Introduction

Conventional MR images are qualitative and rely on subjective interpretation of changes in tissue appearance to diagnose injury or disease. Several inherent tissue properties contribute to a tissue's appearance in an MR image. These properties include the tissue's T1 time, T2 time, and proton density. Specific MR pulse sequences are designed to generate image contrast based on these inherent properties, creating T1-weighted, T2-weighted, or proton density-weighted images, respectively. Depending on the tissue of interest and underlying disease process, these images can be used to qualitatively assess a tissue for the presence of pathology. With respect to cartilage of the TMJ and other joints, conventional MR images are limited to detecting morphological changes, such as thinning or loss, of the articular cartilage. Once cartilage loss is detectable by conventional MR, the joint has already experienced irreversible changes leading toward osteoarthritis.

Due to the qualitative nature of conventional MR, much of what we know about naturally occurring temporomandibular joint disorders (TMD) is morphological in nature. Similar to cartilage disease in other joints, the biochemical and microstructural changes that occur during TMD are rarely characterized until the changes are extensive. Diagnostic imaging techniques capable of accurately detecting subtle biochemical and microstructural changes in the joint tissues are needed to better understand TMD pathophysiology and to diagnose patients early in the course of disease.

Beyond the production of images with different tissue contrast, it is possible to quantify a tissue's inherent MR-related properties, which aids in the detection of subtle tissue pathology. Examples of quantitative MR (qMRI) techniques include T1 mapping, T2 mapping, T1rho mapping, and delayed gadolinium-enhanced MR of cartilage (dGEMRIC), among others. Each of these will be discussed in greater detail later in this chapter. Although the research discussed in this chapter refers to articular cartilage of other joints, it will be also be informative for the TMJ.

Essential Principles of qMRI

Once placed into the strong, primary magnetic field (denoted B_0) of an MR system, protons exhibit important behaviors relevant to understanding quantitative MR:

- Protons align with B_0, creating net magnetization parallel to B_0, referred to as **longitudinal magnetization**
- Protons precess, or wobble, around longitudinal axis with frequency proportional to magnetic field strength; frequency of precession is referred to as **Larmor frequency**
- In equilibrium state, each proton's position along its precessional "orbit" around B_0 is random; collectively, random distribution of protons' positions in their orbits results in no net magnetization perpendicular to B_0; i.e., there is no net transverse magnetization

To create an MR image, the equilibrium state is perturbed by applying a secondary, oscillating magnetic field, known as the radiofrequency (RF) pulse, at the Larmor frequency. The RF pulse decreases the longitudinal magnetization and induces a net transverse magnetization among the protons. A 90° RF pulse, by design, reduces the longitudinal magnetization to zero and induces the maximum possible transverse magnetization. Immediately following the RF pulse, the protons gradually return to the equilibrium state by two, independent processes:

- Longitudinal magnetization recovers according to rate constant known as tissue's T1 time; recovery process is called T1 relaxation or longitudinal recovery
- Transverse magnetization decays according to separate rate constant, tissue's T2 time; decay process is called T2 relaxation or transverse decay

The T1 time or T2 time of a tissue can be measured, pixel-by-pixel, using specialized MR pulse sequences to generate a map illustrating regional variation in T1 or T2 time. Changes in these MR properties may indicate normal regional variation or differences between dissimilar tissues, but they can also detect tissue pathology that may not be apparent on conventional MR images.

Other inherent properties of a tissue that can be assessed using MR include the diffusivity of water, the degree of contrast enhancement, the sodium density, and the T1rho time of the tissue. These tissue properties form the basis of their respective MR techniques: Diffusion-weighted imaging (DWI), dGEMRIC, sodium imaging, and T1rho mapping. For a detailed explanation of the biophysical basis underlying each of these tissue properties, including T1 and T2 times, please refer to this chapter's online content. Each of these MR techniques has been investigated for their ability to predict functional properties of cartilage.

Relationship of qMRI Properties to Functional Properties of Cartilage

Quantitative MR can be used to detect changes in cartilage functional properties. An in-depth review of the functional properties of the cartilaginous tissues of the TMJ will be discussed in another chapter. In general, functional properties of cartilage include its biochemical composition and mechanical properties, such as stiffness and strength. The dependence of MR-related tissue properties, such as T1 time and T2 time, on molecular composition and motion within the tissue make it possible to predict some of the functional properties of cartilage using qMRI. The major macromolecules comprising the ECM of cartilage are collagen and proteoglycans. The major collagen species in hyaline cartilage is type II collagen, while the proteoglycans in hyaline cartilage primarily consist of numerous GAG chains bound to an aggrecan protein backbone. Collagen and GAG make up 50-75% and 15-30% of the solid fraction of the cartilage ECM, respectively. Water makes up 70-80% of the total mass of cartilage and also plays a crucial role in cartilage's mechanical properties. Together, water, GAG, and collagen are responsible for cartilage's ability to resist compressive, tensile, and shear forces.

