Cartilage MRI T2 Relaxation Time Mapping: Overview and Applications

Timothy J. Mosher, M.D.,[1] and Bernard J. Dardzinski, Ph.D.[2,3,4]

ABSTRACT

The sensitivity of magnetic resonance imaging to biochemical and biophysical changes in the extracellular matrix of articular cartilage give it the potential to noninvasively detect the earliest changes of cartilage damage. The transverse relaxation time (T2) of cartilage has been shown to be a sensitive parameter for evaluation of early degeneration in articular cartilage, particularly changes in water and collagen content and tissue anisotropy. Although initial application has been in microimaging of small cartilage explants, in vivo techniques have been developed for cartilage T2 mapping of human joints. In addition to potential application in development of new pharmaceuticals and surgical techniques for preserving cartilage, in vivo cartilage T2 mapping can improve understanding of arthritis, cartilage aging, and response of cartilage to exercise.

KEYWORDS: Articular cartilage, cartilage collagen, arthritis, osteoarthritis, magnetic resonance imaging, cartilage T2

Because magnetic resonance imaging (MRI) can directly visualize articular cartilage, it will likely be an essential tool in the study of arthritis and development of chondroprotective therapy. Currently, development of potential chondroprotective pharmaceuticals is limited by the inability to noninvasively detect and monitor early damage to the cartilage matrix when therapy has the greatest likelihood of being efficacious. Sensitive quantitative or even semiquantitative measures of damage that can be applied longitudinally in clinical trials are needed to evaluate response to therapy. Ideally, these techniques should be noninvasive and capable of detecting localized cartilage damage that precedes structural loss of tissue. Current clinical MRI evaluation of articular cartilage relies primarily on identification of morphological changes in damaged cartilage.[1] These include determination of cartilage thickness and volume using three-dimensional T1-weighted fat-suppressed gradient-echo imaging and detection of superficial cartilage lesions, primarily with two-dimensional proton density-weighted fast spin-echo sequences. In addition to these anatomic techniques, new MRI parametric mapping techniques, such as cartilage transverse relaxation time (T2) mapping, are being developed that exploit the sensitivity of MRI to biophysical properties of tissue.[2] These techniques have the potential to identify the earliest stages of matrix degeneration that precede visible cartilage damage.

Cartilage T2 mapping uses intrinsic cartilage water as a probe to study the structural integrity of the extracellular matrix. Because it has a central role in the biomechanical properties of cartilage, water is an ideal biomarker of cartilage damage. MRI relaxation parameters such as T2 provide a quantitative, noninvasive means for the study of cartilage water and interaction of water with the solid components of the extracellular cartilage matrix at a molecular level.

Imaging in Arthritis; Editors in Chief, David Karasick, M.D., Mark E. Schweitzer, M.D.; Guest Editor, Charles G. Peterfy, M.D., Ph.D. *Seminars in Musculoskeletal Radiology*, Volume 8, Number 4, 2004. Address for correspondence and reprint requests: Timothy J. Mosher, M.D., Department of Radiology/NMR Building M108, Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033. [1]Department of Radiology, The Penn State Milton S. Hershey Medical Center, Hershey Pennsylvania; [2]Imaging Research Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [3]Department of Radiology; [4]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio. 1089-7860,p;2004,08,04,355,368,ftx,en;smr00342x.

OVERVIEW OF CARTILAGE BIOCHEMISTRY, TISSUE STRUCTURE, AND BIOMECHANICS

Unlike anatomic imaging, new parametric mapping techniques such as T2 mapping are sensitive to specific changes in chemical composition and structure of cartilage. Therefore, a brief review of the relevant biochemistry, tissue structure, and biomechanics of cartilage is warranted. For those readers that would like more details, several excellent texts are available.[3–5]

The capacity of cartilage to withstand repetitive compression is a function of restricted movement of cartilage water.[6] The major component of cartilage is water,[7] which is nonuniform in distribution, increasing from 67% near subchondral bone to 74% near the articular surface.[8] The remaining 25 to 35% of the wet-weight of cartilage is solid matrix, primarily type II collagen and large aggregating proteoglycans.[9] Composition and distribution of the solid matrix, which is also nonuniform in distribution,[10] influences tissue permeability,[11] producing regional variation in cartilage compressibility.[12]

Type II collagen fibrils in cartilage are organized into a structural framework that is important for normal cartilage biomechanics. As shown schematically in Figure 1 difference in orientation and structure of the collagen framework divide cartilage into three layers or zones based on depth from the articular surface. In the radial zone, near the cartilage–bone interface, fibrils are woven into large bundles aligned roughly perpendicular to the cortical surface. Toward the articular surface, in the transitional zone, fibers have a more oblique or random orientation. At the articular surface, fine collagen fibers measuring approximately 200 μm in aggregate thickness are oriented parallel to the surface, forming the superficial layer or lamina splendens. Preferential orientation of these superficial fibers varies along the joint surface and can be demonstrated as "splitlines" by puncturing the surface with a fine pointed probe, as initially described by Hultkrantz.[13]

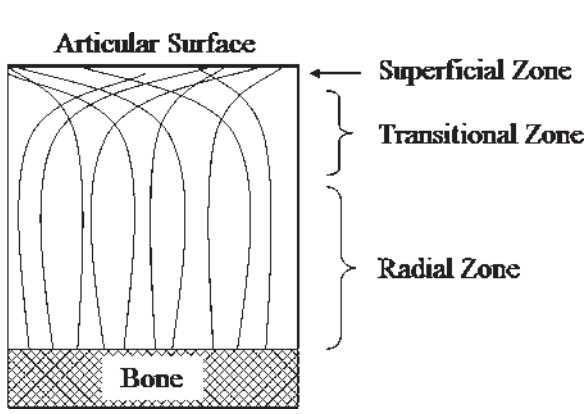

Figure 1 The arrangement of type II collagen fibrils in the extracellular matrix defines zones within cartilage. Near the bone–cartilage interface, collagen fibers in the radial zone are aligned perpendicular to the cortical surface. Random fiber orientation defines the transitional zone, and fibers at the surface are oriented parallel to the articular surface.

Interposed within the framework of the collagen fibrils are proteoglycans. The major proteoglycan aggrecan is comprised of a central core protein with multiple glycosylated side chains, primarily keratan sulfate, and chondroitin sulfate. Once secreted from the chondrocyte, aggrecan binds to hyaluronan to form large proteoglycan aggregates. In the extracellular matrix the negatively charged proteoglycan aggregates bind cations, primarily sodium. This increases the osmolarity of the extracellular matrix, drawing water into cartilage and causing the hydrated proteoglycan to swell. Because proteoglycan aggregates are confined within the collagen matrix, the degree of swelling is constrained, placing the collagen network under tension. At equilibrium, the tension in the collagen network balances the swelling pressure of the proteoglycans and provides cartilage with compressive stiffness.[14] This balance is essential for normal cartilage function.

When normal cartilage is compressed, cartilage water is the major weight-bearing pathway, carrying more than 90% of the load.[15] During compression there is movement of water through the solid matrix and exudation of fluid from the cartilage surface.[6] Because of high osmolarity, interstitial pressure, and fixed charge density of the solid matrix, water movement is counterbalanced by large frictional drag forces, which dissipate energy.[11] The capacity of water to dissipate energy from compressive loads protects the solid components of the extracellular matrix.

T2 OF NORMAL CARTILAGE

The T2 is a measurable MRI time constant that is sensitive to slow molecular motions of water protons[16,17] and anisotropy of the tissue matrix.[18] The limited mobility of cartilage water within a highly anisotropic matrix produces T2 values in the range of 15 ms to 60 ms, relatively short values for such a highly hydrated tissue. Cartilage T2 is relatively insensitive to magnitude of the magnetic field strength (B0) used in the measurement, with slightly lower T2 values observed at higher B0. In a study comparing effects of B0 field strength, Duewell and colleagues obtained a bulk T2 value of 39 ms at 1.5 T compared with 25 ms at 4.0 T.[19] Kaufman and coworkers, who reported in vivo values of human patellar cartilage of 35 ms at 1.5 T and 29 ms at 4.0 T,[20] confirmed this finding.

