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CME

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1. Differentiate the mechanisms used by the individual cartilage prestructural MR imaging techniques to characterize cartilage composition.
2. Apply criteria required for quantitative imaging biomarkers to cartilage prestructural MRI techniques.

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Cartilage loss is irreversible, and to date, no effective pharmacotherapies are available to protect or regenerate cartilage. Quantitative prestructural/compositional MR imaging techniques have been developed to characterize the cartilage matrix quality at a stage where abnormal findings are early and potentially reversible, allowing intervention to halt disease progression. The goal of this article is to critically review currently available technologies, present the basic concept behind these techniques, but also to investigate their suitability as imaging biomarkers including their validity, reproducibility, risk prediction and monitoring of therapy. Moreover, we highlighted important clinical applications. This review article focuses on the currently most relevant and clinically applicable technologies, such as T2 mapping, T2*, T1ρ, delayed gadolinium enhanced MRI of cartilage (dGEMRIC), sodium imaging and glycosaminoglycan chemical exchange saturation transfer (gagCEST). To date, most information is available for T2 and T1ρ mapping. dGEMRIC has also been used in multiple clinical studies, although it requires Gd contrast administration. Sodium imaging and gagCEST are promising technologies but are dependent on high field strength and sophisticated software and hardware.
Level of Evidence: 5

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Rationale for Prestructural/compositional Cartilage Imaging

In 1743, William Hunter published one of the first scientific articles on cartilage composition, he stated "an ulcerated Cartilage is universally allowed to be a very troublesome disease; that it admits of a cure with more difficulty than a carious bone; and that, when destroyed, it is never recovered".[1] Still 273 years later, this statement is true and one of the major challenges in modern medicine is our inability to heal cartilage. To date, no pharmacotherapies are available to effectively treat cartilage and cartilage repair is not universally applicable and has limitations in more advanced disease stages. Prevention of cartilage damage is, therefore, critical in maintaining joint function and avoiding disability, which is socio-economically of growing importance as our society ages. Ideally damage should be detected at a stage when it is still reversible and before cartilage tissue is lost. Moreover, reliable tests should be available that provide an assessment of cartilage quality and allow tailoring life style to prevent disability. Currently, only prestructural/compositional imaging techniques have the potential to provide this information.

Introduction

The current standard classification system to diagnose osteoarthritis (OA) uses anterior–posterior knee radiographs and is nearly 60 years old.[2] The Kellgren-Lawrence classification assesses osteophytes and joint space narrowing to diagnose and grade OA. Although joint space narrowing is only an indirect marker of cartilage degeneration, demonstrating advanced disease stages, it is recommended by regulatory agencies including the United States Food and Drug Administration as the primary imaging endpoint to establish the effectiveness of disease-modifying OA drugs.[3]

The best established imaging technique to visualize cartilage directly is MRI, and over the past 20 years, significant progress has been made to optimize morphological cartilage imaging due to higher field strength, better coils, and advanced imaging sequences.[4] While these technologies allow precise detection of cartilage defects, they image cartilage at a stage, where damage is already irreversible. Ideally cartilage tissue should be characterized before irreversible damage has happened and findings are still reversible. This is where prestructural/compositional cartilage imaging comes in as it analyzes the cartilage matrix providing information on water content, collagen integrity and proteoglycan content. In a clinical setting, prestructural cartilage imaging techniques will allow to diagnose cartilage quality at early disease stages and thus directly impact patient management. This includes life-style interventions related to weight loss and physical activity, but also surgery, e.g., in patients with femoro-acetabular impingement who should be treated at early stages to prevent hip osteoarthritis. These techniques will also allow to sensitively monitor interventions by providing quantitative measurements and thus providing reliable and reproducible imaging biomarkers. Ideally using prestructural cartilage imaging techniques specific measurements should be obtained that would provide intervention thresholds and predict risk of the development of symptomatic osteoarthritis. Several technologies are available to date, with most studies performed using T2 relaxation time measurements.

The goals of this review article are (i) to present the different techniques to measure cartilage composition; (ii) to provide information on validity, reproducibility, and other requirements for imaging biomarkers; and (iii) to illustrate areas of clinical application. The article will conclude with an overall clinical feasibility assessment and a description of obstacles preventing widespread application of quantitative MR imaging biomarkers.

Background: Cartilage Composition on A Biochemical, Histological, And Functional Level

Hyaline, articular cartilage (Fig. 1) is composed of collagen, a proteoglycan-rich matrix and a single cell type: the chondrocyte. Cartilage is unique among connective tissues, in that it lacks blood vessels and nerves and receives its nutrition solely by diffusion. Structurally, hyaline cartilage provides a firm material, which, depending on its subtype, is adapted to resist and damp compressive and tensile forces. The mechanical properties of cartilage are a function of the

extracellular matrix, but it is the chondrocytes that direct the synthesis and composition of the matrix.[5]

As no neurovascular structures penetrate the perichondrium, all nutrition is delivered through diffusion, which limits the thickness of hyaline cartilage surfaces to several millimeters, in rare instances such as the patellar cartilage to more than 1 cm. Cartilage is attached to the underlying bone by a complex network of radial collagen fibers, which, however, do not extend into the subchondral bone.[5] This zone of attachment consists of an approximately 20- to approximately 250-micron-thick layer of calcified cartilage, the tidemark, where perpendicular chondrocyte-derived collagen type II fibers become structurally cemented to collagen type I osteoid deposited by osteoblasts.[6] This zone is a dynamic structure that is of major significance for cartilage health. Moreover, the deep cartilage layer and the subchondral bone have to be considered as a functional unit with biomechanical and biochemical interactions.[7]

