Quantification of longitudinal changes in cartilage following viscosupplementation therapy via $T_{1\rho}$ MRI

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OBJECTIVE: To quantify changes to articular cartilage in patients following viscosupplementation therapy with mild to moderate osteoarthritis using $T_{1\rho}$ MRI.

BACKGROUND: Osteoarthritis (OA) affects nearly 30 million Americans and comprises a significant burden to the healthcare system. Viscosupplementation (VS) is frequently used for the management of mild to moderate OA. VS purportedly increases the viscoelastic properties of synovial fluid and may be a disease modifying treatment through its action on articular cartilage, although the mechanism by which this occurs is not fully understood [1]. The duration that VS remain within the synovial capsule is also not well characterized. Efforts to directly examine the effects of VS on human cartilage have been limited, due to procedural invasiveness and morbidity caused by cartilage biopsy [2]. Therefore, there is a need for a non-invasive means of monitoring cartilage response to potentially disease-modifying therapies. $T_{1\rho}$ MRI can provide quantitative measures of the proteoglycan content of the cartilage matrix [3]. We hypothesize that $T_{1\rho}$ MRI will detect the subtle changes to proteoglycan content of knee articular cartilage by 6 weeks following VS. Additionally, we hypothesize that the treatment effects of the VS will be diminished by 3 months following injection.

METHODS: Following IRB guidelines, 10 subjects (mean age, 56 ± 10 yrs) with Kellgren-Lawrence Grades 1 and 2 OA, and who never had prior VS or knee surgery, were scanned at baseline, 6 weeks post-, and 3 months post-VS using Hylan G-F 20 (3T, Siemens Medical Solutions, Malvern, PA). T_1-weighted isotropic MPRAGE images were acquired for segmentation of cartilage, and $T_{1\rho}$-weighted 3D TrueFISP images were acquired to calculate spatial $T_{1\rho}$ relaxation maps. Sixteen $T_{1\rho}$-weighted slices were acquired in each aspect to allow for volumetric analysis. Image acquisition parameters have been described previously [4]. Isotropic sagittal MPRAGE images were re-sliced along coronal and axial views and interpolated to match the resolution of $T_{1\rho}$- weighted images. Inter- and intra-scan motion was corrected 3D rigid-body co-registration algorithms (Analyze, AnalyzeDirect, Inc., KS). Femoral and tibial images were co-registered separately due to discrepancies in flexion angle between imaging sessions. ROI analysis was performed on the same locations for three time points to accurately quantify changes in $T_{1\rho}$ through mean compartmental analysis and percent change maps from baseline images. Cartilage was segmented using the SliceOMatic (Tomovision, Quebec, CA) software package. Co-registered $T_{1\rho}$-weighted images were fit pixelwise to the linearized, mono-exponential signal decay equation $\ln(S) = -TSL/T1\rho + \ln(S0)$. Volumetric $T_{1\rho}$ means were calculated by layer depth (superficial, middle, deep) as well as by region (medial and lateral patella, femoral condyles, and tibial plateau). Statistical analysis was performed using a one-tailed paired t-test between time points. Additional data to be analyzed but not present for this abstract include the visual analog pain, WOMAC, and IKDC subjective scores before injection and at the time of follow-up MRI. WORMS scoring for each patient is currently being performed and will be correlated to quantitative findings. Statistical significance was accepted when $p<0.05$.

RESULTS:

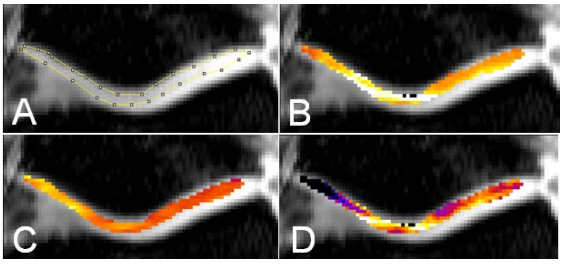


Figure 1 - Anatomical image (A), Baseline $T_{1\rho}$ Map (B), 6 week $T_{1\rho}$ map (C), Percent Difference Map (D, higher values indicate lower $T_{1\rho}$)