Several investigators have demonstrated multiexponential T2 decay of cartilage, suggestive of compartmentalization of cartilage water. Henkelman and associates reported a multiexponential T2 decay with two resolvable major peaks near 20 ms and 80 ms and a minor peak near 160 ms.[18] Mlynarik and colleagues

hypothesized that cartilage T2 decay is biexponential, "with one component decaying rapidly in the first 10 ms or so."[21] Two studies demonstrated multiexponential T2 decay in porcine cartilage plugs, indicative of three T2 populations.[22,23] Lusse and coworkers identified a short T2 component of approximately 1 ms, which they assigned to water inside collagen fibrils, and a minor long T2 component ranging from 150 ms to 300 ms, attributed to free water adsorbed on the cartilage surface. It is unlikely that these components contribute significantly to the cartilage MRI signal observed in clinical imaging or T2 mapping where TE values are generally greater than 10 ms. The major T2 component that was measured with cartilage T2 mapping had values in the range of 5 to 150 ms and was attributed to water within the proteoglycan matrix.[22]

Part of the multiexponential decay observed in bulk T2 measurements of cartilage is due to averaging of spatially different T2 values resulting from regional heterogeneity of the extracellular matrix. Within cartilage, zonal differences in composition and organization of the extracellular matrix produce a spatial variation of T2. When cartilage T2 values are spatially resolved with T2 maps, the decay of transverse magnetization within each individual pixel fits well to a monoexponential curve.[24,25] Several microimaging studies performed on excised cartilage samples demonstrate a reproducible spatial dependency of T2 values in articular cartilage.[21,26,27] Using magnetic resonance microscopy of excised canine articular cartilage plugs, Xia and colleagues demonstrated a relatively uniform distribution of T1 values; however, T2 values were nonuniform, increasing from 10 ms near subchondral bone to 50 ms at the articular surface.[26] A similar pattern of increasing T2 toward the articular surface was described in cartilage T2 maps obtained of excised cartilage samples from porcine humeral head,[27] rat patella,[28] human femoral head,[21] and knee specimens,[29] as well as in surgical specimens analyzed using a 1.5-T clinical magnetic resonance scanner.[25,30]

As demonstrated in Figure 2, this pattern of T2 spatial variation is also observed with in vivo T2 maps of human knees. In the first demonstration of in vivo cartilage T2 mapping, Dardzinski and associates demonstrated an increase in T2 from the deep radial zone (32 ± 1 ms) to the outer transitional zone of cartilage (67 ± 2 ms).[24] Subsequently Smith and colleagues[31] demonstrated there is less spatial variation in femoral and tibial cartilage where T2 increases from 46 ± 3 ms in the radial zone of femoral cartilage to 56 ± 8 ms at the articular surface, and 46 ± 4 ms in the radial zone of tibial cartilage to 55 ± 9 ms at the surface (mean T2 ± 99.99% CI). The in vivo T2 maps in this study also demonstrated a thin zone of high T2 located near the bone tissue interface. This zone is more difficult to interpret due to confounding artifact from volume averaging and chemical shift artifact. A similiar zone of high T2 has been observed in several microimaging studies.[32–35] In a study comparing MRI microscopy T2 maps with polarized light microscopy, Nieminen and coworkers demonstrated that this zone corresponds to a region of cartilage with high chondrocyte density.[33] It is possible that higher water content in the territorial matrix surrounding the chondrocyte results in relatively higher T2 values in this location.

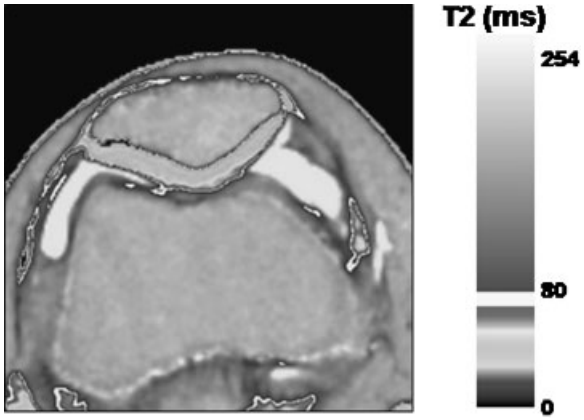

Figure 2 Color-scale T2 map demonstrating spatial variation in normal patellar cartilage T2 relaxation time of a 29-year-old female undergoing arthroscopic anterior cruciate ligament (ACL) repair. In normal cartilage, lower T2 values are observed in the radial zone and increase toward the articular surface.

Although initial in vivo T2 maps were obtained using a 3.0-T research scanner with gradient inserts, Dardzinski and associates recently demonstrated excellent agreement in cartilage T2 maps obtained at 1.5 T using standard clinical hardware.[36] In this study of pediatric patients age 5 to 17 years, patellar cartilage T2 values increased from 40 ± 1 ms in the deep radial zone to 54 ± 1 ms at the articular cartilage, and weight-bearing femoral cartilage T2 relaxation times increased from 46 ± 1 ms to 60 ± 2 ms. Although in vivo T2 mapping in humans has primarily focused on the knee joint where cartilage is thicker, high-resolution cartilage T2 maps of the proximal interphalangeal joint of the finger were recently presented.[37] A spatial variation in cartilage T2 similar to that of knee cartilage was observed with T2 values increasing from a minimum of 38 ms in the radial zone to 71 ms near the articular surface.

There is uniform agreement across all studies that regional differences in the extracellular matrix produce spatial variation in cartilage T2. Despite substantial technical differences between in vivo and ex vivo studies, there is still good agreement in absolute measured T2 values. As a general trend, T2 values of excised cartilage samples at static magnetic field strengths obtained at 7 T and above demonstrate slightly lower values than those observed in lower field strength in vivo studies.

SENSITIVITY OF T2 TO COMPOSITION AND STRUCTURE OF THE EXTRACELLULAR CARTILAGE MATRIX

Dependency of Cartilage T2 on Water Content

Lusse and colleagues have demonstrated a linear relationship between inverse water content and transverse relaxation rates, supporting fast exchange between bound and unbound cartilage water.[22] In a subsequent article these authors correlated spatially resolved cartilage T2 maps with regional water content of the deep and mid zones of cartilage.[25] The high correlation between water content and T2 allows cartilage water content to be estimated using fully relaxed cartilage T2 maps with an error of approximately 2 wt.%.[25] Given that water content in osteoarthritic cartilage increases by approximately 9% compared with normal cartilage,[7,8] the results of Lusse and associates predict T2 should be elevated by about 16 ms based on water content alone. A limitation of this direct calibration is that it does not account for the confounding influence of collagen fiber orientation on cartilage T2, and thus is currently limited to evaluation of cartilage in which fiber orientation is perpendicular to the applied magnetic field. This limitation may be removed if T2 and fully relaxed T1 maps are used to generate absolute proton density images. Using this approach Shapiro and coworkers measured regional water contents of 86% at the articular surface decreasing to 63% at the bone cartilage interface.[38] More recently, Liess and coworkers used in vivo cartilage T2 mapping to detect change in patellar cartilage water content resulting from compressive loading and recovery.[39]

Effect of Proteoglycan Concentration on Cartilage T2

Several studies using either enzymatically degraded or osteoarthritic cartilage specimens found cartilage T2 is insensitive to change in proteoglycan concentration. In a study comparing the effect of proteoglycan depletion on sodium and proton MRI, Borthakur and colleagues found cartilage T2 did not correlate with the degree of proteoglycan loss.[40] Reggate and coworkers found no significant change in cartilage T2 after enzymatic degradation of cartilage proteoglycans in the uncompressed state; however, when proteoglycan-depleted cartilage was placed under compression there was a statistically significant decrease in T2 compared to normal cartilage.[41] This is likely due to greater extrusion of water from the more compressible aggrecan-depleted cartilage. In a study evaluating the effect of proteoglycan depletion on cartilage relaxation properties, Toffanin and coworkers found extraction of proteoglycan and calcium ions from cartilage plugs had little effect on cartilage T2.[42]

Effect of Collagen Concentration on Cartilage T2

Several studies have shown perturbation of cartilage collagen rather than proteoglycan is the key determinant of change in cartilage T2. In a study comparing loaded and unloaded porcine cartilage from the humerus, Fragonas and coworkers found cartilage T2 was strongly influenced by collagen content but not by proteoglycans.[43] In evaluation of human cartilage specimens obtained from osteoarthritic knees, Mylnarik and associates found no significant difference in T2 between normal regions and sites with reduced proteoglycans.[44] However, T2 was elevated in sites of surface fibrillation, suggesting that damage of the collagen network was the cause of increased cartilage T2. In evaluating the effect of skeletal maturation on T2 mapping of rat patellar cartilage, Watrin and coworkers found collagen content was a greater determinant of MRI signal intensity than was proteoglycan concentration.[28] Nieminen and coworkers found no significant change in cartilage T2 following treatment with chondroitinase ABC to remove proteoglycans; however, there was a significant increase in T2 following treatment with collagenase.[45] These reports have led to the conclusion that cartilage T2 is primarily a measure of collagen network integrity and is relatively insensitive to loss of proteoglycan.

