Detection of Proteoglycan Depletion in Mechanically Loaded Cartilage With T1ρ Imaging

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Introduction

The outstanding detail and clarity, rapid acquisition times, and multiple contrast mechanisms achievable with high-field magnetic resonance imaging (MRI) have maintained its position as the gold standard for visualization of cartilage defects and overall assessment of cartilage morphology. However, the earliest markers of cartilage degeneration occur at the tissue level and are therefore not detectable as changes in morphology. In particular, early stages of osteoarthritis (OA) are associated with proteoglycan (PG) loss, which in turn makes the cartilage susceptible to mechanical injury. Routine MRI contrast mechanisms are not sufficiently sensitive to reliably detect and display such biochemical changes. T1ρ relaxation is another MRI-based measurement that shows promise for the early detection of such changes.

Several studies have demonstrated and validated T1ρ relaxation as an indicator for the assessment of PG content [1-3]. The sensitivity of this method has been shown both in vitro and in vivo [4-5]. T1ρ relaxation in tissues is affected by low-frequency interactions between molecules. In cartilage, exchange between water and PG appears to be a primary determinant of T1ρ relaxation time. A decrease in cartilage PG content reduces these interactions and thus reduces the relaxation rate of water molecules. The result is an increase the observed T1ρ relaxation time in areas of PG depletion. In several previous studies, PG depletion was accomplished enzymatically. A potentially more direct model of the mechanisms and progression of PG loss may be achieved with the application of accurately calibrated mechanical loading directly on human cartilage. The purpose of this study was to apply realistic and precisely controlled mechanical stresses to induce PG changes in human cartilage and to assess the ability of T1ρ imaging to accurately detect and assess the resulting PG depletion.

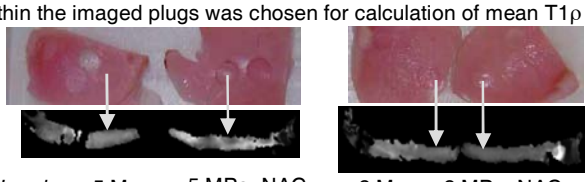
Methods

Fresh human articular cartilage samples were taken from the tibial plateau of three amputation subjects with no known history of OA. From the continuous sheets of cartilage, twelve 4-mm diameter full-thickness (ranging from 1.8 to 3.2 mm) cylindrical plugs were derived from each of the three samples. Mechanical stresses were produced in a load-controlled triaxial compression chamber (TRIAX) at levels representative of normal human gait in vivo. The cartilage plugs received a loading regimen of either 2 MPa or 5 MPa (six plugs each for each subject) lasting one hour (3600 1Hz loading cycles) followed by placement back within the cartilage sheet between TRIAX episodes. The process was repeated on days 1, 5, and 9. Furthermore, in samples derived from two of the three subjects, half of the plugs at each loading were treated with N-Acetylcysteine (NAC) which inhibits loss of PG. In each subject, the remainder of the sheet acted as a common carrier for the explants as well as an unloaded control sample.

After completion of the multiday mechanical loading regime, T1ρ imaging was performed on day 13. Images were acquired from a Varian INOVA 4.7-T small-bore scanner (Varian Medical Systems, Palo Alto, CA) equipped with a 3.75-cm diameter quadrature RF coil. The pulse sequence utilized was fast spin-echo-based with a T1ρ magnetization preparation block prepended. This pulse block included a $+90_x°$ square pulse, a 500 Hz spin lock pulse, a $-90_x°$ square tip-up pulse, and a final crusher gradient to destroy any residual transverse magnetization. Images using spin lock pulses of seven different durations (5 to 80 ms) were recorded. The fast spin-echo pulse sequence parameters were TR/TE=4000/11 ms, echo train length of 4, and 512 x 128 matrix. Depending on the varying geometry and orientation of the samples, the field of view ranged from 25 x 13 mm^2 to 50 x 25 mm^2 with slice thicknesses of 2.5-4 mm. Slices were prescribed so as to pass through one of the plugs for each loading and NAC treatment condition. Localizer images were acquired to determine the plug locations within the slices. A nonlinear curve fitting algorithm estimated the T1ρ parameter on a pixel-by-pixel basis over the region of interest (ROI) of each plug. A 1.5 x 1.5 mm^2 ROI centered within the imaged plugs was chosen for calculation of mean T1ρ values to assure that only tissue subjected to the specified loading conditions was included.

Results

Figure 1 at right shows sample cartilage plugs and the generated T1ρ maps in cartilage derived from a 51-year-old male. For each plug, the computed T1ρ values over the selected region of interest and the PG content derived from biochemical assay are shown. A noticeable depletion of the GAG content can be seen with greater mechanical loading, which is also reflected in the elevated T1ρ measurements for those samples. The NAC treated sample showed a lesser increase in T1ρ and greater retention of PG with 5 MPa loading. Figure 2 displays the comparison between mean T1ρ relaxation time within each plug and measured GAG content for all of the ten cartilage plugs. As can be seen, T1ρ relaxation times were highly correlated with PG content, with increases in T1ρ corresponding to measurably reduced GAG content.



Load	5 Mpa	5 MPa+NAC	2 Mpa	2 MPa+NAC
T1ρ	27.6±2.7	25.8±6.7	21.4±3.2	22.0±2.5
GAG (μg/mg)	37.5	57.2	64.4	70.0

Figure 1: Photographic view (top) of embedded cartilage plugs and corresponding T1ρ maps through the plug (bottom). Mean T1ρ and glycosaminoglycan (GAG) content for each loading and NAC treatment condition are shown below.

Discussion

The significant correlation seen between PG measurements and T1ρ relaxation times suggests that changes in PG content resulting from mechanical loading can be assessed noninvasively with T1ρ imaging. The ability to follow the time course of PG depletion under controlled loading conditions in a non-destructive and noninvasive fashion may serve as the basis for sensitive and accurate assessment of cartilage degradation in vivo in early stages of OA. The development of noninvasive methods such as T1ρ imaging to quantitatively measure cartilage function will permit more objective early stage appraisals of OA and injury as well as followup treatment modalities.

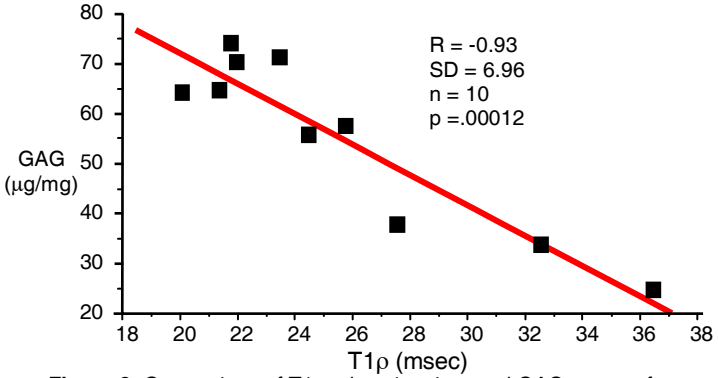


Figure 2: Comparison of T1ρ relaxation time and GAG content from biochemical assay in ten cartilage sample plugs.

References

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