Cartilage Matrix

Cartilage has a matrix, which consists primarily of extracellular water (66–78%) in addition to proteoglycans, collagen, and specialized proteins.[8] Of interest, the water is unevenly distributed through the hyaline cartilage with the highest concentration at the articular surface.[9] The constant diffusion and tidal movement of water in and out of the cartilage matrix with joint compression allow nutrients to reach the chondrocytes, explaining why regular exercise is important to maintain the cartilage matrix. Proteoglycans are directly responsible for the high water content of cartilage. Proteoglycans are composed of high molecular weight proteins with carbohydrate side chains resulting in large, charged molecules that attract water thereby increasing their volume dramatically. Type II collagen predominates in hyaline cartilage and is responsible for the tensile stiffness and strength of the matrix.[10] The expansive pressure of water within the matrix is opposed by the collagen cross-links that restrict expansion and result in a steady-state turgor pressure. This turgor pressure is critical to maintain the viscoelastic properties of the matrix.

Compositional Imaging Techniques To Measure Cartilage

In this section, we outlined "techniques and concept" first and then focused on requirements for imaging biomarkers, which include validation, reproducibility, assessment of disease burden, ability to differentiate patients with and without disease, prediction of risk of disease and monitoring of therapy.[11,12] Validation means that the biomarker measures what it is supposed to measure and that it is accurate in measuring this parameter, for example, that delayed gadolinium (Gd) enhanced MRI of cartilage (dGEMRIC) and T1rho in fact measure the concentration of glycosaminoglycans.

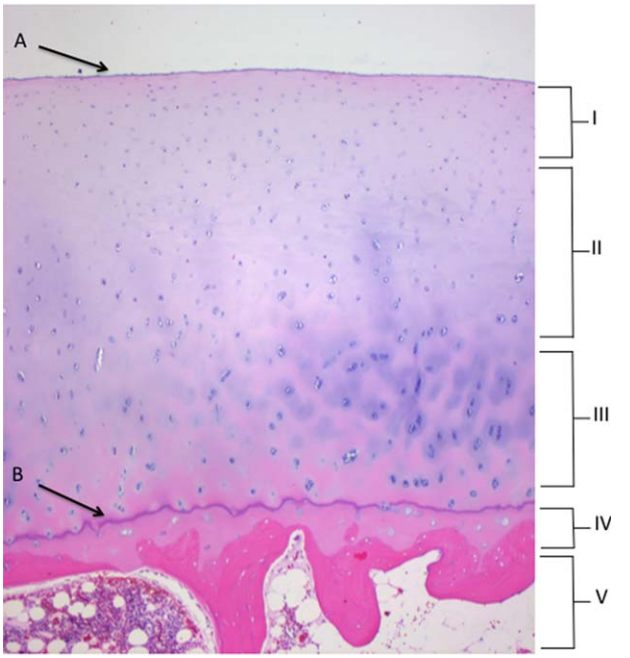

FIGURE 1: Histology slide of healthy articular cartilage, light microscopy with H&E stain. The normal articular cartilage (A) is composed of three zones – the superficial zone (I), the intermediate/middle zone (II) and the deep zone (III). The tidemark (B) distinguishes the deep zone from the calcified cartilage (IV) and the subchondral bone (V). Also note the smooth articular surface (A). (Image courtesy Dr. Andrew Horvai, Department of Pathology at the University of California at San Francisco)

Reproducibility refers to the ability of the biomarker to reproduce the same measurement values in subsequent measurements. Different sequences and MRI scanners and different analysis techniques will affect reproducibility and high reproducibility is critical for longitudinal and multi-center studies. Assessment of disease burden requires exact measurement of disease severity. Ideally an imaging biomarker should also be used to diagnose the disease, e.g., a Kellgren-Lawrence score of 2 and greater is defined as osteoarthritis. Those quantitative cutoff values, however, are not available for prestructural cartilage MRI-based measurements yet. On the other hand, these measurements have been shown to differentiate individuals with and without degenerative joint disease. Finally, imaging biomarkers should also be able to predict incidence of disease and monitor the impact of interventions and therapy in longitudinal studies.

In order for prestructural imaging biomarkers to be applied in clinical practice, the requirements listed above must be met and this review article investigates current literature with regard to these prerequisites going beyond review articles presenting the individual techniques and their clinical applications.

T2 and T2 Mapping*

TECHNIQUE AND CONCEPT. *T2 relaxation times* relate to the rate of transverse magnetization decay, caused by the loss

of phase coherence induced by a preceding radiofrequency pulse. T2 relaxation time, or the spin–spin relaxation time, reflects the ability of free water proton molecules to move and to exchange energy inside the cartilaginous matrix. It has been shown that in normal cartilage this transverse (T2) relaxation is dominated by the anisotropic motion of water molecules in a fibrous collagen network. T2 relaxation times are primarily dependent on water and collagen content of the extracellular matrix as well as the orientation of the collagen fibers.

