

# Quantitative MRI techniques of cartilage composition

Stephen J. Matzat<sup>1</sup>, Jasper van Tiel<sup>2,3</sup>, Garry E. Gold<sup>1,4,5</sup>, Edwin H. G. Oei<sup>1,2</sup>

<sup>1</sup>Department of Radiology, Stanford University, CA, USA; <sup>2</sup>Department of Radiology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; <sup>3</sup>Department of Orthopedic Surgery, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; <sup>4</sup>Department of Orthopedic Surgery, Stanford University, CA, USA; <sup>5</sup>Department of Bioengineering, Stanford University, CA, USA

Corresponding to: Edwin H. G. Oei, MD, PhD. Department of Radiology, Erasmus MC, University Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands. Email: e.oei@erasmusmc.nl.

**Abstract:** Due to aging populations and increasing rates of obesity in the developed world, the prevalence of osteoarthritis (OA) is continually increasing. Decreasing the societal and patient burden of this disease motivates research in prevention, early detection of OA, and novel treatment strategies against OA. One key facet of this effort is the need to track the degradation of tissues within joints, especially cartilage. Currently, conventional imaging techniques provide accurate means to detect morphological deterioration of cartilage in the later stages of OA, but these methods are not sensitive to the subtle biochemical changes during early disease stages. Novel quantitative techniques with magnetic resonance imaging (MRI) provide direct and indirect assessments of cartilage composition, and thus allow for earlier detection and tracking of OA.

This review describes the most prominent quantitative MRI techniques to date—dGEMRIC, T2 mapping, T1rho mapping, and sodium imaging. Other, less-validated methods for quantifying cartilage composition are also described—Ultrashort echo time (UTE), gagCEST, and diffusion-weighted imaging (DWI). For each technique, this article discusses the proposed biochemical correlates, as well its advantages and limitations for clinical and research use. The article concludes with a detailed discussion of how the field of quantitative MRI has progressed to provide information regarding two specific patient populations through clinical research—patients with anterior cruciate ligament rupture and patients with impingement in the hip. While quantitative imaging techniques continue to rapidly evolve, specific challenges for each technique as well as challenges to clinical applications remain.

**Key Words:** Magnetic resonance imaging; cartilage; quantitative; biomarker; osteoarthritis (OA)



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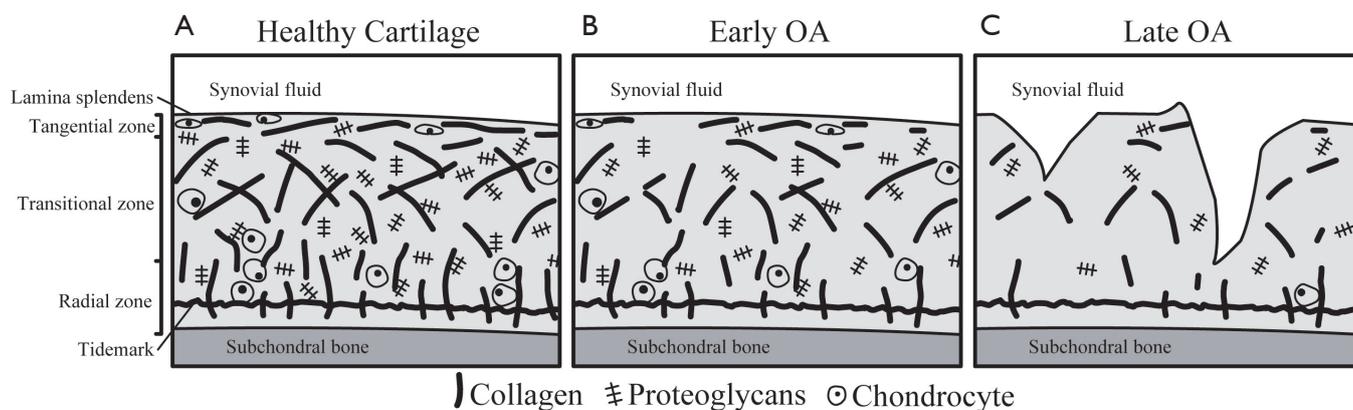
## Introduction

Osteoarthritis (OA) continues to place a large burden on society, most notably in countries with aging populations and rising rates of obesity (1,2). By 2030, 25% of the United States adult population is expected to be diagnosed with arthritis (3). As the number of patients increases, the total medical and productivity costs of the disease will also increase (4). Current research aims to prevent or reverse the effects of OA, so as to limit the individual and societal burden.