Effect of Tissue Anisotropy Cartilage T2

In addition to collagen concentration, the T2 of cartilage is influenced by anisotropy of the collagen framework. Many studies using excised cartilage specimens have demonstrated a strong orientation dependence of T2 of articular cartilage.[18,21,46–49] This orientation effect, first described in tendons,[50] is attributed to the highly structured collagen matrix within the radial zone of cartilage. For tissues such as cartilage that have restricted water mobility, tissue anisotropy provides an efficient T2 relaxation mechanism. However, when collagen fibers are oriented 55 degrees relative to the applied static magnetic field, B0, the nuclear dipole-dipole interaction is minimized resulting in a longer T2 decay.[51] This has been termed the "magic angle effect," derived from the technique of magic angle spinning used to shorten the T2 of crystalline solids in nuclear magnetic resonance (NMR) spectroscopy. In clinical MRI, the magic angle effect has been invoked to explain the etiology of focally increased signal observed on short TE images of cartilage with curved articular surfaces such as the femoral condyle[52] and talar dome.[53]

Using 14-μm resolution T2 maps of excised canine cartilage plugs, Xia identified three distinct zones of cartilage with different orientation dependence.[54] Cartilage immediately beneath the articular surface demonstrated less T2 anisotropy with increasing distance from the surface. A second region corresponding in location to the transitional zone of cartilage did not

demonstrate an orientation dependence of T2, suggesting fiber orientation in this zone was random. The third region, corresponding to the radial zone, demonstrated uniform orientation dependence, with T2 decreasing by approximately 80% when radial collagen fibers were aligned 0 degrees to B0 compared with a 55-degree orientation. Goodwin and colleagues[47] observed a similar orientation dependence of T2 of the radial zone; however, they also demonstrated a measurable orientation dependence in T2 of the transitional zone, suggesting this region contained tissue anisotropy. A more recent study by Xia and colleagues has also demonstrated orientation dependence of cartilage T2 in the transitional zone.[55]

In addition to studies on orientation dependence of cartilage T2, several studies have correlated cartilage T2 with collagen fibril anisotropy as measured with polarized light microscopy. Nieminen and coworkers demonstrated an inverse correlation between T2 and cartilage zones demonstrating collagen birefringence.[33] Xia and colleagues have also established a strong inverse correlation between optical retardation and spatially resolved cartilage T2.[55] The strong orientation dependence of cartilage T2 and correlation with results of polarized light microscopy support the conclusion that the T2 of normal cartilage is very sensitive to the highly anisotropic organization of the collagen matrix.

Few studies have evaluated the orientation dependence of cartilage T2 in the intact joint or in osteoarthritic cartilage. Wacker and coworkers evaluated MRI signal intensity of the femoral condyle as a function of orientation in asymptomatic children age 8 to 12 years.[52] Cartilage oriented 55 degrees to B0 was more homogeneous, with increased signal intensity, and loss of the laminar appearance was observed in cartilage at other orientations. A single study by Mosher and associates evaluated in vivo cartilage T2 of the femoral condyle as a function of orientation with the magnetic field.[56] Although the generally accepted model of collagen fiber orientation illustrated in Figure 1 would predict that the greatest variation in cartilage T2 should occur in the radial zone of cartilage, where anisotropy is greatest, their in vivo results demonstrated the largest variation in T2 as a function of field orientation occurred in the transitional zone. The authors hypothesized this apparent discrepancy was due to regional differences in cartilage compression and structure of the collagen matrix between loaded and unloaded cartilage.

Although cartilage plug studies are excellent models to study the orientation behavior of cartilage T2, the results of these studies should not be widely extrapolated to interpret observations made in the intact human joint. In nearly all ex vivo studies on orientation dependence of cartilage T2, cartilage samples were obtained from load-bearing regions of the joint. In the case of in vivo T2 mapping, regions of cartilage oriented oblique to the magnetic field, such as the posterior femoral condyle, are typically located in non–weight-bearing regions of the joint. There is growing evidence that collagen fibers are organized differently in weight-bearing and non–weight-bearing regions of the joint.[32,35,57] These results clearly indicate that a simplified model of collagen orientation such as that illustrated in Figure 1 is unable to describe the complex orientation dependence of in vivo cartilage T2 for an entire joint. In a recent study using magnetic resonance microimaging T2 maps and polarized light microscopy, Xia and colleagues demonstrated a complex multizone structure of the collagen matrix near the periphery of canine humeral head samples.[58] Near the periphery of the articular surface the MRI and polarized light microscopy results indicate fiber orientation is oblique to the articular surface with anisotropy extending into the transitional zone. These results support a model of collagen fiber orientation that accounts for variation between central and peripheral regions of the humeral head, as illustrated in Figure 3. A similar model of fiber orientation in which collagen fibers are arranged into discrete planes or

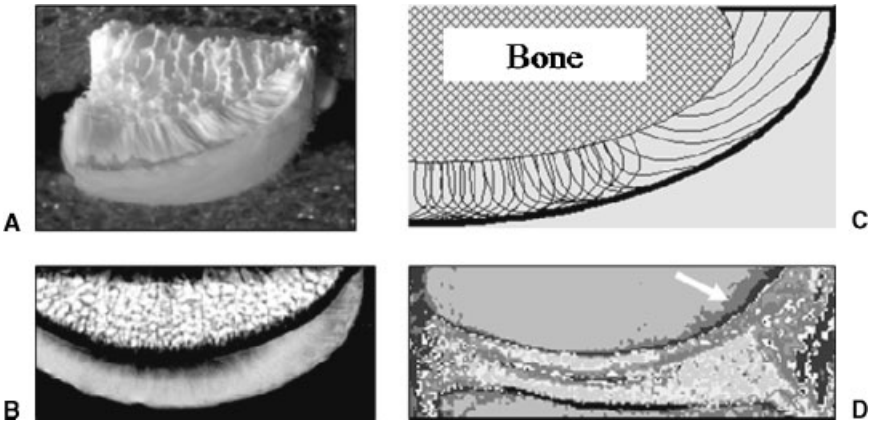

Figure 3 Cartilage freeze fracture pattern (A) and T2 maps (B), courtesy of Douglas Goodwin, Dartmouth Medical School, demonstrate oblique fracturing of cartilage and elevated T2 near the periphery of the articular surface indicative of regional differences in the extracellular matrix. Based on results of Xia and associates,[58] collagen fiber orientation near the periphery of the articular surface is oblique to bone, with anisotropy extending into the superficial transitional zone (C). As shown in (D), these regional differences within the joint are consistent with results of in vivo T2 maps of human femoral cartilage that demonstrate elevated T2 in the superficial cartilage of the posterior femoral condyle.[56]

"leaves" has been suggested by Goodwin and colleagues to explain the correlation of cartilage T2 maps with freeze fracture patterns of cartilage.[32,59] Interestingly, extrapolating this model to the peripheral region of the femoral condyle accurately predicts the in vivo measurements of Mosher and associates.[56]

Summary

Results of studies from several investigators support the theory that cartilage T2 is dependent on several properties of the extracellular cartilage matrix. The dominant factor appears to be tissue anisotropy as characterized by orientation of the collagen matrix. Other important factors include collagen fiber concentration and water content. There is general agreement that the cartilage T2 value is insensitive to changes in proteoglycan concentration.

APPLICATION OF CARTILAGE T2 MAPPING TO EVALUATION OF DAMAGED CARTILAGE

It has been proposed that collagen fatigue and breakdown are the earliest events in a destructive chain of events that leads to development of osteoarthritis.[60,61] The loss of restraint from the collagen framework allows swelling of the proteoglycans, resulting in an increase in cartilage water,[62] and a concurrent increase in cartilage permeability. Compressibility and permeability of cartilage are highly correlated with water content. As water content increases, the matrix of the tissue becomes more compressible,[63] and a greater portion of the load is carried by the solid components of the extracellular matrix. This subsequently leads to increased stress, structural fatigue, fragmentation of cartilage,[64] and ultimately to visible changes such as cartilage fibrillation and ulceration. Cartilage T2 is sensitive to the following processes that occur during the earliest stage of cartilage damage:

1. Fragmentation of the collagen matrix and loss of tissue anisotropy will increase cartilage T2. The strong orientation dependence of cartilage T2 and high correlation with polarized light microscopy suggest cartilage T2 may be a sensitive marker of the integrity of the collagen framework. Loss of collagen and proteoglycan orientation occurs early in canine models of osteoarthritis[65,66] and is observed in human osteoarthritis specimens[67,68]
2. Cartilage T2 increases linearly with cartilage water content with a slope of approximately 1.8 ms/% water content.[22,25] In osteoarthritis specimens, water content is increased by 9% compared to normal cartilage,[7,8] suggesting an increase in T2 of 16 ms. Based on the standard error of in vivo studies,[24,69] this should be within the limits of detection for clinical MRI T2 mapping.
3. Cartilage T2 increases with increasing water mobility.[17] With damage to cartilage there is increased permeability of the extracellular matrix and greater mobility of water.[63,70]

Because these mechanisms of damage occur concurrently, they will likely have a synergistic effect, thereby increasing the sensitivity of T2 to early cartilage degradation. Interestingly, because cartilage T2 appears insensitive to changes in proteoglycan concentration, it provides complementary information to techniques such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC)[71] or T1 rho mapping[72] that are primarily influenced by loss of proteoglycans.

