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Imaging Strategies for Assessing Cartilage Composition in Osteoarthritis

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Abstract

Efforts to reduce the ever-increasing rates of osteoarthritis (OA) in the developed world require the ability to non-invasively detect the degradation of joint tissues before advanced damage has occurred. This is particularly relevant for damage to articular cartilage because this soft tissue lacks the capacity to repair itself following major damage and is essential to proper joint function. While conventional magnetic resonance imaging (MRI) provides sufficient contrast to visualize articular cartilage morphology, more advanced imaging strategies are necessary for understanding the underlying biochemical composition of cartilage that begins to break down in the earliest stages of OA. This review discusses the biochemical basis and the advantages and disadvantages associated with each of these techniques. Recent implementations for these techniques are touched upon, and future considerations for improving the research and clinical power of these imaging technologies are also discussed.

Keywords

Osteoarthritis; Cartilage; Magnetic resonance imaging (MRI); Computed tomography (CT); Imaging; Quantitative

Introduction

Osteoarthritis (OA) is a chronic, degenerative disease of the joint that affects over 26 million people in the United States alone [1]. The effect of OA on joint tissues causes a high degree of morbidity, including loss of mobility and pain. Because of this, OA places a large burden

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on society, with annual medical costs totaling over $185 billion in the US [2]. Moreover, the prevalence and cost of this disease are expected to increase in the coming years due to rising rates of obesity and aging populations across the world. Such alarming numbers have sparked efforts within the scientific and medical communities to better understand the disease and to develop and assess strategies for prevention and treatment. While OA is understood to affect many joint tissues, degeneration of articular cartilage is of primary concern in all stages of the disease [3].

Various imaging strategies are available to observe the biochemical and morphological degradation of cartilage that occurs as the disease progresses. Conventional radiography can indirectly detect gross cartilage loss by revealing a narrowing of the space between two bones [4]. Osteophytes can also be observed, although the diagnostic accuracy with radiography is low relative to other imaging modalities [5]. Alternatively, magnetic resonance imaging (MRI) provides optimal soft tissue contrast for assessing the health of articular cartilage [6]. Conventional use of MRI allows for the visualization of morphological degradation of articular cartilage that is characteristic of acute trauma to the joint and within later stages of OA. However, biochemical changes to the cartilage ultrastructure are known to precede gross morphological changes, and thus more advanced imaging techniques are required for assessing these more subtle changes.

Advanced quantitative imaging technologies provide information relating to cartilage composition that is useful for detecting and monitoring the early stages of OA. The most common and well-validated techniques utilize MRI, and include delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), T_2 relaxation time mapping, $T_{1\rho}$ relaxation time mapping, and sodium MRI. Other MRI techniques include ultrashort echo time (UTE) imaging, chemical exchange saturation transfer sensitive to glycosaminoglycans (gagCEST), and diffusion-weighted imaging (DWI). Lastly, quantitative computed tomography arthrography (CTa) provides an alternative to MRI for capturing biochemical information relating to cartilage.

These imaging methods are employed in clinical research studies to better understand OA as it relates to degradation of cartilage and other joint tissues. Quantitative imaging lends itself best to studying these questions by comparing control to study groups. Within this design, changes in cartilage quality over time can be studied. Typical research objectives include understanding effects of factors such as age, gender, and obesity on cartilage health. Damage after traumatic injury, such as anterior cruciate ligament rupture or meniscal tear, can also be observed. Finally, efficacy of treatments intended to slow down or reverse the progression of OA are often studied with these techniques. In order to appreciate the role of these techniques in current research and practice, it is first important to understand the biochemical composition of articular cartilage and the changes that occur as it begins to break down.

Cartilage Composition

The three components of articular cartilage that are most relevant to imaging the ultrastructure within the extracellular matrix are water, a network of collagen composed

predominantly of type II collagen fibers, and the surrounding proteoglycan (PG) macromolecules. The collagen matrix provides structural support to resist stress at all depths within the cartilage layer, from the articular surface to the chondral plate [7]. Collagen fibrils in superficial regions, closest to the synovial fluid, are oriented parallel to the articular surface to reduce friction and shear stress. In contrast, collagen in deep regions of cartilage is oriented perpendicular to the bone surface in order to anchor itself to the subchondral bone.

Proteoglycans consist of a protein core with many covalently attached glycosaminoglycan (GAG) side-chains that are rich in negatively charged carboxyl and sulfate groups. These create a fixed charged density (FCD) that attracts cations, such as sodium, and generates an osmotic pressure that draws water into the cartilage [8]. Because of this osmotic pull, water constitutes 65–85 % of the total weight of healthy cartilage [9].