A critical aspect of this effort is the detection and

monitoring of disease progression, particularly as it relates to articular cartilage. Pain scores and radiography provide some objective clinical measures, but have demonstrated only weak correlation with actual disease severity and clinical symptoms (5,6).

Magnetic resonance imaging (MRI) has emerged as a useful tool for clinicians and scientists to assess the health of cartilage and other soft tissues. Conventional MRI provides sufficient tissue contrast to detect morphological changes in cartilage where radiography cannot (7). Using these techniques, semi-quantitative scoring systems have provided a means to measure and track progression of



**Figure 1** Representation of articular cartilage composition at three stages of health. Healthy cartilage (A) demonstrates several distinct layers between the articular surface and bone interface, marked by orientation of collagen fibrils. The collagen matrix is highly structured and proteoglycans are abundant. In early stages of OA (B), proteoglycans are initially depleted, and the collagen matrix begins to break down. In later stages of OA (C), proteoglycans become severely depleted and the morphological structure of the cartilage becomes compromised. Current research in quantitative MR applications to cartilage aims to detect early arthritic changes in cartilage before more severe morphological changes occur

OA (8). However, changes in cartilage physiology prior to morphological changes cannot be visualized or measured with conventional MRI (9). Detecting these more subtle changes is a priority due to the importance of detecting and managing disease at its earliest stages.

More advanced MRI techniques offer quantitative assessment of the biochemical composition of cartilage. These measures have a great potential to be used as biomarkers to track cartilage quality in clinical trials and in the study of OA pathogenesis. This article reviews the most common quantitative MR techniques and discusses the technical considerations, biochemical correlates, and advantages and disadvantages of each. Techniques discussed include delayed gadolinium enhanced MRI of cartilage (dGEMRIC), T2 mapping, T1rho mapping, sodium MRI, and a few of the more novel quantitative methods. The paper concludes with a conversation of how the field of quantitative MRI of cartilage has contributed to our understanding of two important clinical scenarios.

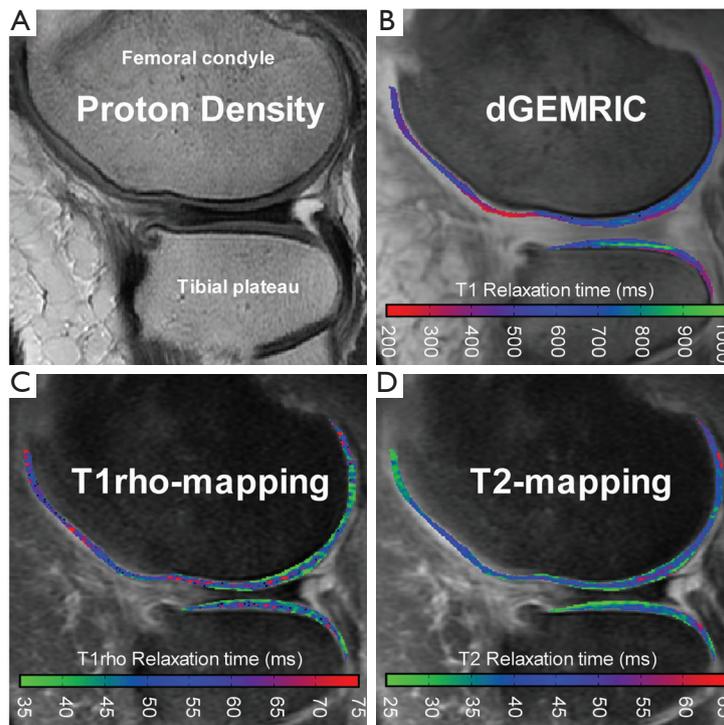
### Physiology of cartilage

Healthy articular cartilage is optimized to reduce friction and distribute weight evenly throughout the joint. It is hypocellular, with only 4% of its wet weight consisting of chondrocytes (10). The main components of articular cartilage are water (65% to 85% of weight) and the