TECHNICAL CONSIDERATIONS FOR IN VIVO CARTILAGE T2 MAPPING

Spatial Resolution of Cartilage T2 Maps

Thus far the majority of spatially resolved cartilage T2 maps were obtained on excised cartilage plugs using microimaging systems operating at 7.0 T or higher.[26,27,29,45,73,74] In these microimaging studies pixel resolution was in the range of 14 to 140 μm. The majority of human cartilage T2 maps obtained in vivo were obtained using a 3.0-T magnet using either a transmit receive surface coil to study patellar cartilage[24,69] or quadrature birdcage coil to evaluate the entire knee.[31,56] These studies were obtained with pixel resolution in the range of 300 to 500 μm, although recently in vivo T2 maps with 39-μm pixel resolution were obtained of cartilage of the proximal interphalangeal joint of the finger.[37] These human studies used specialized small bore gradient inserts and home-built quadrature birdcage or surface coils. More recently human cartilage T2 maps have been published using 1.5-T clinical magnetic resonance scanners with conventional hardware and software.[36,39,75] The pixel resolution of T2 maps in these studies was similar to that obtained at 3.0 T. In evaluation of human cartilage with clinical magnetic resonance instrumentation, it is possible to obtain spatially resolved cartilage T2 maps with approximately 8 to 10 pixels across the thickness of patellar cartilage and 5 to 8 pixels across the thinner femoral cartilage.

T2 Map Acquisition Parameters

For clinical cartilage T2 mapping it is necessary to sample the entire region of the joint in a limited period of time. Thus far T2 maps of knee articular cartilage have used two-dimensional acquisitions. The patellofemoral joint is best evaluated in the axial plane. Because early cartilage

degeneration of the femoral tibial joint often begins along the posterior weight-bearing surface and posterior femoral condyle, it is best evaluated in the sagittal plane. To achieve realistic patient imaging times, multiecho rather than single-echo acquisitions are used, acquiring 4 to 12 images with TE values in the range of 10 to 100 ms. Because of the rapid T2 decay of cartilage it is necessary to use minimum interecho spacing to accurately characterize the exponential decay of cartilage in the radial zone where T2 values can be as low as 10 to 20 ms. This necessitates using large receiver bandwidths. A disadvantage of using large receiver bandwidths to minimize interecho spacing is that it decreases the signal-to-noise ratio (SNR) of the images. Interecho spacing can be further reduced using an extremity transmit/receive coil, which decreases the radio frequency (RF) pulse duration.

The need to minimize interecho spacing while simultaneously maintaining high resolution either by using a small field-of view or a large image matrix places high demand on gradient strength and rise times. High gradient strength is necessary, preferably >3 G/cm (30 mT/m) for clinical scanners. For our studies obtained at 3.0 T, dedicated gradient inserts capable of 6 G/cm were used to allow faster gradient switching and higher bandwidth.[31] Using this system it is possible to obtain interecho spacing of 5 ms. Similar interecho times in fast spin echo (FSE) techniques have been obtained on older clinical systems.[76]

Calculating Cartilage T2 Maps

Once multiecho images are obtained, cartilage T2 maps are generated by fitting the signal intensity (SI) for the i^{th}, j^{th} pixel as a function of time, t, as follows,

$$\mathrm{SI_{i,j}(t)} = \mathrm{S0_{i,j}} \cdot \exp\left(\frac{-\mathrm{t}}{\mathrm{T2_{i,j}}}\right)^{1}$$

where $S0_{i,j}$ is the pixel intensity at $t=0$, and $T2_{i,j}$ is the T2 relaxation time constant of pixel i,j. A proton density map (M0) is generated from the pixel $S0_{i,j}$ data, and a T2 map is generated from the $T2_{i,j}$ data. Because the shortest cartilage T2 values are not visible with standard imaging techniques, most investigators have fit the signal intensity of each pixel to a single exponential decay. Because magnitude images are used in the calculation, the noise is always positive. In cases of poor SNR it is necessary to use a three-parameter fit to characterize the baseline, as the signal will not decay to zero intensity. In addition, as in vivo T2 maps use a multiecho acquisition, the signal in echoes 2 and later contain a significant contribution from stimulated echoes produced by imperfection of the slice refocusing pulse. Except for the first echo, the measured decay curve contains a mixture of T1 and T2 decay. The quality of the fit can be improved by excluding the first echo time.[24] Calculations by Maier and colleagues have shown that in phantom studies excluding the first echo from the fit can improve accuracy of the multiecho T2 measurement.[75] Once T2 values are calculated, a color-coded lookup table can be generated to display the T2 maps. Alternatively, translucent overlays can be superimposed on anatomic images in a method similar to that used in functional magnetic resonance imaging (fMRI). Although ordinal color T2 maps such as that displayed in Figure 3 highlight the underlying spatial variation in cartilage T2, they can overestimate T2 heterogeneity when values are near the transition values of the lookup table. We have found using a combination of a rainbow scale and heat scale map facilitates interpretation.

Although color T2 maps can be directly visualized for qualitative interpretation, dedicated software is necessary to extract quantitative information. We have written our own dedicated software (CCHIPS/IDL) to generate and facilitate quantitative analysis of color T2 maps. This software allows semiautomated segmentation of cartilage regions of interest. Although it is rather simple to calculate a bulk cartilage T2 value, this method of analysis is insensitive to localized areas of cartilage damage and results in large standard deviations due to the inherent spatial variation in T2 of normal cartilage. It is possible to account for the normal spatial variation by generating normalized cartilage T2 profiles, which describe the mean T2 value as a function of normalized distance from bone. With this method of analysis, it is possible to identify small regional differences in cartilage T2 between groups, for example, as a function of age.[69]

Artifacts in Cartilage T2 Mapping

STIMULATED ECHO

Multiple RF pulse sequences and imperfection in the 180-degree refocusing pulse gives rise to formation of stimulated echoes with accumulation of magnetization along the z-axis. As this component decays as a function of T1 rather than T2 decay, this will lead to an overestimation of the T2 value,[75,77] which will be greater for tissues with long T1 relative to T2. In a recent study Maier and colleagues calculated the error from stimulated echoes in the multiecho acquisition to be in the range of 10 to 13% in phantom studies and estimated it to be as high as 48% in measurement of in vivo cartilage T2.[75]

It is important to consider the effect of this error on precision and accuracy of clinical applications. It is well known that any T2 measurement obtained with an imaging technique is inaccurate compared to well-conducted spectroscopic studies.[77] However, with respect to clinical trials, the major concern is not accuracy of the T2 measurement itself but rather the validity, sensitivity,

and reproducibility of the measurement. The excellent agreement observed in T2 mapping studies using a wide range of instrumentation and acquisition parameters suggests that although this error impacts accuracy, it does not degrade precision. However, it is imperative that clinical applications of T2 mapping use appropriate standardization for data acquisition and quality controls to detect random and systematic error in the technique that can influence results in multicenter clinical trials.

MAGNETIZATION TRANSFER

In multislice acquisitions, off-resonance irradiation can produce incidental magnetization transfer that decreases the signal intensity of cartilage. Yao and colleagues[78] have estimated that in multislice FSE acquisitions signal intensity of cartilage can be decreased by as much as 30%. Maier and coworkers[75] have demonstrated incidental magnetization transfer in seven-slice T2 maps decreases the cartilage SNR by 20 to 50% and causes a significant decrease in measured T2 values compared with multiecho single-slice acquisitions. In studies by Dardzinski and associates[24] there was very good agreement between patellar cartilage T2 values obtained with a single-slice multiecho acquisition[24] and those obtained using a five-slice multiecho acquisition,[31,69] suggesting in their experimental protocol there was little effect from incidental magnetization transfer. Fortuitously, although the stimulated echo artifact from the multiecho sequence increases the measured cartilage T2, magnetization transfer from use of a multislice acquisition decreases T2.[75] Although the net effect is that these artifacts partially cancel, it must be noted that they originate from different sources and may behave differently depending on acquisition parameters used in the study.