In the earliest stages of OA, prior to gross cartilage loss, the biochemical composition of cartilage breaks down. The concentration of PGs and GAGs decreases, leading to decreased FCD. Additionally, the structure of the collagen matrix breaks down, leading to an influx of water into these areas [10]. In summary, cartilage in the early stages of OA has reduced PG and GAG content, reduced FCD, and increased water content compared to physiologically normal cartilage. Each of the following imaging techniques relies on one or more of these compositional changes to detect and track OA in its earliest stages.

Imaging Strategies

Delayed Gadolinium-Enhanced MRI of Articular Cartilage (dGEMRIC)

dGEMRIC provides an assessment of GAG concentration through the use of the intravenous contrast agent $Gd(DTPA)^{2-}$. Diffusion of the contrast agent into the cartilage is expedited by exercise and a 90-min delay prior to imaging. Within cartilage, $Gd(DTPA)^{2-}$ molecules encounter repulsive electrostatic forces from the negatively charged GAGs. This causes the contrast agent to distribute in an inverse relationship with GAG content [11]. The paramagnetic properties of $Gd(DTPA)^{2-}$ cause nearby protons to relax more quickly following a radiofrequency (RF) pulse, resulting in shorter T_1 relaxation times. The outcome measure for dGEMRIC is therefore T_1 relaxation time, with higher T_1 relaxation times indicating higher GAG concentration and healthier cartilage.

This relationship between dGEMRIC T_1 relaxation times and GAG content has been validated both in vitro [12] and in vivo [13]. Of note, however, is recent evidence suggesting that the diffusion of $Gd(DTPA)^{2-}$ into the cartilage is not only dependent on GAG distribution but also collagen content and diffusion direction [14, 15]. As is the case with other imaging techniques discussed below, there may not be one precise biochemical correlate that accounts for the entire variation in quantitative results. However, the most important correlate for each technique is clear, and the relationship between dGEMRIC and GAG content is well established.

The dosage of intravenous $Gd(DTPA)^{2-}$ typically ranges from 0.1 to 0.3 mm/kg [16, 17], and intra-articular, rather than intravenous, injection has been used for dGEMRIC in the hip

[18]. The suggested delay time between administration of contrast agent and image acquisition varies between joints [17]. The optimal dosage and delay time may also vary when other tissues, such as the meniscus, are being studied along with cartilage [19]. T_1 relaxation time mapping with dGEMRIC can be achieved with several 2D and 3D MR pulse sequences that generally involve multiple acquisitions with variable flip angles or variable inversion times [20, 21]. Some sequences, however, have demonstrated superior reproducibility compared to others [22]. Post-processing techniques such as 3D image registration can improve the reproducibility of dGEMRIC T_1 relaxation time measurements, allowing this to be a more reliable technique for tracking change over time [23, 24].

Being a well-validated technique for assessing GAG content, dGEMRIC has been used widely in OA research. It has been used to distinguish between healthy and diseased cartilage in the hip [25, 26], finger [27], and knee joints [28]. dGEMRIC T_1 relaxation times have been used as outcome measures following surgical intervention in both the knee and ankle [29–31] and are predictive of progression to late-stage OA [32].

While dGEMRIC is a widely used and well-validated tool for assessment of in vivo GAG content, it has important drawbacks (Table 1). The injection of a contrast agent is an invasive aspect of dGEMRIC that is not required by other quantitative MR techniques. The use of gadolinium contrast agent poses health risks particularly for individuals with renal impairment [33]. Also, the added time necessary to allow the contrast to diffuse into the joint makes the full examination time longer than times needed for other techniques.

T_2 Relaxation Time Mapping

T_2 relaxation time mapping provides an indirect assessment of collagen structure and orientation, as it relates to free water content. The presence of unbound water molecules slows down the loss of transverse magnetization following an RF pulse, such that regions of cartilage with more free water have higher T_2 relaxation times. In healthy cartilage, the collagen matrix traps and immobilizes water molecules. When this structured matrix breaks down, the extra space is filled with free, unbound water. Therefore, elevated T_2 relaxation times are generally indicative of cartilage degeneration.

Correlation between T_2 relaxation time mapping and collagen content has been validated both in vitro [34] and in vivo [35]. As with dGEMRIC, however, there is evidence to suggest that T_2 relaxation may also be dependent on other factors, such as GAG content [36, 37]. Still, this technique is thought to be more sensitive to collagen content than other techniques that are sensitive to loss of GAGs, and it is used in many clinical studies to track early OA.