The T2 relaxation time is measured by fitting signal measured in T2-weighted images acquired with different echo times (TE) to a mono- or multi-exponential decay curve. T2 measurements obtained with different imaging techniques cannot interchangeably be used as shown by Pai et al, who compared T2 mapping techniques in phantoms and in vivo using five different sequences: spin-echo (SE), fast spin-echo (FSE), multi-echo SE (MESE), magnetization prepared 2D spiral, and magnetization prepared 3D spoiled gradient recalled echo (SPGR).[13] T2 measurements showed significant variation, which was explained by different sensitivity of each sequence to system imperfections including stimulated echoes, off resonance signals and eddy currents. Different fitting methods will also introduce bias to T2 quantification.

T2 mapping* is a technique similar to T2 mapping, but with shorter scan times, as gradient-echo signals are used for T2*-weighted images and spin-echo signals for T2 imaging are not required. T2* imaging allows high image spatial resolution and isotropic three-dimensional (3D) cartilage evaluation[14] in clinically practical scan times. T2* mapping has several limitations including higher sensitivity to susceptibility artifacts (for example artifacts at tissue interfaces and postsurgical debris) and magic angle effects.[15] Magic angle affects are found in highly ordered tissues, such as collagen fibers, which are organized parallel, arcade like in the hyaline cartilage. When these fibers are oriented at an angle of 55° to the main magnetic field increase in signal due to T2* elongation is found. This results in artificially higher T2* values overestimating water content and disruption of collagen architecture. Magic angle effects are also found using T2 mapping but to a lesser extent.[16]

T2* mapping can also be used with ultrashort TE (UTE) sequences allowing evaluation of the deep calcified cartilage layer. UTE sequences allow to image tissue components with very short T2 of a few milliseconds or less, which is of particular significance in the deep, calcified layer of the cartilage and the menisci.[17,18] In the calcified zone close to the bone–cartilage interface, the T2 relaxation times can be 10 ms or less. This region forms an important interface between cartilage and bone as it attaches the cartilage to the bone and transmits forces between cartilage and bone. This layer may, therefore, have an important role in the early cartilage degeneration and UTE imaging may allow to better characterize this region and the associated abnormalities. These sequences can be used for quantifying both T2* and T1rho.[18] While these sequences have great promise to explore the osteochondral junction, current clinical application is still limited due to spatial resolution and signal-to-noise ratio (SNR).[19]

VALIDATION. To validate T2 relaxation time measurements specimen studies have been performed using cartilage-bone plugs from fresh cadaveric knees and specimens after knee replacement.[20] Significant differences were found in T2 values between specimens from normal and early OA subjects with intracompartmental variation of the relaxation times and histological patterns. Moreover, T2 values demonstrated a positive correlation with histologic grading scales.[20] Similar correlations validating T2 measurements were found by Regatte et al in specimens obtained from total knee replacements.[21]

REPRODUCIBILITY. Several studies also focused on the reproducibility of T2 measurements, which overall showed good results.[22–24] Mosher et al[22] performed a multicenter multivendor trial involving patients with OA and asymptomatic control subjects; this study found good to high reproducibility of T2 values, with intra-correlation coefficients (ICCs) ranging from 0.61 to 0.98 and root mean square coefficients of variation (RMS CVs) ranging from 4% to 14%.[22] In a multi-site study using the same 3 Tesla (T) MR scanners, Schneider and Nessaiver[24] found minimal longitudinal variations of T2 relaxation time measurements with reproducibilities for phantoms that varied from 1.5% to 5.3% in the Osteoarthritis Initiative (OAI) cohort and Li et al[25] found RMS CVs in the order of 4.4% for human subjects. Overall, these results are encouraging and support the use of cartilage T2 measurements if sequences and equipment are standardized.

OTHER REQUIREMENTS FOR QUANTITATIVE IMAGING BIOMARKERS. So far, however, cutoff values to diagnose patients with OA and to differentiate patients with and without OA have not been defined. Multiple studies have shown that patients with OA, early degenerative changes and risk factors for OA have higher T2 values,[26–29] thus demonstrating that T2 values can measure the disease burden. However, one study also suggested that, once cartilage shows more severe degeneration, T2 values may decrease again, raising concern that T2 measurements may be less suited for more advanced disease stages.[30]

Another important requirement to establish an imaging biomarker is a reference database. Joseph et al recently published a reference database of cartilage 3T MRI T2 values in knees without diagnostic evidence of cartilage degeneration from the OAI.[31] Of interest, in a cohort aged 45–65 years, they found only weak associations with age and gender, but relatively high correlations with body mass