extracellular matrix composed of type II collagen (15-20% of weight) and proteoglycans (PGs) (3-10% of weight) (11). The protein cores of PGs are lined by covalent attachments to glycosaminoglycans (GAGs), which confer negative charge due to the abundance of carboxyl and sulfate groups. This property fixes PGs to the extracellular matrix and attracts cations, such as sodium, which then draw water into the tissue to generate the swelling pressure of cartilage (10).

The biophysical structure of cartilage varies spatially between the bone interface and the articular surface to optimize different physiological characteristics (11). Several distinct layers describe this spatial variation according to depth from the articular surface (*Figure 1A*). The lamina splendens at the most superficial aspect of the articular surface is composed of a smooth, dense network of collagen fibers that work with synovial fluid to decrease friction and shear stress (12). Beneath this the tangential, or superficial, zone is characterized by collagen fibrils oriented parallel to the articular surface. Moving deeper, collagen orientation becomes anisotropic in the transitional zone (13) as it progresses into the radial zone, where fibrils are oriented perpendicular to the bone surface (14). Finally at the tidemark, collagen fibrils anchor cartilage to the subchondral bone.

The layers described above each confer resistance to different kinds of stresses, so variation is observed throughout the joint depending on the loads and stresses applied to particular regions of cartilage. For instance,



**Figure 2** Quantitative MR imaging of osteoarthritis. A number of quantitative MR techniques are increasingly applied to obtain biochemical information regarding cartilage health, especially in the knee. While a conventional MR image may show no major morphological defects in the cartilage (A), quantitative techniques provide evidence of early osteoarthritic changes (B-D). Spatial variation in dGEMRIC T1 and T1rho relaxation times in the anterior weight-bearing femoral cartilage and trochlear cartilage suggests an initial depletion of PGs. T2 mapping reveals minor variations in the posterior weight-bearing femoral cartilage that are also indicative of early OA

weight-bearing regions must resist strong compressive forces and therefore demonstrate thicker radial zones with greater uniformity in collagen orientation (15). Regions around the periphery of the joint are optimized to resist strong shear forces, so the transitional zone is thicker and collagen fibers within this zone are oriented in line with strongest forces (16).

In early OA, this cartilage microstructure breaks down and the tissue begins to lose functional capacity. Indications of these early changes include decreased organization of the collagen matrix, decreased fixed charge density (FCD) due to loss of PGs, and increased water content (*Figure 1B*) (17). These changes compromise the ability of cartilage to resist stress, resulting in further strain on the collagen matrix and leaving cartilage prone to more advanced morphological degenerative changes that conventional MRI techniques are sensitive to (*Figure 1C*) (18).

Quantitative MRI has demonstrated the ability to detect these changes prior to the morphological degradation of cartilage that follows as OA progresses. Thus, these novel

techniques provide numeric measures that correlate with various physiological properties of cartilage and can be used to detect disease earlier than conventional imaging methods.

## Quantitative MRI of cartilage

### *Delayed gadolinium enhanced MRI of cartilage (dGEMRIC)*

dGEMRIC utilizes the FCD within cartilage to indirectly measure GAG content. The contrast agent  $\text{Gd}(\text{DTPA})^{2-}$  is typically injected intravenously and distributed throughout the joint during exercise prior to scanning. Within cartilage, the contrast agent experiences a repulsive force from the negatively charged GAGs and accumulates accordingly in an inverse relationship with GAG content (19).  $\text{Gd}(\text{DTPA})^{2-}$  is also highly paramagnetic and promotes relaxation of nearby protons following a radiofrequency (RF) pulse. This results in a reduced T1 relaxation time in regions with high levels of contrast agent. Thus, T1 relaxation is used as the

quantitative outcome measure for dGEMRIC, with lower T1 indicating reduced GAG content compared to healthy cartilage (Figure 2B).