T_2 relaxation time mapping usually involves imaging at several echo times along the T_2 decay curve [38]. A mono-exponential fit is then typically applied to obtain the desired relaxation time constants. This can be achieved with 2D multi-echo spin and fast spin echo sequences. 3D pulse sequences are also available and achieve shorter scan times [39, 40]. Additionally, the 3D double echo steady state (DESS) sequence has been modified to provide simultaneous estimation of T_1, T_2, and apparent diffusion coefficient (ADC) [41••].

T_2 relaxation times are widely used as quantitative measures in clinical OA research to track cartilage degradation in the knee [42–44], ankle [45, 46], and hip joints [47]. Natural spatial variation along the range of depths from the articular surface has been observed with T_2 relaxation times [48, 49]. Because T_2 can theoretically increase or decrease in disease states, some investigators have looked into the heterogeneity of relaxation times within regions of cartilage [34, 50]. 3D datasets have demonstrated the enhanced ability to detect site-specific variation in cartilage biochemistry that would other-wise be unavailable with 2D sequence [51]. On a larger scale, the Osteoarthritis Initiative uses this technique to assess in vivo cartilage composition in many types of patients [52–54].

An understood drawback to T_2 relaxation time mapping is its susceptibility to the magic angle effect. When collagen fibers are aligned at certain angular orientations to the main magnetic field (B_0), estimations of T_2 relaxation times become elevated and inaccurate [55]. Additionally, this technique may not capture biochemical changes in cartilage as early as GAG-sensitive imaging methods because PG depletion may occur prior to breakdown of the collagen matrix [56].

$T_{1\rho}$ Relaxation Time Mapping

$T_{1\rho}$ relaxation time mapping is an additional quantitative MR technique that is sensitive to GAG content within cartilage. With this technique, a spin-lock RF pulse follows the initial RF pulse to lock protons in phase. Protons then relax in the presence of a B_1 field with the time constant $T_{1\rho}$, and this decay can be sampled similar to that of T_2 decay to obtain quantitative measurements. Water protons that are associated with large macromolecules such as PGs dissipate energy faster than free water protons. Thus, regions of cartilage with more free water as a result of GAG depletion have longer $T_{1\rho}$ relaxation compared to physiologically normal regions [57].

Studies validating the inverse relationship between GAG content and $T_{1\rho}$ relaxation times have been performed both in vitro [58, 59] and ex vivo [36, 60]. MR pulse sequences for $T_{1\rho}$ relaxation time mapping use a $T_{1\rho}$ magnetization preparation pulse [61] followed by either a spin echo [62] or gradient echo readout [63, 64].

This noninvasive assessment of GAG content is used in many research studies. It has been applied primarily to imaging of the knee [65–67] and the hip [68]. As with T_2 relaxation time mapping, findings suggest that increased heterogeneity of $T_{1\rho}$ relaxation times within regions of cartilage is indicative of degenerative changes [69]. $T_{1\rho}$ relaxation is commonly measured along with T_2 relaxation in cartilage studies to obtain information regarding collagen and PG biochemistry [37, 70, 71]. Recently, $T_{1\rho}$ relaxation time mapping has been applied at 7 T to provide higher special resolution [72].

$T_{1\rho}$ relaxation time mapping has the benefit that it provides an assessment of GAG content without the need for invasive contrast agent or specialized hardware. However, this method is not as specific for GAG content as other MR methods. Additionally, the spin-lock RF pulse results in large amounts of energy deposited to tissue, making longer scan times necessary to conform to FDA-regulated specific absorption rates (SAR) [73].

Sodium MRI

Sodium MR imaging captures signal from ^{23}Na ions, rather than the standard ^{1}H protons [74]. Positively charged sodium ions exist in association with the negatively charged GAG side-chains, making sodium MRI an excellent measure of GAG concentration. Cartilage with healthy GAG concentrations, therefore, has high sodium signal relative to cartilage experiencing depletion of GAGs and loss of FCD.

Correlation of sodium MRI with GAG content in cartilage has been validated in vitro [75, 76]. Sodium imaging is typically performed at 7 T, rather than 3 T, in order to obtain sufficient signal from ^{23}Na ions. While this makes the technique less clinically relevant, research studies applying sodium imaging have been able to successfully distinguish between OA and healthy cartilage [77, 78].