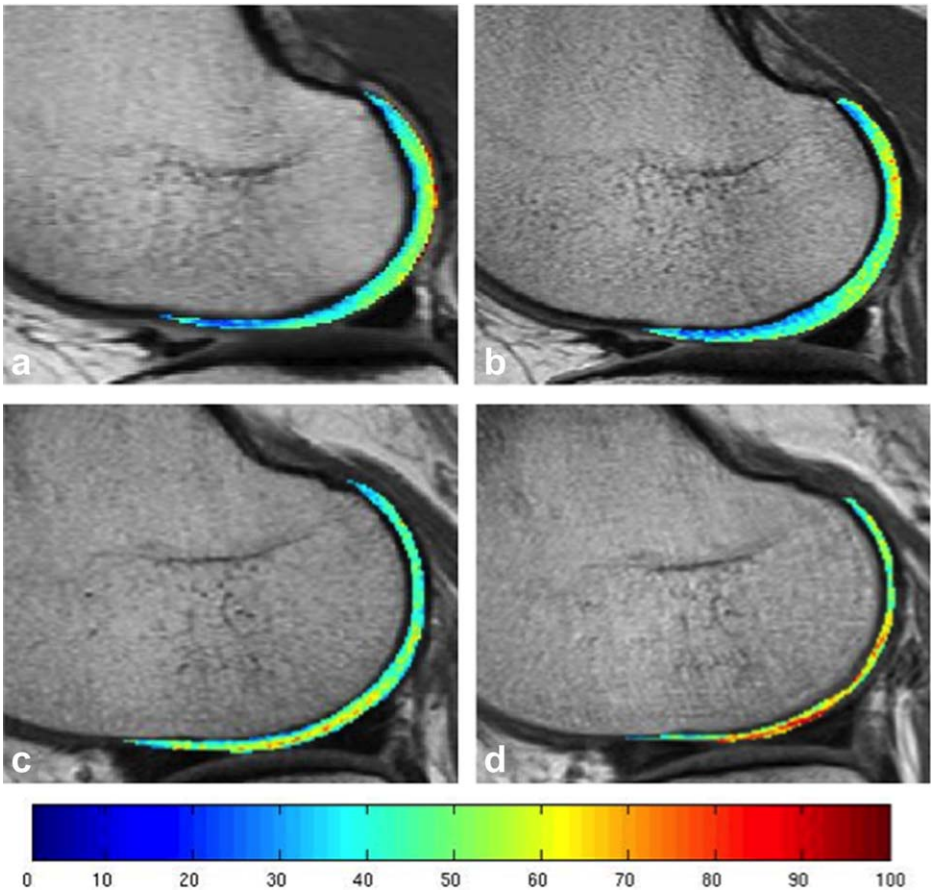

FIGURE 2: T2 color maps of an asymptomatic individual with stable T2 measurements and *an* OA progressor over 4 years. Composite T2 color maps of the lateral femoral cartilage of the right knee obtained in a sagittal plane (at two time points: baseline and 4-year follow-up) in an asymptomatic control subject with stable T2 (A,C) and a patient with progressive knee OA defined by increasing cartilage loss (B,D). T2 values are elevated (orange, yellow, and red) in the weight-bearing area of the lateral femoral condyle in the OA progressor after 4 years (D), indicating progressive cartilage matrix degeneration. The healthy non-progressor shows at both time points similar T2 values with pre-dominantly blue and green cartilage T2 maps.

index. It should be noted, however, that T2 values are dependent on the acquisition technique and reference databases need to be based on standardized techniques. Another important characteristic of an imaging biomarker is its ability to show changes related to interventions or treatment, and multiple studies have shown significant longitudinal changes of T2 measurements to physical activity, weight loss and risk factors for OA.[32–37] Finally, an imaging biomarker should also be able to predict OA and cartilage loss; one study showed that T2 measurements were able to predict radiographic OA[38] and another study demonstrated their ability to predict cartilage loss.[39] Current work in progress focuses on developing a risk score to predict symptomatic OA based on T2 measurements similar to the FRAX score, which predicts osteoporotic fracture risk of the hip and other major fractures after 10 years.

CLINICAL APPLICATIONS. T2 and T2* mapping have been used in multiple clinical studies mostly at the knee, but increasingly also at the hip. Results have been promising in assessing early diseases stages and in monitoring longitudinal changes; Figure 2 shows representative T2 color maps obtained in two subjects with progressive cartilage degeneration and stable cartilage matrix T2 values. Kijowski et al showed the benefit of adding T2 mapping to a routine MR protocol at 3.0T.[40] The investigators found improved sensitivity in the detection of cartilage lesions of the knee joint from 74.6% to 88.9%, with only a small reduction in specificity. Most importantly, they demonstrated the greatest improvement in sensitivity using T2 mapping for the identification of early cartilage degeneration. Su et al[41] analyzed T2 values after ACL injury and before surgical reconstruction in relation to clinical outcomes including the Knee-injury and Osteoarthritis Outcome Score (KOOS) and Marx activity level questionnaires. They found that higher baseline T2 values at the femoral trochlea were associated with worse KOOS activities of daily living at 1 year.

Several studies investigated the relationship between knee pain and T2 measurements, which is the holy grail in imaging of OA.[26,42–44] While one of the studies did not show a difference in cartilage T2 between patients with patellofemoral pain and controls,[42] other studies found a significant

