Contrast-enhanced Computed Tomography Distinguishes Osteoarthritic Disease State in an Equine Patellofemoral Joint

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Introduction: Osteoarthritis (OA) is a shared cause of impaired locomotion among mammals. In racehorses, where athletic performance is of utmost importance, OA is the most common cause of lameness, often leading to an early retirement. The progression of OA in horses follows a trajectory similar to humans. The loss of glycosaminoglycan (GAG) from the cartilage extra-cellular matrix is an early maker for OA, resulting in an increase in the hydraulic permeability and a decrease in the compressive stiffness of articular cartilage. As a consequence of increased cartilage permeability, load support is transferred from the fluid phase to the solid phase, subsequently increasing the load borne by the collagen fibrils, which over time leads to a cascade of tissue fibrillation, loss of tissue volume, fracture, and chondral defects. Clinical management of OA requires diagnosis before these irreversible tissue changes occur. Therefore, a sensitive, minimally-invasive imaging modality that can serially monitor cartilage morphology and composition is necessary to facilitate the timely application of reparative treatments. Radiographs, the standard for evaluating OA, are diagnostic only at later disease stages after irreversible damage has already occurred. While MRI is more sensitive to changes in cartilage morphology and composition diagnostic of early OA, limited availability, decreased image resolution and increased cost have restricted its widespread clinical application. Contrast-enhanced computed tomography (CECT) using anionic iodinated contrast agents (ioxaglate, iothalamate) which function as mobile ionic probes that partition throughout the cartilage in inverse proportion to the GAG content and reflect the mechanical properties of the tissue has been shown to be an effective modality for quantifying these properties. We have developed an alternative strategy which utilizes a cationic contrast agent that exploits its electrostatic attraction to the negatively charged GAGs so that the ionic probe partitions throughout the cartilage in direct proportion to GAG content, thereby improving the ability of CECT to measure subtle changes in GAG content that influence the mechanical performance of the tissue. The aim of this work was to explore the ability of CECT using a cationic contrast agent, CA4+, and a clinical helical CT scanner to minimally-invasively evaluate the clinical stages of OA using an equine cartilage defect model. Our hypotheses are: 1) using a clinical CT scanner, intra-articular injection of CA4+ enhances imaging and segmentation of patellofemoral joint (PFJ) cartilage and facile identification of chondral lesions; 2) CECT attenuation corresponds to OA disease state as measured by Outerbridge scoring, and 3) CECT attenuation is predictive of equilibrium compressive modulus, a surrogate for cartilage mechanical performance.

Methods: All procedures were approved by the Animal Care and Use Committee (IACUC) at Colorado State University. Three full-thickness trochlear ridge cartilage defects (one 15 mm dia. and two 10 mm
Osteochondral plugs (7 mm dia.) adjacent to the chondral defects and from matched regions of the normal contralateral joint were excised and graded for OA severity according to the Outerbridge scoring system (OB). To enable accurate segmentation of CECT attenuation data corresponding to each plug location, the PFJ was re-imaged and registered to the previous CECT images (Analyze®, Overland Park, KS). The osteochondral plugs were rinsed in physiologic saline to remove the CA4+ before mechanical testing. Each plug was rigidly clamped in a mechanical testing apparatus (Enduratec3230, BOSE, Eden Prairie MN) and a compressive pre-load was applied between the cartilage surface and a nonporous UHWPE platen to ensure complete contact between the cartilage and platen. While immersed in saline, each plug was subjected to 4 incremental 5% compressive strain steps (0.333 %/sec) in unconfined compression with stress relaxation (45 minutes) intervening between strain steps. Force and displacement data was recorded at 10 Hz. Linear regression analysis of the stress vs. strain data at each equilibrium step was used to calculate the equilibrium compressive modulus (E) for each cartilage specimen. One-way ANOVA with Tukey's HSD post-hoc analysis was used to assess both E and CECT attenuation over the range of Outerbridge scores (SPSS v17.0, Chicago, IL). Univariate linear regression was used to express the compressive properties of each plug, E, as a function of the corresponding CECT x-ray attenuation (Hounsfield Units, HU).