Compared to other quantitative MR techniques discussed above, sodium imaging is not as common due to several limitations. Firstly, the concentration of ^{23}Na ions in cartilage is significantly lower than that of ^{1}H protons, making it difficult to obtain sufficient SNR. Longer scan times and higher field strengths are two approaches for counteracting the reduced sodium signal. Lowering the spatial resolution with sodium imaging can also help provide sufficient signal within each voxel of cartilage. This may, however, result in partial volume effects with surrounding tissues and lead to artificially decreased measurements of GAG concentration. Lastly, transmit–receive coils made especially for sodium imaging are generally required to capture the sodium signal [79].

Other Imaging Techniques: UTE, gagCEST, DWI, and CT Arthrography

Several other techniques are available for imaging cartilage composition. These are less commonly used for cartilage imaging compared to the techniques discussed above, but are important to note, nonetheless.

Ultrashort echo time imaging (UTE) allows for the assessment of tissues with short intrinsic T_2 relaxation, such as menisci, tendons, ligaments, and the deep radial and calcified layers of cartilage. These tissues have T_2* relaxation times shorter than 5 ms, and do not generate sufficient signal with the standard echo times used for T_2 relaxation time mapping [80]. UTE can be applied to obtain T_1, T_2, T_2*, and $T_{1\rho}$ relaxation time measurements in deep regions of cartilage [81].

While applications of UTE for in vivo cartilage imaging are limited, the technique has demonstrated sufficient repeatability for T_2* mapping of cartilage [82]. T_2* measurements with UTE have recently been used to demonstrate biochemical changes to the deep regions of cartilage following ACL rupture and reconstruction [83•]. The technical requirements for obtaining such short echo times mean that UTE requires lengthy scan times and the use of special MR pulse sequences that are not widely available [84].

Chemical exchange saturation transfer (CEST) is a new MR contrast enhancement technique that enables the indirect detection of molecules with exchangeable protons. CEST makes MRI sensitive to the concentrations of endogenous metabolites and their environments. GAGs in cartilage exhibit a concentration-dependent CEST effect between their hydroxyl (-

OH) protons and bulk water protons [85]. This technique allows for imaging of GAG distribution with high spatial resolution.

The relationship between the gagCEST effect and GAG content has been validated in vivo by comparison to sodium imaging at 7 T [86, 87]. The high specificity to GAG without the need for special hardware or intravenous contrast makes gagCEST a promising method for studying cartilage matrix composition. The major limitation of gagCEST is that it is difficult to perform at 3 T, and, instead, requires a higher B_0 field strength of 7 T [88]. Advanced post-processing tools are also required to correct for field non-homogeneities and to obtain accurate quantitative results.

A final MR technique for assessing cartilage composition is diffusion-weighted imaging (DWI). The translational motion of water protons is measured by a value called the apparent diffusion coefficient (ADC). This is achieved by applying diffusion-sensitizing gradients that break down phase coherence amongst mobile protons, reducing the MR signal from regions with mobile water [79]. Higher ADC values indicate more translational movement of protons. In articular cartilage, the structure and orientation of the collagen matrix influences movement of protons. When the matrix breaks down, there is increased movement of water. Elevated ADC is thus believed to be indicative of early cartilage degeneration [89, 90].

Applications of DWI to clinical research are limited and sometimes involve the use of a semi-quantitative outcome, rather than quantification of ADC [91, 92]. While echo planar imaging is typically used for DWI [93], quantitation of ADC can be achieved simultaneously with T_1 and T_2 relaxation times using a modified version of the double echo steady state (DESS) pulse sequence [41••].

Quantitative CT arthrography (CTa) is an alternative to the many MRI techniques for assessing cartilage composition. CTa takes advantage of the repulsive forces between GAGs in cartilage and the negatively charged contrast agent ioxaglate. Contrast is injected intra-articularly and a delay with exercise is taken prior to scanning. In the scanner, x-ray attenuation in the cartilage is measured in Hounsfield units (HU), with higher HU indicating depletion of GAGs.

The relationship between GAG content and x-ray attenuation measured by CTa has been validated ex vivo [94]. While applications to clinical OA research are very limited, several advantages of CTa over MRI techniques make it a potentially useful tool moving forward. For instance, scan times are short and CT scanners are widely available and relatively less expensive. However, one major limitation is the ionizing radiation that comes with the use of x-ray technology [95].

