MR $T_{1\rho}$ Relaxation Time Quantification Reveals Early Cartilage Degeneration in Osteoarthritic and Acutely Injured Knees

Xiaojuan Li, PhD, Eric T. Han, MS, Richard Souza, PT, PhD, Thomas M. Link, MD, PhD, C. Benjamin Ma, MD, Sharmila Majumdar, PhD

Cartilage and Osteoarthritis

Osteoarthritis (OA) is characterized by the progressive loss of hyaline articular cartilage. Magnetic resonance imaging has been widely applied to visualize cartilage directly. However, conventional MRI is limited to showing morphological changes in cartilage at a stage when cartilage is already irreversibly lost. Standard MR techniques dedicated to cartilage include fat-saturated T_2-weighted, proton density-weighted fast spin echo (FSE) sequences and T_1-weighted spoiled gradient echo (SPGR) sequences. These sequences, however, are inconclusive in quantifying early degenerative changes in the cartilage matrix.

Hyaline articular cartilage is composed of chondrocytes surrounded by a large extracellular matrix (ECM). The ECM is composed primarily of water and two groups of macromolecules: proteoglycan and collagen fibers (mainly type II) (Figure 1). Early events in the development of cartilage matrix breakdown include the loss of proteoglycans, changes in water content, and molecular-level changes in collagen. Early diagnosis of cartilage degeneration would require the ability to non-invasively detect changes in proteoglycan concentration and collagen integrity before gross morphologic changes occur.

The UCSF Department of Radiology and Biomedical Imaging in close collaboration with the Applied Science Laboratory at GE Healthcare have developed novel quantitative MRI, namely $T_{1\rho}$ relaxation time quantification in cartilage. Our goals are to improve early diagnosis of cartilage injury and degeneration, allowing early intervention, and to provide critical evaluation of therapeutic treatment.

MR $T_{1\rho}$ Definition and Quantification Methods

The $T_{1\rho}$ parameter is defined as the time constant describing the spin-lattice relaxation in the rotating frame. It probes the slow-motion interactions between motionally restricted water molecules and their local macromolecular environment, and therefore provides unique biomedical information in the low-frequency regime. The macromolecules in articular cartilage ECM restrict the motion of water molecules. Changes to the ECM, such as loss of proteoglycan, therefore, can be reflected in measurements of $T_{1\rho}$.

The Musculoskeletal Quantitative Imaging Research group within UCSF Radiology is one of the first groups in the field to develop $T_{1\rho}$ quantification techniques in cartilage, and to translate the techniques into clinical applications for patients with osteoarthritic or acutely injured

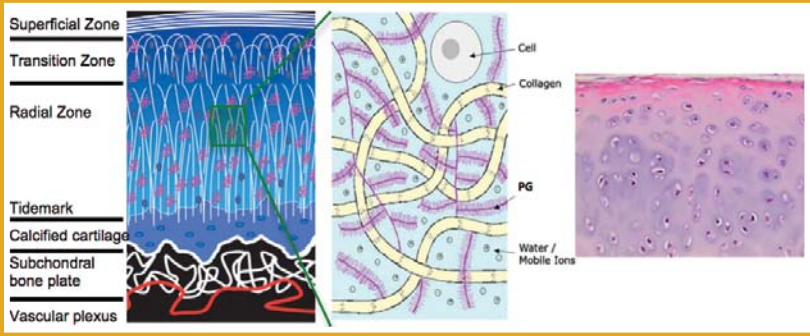


Figure 1. Schematic representation of cartilage molecular organization. Left: Multi-layer structure of hyaline cartilage. Middle: The extracellular matrix (ECM) of hyaline cartilage is composed primarily of water and two groups of macromolecules: proteoglycan (PG) and collagen (mainly type II) fibers. Right: 400X hyaline cartilage histology.

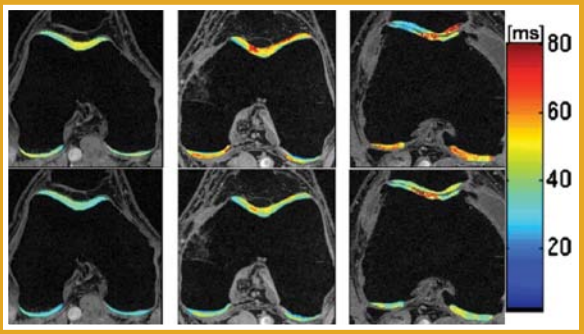


Figure 2. $T_{1\rho}$ maps (first row) and T_2 maps (second row) for a healthy control (left), a patient with mild OA (middle), and a patient with severe OA (right). $T_{1\rho}$ and T_2 values were significantly elevated and become more heterogeneous in OA cartilage. $T_{1\rho}$ and T_2 showed different spatial distribution and may provide complementary information regarding cartilage degeneration in OA.

knees. During the past six years, we have developed novel and robust $T_{1\rho}$ quantification techniques using spin-lock (SL) techniques followed by 2D (spiral or FSE sequences) or 3D (SPGR sequences using transient signal evolving towards the steady-state).