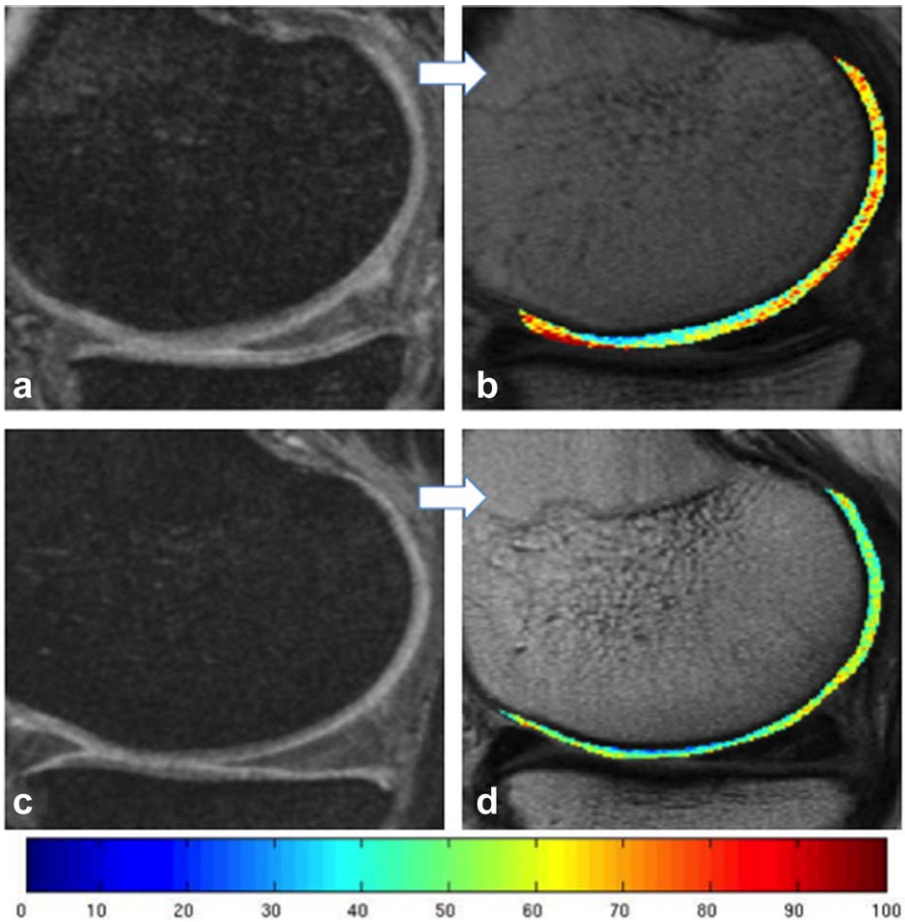

FIGURE 3: Comparison of the T2 color maps of a patient with diabetes and a healthy control, both without focal morphological changes of the cartilage. The 3D dual echo steady-state sequence, obtained in a sagittal plane of the right knee of both subjects (A,C), shows no morphological focal cartilage defects on the medial femoral condyle. The composite T2 color maps of the patient (A), who is suffering from diabetes, shows increased T2 values (predominantly yellow and red) in the area of the medial femoral condyle (B), indicating early cartilage matrix degeneration, whereas the second patient (C), a nondiabetic healthy control, shows no damage of the cartilage matrix (D). Of interest, the cartilage in the diabetic individual appears thicker than in the control subject, suggesting diffuse swelling with higher water content and collagen architecture degeneration.

difference between patients with knee pain and asymptomatic controls.[26,44] Baum et al found that T2 values averaged over all of the compartments were similar in subjects with right knee pain only (mean ± SD 34.4 ± 1.8 ms) and in subjects with bilateral knee pain (mean ± SD 34.7 ± 4.7 ms), but were significantly higher compared with subjects without knee pain (mean ± SD 32.4 ± 1.8 ms; $P < 0.05$).[26] Another study found a relationship between the spatial distribution of cartilage T2 and longitudinal changes in pain.[44]

Studies have also started to investigate cartilage matrix changes in response to metabolic disorders such as obesity and diabetes.[37,45] Figure 3 shows T2 color maps of a patient with diabetes and a healthy control, both without morphological changes of the cartilage. The diabetes subject has generalized higher T2 values than the control, although the cartilage appears thicker, suggesting diffuse swelling with higher water content and collagen architecture degeneration.

More recently, investigators have also focused on T2 and T2* mapping of the hip. Ellermann et al validated T2* measurements using arthroscopy as a standard of reference.[46] These investigators found that T2* relaxation times for normal cartilage were significantly higher than those for cartilage with early changes and cartilage with more advanced degeneration. More importantly, using receiver operating characteristics curve analysis, a T2* value of 28 ms was identified as the threshold for damaged cartilage, with a 91% true-positive and 13% false-positive rate for differentiating normal and damaged cartilage as diagnosed by arthroscopy. Gallo et al demonstrated in a longitudinal study over 18 months that hip OA progressors compared with nonprogressors had significantly higher baseline T2 values, particularly in the posterosuperior and anterior aspects of the femoral cartilage.[47]

T1ρ Relaxation Time Measurements

TECHNIQUE AND CONCEPT. The spin lattice relaxation time in the rotating frame technique, known as T1ρ, is sensitive to regional changes in proteoglycans.[48] It quantifies

the interactions between motion-restricted water molecules with their local macromolecular environment. The macromolecules in the articular cartilage matrix restrict the motion of water molecules. Damage to the cartilage matrix, accompanied by proteoglycan (PG) loss, will result in higher T1ρ measurements.