VOLUME AVERAGING

In clinical cartilage T2 mapping spatial resolution is limited by time and SNR constraints. As nearly all articular surfaces possess some degree of curvature, there is inherent volume averaging at the bone–cartilage interface and articular surface that varies with location in the joint. Additionally, spatial heterogeneity in curvature of the collagen matrix will result in volume averaging of cartilage with differing orientation dependence.[78]

CHEMICAL SHIFT ARTIFACT

The effect of chemical shift from fatty marrow can produce artifacts at the bone–cartilage interface. This can be especially problematic at 3 T (125 MHz), where the fat to water separation of 3.5 ppm produces a shift of 438 Hz. Because there is a smaller bandwidth per pixel, this artifact is reduced by using a large receiver bandwidth necessary to minimize the interecho spacing. For example, using a 25-kHz bandwidth and a field of view of 12 cm in the frequency encoding direction, the fat resonance is shifted approximately 2.1 mm relative to water. However, increasing the bandwidth to 75 kHz decreases the shift to 0.7 mm. Chemical shift fat suppression can be used to reduce the artifact; however, additional studies are needed to determine how this will impact the measured T2 value. In some cases the effect of chemical shift in patellar cartilage can be further reduced by choosing the frequency encoding in the left-to-right direction; however, this can lead to pulsation artifact from the popliteal vessels.

APPLICATIONS OF T2 MEASUREMENTS TO STUDY OF CARTILAGE

Identification of Cartilage Damage

Increased cartilage T2 has been correlated with cartilage damage in both animal and clinical studies. Elevated T2 has been reported in a spontaneous model of osteoarthritis in the guinea pig,[79] Rhesus monkey,[80] and following proteolytic degradation of cartilage.[81] Nieminen has shown a significant increase in T2 of cartilage samples treated with collagenase.[45] Using magnetic microscopy T2 maps, Goodwin and Dunn associated foci of increased T2-weighted signal with cartilage damage.[74]

The majority of clinical studies have evaluated T2-weighted imaging in diagnosis of surface pathology. McCauley and coworkers[82] correlated foci of abnormal T2 signal or contour defect with the arthroscopic diagnosis of chondromalacia. Brown and Quinn found the most reliable indicators of chondromalacia are focal contour irregularities of hyaline cartilage and/or thinning of the hyaline cartilage associated with high signal intensity changes on T2-weighted images.[83] In a retrospective study of 75 patients, De Smet and coworkers found hyperintense signal abnormalities or fissures on sagittal T2-weighted images had high specificity but low sensitivity in diagnosis of patellar chondromalacia.[84] Bredella and colleagues reported similar results.[85] In a study comparing several MRI and computed tomography techniques in detection of patellar cartilage degeneration, Gagliardi and associates found T2-weighted images had sensitivity similar to that of computed tomography or magnetic resonance arthrography but noted that the T2-weighted images had a large number of false-positive studies when using arthrography as the gold standard.[86]

The primary focus of clinical evaluation of T2-weighted imaging in assessment of cartilage has been identification of focal surface defects. In this scenario, the primary consideration is contrast resolution between cartilage and synovial fluid. Thus far, there has not been a human clinical study correlating in vivo cartilage T2 maps with a measure of cartilage damage. Mosher and colleagues have presented preliminary results demonstrating abnormal cartilage T2 maps in patients with

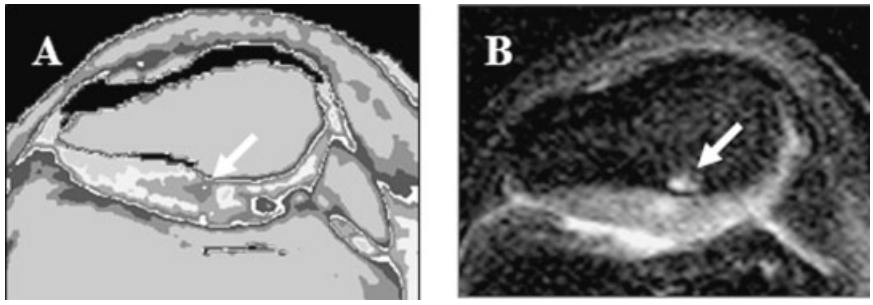

Figure 4 (A) Color T2 map demonstrating focally elevated cartilage T2 localized to the radial zone of cartilage in a patient with chronic anterior knee pain. (B) Corresponding clinical FSE T2-weighted image with fat suppression demonstrates elevated signal intensity at the site of measured high T2 values and associated high signal in the adjacent subchondral marrow.

clinical presentations of anterior knee pain and osteoarthritis.[69] They describe three patterns of abnormal T2 in patellar cartilage. The first pattern is focally elevated cartilage T2 limited to the radial zone (Figure 4). This pattern was associated with slightly elevated signal intensity on T2*-weighted gradient-echo images and loss of radial striation. The second pattern was that of heterogeneously elevated T2 associated with loss of the normal spatial variation in T2 seen in normal cartilage (Figure 5). This pattern was associated with surface irregularity on T2*-weighted imaging suggesting it may represent a more advanced stage of degeneration. A third pattern was superficial elevated T2 associated with a cartilage flap tear identified on anatomic imaging (Figure 6). Although these preliminary findings are encouraging, additional validation studies are needed to determine if sites of abnormal cartilage T2 are associated with structural cartilage damage and, more importantly, if sites of elevated T2 are prognostic for disease progression.

Aging

Several investigators have studied the age dependency of cartilage T2 maps. Most studies evaluated changes in cartilage T2 in animal models during the period of skeletal maturation. In a longitudinal study of Dunkin-Hartley guinea pigs, Watson and coworkers demonstrated increasing bulk cartilage T2 values from age 18 weeks to age 1 year.[79] Watrin and coworkers studied excised patellar cartilage of rats age 4 weeks to 6 months using magnetic resonance microscopy T2 maps that were correlated with biochemical analysis of the extracellular matrix.[28] Unlike the results of Watson's group, in this study maturation resulted in a decrease in cartilage T2 values. Biochemical analysis demonstrated a corresponding decrease in proteoglycan and increase in collagen content. The authors felt maturation changes in collagen content and organization were the primary determinants of age-related differences in cartilage T2. In a study of bovine cartilage, Olivier and coworkers found that variation in T2-weighted signal intensity correlated well with the proteoglycan/collagen ratio in animals 3 months of age but did not correlate in animals 3 years and 13 years of age.[87] They suggest that in skeletally mature animals other factors such as collagen fiber orientation or hydration may be greater determinants of cartilage T2.

As osteoarthritis is primarily a disease of the elderly, it is important to characterize cartilage T2 in the aged population. There has only been one study evaluating age-dependent changes of cartilage T2 in humans. In a study of asymptomatic male volunteers Mosher and colleagues demonstrated cartilage T2 values of the superficial transitional zone of individuals age 45 to 60 was elevated compared to individuals under age 45 years[69] (Figure 7). Given the strong dependency of cartilage on collagen fiber integrity, it is hypothesized that this observation reflects senescent denaturation of the collagen fiber matrix. The age dependency of cartilage T2 is compatible with the recognized pattern of development for osteoarthritis, which begins in the superficial layer of cartilage.[8] Prior immunohistochemistry studies have demonstrated a similar age-associated

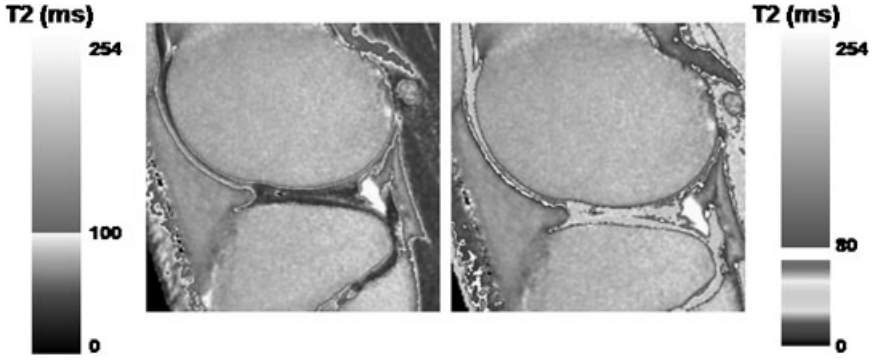

Figure 5 Heat scale (A) and color T2 (B) map demonstrating heterogeneously elevated cartilage T2 with loss of normal spatial variation compatible with diffuse cartilage degeneration. At arthroscopic surgery for repair of a torn medial meniscus, this region demonstrates fibrillation and deep erosion (Beguin and Locker grade III).