In an SL experiment, spins are flipped into the transverse plane along one axis, immediately followed by an SL pulse applied along the same axis. Under locking condition, the spins will relax with a time-constant $T_{1\rho}$ along B_1 of locking pulses in the transverse plane. The amplitude of the SL pulse is defined as SL frequency, normally ranging from a few hundreds hertz to a few kilohertz. The duration of the SL pulse is defined as time of SL (TSL). $T_{1\rho}$ relaxation phenomena are sensitive to physicochemical processes with inverse correlation times on the order of the nutation frequency of the SL pulse. By setting the amplitude of the SL pulse to coincide with the frequency of the molecular processes of interest, the signal from the SL-MRI sequence becomes heavily $T_{1\rho}$-weighted. $T_{1\rho}$ can be computed by acquiring a series of $T_{1\rho}$-weighted images at various TSL by fitting the exponential decay curve.

Using specimens collected from patients who underwent total knee arthroplasty (TKA) due to severe OA, we demonstrated a significant, negative correlation between $T_{1\rho}$ quantification and the concentration of proteoglycan in the cartilage matrix. The *in vivo* average coefficient-of-variation (CV) of mean $T_{1\rho}$ values for cartilage was 1.6%, with regional CV ranging from 1.7% to 8.7%, indicating excellent reproducibility.

In vivo MR $T_{1\rho}$ Quantification in Osteoarthritic Knees

Using developed techniques, we demonstrated significantly elevated cartilage $T_{1\rho}$ values in OA subjects compared to controls (Figure 2). Increased $T_{1\rho}$ were also correlated with increased disease severity shown with X-rays and MRI. Furthermore, we observed biochemical, degenerative cartilage changes, as indicated by elevated $T_{1\rho}$, in morphologically normal appearing knees with standard MRI. Compared with more established T_2 quantification, $T_{1\rho}$ has a larger dynamic range and higher effect size in distinguishing between OA and control cartilage. $T_{1\rho}$ and T_2 also show different spatial distribution (Figure 2) and may provide complementary information regarding cartilage degeneration in OA.

In addition to average values, texture analysis has been applied to quantify the heterogeneity in $T_{1\rho}$ maps. We demonstrated that OA cartilage had significantly higher $T_{1\rho}$ contrast and entropy compared to controls, indicating that $T_{1\rho}$ values are not only increased, but are more heterogeneous in osteoarthritic cartilage.

We also applied $T_{1\rho}$ measurements in physically active and sedentary healthy subjects, as well as in patients with early OA. $T_{1\rho}$ values in active subjects with and without focal cartilage abnormalities differed significantly (Figure 3 on the next page), even in the regions where no cartilage abnormalities were observed with clinical MRI. $T_{1\rho}$ were significantly higher in early OA patients compared to healthy subjects. These results suggest that $T_{1\rho}$ could be a parameter suited to identify active healthy subjects at higher risk for developing cartilage pathology. This non-invasive imaging marker would be valuable for developing preventive interventions or strategies for OA.

It is well known that OA is a multi-factorial disease involving not only cartilage, but other tissues, such as meniscus and subchondral bone. We observed that the increase of cartilage $T_{1\rho}$ correlated significantly with a decrease of trabecular bone structures in subjects with mild OA. In addition, cartilage $T_{1\rho}$ quantification can not only distinguish between subjects with a normal meniscus and those with a meniscal tear, it can also distinguish between subjects with increased intra-substance signal and those with a meniscal tear, providing a more sensitive stratification of joint degeneration compared to conventional MRI. These stud-