The T1ρ-weighted imaging sequences are composed of two parts: magnetization preparation with T1ρ weighting using spin-lock pulse cluster, followed by two-dimensional (2D) (based on spiral, or fast spin-echo or echo planar imaging) or 3D (based on gradient echo or 3D fast spin echo) data acquisition.[49] Compared with 2D acquisition, 3D sequences have the advantage of higher image resolution, especially in the slice direction. Among 3D sequences, the method using transient signals immediately after T1ρ preparation either based on SPGR acquisition[50] (magnetization-prepared angle-modulated partitioned *k*-space spoiled gradient echo snapshots, MAPSS) or based on balanced gradient echo (GRE) acquisition[51] are more SNR efficient and less specific absorption rate intensive compared with the method based on the steady state GRE acquisition.[52] These sequences have been implemented at both 1.5T and 3T on scanners from different manufactures.

VALIDATION. Previous studies validated T1ρ sequences in their ability to measure the cartilage proteoglycan concentration.[48,53,54] Wheaton et al[54] performed a pig study with intra-articular injection of recombinant porcine interleukin-1β (IL-1β) into the knee joint before imaging to induce changes in cartilage by means of matrix metalloproteinase. Compared with controls the average $T_{1\rho}$ relaxation rate, $R_{1\rho}$ ($1/T_{1\rho}$) of the IL-1β-treated joints was measured to be on average 25% lower than that of saline-injected joints consistent with a loss of proteoglycans. The loss of proteoglycans induced by IL-1β was confirmed by histological and immunochemical analyses. Another study[55] used 33 cartilage specimens, which were collected from patients who underwent total knee arthroplasty and were scanned with a 3T MR scanner. T1ρ values had a significant but moderate correlation with proteoglycan content ($R = .45$; $P = 0.002$) in these cartilage specimens and T1ρ values of specimen sections with high Mankin scores were significantly higher than those with lower Mankin scores ($P < 0.05$).

REPRODUCIBILITY. Multiple studies have analyzed the reproducibility of different techniques to measure T1ρ.[22,25,56] Jordan et al[56] examined eight healthy subjects at 3T at baseline, 1 day, 5 months, and 1 year and found average intra-subject RMS CV of 4.6%, 6.1%, and 6.0% with intra-observer and inter-observer RMS CVs of 3.8% and 5.7%. In a multi-center study Li et al[25] analyzed the longitudinal reproducibility of T1ρ measurements using phantoms and human subjects. Across three sites with the same model of MR systems and coils, and identical imaging protocols the RMS CV was 3.1% for phantoms and 4.9% for the human subjects. Mosher et al[22] investigated reproducibility across different vendor platforms and found fairly limited reproducibility with RMS CVs ranging from 7% to 19% for femorotibial joints.

OTHER REQUIREMENTS FOR QUANTITATIVE IMAGING BIOMARKERS. While no studies so far have identified a threshold suitable to diagnose OA based on T1ρ, T1ρ has been identified as a measure to assess disease burden in OA at the knee.[57,58] Li et al showed that T1ρ values were correlated with increased severity in radiographic and MR grading of OA,[57] while Rauscher et al showed significant differences in meniscal T1ρ between normal volunteers and patients with mild and severe OA.[58] A study analyzing T1ρ of the hip in subjects without, and with mild and moderate OA found significant differences in T1ρ in acetabular cartilage with and without focal defects.[59]

T1ρ baseline measurements have also been shown to be predictors of progression of knee and hip OA.[39,47] In a longitudinal study over 2 years, it was found that baseline T1ρ was higher in those subjects that had progressive cartilage lesions compared with those that did not progress.[39] In a similar study comparing baseline T1ρ of the hip joint in subjects with and without incident or progression of morphological abnormalities measured using semi-quantitative scores at 18 months, significantly higher T1ρ values were found in the hip progressors.[47] Several longitudinal studies were performed assessing the impact of ACL tears[41,60] and marathon running[36,61] as well as the impact of viscosupplementation.[62] All of these studies showed that T1ρ was a suitable biochemical imaging biomarker to sensitively assess longitudinal changes in the cartilage matrix.

CLINICAL APPLICATIONS. T1ρ has been used mostly to assess the knee cartilage, especially in early stages of OA,[52,63] but feasibility and clinical relevance in the menisci[36,58,64,65] and the hip have also been reported.[66,67] Figure 4 shows representative T1ρ color maps of the hip in an asymptomatic individual and a patient with OA of the hip. Several studies focused on showing the impact of ACL injury and reconstruction on the knee cartilage.[41,60,65,68] Studies have shown how ACL injury impacted the cartilage matrix and longitudinal changes in the cartilage matrix after ACL reconstruction (Fig. 5).

More recently, there has been an increasing number of studies focusing on femoroacetabular impingement.[66,69–71] Anwander et al showed in asymptomatic individuals with a cam deformity that the mean T1ρ value of the entire weight-bearing cartilage in hips with a cam deformity (34.0 ± 4.6 ms) was significantly higher compared with control hips without deformity (31.3 ± 3.2 ms; $P = 0.050$). Studies were also performed to identify the best suited regions of interest to measure cartilage matrix abnormalities related to