There has been some variation in the contrast administration and imaging protocol for dGEMRIC. Usually, 0.2 mmol/kg Gd(DTPA)<sup>2-</sup> is injected intravenously (20) and given time to distribute to the joint during exercise. However, alternative doses [0.1, 0.3 mmol/kg Gd(DTPA)<sup>2-</sup>] have been used (20,21) and injection is sometimes performed intra-articularly for hip imaging (22,23). The optimal delay time between injection of contrast and image acquisition also differs between joints (21). Several MRI pulse sequences can be used for dGEMRIC, most of which utilize multiple acquisitions with variable flip angles (24) or variable inversion times (25). These methods can be executed with gradient echo, spin echo, and look locker type techniques (25-27). Any of these techniques can yield T1 maps that can supply the dGEMRIC index for cartilage by averaging T1 relaxation times.

Correlation of dGEMRIC with GAG content has been validated through *in vitro* experiments (19,28) and has begun to be validated *in vivo* (29). Due to its robustness and its ability to be used in longitudinal research (30-32), dGEMRIC has been successfully applied to a wide range of clinical studies. These include tracking cartilage change after anterior cruciate ligament tear (33), performing regional analysis of patients with femoroacetabular impingement (34), and measuring damage to finger cartilage in rheumatoid arthritis (35).

While dGEMRIC remains the most established imaging tool for indirect measurement of GAG content *in vivo*, there are several limitations that must be considered. First, administration of contrast agent adds an invasive and potentially risky element to the protocol that is not present in other quantitative MR methods. Additionally, the delay required for the contrast to distribute throughout the joint makes for a long examination time.

### T2 mapping

T2 relaxation time relates to the speed by which nuclei lose phase coherence following excitation (36). This loss of coherence results in an exponential decay of transverse magnetization and NMR signal. The rate of this decay is largely influenced by the presence of free water molecules, which slow down the loss of transverse magnetization.

Due to this relationship between T2 relaxation and free water, T2 mapping is a commonly used tool for measuring

water content in cartilage (37). This method allows for the indirect assessment of collagen content and orientation, which are important indicators for early OA (38). The collagen matrix of healthy cartilage traps and immobilizes water protons, so signal intensity on T2-weighted images is low. In the earliest stages of OA, the matrix begins to break down and becomes more permeable to water, causing an elevation in T2 relaxation times (Figure 2D) (39).

T2 mapping typically involves imaging with multiple spin echo sequences at different echo times (37). 2D sequences suffer from long acquisition times and have begun to be replaced by several 3D sequences that capture the whole joint in shorter time (40-43). An additional 3D sequence known as the Double Echo Steady State (3D-DESS) allows for simultaneous estimation of T2 and apparent diffusion coefficient (ADC) values in cartilage (44,45).

The sensitivity of T2 mapping to detect changes in collagen content and orientation has been validated both *in vitro* (46,47) and *in vivo* (39,48,49). While this relationship between T2 and collagen is well-established, new evidence suggests that T2 may also be sensitive to proteoglycan content (50-52), indicating that negatively charged GAGs influence the interaction of water protons. Regardless of the precise biochemical correlate, T2 mapping has proven useful in many clinical studies. To provide a few examples, it has been used to track cartilage quality in the hips of patients with congenital hip dysplasia (53), in the knee after ACL reconstruction (54), and in the ankle after cartilage repair surgery (55).

T2 mapping is a powerful tool because it provides information regarding cartilage health without the need for contrast. However, one drawback that must be understood is the susceptibility of T2 relaxation to the magic angle effect (56). Collagen fibers at certain orientations to the B<sub>0</sub> field influence the estimation of T2 relaxation and render T2 mapping inaccurate for these regions of cartilage. Additionally, depletion of proteoglycans is believed to occur prior to degradation of the collagen matrix in OA progression (57), so T2 mapping may not detect changes as early as techniques sensitive to GAG content, such as dGEMRIC or T1rho.

### T1rho mapping

T1rho relaxation, or relaxation in the rotating frame, refers to the dissipation of energy by protons under the constant influence of a weak RF, or spin lock, pulse in the transverse plane (58). This pulse locks protons in phase to sequester

T2 relaxation, and protons instead relax with the time constant T1rho.