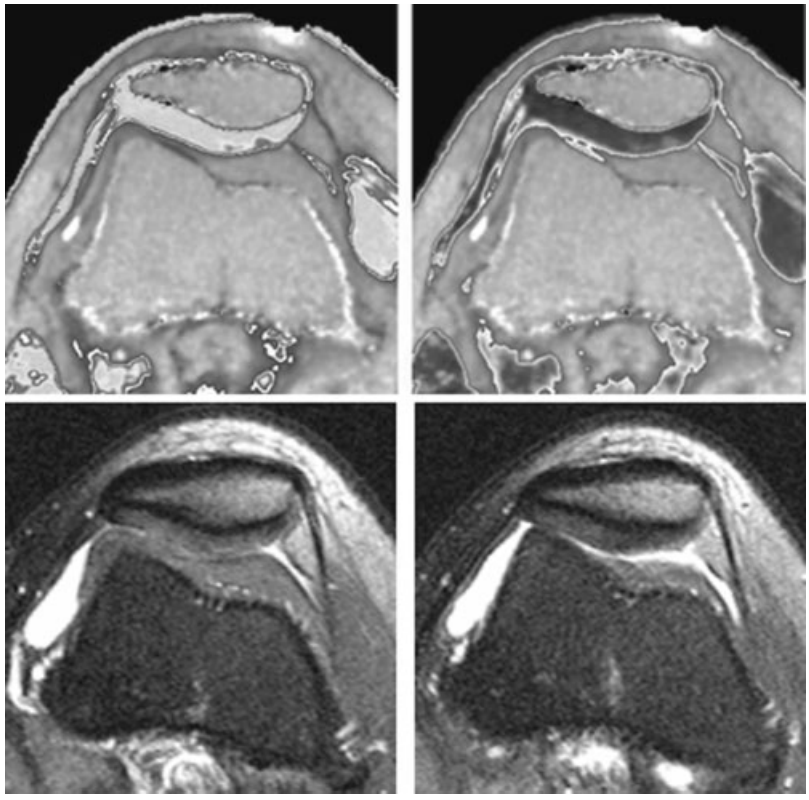

Figure 6 Superficial elevated T2 in 25-year-old male demonstrating focal superficial elevation in T2 of the medial facet of the patella. This finding is not apparent on the clinical MRI study obtained at 1.0 T (TR/TE: 3500 ms/45 ms). At arthroscopic surgery for ACL reconstruction, this site demonstrated focal cartilage fibrillation and superficial erosion (Beguin and Locker grade I/II).

pattern of type II collagen denaturation beginning superficially and progressing to deeper layers with age.[88] Although preliminary, results of in vivo T2 mapping suggest this may serve as a useful noninvasive tool to study age-related changes in the collagen fiber matrix.

Cartilage Biomechanics

A few studies have demonstrated that elevated cartilage T2 is associated with a change in the biomechanical response of cartilage to compression. In a study of enzymatically degraded cartilage, Nieminen and coworkers demonstrated that cartilage treated with collagenase had an elevated T2, which was associated with a statistically significant decrease in Young's modulus.[45] Similarly, Reggate and associates found a significant decrease in T2 when proteoglycan-depleted cartilage was placed under compression compared with untreated cartilage,[41] likely due to greater cartilage permeability. There has been limited application of cartilage T2 mapping to study of cartilage biomechanics in vivo. Liess and colleagues have reported using cartilage T2 mapping to monitor changes in patellar cartilage in response to exercise.[39] In this study, performed at 1.5 T, cartilage T2 maps performed after 45 minutes of recovery demonstrated a small but measurable increase in bulk T2 values compared with those obtained immediately after performing knee bend exercise.

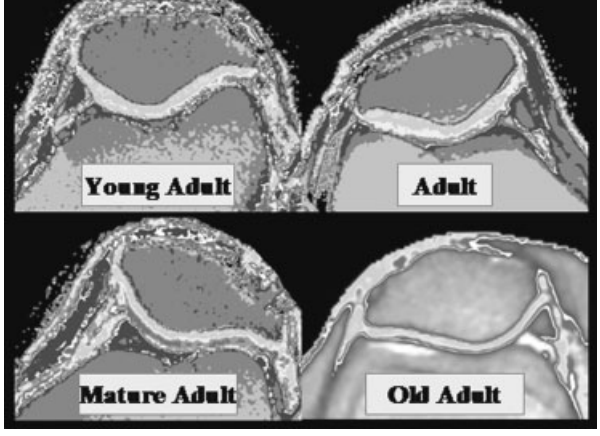

Figure 7 In asymptomatic individuals, differences in cartilage T2 are observed with increasing age. Individuals age 45 to 65 (mature adult) demonstrate longer T2 values in superficial cartilage. In individuals over age 65 (old adult) the elevation in T2 is observed throughout the entire thickness of cartilage.

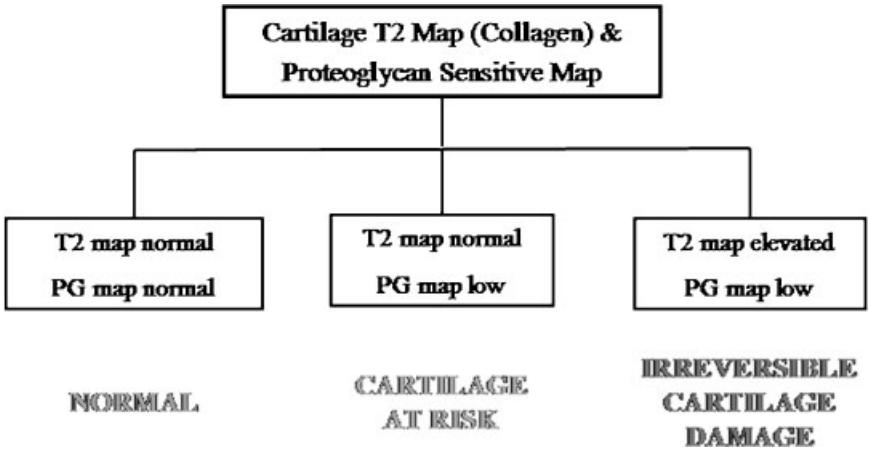

Figure 8 Proposed multispectral paradigm for identifying ''cartilage at risk'' that may be amenable to evaluation of chondroprotective therapy. Using a combination of cartilage T2 mapping and proteoglycan-sensitive techniques such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC)[71] or T1 rho mapping[72] it may be possible to differentiate cartilage with isolated proteoglycan depletion from cartilage with structural damage of the collagen matrix that may be less amenable to repair.

Future Application: Identifying ''Cartilage at Risk''

In development of chondroprotective therapy it will be desirable to develop MRI techniques that can identify cartilage that is capable of restoration. A similar approach is currently used in evaluation of neuroprotective agents in the treatment of stroke, where a combination of perfusion and diffusion-weighted imaging are used to differentiate "brain at risk" in the peri-infarct penumbra from irreversible tissue damage. Potentially a similar multispectral approach could be developed to identify "cartilage at risk." For example, using a combination of cartilage T2 mapping with proteoglycan-sensitive MRI techniques such as dGEMRIC[71] or T1 rho imaging,[72] it may be possible to categorize cartilage according to proteoglycan content and collagen matrix integrity. In theory, cartilage with isolated proteoglycan depletion and an intact collagen framework is less able to restrict water movement and thus "at risk" due to greater stress on the solid matrix; yet may be capable of functional recovery if proteoglycan synthesis is increased. Cartilage with substantial damage to the collagen matrix is unlikely to recover the fiber content and structural organization necessary for normal biomechanical function. As outlined in Figure 8, using a combination of cartilage T2 mapping and proteoglycan-sensitive parametric mapping it may be possible to identify cartilage in which there is irreversible damage to the collagen matrix (elevated T2) from that in which the collagen matrix is intact but proteoglycan concentration is low (normal cartilage T2, low proteoglycan score).

SUMMARY

The sensitivity of cartilage T2 relaxation time to biochemical and biophysical changes in the extracellular matrix make it a potential biomarker to study the structural integrity of the collagen matrix and changes in cartilage water content. Although the majority of cartilage T2 mapping studies have been performed using ultra-high field microscopy systems, preliminary results obtained from in vivo human cartilage demonstrate the feasibility of using these techniques for human imaging. Additional studies will be needed to determine the prognostic significance of elevated cartilage T2 and define the role of cartilage T2 mapping in the study of cartilage physiology and the efficacy of therapeutic intervention.

ACKNOWLEDGMENTS

The authors acknowledge grant support from NIH grant RO1 AR47179 and the Arthritis Foundation.