Correlations Between qMRI and Cartilage Composition

Proteoglycans/Glycosaminoglycans

The ability to detect changes in cartilage proteoglycans or GAG has been the focus of considerable research because a decrease in GAG content is an early event in the development of osteoarthritis. Multiple qMRI approaches have been investigated for the ability to detect loss of GAG in cartilage. Of the various qMRI approaches to imaging cartilage, dGEMRIC has been the most widely adopted and shown to strongly correlate with cartilage GAG content. dGEMRIC is unaffected by the content and organization of other cartilage

ECM macromolecules. By comparing pre- and postcontrast T1 times of cartilage, dGEMRIC can produce a map showing spatial variation of GAG. Although there is some variation of precontrast cartilage T1 times, research has shown that the change in T1 time between pre- and post-contrast images highly correlates with the postcontrast T1 time alone. Further research has demonstrated the ability to evaluate GAG content and cartilage health using only a postcontrast T1 time measurement. This ability is an important advantage for clinical application as measuring only postcontrast T1 times significantly reduces the image acquisition time.

Sodium density imaging is also highly specific and correlates with cartilage GAG content. Currently, few clinical studies exist due to limitations associated with sodium imaging. Sodium imaging requires long acquisition times and results in poor signal:noise ratios in typical clinical MR scanners. Specialized RF coils are required to perform sodium imaging and most research involving sodium density imaging of cartilage is carried out using in vitro or ex vivo samples in high-field research MR scanners. Nonetheless, as MR technology and higher-field MR systems become more available, sodium density imaging remains an attractive potential option for noninvasively evaluating cartilage health.

T1rho imaging is another qMRI technique that seems to be relatively specific to cartilage proteoglycan or GAG content. T1rho measurements are also insensitive to zonal variations in ECM organization. Although T1rho times of cartilage may be influenced by water or collagen to some extent, research has found an inverse relationship between T1rho time and GAG content of in vitro and ex vivo cartilage samples. Attempts to apply T1rho imaging to in vivo cartilage evaluation have yielded mixed results with generally weaker correlations between in vivo T1rho times and cartilage GAG content. Research has shown that T1rho imaging of cartilage is possible within safe limits for patients and additional research is necessary to fully understand the relationship between cartilage composition and T1rho times measured in vivo.

Diffusion of water is also related to GAG content in cartilage and can be measured using DWI. Loss of GAG results in freer diffusion of water and increased apparent diffusion coefficients (ADC). Using DWI, an ADC map can be created that depicts regions of relatively increased diffusion in cartilage. Although DWI seems to correlate with cartilage GAG content in ex vivo studies, diffusivity of water is also influenced by collagen content and orientation. Furthermore, it has proven difficult to obtain meaningful diffusion maps of cartilage in vivo using standard DWI pulse sequences. Recent development of a specialized pulse sequence, dual echo steady state (DESS), allows simultaneous acquisition of T2 maps and DWI of cartilage. Using DESS to create ADC maps may facilitate using DWI for detecting cartilage injuries in vivo.

Other qMRI properties are likely influenced by proteoglycans but are generally not considered to be specific for cartilage proteoglycan or glycosaminoglycan content. Cartilage T1 and T2 times decrease from the superficial to deep zones of cartilage, consistent with depth-dependent variations in water and glycosaminoglycan content. Although T1 time is believed to relate more to proteoglycan content than to other factors, T2 time strongly correlates with collagen content and orientation and is minimally affected by proteoglycans. Neither T1 nor T2 time is believed to be specific for cartilage glycosaminoglycan content.