The relaxation behavior of water in close proximity to large macromolecules (i.e., PGs) is affected by the presence of the spin lock pulse. These water protons dissipate energy faster than free water not associated with macromolecules. Due to these properties of T1rho relaxation, this quantitative measure is believed to be inversely correlated with PG or GAG content, providing an indication of early OA (Figure 2C) (59).

T1rho mapping can be accomplished with spin echo or gradient echo type pulse sequences.

The inverse relationship between T1rho relaxation time and PG/GAG content has been validated *in vitro* with bovine cartilage (60,61) and *ex vivo* with human cartilage specimens (50,62), which demonstrated a moderate to good correlation. More recent research attempting to validate this relationship *in vivo* has offered mixed results with weaker correlations than *in vitro* and *ex vivo* studies (51,52,63). Still, T1rho mapping has been used in a number of clinical research studies to track cartilage degradation, including patients with ACL reconstruction (64) and cartilage repair surgeries (65,66). Studies of healthy cartilage indicate that T1rho increases with age (67) and to decreases immediately following running and jumping tasks (68,69).

The major advantage of T1rho is it allows for noninvasive measurement of GAG content. One notable drawback of this method is the relatively high specific absorption rate (SAR) and potential tissue heating that results from the RF power during the spin lock preparation pulse (70).

### Sodium MRI

Sodium MRI provides an additional technique for quantifying the biochemical composition of cartilage. As discussed above, sodium cations ( $^{23}\text{Na}$ ) are attracted to negatively charged GAGs and are therefore distributed in accordance with GAG content. Similar to  $^1\text{H}$ ,  $^{23}\text{Na}$  generates an MR signal (71) that can be used to indirectly assess GAG distribution.

The ability of sodium MRI to detect differences in GAG concentration has been validated *in vitro* (72,73).

Numerous limitations of sodium MRI make it a less popular technique for tracking OA progression in clinical research. It is more difficult to generate an MR signal with sodium because  $^{23}\text{Na}$  ions exist at much lower concentrations than  $^1\text{H}$  ions within the body. In general,

sufficient signal-to-noise ratio can only be achieved at higher magnetic field strengths, with special transmit and receive coils, and with long imaging times (74).

### Ultrashort TE, gagCEST, and diffusion-weighted imaging (DWI)

Several other MR techniques exist that show promise in providing reliable quantitative analysis of cartilage composition. These are more novel than the aforementioned techniques and have not yet undergone rigorous validation experiments. Still, these will be of great importance looking to the future in cartilage imaging, as they likely provide new biochemical correlates and may prove more sensitive to early disease progression.

Tissues with short intrinsic relaxation times cannot be adequately assessed with the aforementioned techniques because they do not generate enough signal with MRI. These tissues include menisci, tendons, ligaments, entheses, and deep radial and calcified layers of cartilage, which all have T2\* relaxation times below 5 ms (75). Ultrashort TE (UTE) pulse sequences enable T2- and T2\* weighted imaging of these tissues by using an extremely short echo time (TE). T1 and T1rho measurements may also be obtained from deep cartilage layers with UTE (76).

UTE has yet to be applied in clinical research, and its correlation with aspects of cartilage composition still must be validated. A repeatability study of T2\* mapping with UTE reported positive results *in vivo* with healthy volunteers (77). Further application of this technique to the deep radial and calcified layers of cartilage may provide critical information regarding OA pathogenesis and progression. Still, it is important to note that UTE requires lengthy scan times and will likely require development of specialized MR equipment to overcome technical challenges affecting image quality (78).

gagCEST is another novel quantitative MR technique that takes advantage of a principle known as magnetization transfer contrast (MTC) (79). MTC involves an off-resonance preparatory pulse that selectively excites and saturates immobile protons bound to macromolecules. Some of this induced transverse magnetization transfers to nearby free water protons, resulting in faster dephasing and reduced signal in free water. This creates contrast between regions with variable rates of magnetization transfer. Chemical exchange saturation transfer (CEST) is a similar technique that saturates exchangeable protons that move from macromolecules to free water, rather

than transferring magnetization to free water. In articular cartilage, hydroxyl residues on GAGs are selectively excited to provide contrast between regions of high and low GAG content—gagCEST (80). This provides a direct measurement of GAG content, expressed as a magnetization transfer asymmetry value/percentage. Regions of low GAG content have low magnetization transfer and low asymmetry value.