Future Considerations

As imaging technologies for assessing cartilage composition continue to evolve, several broader considerations are being investigated. One question that arises is how these techniques perform between scanners and across vendors. Several studies have recently begun looking at this question. An analysis of in vivo $T_{1\rho}$ and T_2 relaxation time mapping

between study sites found that reproducibility was generally moderate to excellent, but better in some regions of cartilage than others [96]. These differences need extensive further study before large-scale clinical studies can involve imaging with equipment from different vendors.

Another question relating to quantitative imaging of cartilage is how best to process and interpret data, especially with so many 3D sequences becoming available. Data are conventionally collected from one or more slices within the joint of interest, but the selection of slices can have a substantial impact on the results [22]. New methods for better utilizing 3D data sets are being developed and tested [97], and will likely provide better sensitivity to detect regional changes in cartilage quality.

Finally, multiple imaging techniques within single studies may provide assessments of both the collagen matrix and the concentration of GAG molecules to yield a better understanding of early changes in OA (Fig. 1). For instance, T_2 and $T_{1\rho}$ relaxation time mapping are commonly applied together in clinical studies [98, 99•], and sometimes provide different results among study participants [100]. An interventional study utilizing both dGEMRIC and T_2 relaxation time mapping suggests that dGEMRIC may be more sensitive to the earliest biochemical changes in cartilage [101], possibly attributable to the suggestion that GAG loss precedes breakdown of the collagen matrix in OA [56]. This is further supported by a study comparing $T_{1\rho}$, T_2, and dGEMRIC T_1 relaxation times between healthy and early arthritic cartilage [102], in which $T_{1\rho}$ and T_1 relaxation times were more sensitive to differences between these two groups than T_2 relaxation times. Results from another study that used these two techniques suggest that combining datasets from dGEMRIC and T_2 relaxation time mapping provides useful information that is otherwise unavailable from only one technique [103].

Conclusions

Imaging with MRI and CT is becoming increasingly important in studies of cartilage degeneration and in testing new therapies for prevention or delaying the progression of OA. Real progress in understanding how best to treat and manage OA has been facilitated by these techniques. While each technique provides advantages over others, several drawbacks are yet to be overcome or circumvented. Finally, new directions of research show promise in boosting the strength of these imaging techniques to be more sensitive to arthritic changes and to be used in larger-scale research studies.

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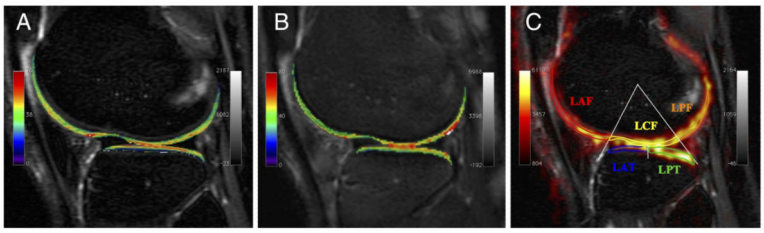

Fig. 1.

Compositional techniques in cartilage to evaluate cartilage health. Compositional markers studied here were **a** T_2 (collagen and water), **b** $T_{1\rho}$ (glycosaminoglycan, collagen, water), and **c** sodium (glycosaminoglycan)

Table 1

Techniques for imaging cartilage composition and their pros/cons

Technique	Outcome measure	Biochemical correlate	Advantages	Disadvantages
dGEMRIC	T_1 relaxation time	GAG content	Well validated	Long exam time Requires use of contrast agent
T_2 relaxation time mapping	T_2 relaxation time	Collagen content/ orientation	Assessment of collagen content without contrast Widely available	Magic angle effect May not capture initial biochemical changes to cartilage
$T_{1\rho}$ relaxation time mapping	$T_{1\rho}$ relaxation time	GAG content	Assessment of GAG content without contrast	SAR limits due to high RF power
Sodium MRI	^{23}Na signal intensity/ concentration	GAG content	High specificity to GAG content without contrast	Requires specialized MRI hardware Long scan time Low SNR Better results at 7 T
UTE	T_1, T_2, T_2*, and $T_{1\rho}$ relaxation times	Variable	Assessment of deep regions of cartilage	Long scan time Requires specialized MRI sequences
gagCEST	CEST asymmetry	GAG content	High specificity to GAG content without contrast	Difficult to perform at 3 T and below Requires advanced post-processing tools
DWI	ADC	Collagen content/ orientation	Assessment of collagen content without contrast Widely available	Low SNR Limited evaluation of deep cartilage regions
CTa	X-ray attenuation	GAG content	Useful for patients who cannot undergo MRI Short scan times	Ionizing radiation Requires use of contrast agent