Assessment of glycosaminoglycan distribution in human lumbar intervertebral discs using chemical exchange saturation transfer

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Objective: Low back pain is a global concern with tremendous socioeconomic implications which may severely diminish functional activity, decrease quality of life, lead to loss of wages, and increase health-care costs [1]. Intervertebral disc (IVD) degeneration is a factor strongly associated with low back pain. Composed of a central nucleus pulposus (NP) rich in proteoglycan (PG) content (protein core with glycosaminoglycans (GAGs)) and an outer fibrous annulus fibrosus (AF), the IVD has been noted to degenerate as characterized by biochemical and morphological changes [2-3]. Loss of GAGs is known as an initiating factor in degenerative disc disease (DDD), followed by the reduction of the osmotic pressure and shrinkage of the disc height as a consequence. As it has been suggested that treatment can only stop disc degeneration but not reverse it, it is essential to diagnose early degenerative changes at the stage of GAGs loss by non-invasively quantifying the GAGs content. This is not possible using the sequences currently used in routine practice. Recent studies have proposed that chemical exchange saturation transfer (CEST) can be specific for GAGs content (gagCEST) [4, 5]. However, gagCEST of the large volume of body parts is challenging at a standard clinical magnetic resonance (MRI) scanner. This is because low spectral resolution at 3 Tesla (3T) makes correction of magnetic field inhomogeneity difficult, especially when the chemical shift difference between solute protons and water frequency is relatively small, as is the case for the hydroxyl (OH) protons of GAGs. The purpose of this study is to show the feasibility of quantifying gagCEST values in human IVDs using a 3T clinical MRI system for the first time, to our best knowledge.

Materials and Methods: After informed written consent was obtained, twelve healthy volunteers (5 females, 7 males; mean age = 30; ± standard deviation (SD) = 9 years; age range = 25-53 years) with no history of lumbar DDD were recruited. Axial images of L3/L4, L4/L5 and L5/S1 levels of each subject were acquired using a 3T Achieva scanner (Philips Healthcare, Best, The Netherlands) with body coil transmission, phased-array coil reception and high order shimming. Thirty non-degenerated discs of the lumbar spine with DDD = 0 graded on T_2-weighted (T_2W) MRI according to Schneiderman's classification [6] by two raters were selected (10 discs for each level) and six discs with DDD = 1 or above were excluded for data analysis. For series of consecutive water saturation shift referencing (WASSR) [7] as for B_0 inhomogeneity correction and CEST scans, saturation was accomplished using a block pulse before the turbo spin echo (TSE) acquisition. Single-slice TSE imaging was performed using 36 offsets for both WASSR (range: 1 to -1 ppm) and CEST (range: 2 to -2 ppm). Imaging parameters: TR, 2000 ms; TE, 6 ms; TSE factor, 34; slice thickness, 8 mm, pixel size, 2 x 2 mm^2. RF saturation pulses: 100 ms and 0.1 μT for WASSR, and 400 ms and 0.75 μT for CEST). Total scan time was 2 min. 26 sec. for each scan. For data analysis, a custom-written program in Matlab (Mathworks, Natick, MA, USA) was used. For each voxel, CEST curves were shifted using the frequency shift from the WASSR map. The magnitude of the CEST effect was quantified as $MTR_{asym} = S(\text{-freq})/S_0 - S(\text{freq})/S_0$ where S and S_0 are the saturated and non-saturated intensities. CEST signal was integrated from 0.5 to 1.5 ppm, where OH groups resonate.

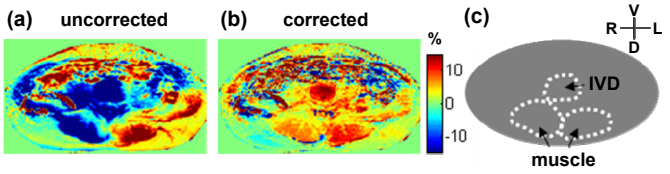

Fig. 1. CEST maps of abdomen including IVD and muscle (a) before-, (b) after-WASSR correction and (c) layout of anatomical regions. Abbreviations: R, right; L, left; V, ventral; D, dorsal.

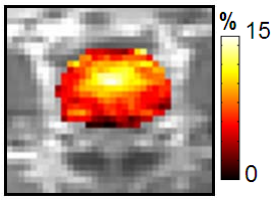

Fig. 2. Axial CEST color map of the IVD (L3/L4).

Results: Fig. 1 shows CEST maps of human abdomen including lumbar IVD before and after WASSR correction and demonstrates that large spatial intensity fluctuation over the entire abdomen was remarkably improved. Note that symmetric CEST signal especially over the muscle indicates that inhomogeneity correction was well performed and that CEST value on the IVD is reliable for our purposes. Fig. 2 illustrates a representative color map of *in vivo* human IVD, showing the spatial distribution of the CEST signal as well as robust contrast between NP and AF regions. Mean CEST values of [NP, AF] for L3/L4, L4/L5 and L5/S1 were [7.95 %, 6.50 %], [6.02 %, 5.22 %] and [3.08 %, 1.98 %], respectively (Fig. 3). CEST values were significantly greater in the NP than in the AF for all three IVD levels ($p < 0.005$ at L3/L4; $p < 0.05$ at both L4/L5 and L5/S1 using two-tailed paired student's t-test). A trend of decreasing CEST values from L3/L4 to L4/L5 to L5/S1 was evident.

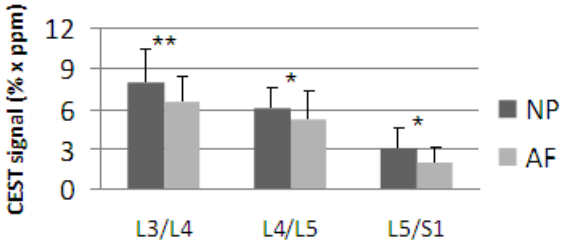

Fig. 3. Mean CEST signal of NP and AF (N = 12; 30 discs). The error bar represents the SD. Significant differences between groups are indicated by * $p < 0.05$ and ** $p < 0.005$.

Conclusion: The results of this study suggest that *in vivo* gagCEST quantification in human lumbar IVDs is feasible at 3T with the successful magnetic field inhomogeneity correction and may potentially be a useful clinical tool in identifying early degenerative changes in the IVDs.

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