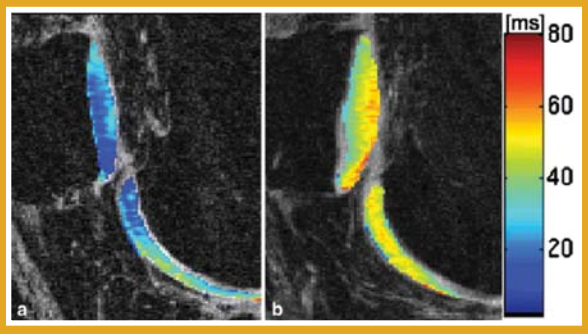


Figure 3. Color-coded $T_{1\rho}$ maps overlaid on SPGR images from a central section of the patello-femoral cartilage. (a) demonstrates the $T_{1\rho}$ map of am active, asymptomatic 25-year-old male subject without focal cartilage abnormalities anywhere in the knee. The average $T_{1\rho}$ of the patello-femoral compartment was 33.7±0.73 ms. (b) shows the $T_{1\rho}$ map of an active, asymptomatic 36-year-old female subject at the central femoro-patellar joint who had a cartilage lesion at the lateral patella. The average $T_{1\rho}$ of the patello-femoral compartment was 45.9±1.68 ms. Interestingly, compared to subject (a), the $T_{1\rho}$ values at the central patella and at the trochlea are globally increased not only in the region of the defect, yet have a similar distribution.

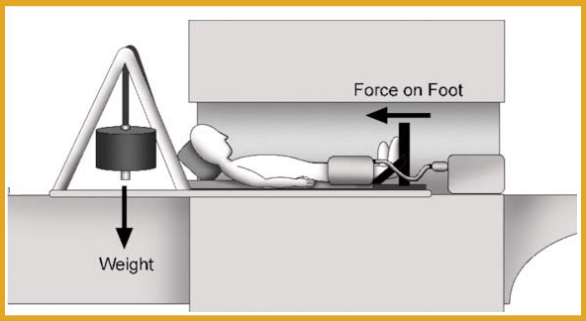
ies suggest that there is a complex interrelationship among cartilage, meniscus, and trabecular bone degeneration in OA knees, and that MR $T_{1\rho}$ is a valuable tool to quantify such correlations.

More recently, we evaluated $T_{1\rho}$ measurements in cartilage with simulated acute loading, using an MR-compatible loading device developed in-house (Figure 4). We demonstrated that acute loading resulted in a significant decrease in $T_{1\rho}$ of the medial compartment, with greater change of values observed in cartilage regions with small focal lesions. These data suggest that changes of $T_{1\rho}$ values with loading may be related to cartilage biomechanical properties and may be a valuable tool for identifying early cartilage disease.

In vivo MR $T_{1\rho}$ Quantification in Knees with Acute Injuries

In addition to patients with OA, $T_{1\rho}$ quantification techniques have been applied to patients with acutely injured knees, in particular patients with acute anterior cruciate ligament tears. Previous cohort studies showed that more than half of patients with ACL tears will develop OA later in life, even after ACL reconstruction. There is a profound need for early detection of joint degeneration in such knees.

Using developed techniques, we demonstrated significantly increased $T_{1\rho}$ values in the posterior lateral tibia. This sub-compartment overlies the commonly seen bone bruise during ACL tear. The elevation of $T_{1\rho}$ in these regions indicated cartilage damage due to translational injury when the ACL was ruptured. Two patients have been confirmed to have cartilage damage in these regions with elevated $T_{1\rho}$ values using arthroscopic images. (Figure 5) Interestingly, at one year after ACL reconstruction, despite the resolution of BMEL, cartilage overlying the baseline BMEL still shows significantly higher $T_{1\rho}$. This suggests potential irreversible damage of cartilage in these regions. Previous histological studies revealed a loss of the proteoglycan component in



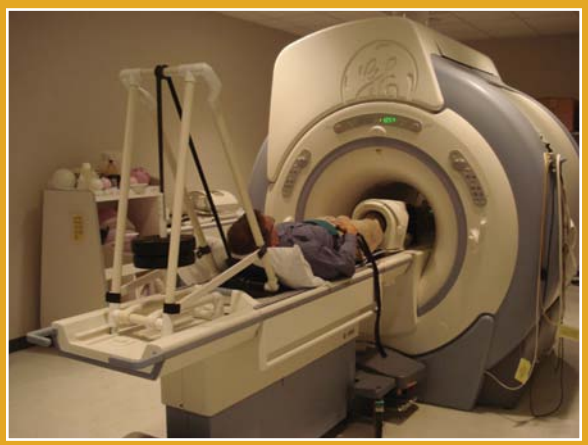


Figure 4. Schematic (above) and photo (right) of the MR-compatible loading device developed in-house.

cartilage matrix overlying BMELs. We have, for the first time, detected and followed up such changes in cartilage matrix non-invasively using advanced MR techniques. In addition, at one-year follow up, we observed significantly elevated $T_{1\rho}$ values in the medial femorotibial cartilage, in particular the contact areas of medial femoral condyle and medial tibia.