Collagen

Collagen makes up the majority of the solid portion of the cartilage ECM and also influences its qMRI characteristics. Loss of collagen and disruption of the normal collagen architecture in cartilage precede radiographically apparent joint damage, making noninvasive, in vivo characterization of collagen a potential biomarker of early cartilage injury. Of the clinically applicable qMRI techniques to date, T2 mapping best reflects cartilage collagen content and organization. Importantly, zonal variations in collagen alignment significantly impact cartilage T2 times. Collagen fiber alignment in the superficial and deep zones of cartilage tends to cause short T2 times. In contrast, collagen fiber disruption causes prolonged T2 times. It is important to note that the T2 time of tissues with highly aligned collagen fibers is prolonged when the fibers are oriented at approximately $55° ± 10°$ relative to the axis of B_0 due to a phenomenon known as the magic angle effect. The magic angle effect can create the appearance of increased T2 times in healthy cartilage with normal collagen. The ability of T2 mapping to detect changes in collagen content and architecture with relatively short MR acquisition time and straightforward data processing have led to commercially available T2 mapping pulse sequences for cartilage MR. Researchers and clinicians should interpret cartilage T2 maps carefully while accounting for the potential influence of collagen alignment and orientation that varies between cartilage zones, geographic location, and joint position.

Other pulse sequences have been investigated for the potential to assess collagen in cartilage. At least one study has reported an association between cartilage collagen content and T1rho time, but most MR studies involving T1rho have found little or no correlation between T1rho and collagen. In an ultra-high field MR system, a specialized DWI technique called diffusion tensor imaging is capable of mapping collagen fiber orientation and changes in the collagen network associated with cartilage deformation. This technique requires highly specialized MR hardware, long acquisition times, and intensive data analysis, making it unlikely to see clinical translation in the near future.

Correlations Between qMRI and Mechanical Properties

Besides using qMRI to quantify changes in cartilage composition, a number of researchers have attempted to correlate various qMRI metrics with the biomechanical properties of cartilage. Cartilage possesses a unique viscoelastic mechanical behavior that allows it to resist compression, shear, and tension while dissipating joint forces and providing a nearly frictionless surface for joint movement. Deterioration of cartilage mechanical properties occurs early in the onset of osteoarthritis and precedes cartilage structural damage. Noninvasive measurement of cartilage mechanical properties may help clinicians identify cartilage disease at a stage when early intervention could prevent the progression of osteoarthritis.

The biomechanical property of cartilage that has received the most attention with respect to qMR research is compressive stiffness. It should be noted that multiple different measurements of cartilage compressive stiffness are possible depending on the way the cartilage stiffness is tested. This makes comparison between studies using different methodologies difficult; however, multiple studies have found

correlations between qMRI and cartilage compressive stiffness.

Measuring T1 time and T1rho time of cartilage have both been found to correlate with cartilage compressive properties. Specifically, shorter T1 times correlate with greater cartilage compressive stiffness. Researchers have suggested that shorter T1 times observed in stiff cartilage samples are associated with greater cartilage macromolecule content and less water content. Similarly, the T1rho relaxation rate (i.e., 1/T1rho time) was found to be proportional to the compressive modulus and permeability of bovine cartilage. Other qMRI methods have had mixed success in predicting cartilage biomechanical properties. Despite the strong correlation between dGEMRIC and cartilage GAG content, this method has not been found to consistently correlate with cartilage stiffness. At least one study, however, found a high degree of correlation between dGEMRIC and the instantaneous and equilibrium moduli of human cartilage. Multiple studies have reported a lack of correlation between cartilage T2 time and compressive stiffness. It is possible that the effect of collagen orientation on cartilage T2 time confounds any relationship between T2 time and cartilage stiffness.

Several other novel techniques for using MR to measure cartilage compressive stiffness have been proposed. These other techniques employ some means of directly or indirectly applying a load to the cartilage surface and using MR to measure the resulting cartilage deformation. The described methods that quantify cartilage deformation upon stress application are generally technically difficult and require specialized hardware. Nevertheless, it may become feasible in the future to generate maps of cartilage deformation and mechanical properties rather than infer cartilage properties from qMRI metrics that are influenced by a number of factors.

Clinical Applications of qMRI for Assessing Cartilage Health

The ability of qMRI to predict cartilage characteristics, such as proteoglycan content, collagen organization, and compressive stiffness, has paved the way for researchers to examine the potential for qMRI to accurately assess cartilage health in vivo. T1rho mapping in clinical patients has been shown to be comparable to arthroscopy for detecting posttraumatic, preradiographic cartilage injuries. When T1rho and T2 mapping were compared for evaluating cartilage health in patients with ACL injuries, T1rho was found to be a more sensitive indicator of cartilage changes. In another study, both T2 mapping and T1rho mapping were found to be more sensitive than dGEMRIC for detecting changes in cartilage following ACL injury. Although a single qMRI metric may be capable of detecting changes in injured cartilage, it is likely that more than one qMRI approach will be necessary to create a robust understanding of the pathophysiology in the cartilage of any given joint. For example, T1rho mapping may indicate proteoglycan and overall macromolecular content, T2 mapping may provide insight into the integrity of the cartilage collagen network, and dGEMRIC or sodium imaging specifically quantifies the cartilage GAG content. It is important to note that any qMRI should be interpreted in conjunction with conventional, morphologic images in clinical patients. Further research is necessary to determine which individual or combination of qMRI techniques provides the greatest clinical benefit.