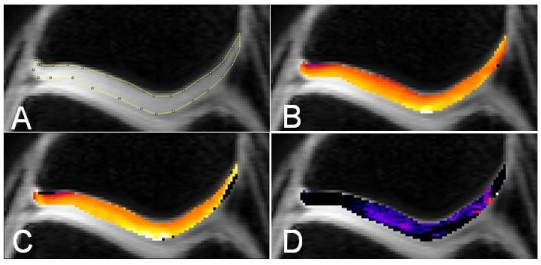
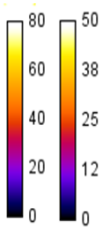


Figure 2 - Anatomical image (A), Baseline $T_{1\rho}$ Map (B), 6 week $T_{1\rho}$ map (C), Percent Difference Map (D, higher values indicate lower $T_{1\rho}$)



$T_{1\rho}$ Color Bar (0-80 ms)
Percent Color Bar (0-50%)

Individual		
Times	p	Location
1--3	0.0282	Tib. Lat. Deep.
1--3	0.0350	Tib. Med. Midl.
1--2	0.0243	Tib. Lat. Deep.
1--3	0.0258	Tib. Lat. Deep.
1--3	0.0371	Tib. Lat. Midl.
Aggregated		
Times	p	Location
1--2	0.03138	Middle.
1--2	0.00091	Super.
1--3	0.01361	Super.
1--2	0.00243	Medial
1--2	0.00153	All

Table 1 – Compartments with Significant difference ($p<0.05$) in mean $T_{1\rho}$ score across different time points

There were significant differences in volumetric $T_{1\rho}$ scores in both the medial and lateral compartments of the superficial patella ($p< 0.05$) 6 weeks following but not after three months (Med. - $p<0.1$, Lat. - $p<0.06$). Table 1 lists several regions with significant differences between individual or aggregated compartments {by depth level, all medial or all lateral or total joint}) between various time point (1^{st} and 2^{nd} or 1^{st} and 3^{rd}). Visual inspection of the $T_{1\rho}$ images and percent change maps demonstrate a varied physiological response to the VS injection between individuals. The $T_{1\rho}$ signal can change uniformly or regionally throughout joint as shown in Figure 1 and Figure 2. Figure 1 data demonstrates volumetric mean drop in $T_{1\rho} > 20\%$ across the entire patella while Figure 2 has no significant difference in average between two following time points. There is a large region across the middle of the lateral facet with an average $T_{1\rho}$ score < 20% versus the volumetric mean. This trend of non-uniform spatial changes to $T_{1\rho}$ following VS regiments is prevalent among all patients.

CONCLUSIONS: These data suggest that VS has a quantifiable physiological effect on knee articular cartilage. This effect is greater in the superficial layers than in the deep layers. Intuitively, direct contact between VS and cartilage occurs at the superficial layer, and there may be a subsequent physical mechanism of action for VS. Interestingly, the greatest effects were observed in the patella-femoral compartment which may be due to lower load-bearing activities and increased cartilage thickness. Future work will assess methods to predict homo- or heterogeneous changes within the articular cartilage through correlation analysis with WORMS, WOMAC, and other qualitative assessments. While some patients responded positively to the VS, as calculated through lower $T_{1\rho}$ scores, there were some who did not or had higher $T_{1\rho}$ values. There may be both placebo effects as well as anti-inflammatory mechanisms associated with the VS which allowed patients to push through pain more than before thereby causing increased damage to the cartilage tissue. We will follow this cohort to determine whether this improvement in cartilage $T_{1\rho}$ is sustained and whether these changes continue to associate with improved patient reported outcomes. $T_{1\rho}$ MRI is a feasible non-invasive method of studying human *in vivo* articular cartilage changes following this routine clinical intervention. This is the first *in vivo* human study to demonstrate a potentially disease modifying effect of VS on early stage knee OA. It further demonstrates the utility of $T_{1\rho}$ MRI as a noninvasive technique for assessing changes in cartilage proteoglycan content in response to an intervention. This modality and protocol may have utility in studying the disease modifying effects of therapeutic agents used in the treatment of osteoarthritis.

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REFERENCES: [1] Creamer+, OA and Cartilage 1994 [2] Pasquali Ronchetti+, Rheumatology 2001 [3] Borthakur+, NMR Biomed 2006 [4] Witschey+, JMRI 2008