REFERENCES

1. McCauley TR, Recht MP, Disler DG. Clinical imaging of articular cartilage in the knee. Semin Musculoskelet Radiol 2001;5:293–304
2. Gray ML, Burstein D, Xia Y. Biochemical (and functional) imaging of articular cartilage. Semin Musculoskelet Radiol 2001;5:329–343
3. Moskowitz RW. Osteoarthritis: Diagnosis and Medical/Surgical Management. 3rd ed. Philadelphia: Saunders; 2001
4. Brandt KD, Doherty M, Lohmander LS. Osteoarthritis. Oxford Medical P. Oxford New York: Oxford University Press; 1998
5. Mow VC, Hayes WC. Basic Orthopaedic Biomechanics. 2nd ed. Philadelphia: Lippincott-Raven; 1997
6. Mow VC, Holmes MH, Lai WM. Fluid transport and mechanical properties of articular cartilage: a review. J Biomech 1984;17:377–394
7. Mankin HJ, Thrasher AZ. Water content and binding in normal and osteoarthritic human cartilage. J Bone Joint Surg Am 1975;57:76–80
8. Venn M, Maroudas A. Chemical composition and swelling of normal and osteoarthrotic femoral head cartilage. I. Chemical composition. Ann Rheum Dis 1977;36:121–129
9. Mankin HJ, Brandt KD. Biochemistry and metabolism of articular cartilage in osteoarthritis. In: Moskowitz RW, Goldberg VM, Mankin HJ, eds. Osteoarthritis: Diagnosis

and Medical/Surgical Management Philadelghia: W.B. Saunders; 1992:109–154
10. Lipshitz H. Etheredge RD, Glimcher MJ. Changes in the hexosamine content and swelling ratio of articular cartilage as functions of depth from the surface. J Bone Joint Surg Am 1976;58:1149–1153
11. Lai WM, Hou JS, Mow VC. A triphasic theory for the swelling and deformation behaviors of articular cartilage. J Biomech Eng 1991;113:245–258
12. Guilak F, Ratcliffe A, Lane N, Rosenwasser MP, Mow VC. Mechanical and biochemical changes in the superficial zone of articular cartilage in canine experimental osteoarthritis. J Orthop Res 1994;12:474–484
13. Hultkrantz W. Uber die spaltrichtungen der gelenkknorpel. Verhandlungen der anatomischen gesellschaft 1898;12:248
14. Maroudas A. Balance between swelling pressure and collagen tension in normal and degenerate cartilage. Nature 1976;260: 808–809
15. Mow VC, Kuei SC, Lai WM, Armstrong CG. Biphasic creep and stress relaxation of articular cartilage in compression? Theory and experiments. J Biomech Eng 1980;102:73–84
16. Harrison R, Bronskill MJ, Henkelman RM. Magnetization transfer and T2 relaxation components in tissue. Magn Reson Med 1995;33:490–496
17. Packer KJ. The dynamics of water in heterogeneous systems. Philos Trans R Soc Lond B Biol Sci 1977;278:59–87
18. Henkelman RM, Stanisz GJ, Kim JK, Bronskill MJ. Anisotropy of NMR properties of tissues. Magn Reson Med 1994;32:592–601
19. Duewell SH, Ceckler TL, Ong K, Wen H, Jaffer FA, Chesnick SA, et al. Musculoskeletal MR imaging at 4 T and at 1.5 T: comparison of relaxation times and image contrast. Radiology 1995;196:551–555
20. Kaufman J, Cecil KM, Kneeland J, Bolinger L. Structure in Images of articular cartilage at 4T. In: International Society for Magnetic Resonance in Medicine. New York: ISMRM; 1996
21. Mlynarik V, Degrassi A, Toffanin R, Vittur F, Cova M, Pozzi-Mucelli RS. Investigation of laminar appearance of articular cartilage by means of magnetic resonance microscopy. Magn Reson Imaging 1996;14:435–442
22. Lusse S, Knauss R, Werner A, Grunder W, Arnold K. Action of compression and cations on the proton and deuterium relaxation in cartilage. Magn Reson Med 1995;33:483–489
23. Mosher T, Dardzinski B, Smith M. Characterization of Multiple T2 Components in Articular Cartilage. In: Proceedings of the International Society for Magnetic Resonance in Medicine. Vancouver; International Society for Magnetic Resonance in Medicine: 1997
24. Dardzinski BJ, Mosher TJ, Li S, Van Slyke MA, Smith MB. Spatial variation of T2 in human articular cartilage. Radiology 1997;205:546–550
25. Lusse S, Claassen H, Gehrke T, Hassenpflug J, Schunke M, Heller M, et al. Evaluation of water content by spatially resolved transverse relaxation times of human articular cartilage. Magn Reson Imaging 2000;18:423–430
26. Xia Y, Farquhar T, Burton-Wurster N, Ray E, Jelinski LW. Diffusion and relaxation mapping of cartilage-bone plugs and excised disks using microscopic magnetic resonance imaging. Magn Reson Med 1994;31:273–282
27. Mlynarik V, Degrassi A, Toffanin R, Jarh O, Vittur F. A method for generating magnetic resonance microimaging T2 maps with low sensitivity to diffusion. Magn Reson Med 1996;35:423–425
28. Watrin A, Ruaud JP, Olivier PT, Guingamp NC, Gonord PD, Netter PA, et al. T2 mapping of rat patellar cartilage. Radiology 2001;219:395–402
29. Freeman DM, Bergman G, Glover G. Short TE MR microscopy: accurate measurement and zonal differentiation of normal hyaline cartilage. Magn Reson Med 1997;38:72–81
30. Frank LR, Wong EC, Luh WM, Ahn JM, Resnick D. Articular cartilage in the knee: mapping of the physiologic parameters at MR imaging with a local gradient coil—preliminary results. Radiology 1999;210:241–246
31. Smith HE, Mosher TJ, Dardzinski BJ, Collins BG, Collins CM, Yang QX, et al. Spatial variation in cartilage T2 of the knee. J Magn Reson Imaging 2001;14:50–55
32. Goodwin DW, Zhu H, Dunn JF. In vitro MR imaging of hyaline cartilage: correlation with scanning electron microscopy. AJR Am J Roentgenol 2000;174:405–409
33. Nieminen MT, Rieppo J, Toyras J, Hakumaki JM, Silvennoinen J, Hyttinen MM, et al. T2 relaxation reveals spatial collagen architecture in articular cartilage: a comparative quantitative MRI and polarized light microscopic study. Magn Reson Med 2001;46:487–493
34. Grunder W, Kanowski M, Wagner M, Werner A. Visualization of pressure distribution within loaded joint cartilage by application of angle-sensitive NMR microscopy. Magn Reson Med 2000;43:884–891
35. Xia Y. Heterogeneity of cartilage laminae in MR imaging. J Magn Reson Imaging 2000;11:686–693
36. Dardzinski BJ, Laor T, Schmidthorst VJ, Klosterman L, Graham TB. Mapping T2 relaxation time in the pediatric knee: feasibility with a clinical 1.5-T MR imaging system. Radiology 2002;225:233–239
37. Lazovic-Stojkovic J, Mosher TJ, Smith HE, Yang QX, Dardzinski BJ, Smith MB. In vivo T2 mapping of the proximal interphalangeal (PIP) joint at 3T. In: International Society for Magnetic Resonance in Medicine. Honolulu, HI; 2002
38. Shapiro EM, Borthakur A, Kaufman JH, Leigh JS, Reddy R. Water distribution patterns inside bovine articular cartilage as visualized by 1H magnetic resonance imaging. Osteoarthritis Cartilage 2001;9:533–538
39. Liess C, Lusse S, Karger N, Heller M, Gluer CC. Detection of changes in cartilage water content using MRI T(2)-mapping in vivo. Osteoarthritis Cartilage 2002;10:907–913
40. Borthakur A, Shapiro EM, Beers J, Kudchodkar S, Kneeland JB, Reddy R. Sensitivity of MRI to proteoglycan depletion in cartilage: comparison of sodium and proton MRI. Osteoarthritis Cartilage 2000;8:288–293
41. Regatte RR, Kaufman JH, Noyszewski EA, Reddy R. Sodium and proton MR properties of cartilage during compression. J Magn Reson Imaging 1999;10:961–967
42. Toffanin R, Mlynarik V, Russo S, Szomolanyi P, Piras A, Vittur F. Proteoglycan depletion and magnetic resonance parameters of articular cartilage. Arch Biochem Biophys 2001;390:235–242
43. Fragonas E, Mlynarik V, Jellus V, Micali F, Piras A, Toffanin R, et al. Correlation between biochemical composition and magnetic resonance appearance of articular cartilage. Osteoarthritis Cartilage 1998;6:24–32
44. Mlynarik V, Trattnig S, Huber M, Zembsch A, Imhof H. The role of relaxation times in monitoring proteoglycan depletion in articular cartilage. J Magn Reson Imaging 1999; 10:497–502