The sensitivity of gagCEST to GAG content has been validated *in vitro* by comparison to sodium MRI of both healthy and diseased cartilage (81). A recent application to clinical research includes tracking change after cartilage repair with osteochondral transplantation in the knee (82). While gagCEST will continue to be applied to clinical research, several drawbacks of this technique should be understood. First, imaging at 3T is difficult due to low SNR and susceptibility of the technique to  $B_0$  inhomogeneities (83). Additionally, data analysis necessitates sophisticated post-processing tools.

Diffusion-weighted imaging (DWI) has recently provided yet another quantitative technique for measuring cartilage composition. This technique measures the translational motion of extracellular water molecules by applying diffusion-sensitizing gradients that cause mobile water protons to lose phase coherence and MR signal (84). The outcome measure for DWI is called the apparent diffusion coefficient (ADC), with higher ADC values indicating more translational motion of protons. In cartilage, this movement of free water is dependent upon the quality and orientation of collagen fibers. In cartilage, elevated ADC is believed to result from degradation of the collagen matrix, thus indicating early degeneration of cartilage (85).

As mentioned earlier, the Double Echo Steady State (DESS) is a recently developed sequence that allows for the estimation of both T2 and ADC (44). DWI has been used in a handful of clinical studies to track cartilage composition following repair surgery (55,86,87). Still, applications of DWI to cartilage imaging have proven challenging due to technical considerations for cartilage imaging, and no biochemical correlation has yet been verified.

### Quantitative MRI and clinical research

Each of the above techniques has contributed to the growing body of research on OA, cartilage degradation, and treatment of focal cartilage lesions. Some of the successful clinical applications of each have briefly been mentioned, but it is also important to step back and see how the field

of quantitative MRI has worked to provide knowledge regarding specific patient groups and pathologies. Two examples that are representative of this work include the growing body of research in patients with anterior cruciate ligament (ACL) tear in the knee and patients with femoroacetabular impingement (FAI) in the hip. Both of these patient groups are believed to be predisposed to early development of OA, making them ideal subjects for research of cartilage biochemistry.

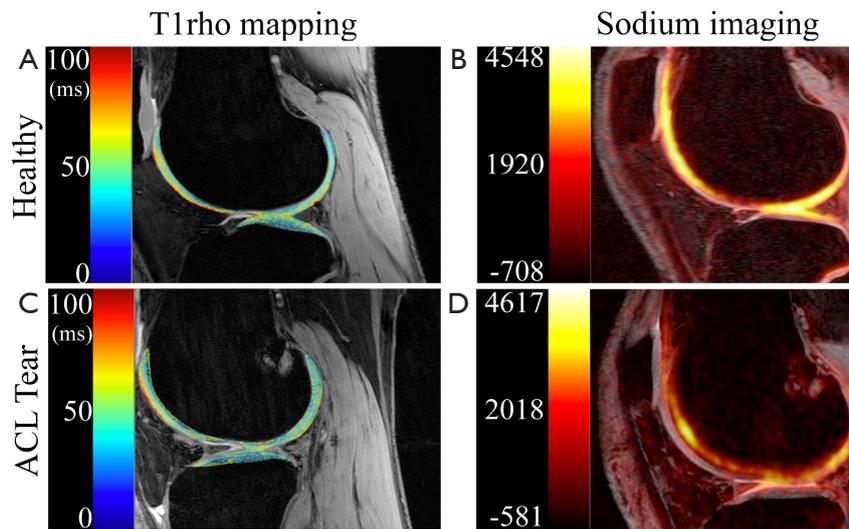
#### ACL tear patients

Acute ACL rupture is a common traumatic injury in the active population and many of these patients develop OA in the knee (88). In a recent report on 121 ACL rupture patients five years following injury, 12% demonstrated radiographic tibiofemoral OA and 19% demonstrated radiographic patellofemoral OA (89). Ten years following ACL rupture, up to 38% of patients have presented with radiographic OA (90). These relatively high rates of OA motivate research in early detection of cartilage degradation and quantitative MRI provides a promising route to accomplish this. Even within weeks of an ACL rupture, quantitative MRI has been able to demonstrate changes in the biochemical composition of cartilage (*Figure 3*). These effects, along with potential recovery and longer term progression of OA, are of interest to clinicians monitoring cartilage health.

