SPT with B_{1rms} of 0.13 μT was used in all cases. For z-spectral data, a 0.5 s SPT with a B_{1rms} of 2.2 μT was used with the same volunteers (n = 2) at 3T and 7T. For investigating the effects of saturation parameters, multiple CEST images were collected on two volunteers at both 3T and 7T using saturation pulses with B_{1rms} of 0.4 μT, 0.7 μT, 1.4 μT, 2.2 μT and 2.9 μT over a duration range of 0.1–2s. CEST imaging was performed with 4 volunteers on both 3T and 7T using the imaging protocol as described above with an optimal saturation duration of 0.5 s and B_{1rms} of 2.2 μT.

***Data analysis*:** All image processing and data analysis was performed using in-house programs written in MATLAB. Acquired CEST data (at $\Delta\omega = \pm 1.0$ ppm) or z-spectral data (typically -5.0 to +5.0 ppm) were directly used to generate gagCEST maps or z-spectral asymmetry curves using Eq. [1] to get data without B_0 correction. The mean and SD of gagCEST or CEST asymmetry values were calculated over the small ROI drawn on cartilage in the image. The gagCEST map was overlaid on off-resonance image. B_0 map was computed using WASSR data (4). Acquired CEST data (at offset frequencies, typically +0.3 to +1.7 ppm and -0.3 to -1.7 ppm) or z-spectral data (typically -5.0 to +5.0 ppm) were smoothed and interpolated using a cubic spline to generate data with a step size of 0.01 ppm. For B_0 inhomogeneity correction, each voxel data value at $\Delta\omega$ ppm was replaced by the interpolated data value from ($\Delta\omega - \delta\omega$) ppm. Either z-spectral asymmetry curves or CEST maps (based on the data from ±1.0 ppm) were generated using Eq. [1].

***Simulations*:** Bloch McConnell equation solvers with two exchanging components (water and GAG) were written in MATLAB for analyzing the effects of CEST and DS with the same saturation pulses as used in the experiments (14). Simulation parameters: for water, concentration = 88M, T1 = 1.2s at 3T and 1.5 s at 7T, T2 = 0.038s at 3T and 0.032s at 7T. For GAG, exchange rate (k_{ex}) = 1000Hz, concentration = 0.3M, T1 = s, T2 =0.01s and chemical shift =1 ppm.

RESULTS AND DISCUSSION

gagCEST contrast calculated using optimal saturation parameters without B_0 correction show large effects (>20%) while after B_0 correction it was negligible at 3T and ~6% at 7T. Simulated CEST asymmetry spectra show that the theoretical gagCEST expected at 3T is 0.5% at 1.0 ppm while at 7T it is 5.8%. This is in line with the experimental results reported above. The reported –OH protons exchange rate k_{ex} of 1000 s^{-1} (7) is in fast exchange regime at 3T whereas it is in slow exchange regime at 7T. Additionally, at 3T, higher DS of water protons and DS of GAG protons when saturating at -1ppm reduce gagCEST sensitivity. Since GAG loss from cartilage is expected to result in a further reduction in gagCEST, this method is not expected to lead to accurate quantification of GAG content in healthy or degenerated cartilage at 3T. Given its magnitude (~6%) gagCEST at high fields such as 7T holds promise as a clinically viable technique.

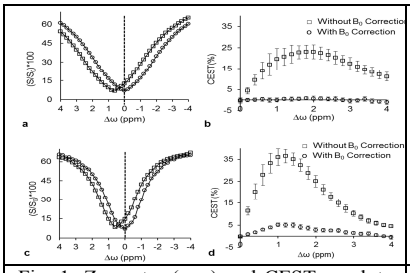

Fig. 1: Z-spectra (a, c) and $CEST_{asym}$ plots (b, d) of human knee cartilage obtained at 3T and 7T respectively.

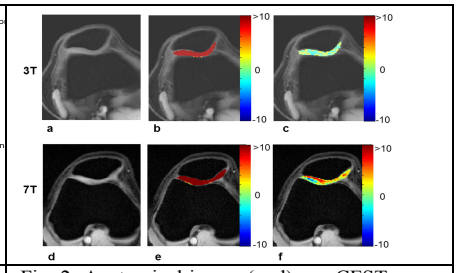

Fig. 2: Anatomical image (a, d), gagCEST maps of cartilage obtained without (b, e) and with correction (c, f) for B_0 inhomogeneity.

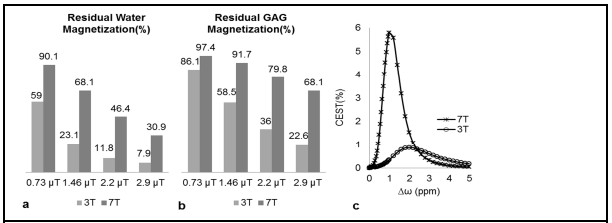

Fig. 3: Simulation results. (a) Residual water magnetization (%) after a 0.5s saturation duration with different B_{1rms} values applied at a 1ppm offset symmetrically around water (b) Residual GAG magnetization (%) at -1 ppm offset from water. (c) Asymmetry plot for a 0.5s duration saturation with B_{1rms} =2.2μT.

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