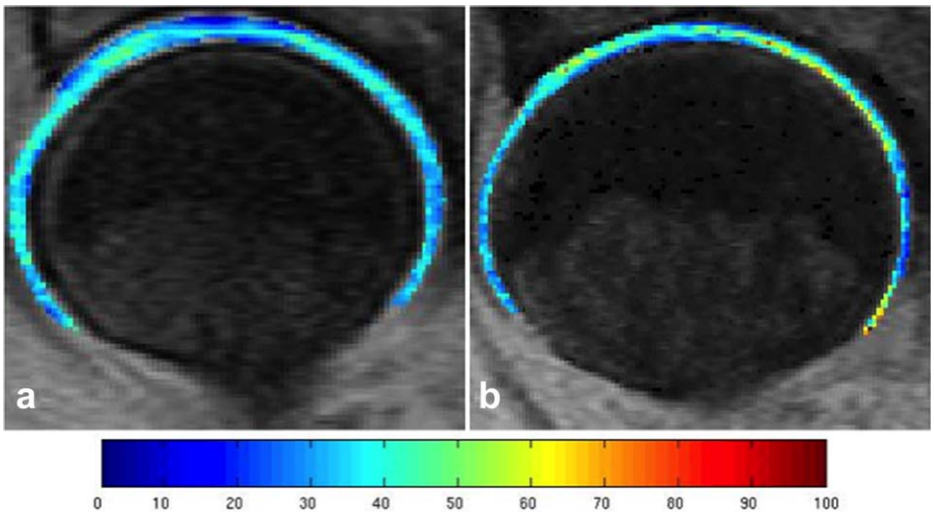

FIGURE 4: T1ρ color maps of the acetabular and femoral articular cartilage. Composite T1ρ color maps of the right hip obtained in the sagittal plane in a healthy control subject (A) and a patient with OA of the hip (K-L grade 3) (B). Thinning of cartilage and joint space narrowing are shown in the patient with advanced OA (B) with at the same time increased T1ρ values (yellow, red), consistent with cartilage matrix degeneration. (Image courtesy Dr. Richard B. Souza, Department of Physical Therapy & Rehabilitation Science, University of California at San Francisco; Dr. Michael Samaan and Matt Tanaka, MS, Department of Radiology and Biomedical Imaging, University of California at San Francisco)

femoroacetabular impingement[66,70] with one study favoring the anterior–superior region as most useful. Figure 6 shows cartilage abnormalities in a patient with CAM type femoroacetabular impingement on a standard intermediate-weighted MRI sequence and on the T1rho map.

Delayed Gd Enhanced MRI of Cartilage

TECHNIQUE AND CONCEPT. dGEMRIC uses a T1 mapping technique after intravenous application of Gd-DTPA.[72] It is based on the fact that proteoglycans and the associated glycosaminoglycans have negatively charged carboxyl and sulfate groups. Negatively charged contrast agents such as Gd-DTPA^{2-} (Magnevist®; Bayer Schering Pharma Ag, Berlin, Germany), are injected intravenously (or intraarticularly) and distributed in the cartilage by diffusion. The diffusion time depends on the cartilage thickness and is approximately 2 h in femoral weight-bearing cartilage. Due to their negative charges, Gd-based contrast agents will only show minimal enhancement in healthy cartilage, which is rich in glycosaminoglycans; however, there will be higher concentrations and higher enhancement in regions with degenerated cartilage matrix with lower concentrations of glycosaminoglycans.[73–75] Gd-DTPA concentration has a direct effect on the MR parameter T1 and thus allows to assess the glycosaminoglycan concentration based on a modified electrochemical equilibrium theory, assuming the Gd-DTPA concentration is equilibrated in the tissue.[76] However, in addition to an intravenous injection of Gd-DTPA, standard dGEMRIC scans also require exercise and relatively long wait times to distribute the contrast agent sufficiently through the cartilage.

VALIDATION. dGEMRIC measures have been validated using biochemical and histologic measurements of glycosaminoglycan concentration in cartilage with ex vivo studies.[77] The in vivo validation of dGEMRIC techniques, however, is not straightforward especially for the conversion from T1 quantification to glycosaminoglycan concentration; therefore, the direct T1 measure of "dGEMRIC index" is normally reported for clinical studies.[77] Loss of glycosaminoglycans will result in a decreased T1, and a decreased "dGEMRIC index." One recent study analyzed cartilage specimens obtained from 12 patients that underwent dGEMRIC knee imaging before total joint replacement and found a strong correlation of dGEMRIC with cartilage sulphated glycosaminoglycan content ($r = 0.73$; 95% credibility interval [CI] = 0.60, 0.83).[78] Another study validated hip dGEMRIC using histology in 21 patients undergoing total hip arthroplasty with good results.[79]

REPRODUCIBILITY. Several studies showed good reproducibility of dGEMRIC in vivo.[80–82] All these studies demonstrated moderate to good results with high ICCs ranging between 0.45 and 0.98. RMS correlation coefficients were typically below 10%. Multanen et al calculated RMS correlation coefficients and ICCs for bulk measurements of 4.2% and 0.95 for the femur, 5.5% and 0.87 for the tibia, and 4.8% and 0.97 for the patella.