Following ACL rupture, studies have revealed elevated T1rho relaxation times in regions near bone marrow edema-like lesions (91,92), indicating rapid biochemical changes to cartilage near the site of trauma that persist up to a year following injury (93).

Recently, a study applied dGEMRIC, T2, and T1rho mapping to ACL rupture patients shortly after injury (94). Results revealed elevated T1rho and T2 relaxation times, but no focal GAG loss detected by dGEMRIC. These data suggest the traumatic event may cause an influx of water into cartilage but cause no substantial change to the supporting GAGs. This demonstrates how applications of multiple quantitative techniques can provide novel information regarding OA progression that cannot be inferred with results from a single technique.

Longitudinal studies have revealed these quantitative changes don't necessarily recover up to one year after the initial traumatic event (95). This suggests that biochemical damage induced by ACL rupture persists, and that progression towards OA begins soon after the injury.



**Figure 3** Quantitative MR imaging of ACL tear knees. T1rho mapping (A,B) is applied to demonstrate the traumatic effects of ACL tear on cartilage biochemistry, compared to healthy controls. Increased heterogeneity of T1rho relaxation times within weeks of injury (B) suggests these changes occur along with the traumatic event. Sodium imaging (C,D) is also applied to reveal the impact of ACL tear on GAG content (Courtesy of Caroline Jordan, Ph.D., Stanford Dept. of Bioengineering)

The cumulative results from quantitative MRI experiments have revealed much about cartilage damage following ACL tear. These methods will continue to be applied to track the success of clinical decisions and to supply further information regarding pathogenesis of OA in the knee.

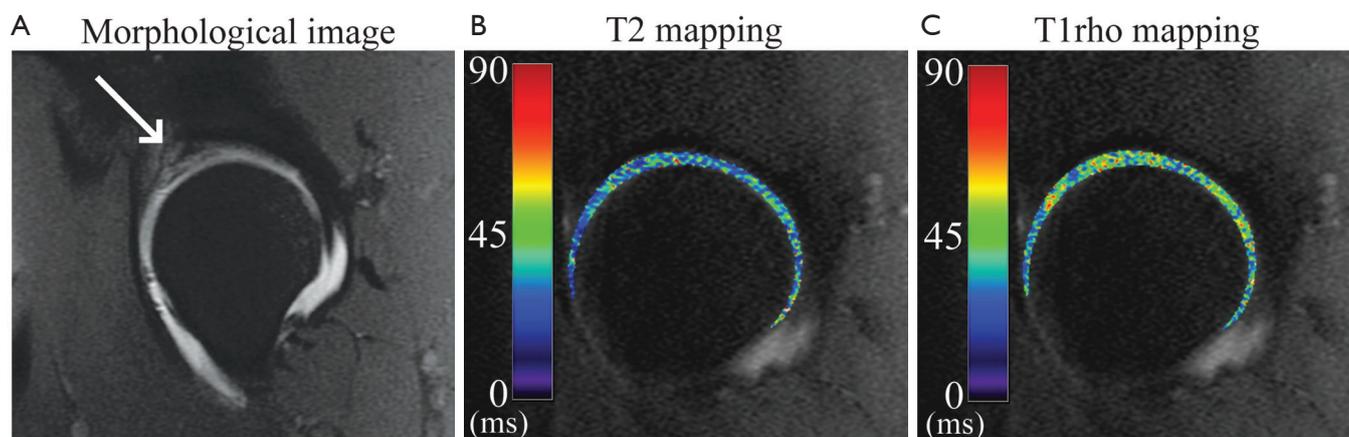
### *Femoroacetabular impingement (FAI)*