To explore potential mechanisms of post-traumatic OA development in ACL-injured knees, we developed techniques to simultaneously quantify knee kinematics (under simulated acute loading) and cartilage $T_{1\rho}$. Abnormal kinematics following ACL reconstruction are thought to be a cause of post-traumatic OA. However, it has been difficult to show a direct relationship between changes in knee kinematics and the development of OA, primarily due to the long lag time between injury and resultant morphological cartilage changes seen in radiographs. Using $T_{1\rho}$ MRI, we observed that the $T_{1\rho}$ increase in medial femorotibial cartilage, in particular the weight-bearing regions, was significantly correlated with abnormal anterior tibial translation and abnormal internal tibial rotation, in ACL-injured subjects at one year after their ACL reconstruction.

These results suggest that cartilage damage after acute knee injuries can be risk factors for predisposing these knees to OA. Abnormal kinematic changes following ACL reconstruction appear to lead to accelerated cartilage degeneration. Quantitative $T_{1\rho}$ can probe these degenerations as early as one year post surgery. In fact, ACL-injured knees may serve as a valuable *in vivo* model for "early OA," and, due to its sensitivity to protoglycan loss, $T_{1\rho}$ can be an extremely valuable tool for evaluating and monitoring early degeneration in such joints.

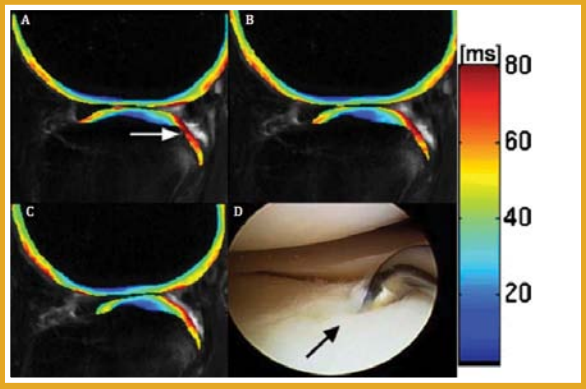


Figure 5. A, B, and C shows a color-coded $T_{1\rho}$ map overlaid on 3-T magnetic resonance images, demonstrating the increased $T_{1\rho}$ relaxation times along the posterolateral aspect of the tibial plateau at the site of the tibial plateau bone bruise (white arrow). The mean $T_{1\rho}$ value of the cartilage directly over the bone bruise was 60.2 ± 13.7 ms, whereas the mean $T_{1\rho}$ value of the remaining cartilage was 37.5 ± 14.3 ms. D is an arthroscopic image demonstrating Outerbridge grade-1 softening of the articular cartilage overlaying the posterolateral aspect of the tibial plateau with a focal area of grade-2 fissures in the region of the bone bruise (black arrow).

Summary

$T_{1\rho}$ quantification in cartilage can provide valuable information related to biochemical degeneration of the cartilage matrix prior to morphological change demonstrated with conventional MRI. Because these techniques will be able to detect cartilage damage at a stage when changes are potentially still reversible, $T_{1\rho}$ quantification in cartilage may have significant clinical implications, allowing opportunities for early intervention or prevention of OA. $T_{1\rho}$ quantification requires no contrast agent injection and no special hardware. Technical challenges of $T_{1\rho}$ quantification include relatively high energy deposited into tissue during the scan and relatively long acquisition times. Ongoing efforts at UCSF Radiology include further technical development, exploration of the relationship among cartilage, bone, and meniscus in osteoarthritis, between cartilage health, gait and physical activities, between imaging measures and genetic profiles in degenerative cartilage, and eventually, clinical translation of the techniques developed.

Xiaojuan Li, PhD, is an associate professor in residence, Department of Radiology and Biomedical Imaging. Eric T. Han, MS, was research manager at the Applied Science Laboratory, GE Healthcare. Richard Souza, PT, PhD, is an assistant professor in residence, Department of Physical Therapy and Rehabilitation Science, and Department of Radiology and Biomedical Imaging. Thomas M. Link, MD, PhD, is a professor in residence, the Clinical Director of MQIR and the Chief of Musculoskeletal Radiology. C. Benjamin Ma, MD, is an associate professor in residence, and the Chief of Sports Medicine at the Department of Orthopaedic Surgery. Sharmila Majumdar, PhD, is a professor in residence, the director of the Musculoskeletal and Quantitative Imaging Research Interest Group and the vice-chair of research for the Department of Radiology and Biomedical Imaging.