Results: The CA4+ was highly taken up by the PFJ cartilage and enabled facile identification of the chondral lesions (Figure 1). The mechanical performance of the cartilage measured by E corresponded to the Outerbridge score (OB), with moderately degenerated cartilage OB=2 exhibiting statistically different compressive properties than healthy cartilage OB=0 (p = 0.013, Figure 2A). The CECT attenuation also corresponded to OB, with moderately degenerated cartilage OB=2 exhibiting statistically different CECT attenuation compared to healthy cartilage OB=0 (p = 0.001, Figure 2B) and minimally degraded cartilage OB=1 (p = 0.003). CECT attenuation predicted 44% of the variability in E, a direct measure of the mechanical performance of the cartilage (R2 = 0.44, Figure 2C).

Discussion: Previous reports have demonstrated that CECT using anionic or cationic contrast agents performed with high resolution microCT scanners robustly reflects the GAG content and mechanical properties of isolated osteochondral plugs. The results of this study demonstrate that CA4+-enhanced cartilage images obtained with a clinical helical CT scanner in a clinically relevant large animal model of OA: 1) improves the imaging and segmentation of articular cartilage and facile identification of chondral lesions; 2) indicates OA disease staging by reflecting Outerbridge scores; 3) predicts the equilibrium compressive modulus, a surrogate for cartilage mechanical performance. The ability to distinguish between early (OB 0-2) stages of OA suggests the clinical applicability for CECT to sensitively monitor OA in the earliest stages of the disease when reparative and chondroprotective treatments will have the best chance of success.

Significance: Whole-joint CECT imaging obtained with a clinical helical CT scanner using a cationic contrast agent in a clinically relevant large animal model of OA accurately predicted the progressive
stages of OA, thereby supporting further efforts to develop CECT as an in vivo diagnostic tool for OA to facilitate the selection of appropriate reparative and chondroprotective treatments based on disease stage.

Figure 1: A full-thickness cartilage defect (right) is visible using CECT and is distinguishable from healthy cartilage (left).

Figure 2: (A) $E$ corresponds to Outerbridge score, with OB=2 being distinct from OB=0 ($p = 0.013$). (B) CECT attenuation corresponds to Outerbridge score, with OB=2 being distinct from both OB=0 and OB=1 ($p = 0.003$, $p = 0.001$ respectively). (C) $E$ correlates to CECT attenuation ($R^2 = 0.44$, $p < 0.001$).

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Evaluation of the Acetabular Labrum in Patients with Acetabular Dysplasia Using T2 Mapping with Arthroscopic Verification

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Introduction: Acetabular labral tears are a common cause of hip pain and are thought to be a precursor to the progression of osteoarthritis. These tears can be associated with various pathogeneses including hip trauma, high levels of sports activity, degenerative osteoarthritis, acetabular dysplasia, and femoroacetabular impingement. Arthroscopic examinations of intra-articular lesions in acetabular dysplasia have found a high prevalence of labral tears. Hip arthroscopy is considered the gold standard for diagnosing acetabular labral abnormalities. However, the cost and invasive nature of that procedure are reasons to investigate new methods for diagnosing intra-articular hip pathologies, including labral lesions. Several reports using magnetic resonance (MR) arthrography have demonstrated its effectiveness in detecting acetabular labral pathological changes. However, other study reported MR arthrography has a poor negative predictive value and cannot be used to rule out labral lesions.[1] Recently, several quantitative MR imaging techniques for cartilage assessment have been developed, including delayed gadolinium-enhanced MR imaging and T2 mapping of the hip joint.[2, 3] Evaluation of the T2 values of the articular cartilage shows great potential for the quantitative assessment of collagen and water content and indicates its clinical utility for assessing the hip joint.[4] However, to the best of our knowledge, there have been no reports that assess the acetabular labrum using T2 values. The purpose of this study was to evaluate the diagnostic capability of T2 mapping for the acetabular labrum by comparing it with arthroscopic findings as the gold standard in patients with acetabular dysplasia.