Challenges for Application of qMRI to TMJ Imaging

Three major challenges exist for the application of qMRI to imaging the fibrocartilaginous tissues of the TMJ

- Fibrocartilage typically has short T2 time and rapid decay of MR signal compared to hyaline cartilage
- Fibrocartilage of mandibular condyle is thin, requiring fine spatial resolution
- It is difficult for clinical patients to keep their TMJ completely motionless for prolonged periods of time, necessitating short MR acquisition times

It is difficult to apply qMRI to tissues with short T2 times. Highly organized, collagenous tissues, such as tendon, ligament, and fibrocartilage, tend to have very short T2 times. A tissue with short T2 time will experience rapid loss of MR signal, creating a dark gray or black appearance on conventional MR images. Furthermore, rapid loss of transverse magnetization in tissues with short T2 times may result in insufficient signal to allow measurement of qMRI parameters. The development of MR pulse sequences with ultra-short echo times (UTE) preserves signal in fibrocartilage and theoretically will permit qMRI; however, UTE pulse sequences are not widely available and are currently limited to research applications.

The thin cartilage and shape of the mandibular condyle, as well as the TMJ disc, requires fine spatial resolution for visualization and qMRI. Fine spatial resolution can be achieved using 3D imaging techniques, high MR field strengths, &/or long MR acquisition times. This problem is compounded by the need for the patient to remain motionless during MR acquisition. The longer the MR acquisition time, the greater the likelihood that minor patient motion will cause artifacts that prevent accurate qMRI. Motion correction of MR images is possible with specialized pulse sequences and data processing, but these methods are technically difficult.

Significant hurdles must be overcome before qMRI can be successfully applied to characterizing TMJ disorders in clinical patients; however, increasing availability of high-field MR and ongoing research and development of qMRI may make it possible to apply qMRI to the TMJ in the future. qMRI has the potential for detecting biochemical and microstructural changes in the TMJ cartilage that precede irreversible morphologic changes. Thus, qMRI may provide insight into the pathophysiology of TMJ disorders and facilitate identification of patients that will benefit from early intervention.