FAI is a condition caused by bone abnormalities in the hip that lead to excess friction between the femoral head, neck, and acetabular rim. Two different mechanisms of impingement are associated with FAI (cam and pincer impingement), and both are believed to be responsible for different distributions of stress around the joint. Cam impingement is caused by a lesion on the head/neck junction of the femur that causes the femoral head to be non-spherical (96). During flexion, this eccentric lesion is forced into the anterior rim of the acetabulum, compressing acetabular cartilage at its junction with the labrum (97). This stress can cause a separation of articular cartilage from the labrum and eventually lead to hip OA (98). Pincer impingement results from an overly-deep acetabulum with excessive coverage around the femoral head. Such over-coverage causes circumferential abutment between the neck of the femur and the acetabular rim, commonly

resulting in compression of the labrum and increased stress to nearby acetabular cartilage around the periphery of the joint (97). While FAI may present as a single mechanism of impingement, most cases demonstrate characteristics of both cam and pincer impingement, referred to as mixed impingement (99).

It is important to note several challenges specific to imaging of hip cartilage. It is difficult to get adequate MR signal due the depth of the hip joint within the body, and relatively high spatial resolution is required to distinguish the layers of femoral and acetabular cartilage since they are only 1-3 mm thick (100). Additionally, the strong curvature of the articular surface renders hip cartilage prone magic angle effects in regions with certain orientation to  $B_0$  (101). Both in-plane and out-of-plane partial volume effects resulting from this curvature also make hip imaging challenging.

dGEMRIC has been one of the leading quantitative techniques for hip cartilage imaging. In a study by Bittersohl *et al.*, dGEMRIC was applied to 26 symptomatic FAI patients and ten asymptomatic volunteers (102). Comparison between groups revealed significantly lower T1 relaxation times in FAI cartilage, suggesting a marked reduction in GAG content. Additionally, regional analysis of purely cam- and pincer-types revealed concentration of GAG depletion in the anterior-superior region for cam-



**Figure 4** Quantitative MRI of hip impingement. Sagittal T1-weighted image (A) of a patient with mixed impingement demonstrates swelling and increased signal in the anterior-superior labrum, suggesting a tear. T2 (B) and T1rho (C) maps of the same patient demonstrate applications of quantitative imaging to the hip

type and more circumferential GAG depletion for pincer-type. A later study by the same group compared dGEMRIC imaging to intra-operative findings and found reduced T1 values in damaged cartilage (103). Still, T1 values were only weakly correlated with intra-operative determination of healthy versus damaged cartilage. Overall, applications of dGEMRIC suggest that GAG depletion occurs in patients with FAI, and that these effects may vary regionally according to the mechanism of impingement.

T2\* mapping has also made a contribution to research on cartilage damage with FAI. A recent study demonstrated a significant reduction in T2\* relaxation time for morphologically normal-appearing cartilage in FAI patients compared to cartilage of asymptomatic volunteers (104). This suggests that early biochemical changes to cartilage are occurring with impingement, and that novel quantitative MR techniques may be sensitive to such changes.

T1rho and T2 mapping also continue to be applied to image cartilage in the hip (Figure 4), and provide a non-invasive measure of cartilage composition.

One major difficulty in validating quantitative MRI is that there is no highly-sensitive reference standard with which to compare. As demonstrated by the studies above, quantitative outcomes were compared with morphological findings from conventional MRI, with intra-operative findings, or with data from healthy subjects. None of these are sensitive to early biochemical degradation of cartilage, so it is difficult to firmly establish that quantitative differences are due to changes such as PG loss, collagen matrix decomposition, and increased water content. Future validation with histological grading of cartilage will serve as

a powerful test of quantitative techniques in hip cartilage.

## Conclusions

The field of quantitative MRI is rapidly evolving, and while more established techniques are applied to clinical research, new techniques continue to be tested as methods for capturing cartilage composition. Each offers unique advantages and disadvantages for cartilage imaging. Looking to the future, determination of biochemical correlates for each quantitative technique will be essential in developing and tracking interventions to prevent OA progression. Finally, while research often focuses on developing and validating single techniques, successful applications to clinical research may come best when combining multiple quantitative methods.

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