Methods: Forty-five symptomatic patients with acetabular dysplasia who underwent preoperative MR imaging and periacetabular osteotomy combined with an arthroscopy were included in this study. The cohort included two males and forty-three females, and the mean patient age at the time of surgery was 37.4 years (range: 17-59). On the preoperative plain radiographs, the mean lateral center edge angle was 11.4° (range: −10-18°), and the Tönnis osteoarthritis grade was grade 0 in 28 hips and grade 1 in 17 hips. Informed consent for participation in this study was obtained from all patients, and the study protocol was approved by the local Institutional Review Board.

MR imaging of the hip was performed on a 1.5-T magnet system (Achieva 1.5T; Philips Medical Systems, Best, The Netherlands) using a dedicated transmit-receive coil. Coronal T2 maps were obtained from two-dimensional fast spin-echo images acquired with the following parameters: TR: 1500 ms; TE: 8 echoes between 15 and 120 ms; FOV: 20 cm; matrix: 512×256 interpolated to 512×512; and slice thickness: 5 mm. A region of interest (ROI) in each acetabular labrum was defined within a single coronal
section from the center of the femoral head using the Philips Research Integrated Development Environment (PRIDE) software (Philips Medical Systems, Best, The Netherlands) (Fig 1). Arthroscopic examinations of the hips were conducted on the superior labral lesions in areas corresponding to the ROI. The condition of the acetabular labrum was classified according to the classification of Beck as normal, degeneration, full-thickness tear, or detachment. Acetabular labral tears were defined as the presence of a full-thickness tear or detachment. We used receiver operating characteristic (ROC) analysis to determine the sensitivity, specificity, negative predictive value, and positive predictive value of T2 mapping, and to define a threshold T2 value that indicated a labral tear.

**Results:** During arthroscopy, 29 labral tears were identified in the 45 hips. The mean T2 value of the acetabular labrum by Beck classification was 7.6 ± 6.8 ms for normal (n=8), 11.4 ± 6.1 ms for degeneration (n=8), 25.0 ± 11.4 ms for full-thickness tears (n=12), and 38.5 ± 10.5 ms for detachment (n=12). The mean T2 values of the full-thickness tear and detachment groups were significantly higher than those in the normal and degeneration groups (p<0.05, Fig 2). The ROC curve analysis showed a sensitivity of 79%, specificity of 94%, negative predictive value of 71%, and positive predictive value of 96%, indicating a threshold T2 value of 21 ms for defining a labral tear. This value corresponded to an estimated probability of disease of 0.9.

**Discussion:** The ability of T2 mapping to diagnose acetabular labral tears was evaluated by comparison with arthroscopy as the gold standard. Acetabular labral tears were detected with a sensitivity of 79% and specificity of 94%, which are similar to, or superior than, previously reported sensitivities of 71-100% and specificities of 44-71% using MR arthrography. The T2 values of articular cartilage are closely correlated with the collagenous architecture and water content. Histologically, the acetabular labrum contains two different tissue phenotypes: fibrocartilage and dense connective tissue. The dense connective tissue contains types I and III collagen, and the fibrocartilaginous zone contains cartilage-specific type II collagen. Additionally, the tears and lesions of the intra-articular structures, such as the acetabular labrum, are highly dependent on the architecture of the collagen fibrils.[5]

In conclusion, T2 mapping was useful for evaluating acetabular labral tears in patients with acetabular dysplasia. In future studies, it will be important to determine the association between the T2 values of the acetabular labrum and the pathological findings among patients with acetabular dysplasia and normal volunteers.

**Significance:** T2 mapping as a non-invasive method for evaluating labral tears showed a sensitivity of 79%, specificity of 94%, negative predictive value of 71%, and positive predictive value of 96%; a T2 value of 21 ms was identified as the threshold for identifying such tears.