45. Nieminen MT, Toyras J, Rieppo J, Hakumaki JM, Silvennoinen J, Helminen HJ, et al. Quantitative MR microscopy of enzymatically degraded articular cartilage. Magn Reson Med 2000;43:676–681
46. Rubenstein JD, Kim JK, Morova-Protzner I, Stanchev PL, Henkelman RM. Effects of collagen orientation on MR imaging characteristics of bovine articular cartilage. Radiology 1993;188:219–226
47. Goodwin DW, Wadghiri YZ, Dunn JF. Micro-imaging of articular cartilage: T2, proton density, and the magic angle effect. Acad Radiol 1998;5:790–798
48. Xia Y, Farquhar T, Burton-Wurster N, Lust G. Origin of cartilage laminae in MRI. J Magn Reson Imaging 1997;7: 887–894
49. Kim DJ, Suh JS, Jeong EK, Shin KH, Yang WI. Correlation of laminated MR appearance of articular cartilage with histology, ascertained by artificial landmarks on the cartilage. J Magn Reson Imaging 1999;10:57–64
50. Fullerton GD, Cameron IL, Ord VA. Orientation of tendons in the magnetic field and its effect on T2 relaxation times. Radiology 1985;155:433–435
51. Hayes CW, Parellada JA. The magic angle effect in musculoskeletal MR imaging. Top Magn Reson Imaging 1996;8:51–56
52. Wacker FK, Bolze X, Felsenberg D, Wolf KJ. Orientation-dependent changes in MR signal intensity of articular cartilage: a manifestation of the "magic angle" effect. Skeletal Radiol 1998;27:306–310
53. Erickson SJ, Prost RW, Timins ME. The "magic angle" effect: background physics and clinical relevance [editorial]. Radiology 1993;188:23–25
54. Xia Y. Relaxation anisotropy in cartilage by NMR microscopy (muMRI) at 14- microm resolution. Magn Reson Med 1998; 39:941–949
55. Xia Y, Moody JB, Burton-Wurster N, Lust G. Quantitative in situ correlation between microscopic MRI and polarized light microscopy studies of articular cartilage. Osteoarthritis Cartilage 2001;9:393–406
56. Mosher TJ, Smith H, Dardzinski BJ, Schmithorst VJ, Smith MB. MR imaging and T2 mapping of femoral cartilage: in vivo determination of the magic angle effect. AJR Am J Roentgenol 2001;177:665–669
57. Gomez S, Toffanin R, Bernstorff S, Romanello M, Amenitsch H, Rappolt M, et al. Collagen fibrils are differently organized in weight-bearing and not-weight-bearing regions of pig articular cartilage. J Exp Zool 2000; 287:346–352
58. Xia Y, Moody JB, Alhadlaq H, Hu J. Imaging the physical and morphological properties of a multi-zone young articular cartilage at microscopic resolution. J Magn Reson Imaging 2003;17:365–374
59. Goodwin DW. Visualization of the macroscopic structure of hyaline cartilage with MR imaging. Semin Musculoskelet Radiol 2001;5:305–312
60. Maroudas AI. Balance between swelling pressure and collagen tension in normal and degenerate cartilage. Nature 1976;260: 808–809
61. Maroudas A, Venn M. Chemical composition and swelling of normal and osteoarthrotic femoral head cartilage. II. Swelling. Ann Rheum Dis 1977;36:399–406
62. Venn M. M.A., Chemical composition and swelling of normal and osteoarthritic femoral head cartilage. Ann Rheum Dis 1977;36:121–129
63. Armstrong CG, Mow VC. Variations in the intrinsic mechanical properties of human articular cartilage with age, degeneration, and water content. J Bone Joint Surg Am 1982; 64:88–94
64. Mow VC, Zhu W, Ratcliffe A. Structure and function of articular cartilage and meniscus. In: Mow VC, Hayes HC, eds. Basic Orthopedic Biomechanics. New York: Raven Press; 1991:143–189
65. Dunham J, Chambers MG, Jasani MK, Bitensky L, Chayen J. Changes in the orientation of proteoglycans during the early development of natural murine osteoarthritis. J Orthop Res 1990;8:101–104
66. Dunham J, Shackleton DR, Nahir AM, Billingham ME, Bitensky L, Chayen J, et al. Altered orientation of glycosaminoglycans and cellular changes in the tibial cartilage in the first two weeks of experimental canine osteoarthritis. J Orthop Res 1985;3:258–268
67. Mori Y, Kubo M, Okumo H, Kuroki Y. A scanning electron microscopic study of the degenerative cartilage in patellar chondropathy. Arthroscopy 1993;9:247–264
68. Muir H, Bullough P, Maroudas A. The distribution of collagen in human articular cartilage with some of its physiological implications. J Bone Joint Surg Br 1970;52: 554–563
69. Mosher TJ, Dardzinski BJ, Smith MB. Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2—preliminary findings at 3 T. Radiology 2000;214:259–266
70. Hoch DH, Grodzinsky AJ, Koob TJ, Albert ML, Eyre DR. Early changes in material properties of rabbit articular cartilage after meniscectomy. J Orthop Res 1983;1:4–12
71. Burstein D, Velyvis J, Scott KT, Stock KW, Kim YJ, Jaramillo D, et al. Protocol issues for delayed Gd(DTPA)(2-)-enhanced MRI (dGEMRIC) for clinical evaluation of articular cartilage. Magn Reson Med 2001;45:36–41
72. Akella SV, Regatte RR, Gougoutas AJ, Borthakur A, Shapiro EM, Kneeland JB, et al. Proteoglycan-induced changes in T1rho-relaxation of articular cartilage at 4T. Magn Reson Med 2001;46:419–423
73. Grunder W, Wagner M, Werner A. MR-microscopic visualization of anisotropic internal cartilage structures using the magic angle technique. Magn Reson Med 1998;39:376–382
74. Goodwin DW, Dunn JF. High-resolution magnetic resonance imaging of articular cartilage: correlation with histology and pathology. Top Magn Reson Imaging 1998;9:337–347
75. Maier CF, Tan SG, Hariharan H, Potter HG. T2 quantitation of articular cartilage at 1.5 T. J Magn Reson Imaging 2003;17:358–364
76. Vinitski S, Mitchell DG, Einstein SG, Rao VM, Flanders AE, Schweitzer ME, et al. Conventional and fast spin-echo MR imaging: minimizing echo time. J Magn Reson Imaging 1993;3:501–507
77. Poon CS, Henkelman RM. Practical T2 quantitation for clinical applications. J Magn Reson Imaging 1992;2:541–553
78. Xia Y, Moody JB, Alhadlaq H. Orientational dependence of T2 relaxation in articular cartilage: a microscopic MRI (microMRI) study. Magn Reson Med 2002;48:460–469
79. Watson PJ, Carpenter TA, Hall LD, Tyler JA. Cartilage swelling and loss in a spontaneous model of osteoarthritis visualized by magnetic resonance imaging. Osteoarthritis Cartilage 1996;4:197–207

80. Gahunia HK, Lemaire C, Babyn PS, Cross AR, Kessler MJ, Pritzker KP. Osteoarthritis in rhesus macaque knee joint: quantitative magnetic resonance imaging tissue characterization of articular cartilage. J Rheumatol 1995;22:1747–1756
81. Jelicks LA, Paul PK, O'Byrne E, Gupta RK. Hydrogen-1, sodium-23, and carbon-13 MR spectroscopy of cartilage degradation in vitro. J Magn Reson Imaging 1993;3:565–568
82. McCauley TR, Kier R, Lynch KJ, Jokl P. Chondromalacia patellae: diagnosis with MR imaging [see comments]. AJR Am J Roentgenol 1992;158:101–105
83. Brown TR, Quinn SF. Evaluation of chondromalacia of the patellofemoral compartment with axial magnetic resonance imaging. Skeletal Radiol 1993;22:325–328
84. De Smet AA, Monu JU, Fisher DR, Keene JS, Graf BK. Signs of patellar chondromalacia on sagittal T2-weighted magnetic resonance imaging. Skeletal Radiol 1992;21:103–105
85. Bredella MA, Tirman PF, Peterfy CG, Zarlingo M, Feller JF, Bost FW, et al. Accuracy of T2-weighted fast spin-echo MR imaging with fat saturation in detecting cartilage defects in the knee: comparison with arthroscopy in 130 patients. AJR Am J Roentgenol 1999;172:1073–1080
86. Gagliardi JA, Chung EM, Chandnani VP, Kesling KL, Christensen KP, Null RN, et al. Detection and staging of chondromalacia patellae: relative efficacies of conventional MR imaging, MR arthrography, and CT arthrography. AJR Am J Roentgenol 1994;163:629–636
87. Olivier P, Loeuille D, Watrin A, Walter F, Etienne S, Netter P, et al. Structural evaluation of articular cartilage: potential contribution of magnetic resonance techniques used in clinical practice. Arthritis Rheum 2001;44:2285–2295
88. Hollander AP, Pidoux I, Reiner A, Rorabeck C, Bourne R, Poole AR. Damage to type II collagen in aging and osteoarthritis starts at the articular surface, originates around chondrocytes, and extends into the cartilage with progressive degeneration. J Clin Invest 1995;96:2859–2869