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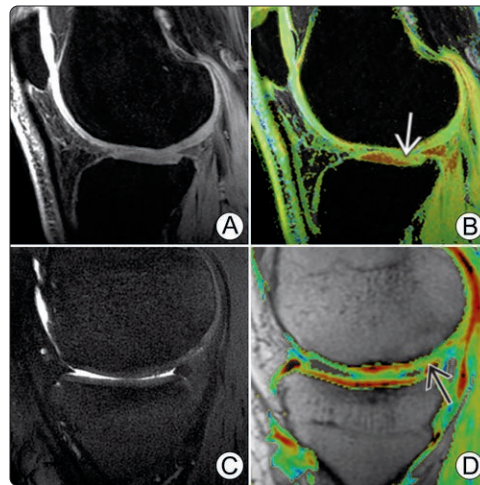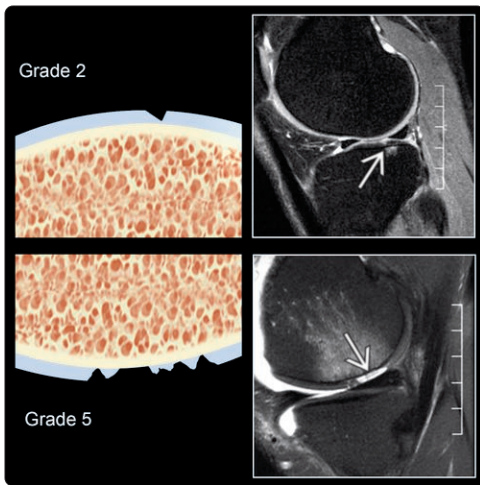
(Left) *Conventional MR of the femorotibial joint detects cartilage loss ➡ associated with osteoarthritis (OA). Once cartilage loss is apparent by conventional MR, the damage is irreversible. (Modified with permission from Li, 2013.)* **(Right)** *Conventional MR of the knee depicts morphologically normal cartilage (A, C). Prolonged T1rho time in tibial cartilage (B, ➡) and prolonged T2 time in the femoral cartilage (D, ➡) indicates cartilage degeneration. (Modified with permission from Kijowski, 2014.)*
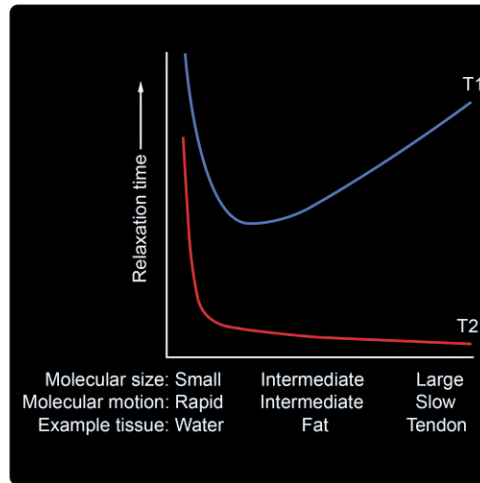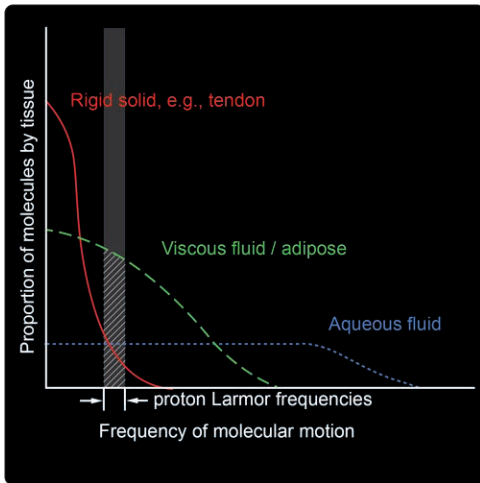
(Left) *Tissues with molecular motion overlapping the Larmor frequency will experience more rapid longitudinal recovery and shorter T1 times than tissues with little overlap. (Redrawn from Bushberg, 2002.)* **(Right)** *Fluids with small, rapidly moving molecules will have long T1 and T2 times. Tissues composed of large, rigidly held molecules will have long T1 times and short T2 times. Intermediate tissues will have short T1 and T2 times. (Redrawn from Bushberg 2002.)*
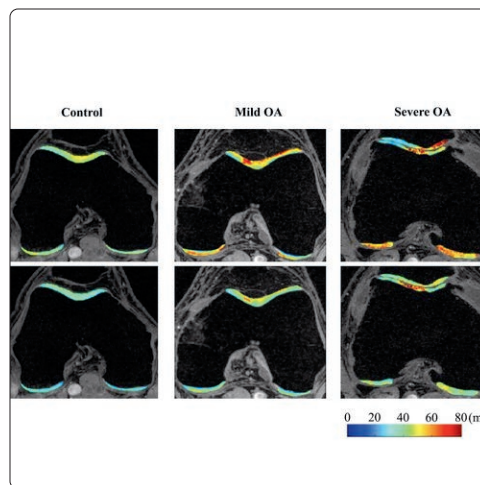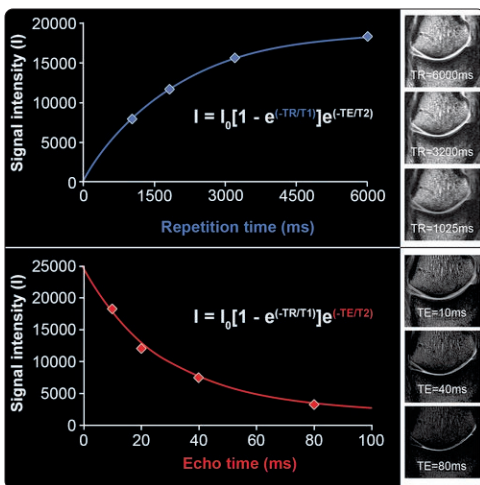
(Left) *Tissue signal intensity will increase with increasing repetition time (TR) and decrease with increasing echo time (TE). The T1 time and T2 time of a tissue can be calculated from MR images with varying TR and TE, respectively.* **(Right)** *T1rho (top row) and T2 (bottom row) maps of the femoropatellar joint are shown. Subjects with OA demonstrate prolonged T1rho time and T2 time of the femoropatellar cartilage, suggesting GAG depletion and collagen disruption, respectively. (Modified with permission from Li, 2013.)*