Assessment of glycosaminoglycan content in lumbar intervertebral discs with chemical exchange saturation transfer imaging: comparison with T1-rho measurement

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Target audience: Researchers and clinicians interested in CEST imaging and T1-rho measurement especially in musculoskeletal area.

Purpose: The degeneration of IVDs is the most common cause of low back pain. Glycosaminoglycan (GAG) is one of the major components of discs and plays a crucial role in spinal physiology. Reduction of GAG is thought to occur at early stage of IVD degeneration. So far, there have been several methods for classifying degree of IVD degeneration previously including qualitative morphological assessment and quantitative measurements such as relaxation times. Previous studies showed that T1-rho correlated with GAG content in the nucleus pulposus[1], and had wider dynamic range than T2 to detect early degeneration of IVD[2]. Glycosaminoglycan CEST (gagCEST) imaging is an emerging molecular MR imaging technique to directly measure in-vivo GAG content in cartilaginous tissue[3]. The feasibility of this method for IVD degeneration has been demonstrated in several studies; however, its reliability for quantitative assessment has not been evaluated. Therefore, the purpose of this study was to evaluate the utility of this method in assessments of lumbar intervertebral disc degeneration (IDD) by comparing with T1-rho, an established quantitative biomarker of IDD, and conventional morphological assessments.

Methods: *Subjects:* Sixty-four IVDs (L2-3, L3-4, L4-5, L5-S1) in 16 volunteers (35.7±7.4 year-old, 15 males and 1 female) were examined with both gagCEST imaging and T1-rho measurements.

MRI: MRI was conducted in a 3T clinical scanner (Achieva TX 3.0T, Philips Healthcare, NL) using an 8-channel head coil for signal reception and 2-channel parallel transmission via the body coil. Acquisition software was modified to alternate the operation of the two transmission channels during the RF saturation pulse and to allow a special RF shimming for the saturation homogeneity of the alternated pulse (identical mean B1 level per channel)[4]. Saturation pulse-trains: 50ms sinc-gaussian elements, $B_{1,rms}$=0.8μT. 2D fast spin-echo sequences with driven equilibrium refocusing were used. The imaging parameters were as follows: T_{sat}=1.0s, TR/TE=5500ms/6ms, FOV (250 mm)^2, matrix 168^2, resolution 1.5×1.5×5 mm, 25 saturation frequency offsets S[ω], ω=-3 to 3ppm (step 0.25ppm) and S_0 (ω=-160ppm), affording scan time of 2min34s. ΔB_0 maps for off-resonance correction were acquired separately (identical geometry, 2D GRE, ΔTE=10ms, TR/TE=24ms/8.1ms, 16 averages, 55s). T1-rho measurements were performed with 3D gradient-echo sequence with 5 spin lock times (TSLs = 1, 25, 50, 75, 90ms). The other imaging parameters are as follows: shot interval=6s, TR/TE=4.7ms/2.4ms, FOV (250 mm)^2, matrix 128^2, resolution 1.8×1.8×5 mm, number of slice = 3, NSA = 1.

Image Analysis: Maps of the magnetization transfer ratio asymmetry: (MTR_{asym})=(S[- α ppm]-S[+ α ppm])/S0 were calculated with a point-by-point δB0 correction using a with the software program ImageJ (version 1.43u; National Institutes of Health, Bethesda, MD) and a self-made plugin. The gagCEST (%) was defined as an average MTR_{asym} obtained at from +0.5 to +1.5 ppm. The T1ρ imaging signals corresponding to 5-different TSLs were fitted mono-exponentially. The signal intensity S in T1ρ weighted image was represented by the following formula: $S = S_0 \times \exp(-TSL/T_{1\rho})$, where S_0 is the signal intensities when the TSL is zero. Quantitative T1ρ maps were generated using Philips Research Integrated Development Environment (PRIDE) software written in Interactive Data Language (IDL 6.3, ITT Inc., Boulder, CO). Region-of-interests were placed to include the nucleus pulposus of each IVD.

