Effects of Ionic and Non-Ionic Clinical CT Contrast Agents on Swelling Behavior of Sheep Meniscus Fibrocartilage

Hollis A. Crowder¹, Christina Martin¹, Eva G. Baylon², Garry E. Gold³, Marc E. Levenston¹

¹Stanford University, Dep. of Mechanical Engineering, Stanford, CA; ²UCSF, Dep. of Orthopedic Surgery, San Francisco, CA; ³Stanford University, Dep. of Radiology, Stanford, CA
hcrowder@stanford.edu

Disclosures: Hollis A. Crowder (N), Christina Martin (N), Eva G. Baylon (N), Garry E. Gold (GE Healthcare), Marc Levenston (N)

Introduction: Osteoarthritis of the knee is a chronic, debilitating joint disease characterized by degenerative changes in the articular cartilage and menisci in the knee joint¹. Although Magnetic Resonance Imaging (MRI) is the most accurate and least invasive method for assessing lesions in the knee joint, some patients (those who are claustrophobic, have pieces of metal in their bodies, or have pacemakers) are ineligible for MRI, and Computed Tomography (CT) arthrography is a common alternative². Contrast agents at clinically-relevant dilutions were recently shown to induce transient swelling and deswelling of articular cartilage, but the effects on joint tissues, such as the meniscus, are not yet fully understood³,⁴. This study examined the mechanical effects of two iodinated contrast agents (non-ionic Omnipaque 350 (Iohexol) and ionic Cysto-Conray II) on sheep meniscus explants.

Methods: Meniscus explants were taken from the surface of four immature sheep stifles using an 8mm biopsy punch, after which they were trimmed to 2mm thickness while keeping the surface of the samples intact. Explants were stored at -20°C in Phosphate Buffered Saline (PBS) until mechanical testing. Before testing, samples were thawed to a final temperature of 25°C, trimmed to a final diameter of 6mm, and randomly assigned to one of five testing groups: 1XPBS, 0.1XPBS, 10XPBS, 100% Omnipaque (Omnii), 100% Cysto-Conray II (Conray). Mechanical Testing: Samples (n=3/group) were placed in a rubber confining ring and tested on an Instron 5940 microtester using a 10N load cell and an hemispherical indenter tip (radius 1mm). Once in the rubber ring, samples were placed in a bath of 1XPBS while being pre-loaded to 0.02N. Samples were then loaded at a rate of 0.002mm/s to 15% strain followed immediately by an unloading step of the same rate and then a 15-minute recovery period. After 3 cycles in 1XPBS (previously shown to be a sufficient number of cycles for equilibration) the bath was changed to the assigned solution group, and the sample was indented for 4 more cycles to monitor the equilibrium response of the tissue (contrast agent equilibrium). The bath was then changed once more back to 1XPBS and indented for 4 cycles to monitor tissue recovery (recovery equilibrium). Analysis: The peak force from each cycle was normalized by the peak force value of the third initial cycle in 1XPBS. Data were analyzed using one-way ANOVA followed by Bonferroni post-hoc test for pairwise comparisons. Results are presented as mean±SEM.

Results: Normalized peak force (N) in the control (1XPBS) group did not vary (Figure 2), which indicates the testing protocol did not damage the meniscus tissue. Normalized peak force data for contrast agent equilibrium show an overall deswelling trend for contrast agents, 10XPBS, and an overall swelling trend for 0.1XPBS (Figure 2). Normalized peak force data for recovery equilibrium show a deswelling trend for both contrast agents and 10XPBS with little change for 0.1XPBS (Figure 2). Normalized peak force data for cycle 4 contrast agent equilibrium show the Omnii group (0.1178N/N±0.04996) to be significantly lower than all other groups, Conray (0.7142N/N±0.2940) to be significantly lower than 0.1XPBS (1.2321N/N±0.0516), and 0.1XPBS to be significantly higher than 1XPBS (0.9738N/N±0.0306) and 10XPBS (0.5170N/N±0.0278) (Figure 3). No significant difference was detected between Conray and 1XPBS. Normalized peak force data for recovery equilibrium show Omnii (0.2915N/N±0.2137) to be significantly lower than all other groups and no other significant differences between groups (1.0059N/N±0.0553) (Figure 3).

Discussion: A substantial deswelling response was observed in meniscus tissue equilibrated in Omnipaque 350 (Iohexol) compared to control conditions. Omnipaque 350 is hyperosmolar (844mOsm/kg) but is also hypotonic due to the lack of ions. In articular cartilage, the net effect is a swelling response, but due to the lower fixed charge density of meniscus tissue, the toxicity is less impactful and the net effect is a deswelling response. Cysto-Conray II (400mOsm/kg) did not induce a response significantly different from 1XPBS, likely because both the osmolality and toxicity are only modestly above that of 1XPBS. Preliminary studies with Omnipaque diluted 50% in H2O (and therefore having similar osmolality to Cysto-Conray II) found a strong deswelling effect as well, indicating that both the osmolality and toxicity of contrast solutions are important⁴. There was also an incomplete recovery of meniscus tissue in 1XPBS within a one-hour time frame post-contrast agent equilibration, which bears consideration in a clinical context. These results indicate that exposure to different clinical contrast agent solutions affects the mechanical properties of meniscus tissue in significantly different ways that may differ substantially from effects on cartilage, potentially altering the physical properties of meniscus tissue and ability to withstand loading to different extents.

Significance/Clinical Relevance: These results show exposure to iodinated CT contrast agents has a significant and varied mechanical effect on meniscus tissue in the knee, which illustrates the need for the development of robust clinical protocols to prevent damage to the meniscus surface after exposure to iodinated contrast agents.


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Images and Tables:

Figure 1: Experimental set-up.

Figure 2: Representative normalized peak force data (N/N±) of samples in [A] contrast agent equilibrium and [B] recovery in PBS.

Figure 3: Normalized peak force data for cycle 4 for [A] contrast agent equilibrium and [B] recovery equilibrium.