

## T<sub>2</sub>, T<sub>1ρ</sub>, and Sodium MRI of Articular Cartilage in Patients with Osteoarthritis Treated with Arthritis Relief Plus Cream

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### Introduction

The bulk of current pharmacologic osteoarthritis (OA) relief focuses on alleviating symptoms instead of altering joint morphology [1]. Interestingly, Arthritis Relief Plus Cream (ARP, Taber Herbals, Queensland, Australia) has been shown to relieve joint pain in two separate studies, even after discontinued treatment [2,3], so it may have a disease modifying effect. Advanced MRI methods such as T<sub>2</sub>, T<sub>1ρ</sub>, and sodium imaging techniques can assess the macromolecule content of cartilage. T<sub>2</sub> measures changes in cartilage water content and collagen structure [4]. Sodium imaging allows a direct measure of glycosaminoglycan (GAG) content [5]. T<sub>1ρ</sub> has been shown to provide an accurate measure of GAG content [6]. The purpose of this study was to use advanced MRI to evaluate participants after a twelve-week course of topical ARP Cream application.

### Methods

Eight subjects (3 women, 5 men, ages 51-70) were recruited after demonstrating good health and early Kellgren-Lawrence grade 1 or 2 radiographic OA of one knee. Three subjects (2 men, 1 woman) were randomly assigned to the placebo cohort, and five subjects (3 men, 2 women) were randomly assigned to the experimental group. All participants applied topical cream to the affected knee three times daily for twelve weeks and completed the WOMAC questionnaire and Visual Analog Scale to establish functionality and pain levels before and after cream application. All knees were imaged pre- and post-cream application in the sagittal plane using a 3.0T scanner (GE Healthcare) and an 8-channel proton (T<sub>1ρ</sub> & T<sub>2</sub>) or custom sodium quadrature knee coil. A prototype magnetization-prepared spoiled gradient echo sequence with a 500 Hz spin-lock pulse (TR/TSL 5.1/0, 10, 30, 70ms, 256x192 matrix, 3mm slices, 16cm FOV, 70° flip angle, BW ±62 kHz, 10 min imaging time) was used to obtain T<sub>1ρ</sub> images in 10 min. T<sub>2</sub> data was acquired using 2D-FSE with TR/TE 2000/8, 16, 26, 35, 43, 52, 61, 70ms, 320x160 matrix, 3mm slices, 16cm FOV, BW ± 41 kHz in 10 min. Sodium images were obtained using a fast gradient-spoiled sequence with the 3D cones *k*-space trajectory (TR/TE 35/0.6 ms, 70° flip angle, 28 signal averages, 1.25x1.25x4 mm resolution, 21 min scan time). Sodium levels were normalized using a 100 mM saline test tube within the coil.

Sodium signal and relaxation times were measured by two independent, blinded observers using OsiriX. The following ROIs were evaluated: medial/lateral anterior, central, and posterior femoral condyle, medial/lateral anterior and posterior tibia, and medial/lateral superior and inferior patellar cartilage. A musculoskeletal radiologist used a semi-quantitative scoring system on routine 2D-FSE sequences to assess morphologic cartilage change, synovitis, and effusion [7]. Agreement between observers was measured by Pearson correlation. Paired t-tests were used to determine the significance of differences in pain and functionality. Paired t-tests and a mixed effects regression model were used to evaluate the significance of differences between pre-and post-treatment T<sub>2</sub>, T<sub>1ρ</sub>, and sodium values (Excel 2008, Stata 9.2).

### Results

Normalized sodium signal intensity showed a significant increase over time in the MCF of the treatment group using both the paired t-test and mixed effects regression (Figure 1, p=0.03). No significant effect was seen for treatment or time for both T<sub>2</sub> and T<sub>1ρ</sub> measurements. Interobserver variability showed good correlation (Pearson coefficient 0.7). Semi-quantitative scoring revealed no observable changes in cartilage. No significant differences were present in overall average effusion or synovitis between placebo and experimental groups (p=0.177, 0.105). There were no significant differences in pain in either the treatment or placebo groups (p=0.148, 0.212), but a significant increase in activity was observed in the treatment group (p=0.038).

### Conclusion

The significant effect seen using sodium MRI in the MCF suggests there may be changes in the cartilage at the molecular level. Moderate exercise can have beneficial effects on cartilage GAG, so the increase in activity of the treatment group may be related to these findings [8]. The lack of a significant effect from the cream seen in the T<sub>1ρ</sub> and T<sub>2</sub> data may be a result of lack of treatment effect, sensitivity of the measure to change, or the small sample size. Unlike previous studies, this investigation did not reveal significant analgesic effects of ARP cream use [2,3], but a larger sample size may have shown a more definitive analgesic effect. Future studies with a larger sample size are needed to investigate these results further.

### References

1. Lohmander LS. *Arthritis Res* 2000; 2:95-100
2. Gemmell HA, et al. *J Manipulative Physiol Ther* 2003; 26:e15.
3. McKay L et al. *J Clin Rheumatol* 2003; 9:164-169.
4. Gold et al. *AJR* 2009;1193:628-38.
5. Shapiro et al. *Magn Resn Med* 2002; 47(2): 284-91.
6. Regatte et al. *Acad Radiol* 2002; 9(12):1388-94.
7. Baker et al. *Ann Rheum Dis*. 2010 Oct;69(10):1779-83.
8. Roos, et al. *Arth Rheum* 2005; 52(11): 3507-2514.

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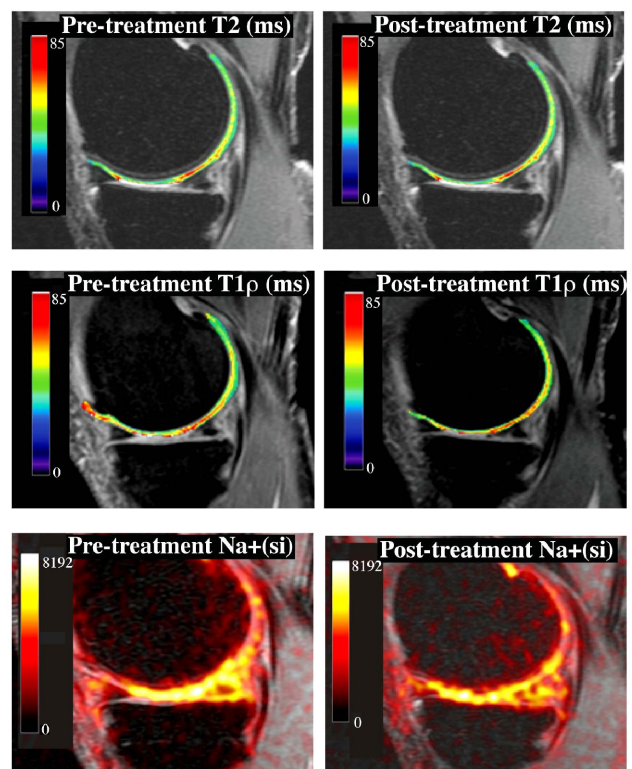


Figure 1: Images of the medial femur pre (left) and post (right) 12-week course of ARP Cream treatment. From top to bottom, T<sub>2</sub> (ms), T<sub>1ρ</sub> (ms), and sodium signal (signal intensity, si) overlaid onto proton images are shown.