

Magnetic Resonance Imaging of Viscosupplements: A Preliminary Report

Mohammad Haris^{1,2}, Anup Singh¹, Kejia Cai^{1,3}, J. Bruce Kneeland⁴, Fotios Tjoumakaris⁵, Hari Hariharan¹, and Ravinder Reddy¹

¹CMROI, Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States, ²Research Branch, Sidra Medical and Research Center, Doha, Qatar,

³CMRR 3T Research Program, University of Illinois at Chicago, Chicago, IL, United States, ⁴Radiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States, ⁵Sports Medicine at Rothman Institute, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, United States

Background:

Osteoarthritis (OA) is a chronic progressive condition characterized by loss of cartilage, changes in synovial fluid within the affected joint and increasing pain and disability. With increased understanding of the pathogenesis of OA, new therapies are being developed, one of which is intra-articular injection of viscosupplementation with hyaluronic acid. In recent years, the concept of viscosupplementation has gained widespread acceptance as a new treatment for the management of OA of the knee. Although these agents were originally developed to increase lubrication for the joints, the anecdotal observation of much longer treatment effect than believed likely from that mechanism has long suggested the existence of an additional mechanism, likely involving an effect on the glycosaminoglycans. Studies have revealed that exogenous hyaluronic acid stimulates *de novo* synthesis of hyaluronic acid, and inhibits the expression and quantity of cartilage degrading enzymes. In a recent study, decreased cartilage T2 relaxation time has been shown after intra-articular injection of hyaluronic acid in a rat model of OA. However, to date there are no *in vivo* studies demonstrating the potential of these molecules in influencing molecular changes in articular cartilage. Recently, feasibility of mapping the glycosaminoglycan (GAG) concentration in human knee cartilage through chemical exchange saturation transfer (CEST)¹ has been evaluated both at 3T and 7T human scanner². Therefore, using the CEST it is possible to probe the changes in knee cartilage GAG concentration *in vivo* after intra-articular injection of viscosupplementation at 7T. In the current study, our objective is to evaluate the CEST effect from the two popular viscosupplements (Hylan gf-20 (Synvisc) and hyaluronan (Orthovisc)) by exploiting the exchangeable hydroxyl groups present on these molecules at 7T human scanner.

Materials and Methods:

For this study we used two brands of viscosupplements i.e. hylan gf-20 (Synvisc, Genzyme Biosurgery) and high molecular weight hyaluronan (Orthovisc, DePuy Mitek). Orthovisc has a lower molecular weight than Synvisc but contains a higher concentration of hyaluronic acid per injection than Synvisc. Both products have already shown their treatment efficacy in reducing pain associated with OA and are considered high molecular weight hyaluronic acid compounds^{3,4}. The CEST imaging was performed on a 7T Siemens whole body MRI scanner (Siemens Medical Systems, Malvern, PA, USA). During the course of experiments temperature was maintained at $37 \pm 1^{\circ}\text{C}$. A new pulse sequence was written that uses a frequency selective saturation pulse followed by a segmented RF spoiled gradient echo (GRE) readout sequence. The sequence parameters were: slice thickness = 10 mm, GRE flip angle = 10° , GRE readout TR = 5.6 ms, TE = 2.7 ms, field of view = 100×100 mm², matrix size = 192×192 , and one saturation pulse and 64 segments acquired every 10 s. CEST images were collected with different combination of saturation pulse $B_{1\text{rms}}$ and saturation duration. Z-spectra were collected at $B_{1\text{rms}}$ of 155 Hz and 1s duration by varying the frequency from -4 to +4 ppm in step size of 0.1 ppm. The B_0 and B_1 maps were also gathered. For CEST contrast map was generated using equation $\text{CEST} = 100 * [(S_{-ve} - S_{+ve})/S_0]$, where S_{-ve} and S_{+ve} are the B_0 corrected MR signals respectively at -1 p.p.m., +1 p.p.m from water resonance, while S_0 is the image obtained without application of any saturation pulse. The CEST contrast map was further corrected for any B_1 inhomogeneity. The gagCEST map was also obtained from normal human volunteers under an approved institutional review board protocol using the methods described previously.²

Results and Discussion:

The Z-spectra and Z-spectra asymmetry curve show the broad peak center around 1 ppm in both viscosupplements (Figure 1). The Z-spectra asymmetry curve clearly shows higher CEST contrast from Orthovisc compared to Synvisc. The CEST map at $B_{1\text{rms}}$ of 155Hz and 1s saturation duration (figure 2), which clearly depicts the ~ 20% higher CEST contrast from Orthovisc. The higher CEST contrast from Orthovisc may be due to its higher concentration of hyaluronic acid and thus possesses more exchangeable hydroxyl group than Synvisc. Figure 3 shows the $B_{1\text{rms}}$ and saturation duration dependent CEST effect from these molecules. Increase in CEST contrast was observed with increased $B_{1\text{rms}}$ and saturation duration. The graphs clearly show that the optimal $B_{1\text{rms}}$ is 155Hz to observe the maximum CEST contrast from both molecules. In the previous study, it has been shown that the optimal $B_{1\text{rms}}$ and saturation duration to get maximum contrast from knee cartilage is 93 Hz and 500ms saturation duration². These results demonstrate the potential of CEST to monitor and track the course of these viscosupplementation *in vivo*. Furthermore, using the CEST technique with optimal parameters it may possible to map the fate of the injected viscosupplementation in knee joints of OA patients over time as well as their effect on knee cartilage GAG concentration. Further studies in these lines are currently in progress in our laboratory.

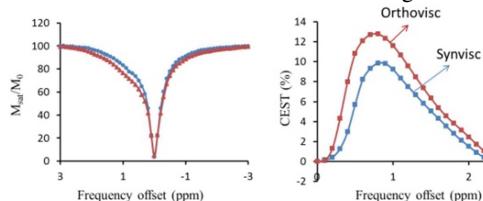


Figure 1: Z-spectra and z-spectra asymmetry curve from Orthovisc and Synvisc shows CEST effect around 1ppm.

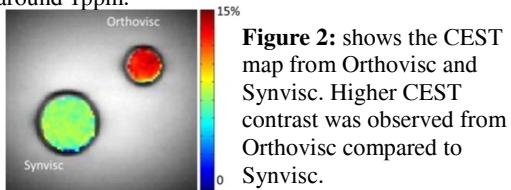


Figure 2: shows the CEST map from Orthovisc and Synvisc. Higher CEST contrast was observed from Orthovisc compared to Synvisc.

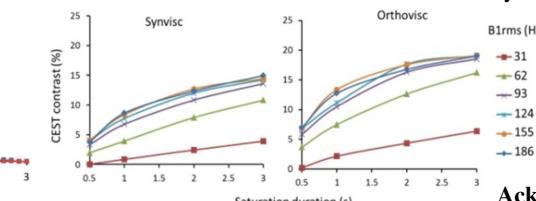


Figure 3: Graphs show the saturation pulse amplitude ($B_{1\text{rms}}$) and saturation duration dependent CEST contrast.

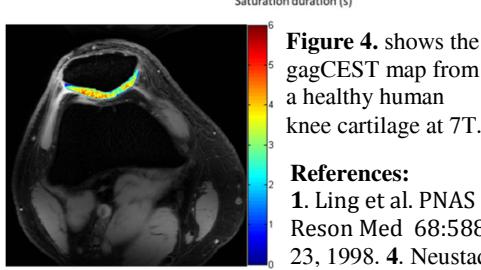


Figure 4. shows the gagCEST map from a healthy human knee cartilage at 7T.

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References:

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