Results and Discussion: The number of intervertebral discs with Pfirrmann grading 1, 2, 3, 4, and 5 was 19, 22, 7, 13, and 3, respectively. Z-spectrum analysis (**Fig. 1A**) demonstrated that degenerated IVDs (Pfirrmann grade 3-5) showed reduced S/S0 in all frequency range compared with non-degenerated IVDs (Pfirrmann grade 1 and 2). The peaks of MTR_{asym} were observed at 0.65, 0.86, and 0.78 ppm in Pfirrmann grade 1, 2, 3, respectively, and the values decreased with the grade (**Fig. 1B**). Both gagCEST and T1-rho decreased with the degeneration of IVDs (**Fig. 2**). GagCEST imaging was able to detect the difference in MTR_{asym} between grade 1 and 2. GagCEST value in Pfirrmann grade 3 is around zero and those in grade 4 and 5 were negative. Both gagCEST values (R^2 = -0.62, P < 0.0001, Spearman rank correlation) and T1-rho (R^2 = -0.79, P < 0.0001, Spearman rank correlation) correlated with Pfirrmann grades. GagCEST values significantly correlated with T1-rho (r = 0.63, P< 0.0001, linear regression) in lumbar intervertebral discs (**Fig. 3**). **Figure 4** demonstrates that the degenerated IVD at L4-5 shows shortened T1-rho and reduced gagCEST. GagCEST was able to detect early degeneration of IVDs. GagCEST can be a reliable and quantitative marker to monitor the IVD degeneration and thus treatment effect (e.g. stem cell therapy).

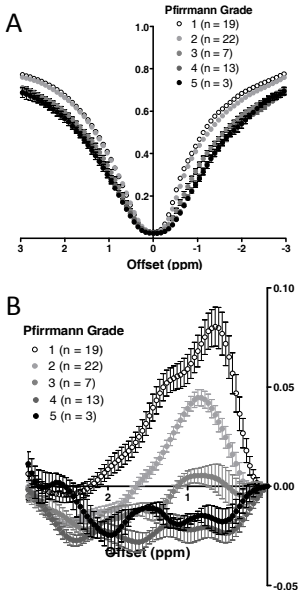

Figure 1. Z-spectra (**A**) and MTR asymmetry (**B**) in the progression of IVD degeneration.

Conclusion: GagCEST correlated with T1-rho and Pfirrmann grades in lumbar IDD. GagCEST can provide a quantitative measure to assess degeneration of IVDs.

References: 1. Johannssen W et al., Spine (2006), 2. Blumenkrantz G et al. MRM (2010), 3. Ling W et al. PNAS (2008), 4. Keupp J et al. ISMRM (2011)

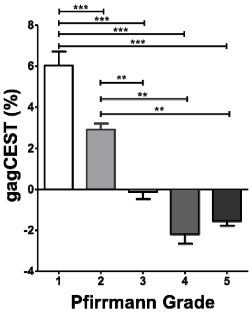

Figure 2. GagCEST at each Pfirrmann grade. GagCEST decrease with the degeneration.

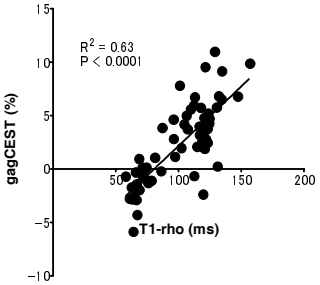

Figure 3. Correlation between T1-rho and gagCEST

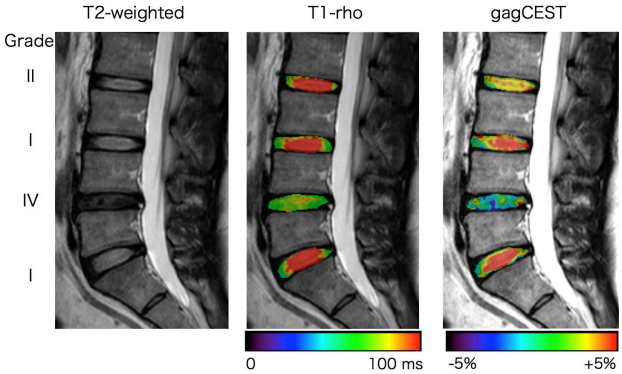

Figure 4. 29-year-old- man with low back pain. Note that the degenerated IVD (Pfirrmann grade 4) at L4-5 shows shortened T1-rho and reduced gagCEST compared with other normal IVDs.