Other Requirements for Quantitative Imaging Biomarkers

Similar to T1ρ and T2, no cutoff values have been defined for dGEMRIC values to define OA. However, dGEMRIC has been shown to be associated with the severity of the disease and the disease burden at the knee cartilage and

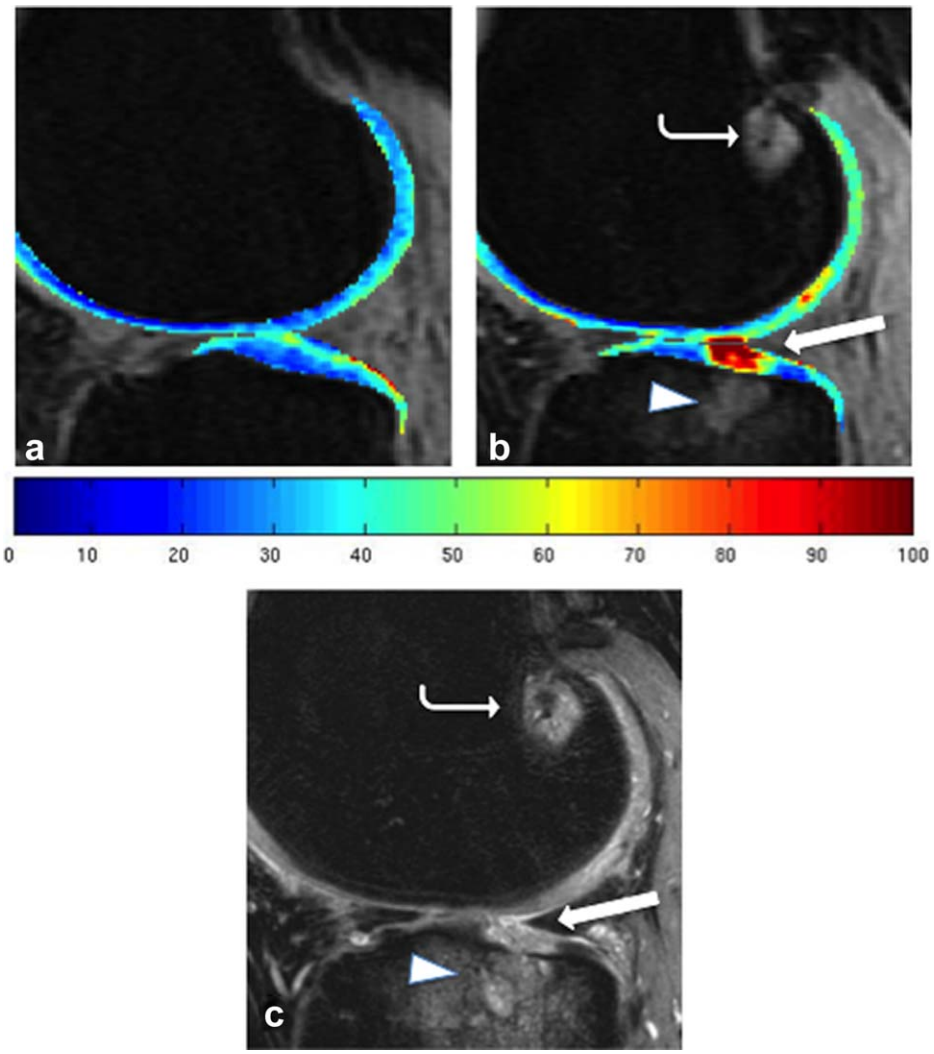

FIGURE 5: T1ρ color maps of the medial femoral and tibial articular cartilage of a patient undergoing ACL reconstruction and 2-year follow-up. T1ρ color map of a patient 3 weeks after complete tear of the right ACL (A), T1ρ color map 2 years after undergoing ACL reconstruction (B), and concurrent sagittal intermediate-weighted fat-saturated 3D fast spin-echo (CUBE) (C). Initial imaging of the femoral and tibial cartilage shows no cartilage matrix damage (blue and green = normal composition). Following ACL reconstruction, 2 years after the initial trauma, the tibial cartilage shows focal increased (red) T1ρ values (B; white arrow) with also elevated T1ρ values (yellow and orange) along the dorsal side of the medial femoral condyle. 3D fast spin-echo sequence shows focal cartilage degeneration (C; white arrow) and subarticular cysts with surrounding edema (B,C; white arrowhead). Femoral tunnel placement of the ACL graft (B,C; curved white arrow).

menisci,[83,84] although the number of studies systematically investigating the disease burden with dGEMRIC is limited. Several studies demonstrated that dGEMRIC indices were useful in predicting knee radiographic OA changes,[85,86] predicting early failure of periacetabular osteotomy for hip dysplasia and in predicting clinical outcomes in patients undergoing therapeutic hip arthroscopy after 2 years.[87] dGEMRIC was also found helpful in monitoring therapy and interventions such as cartilage repair[88] and oral medications.[89]

CLINICAL APPLICATION. dGEMRIC has been used in multiple clinical studies, although the study designs overall appeared less rigorous than those used in the studies with T2 and T1ρ relaxation time measurements. While one multi-center study was performed,[90,91] rigorous assessment of inter-site and inter-scanner reproducibility was not reported. Also, it should be noted that Gd-based contrast agents have potential side effects, such as nephrogenic systemic fibrosis in patients with renal insufficiency and some effects of Gadolinium based contrast agents, such as the deposition of Gd in the brain and other tissues, are still poorly understood.[92] Other limitations are double dose regimens and lack of standardization of required physical activity.

Nevertheless dGEMRIC has been applied to multiple conditions at different anatomical sites such as the knee, the hip, the hand and the shoulder. It has been used to assess several conditions such as cartilage repair,[93] surgical joint interventions for hip dysplasia,[94] femoroacetabular impingement,[95] OA[84] and inflammatory joint disorders.[96] Figure 7 shows an

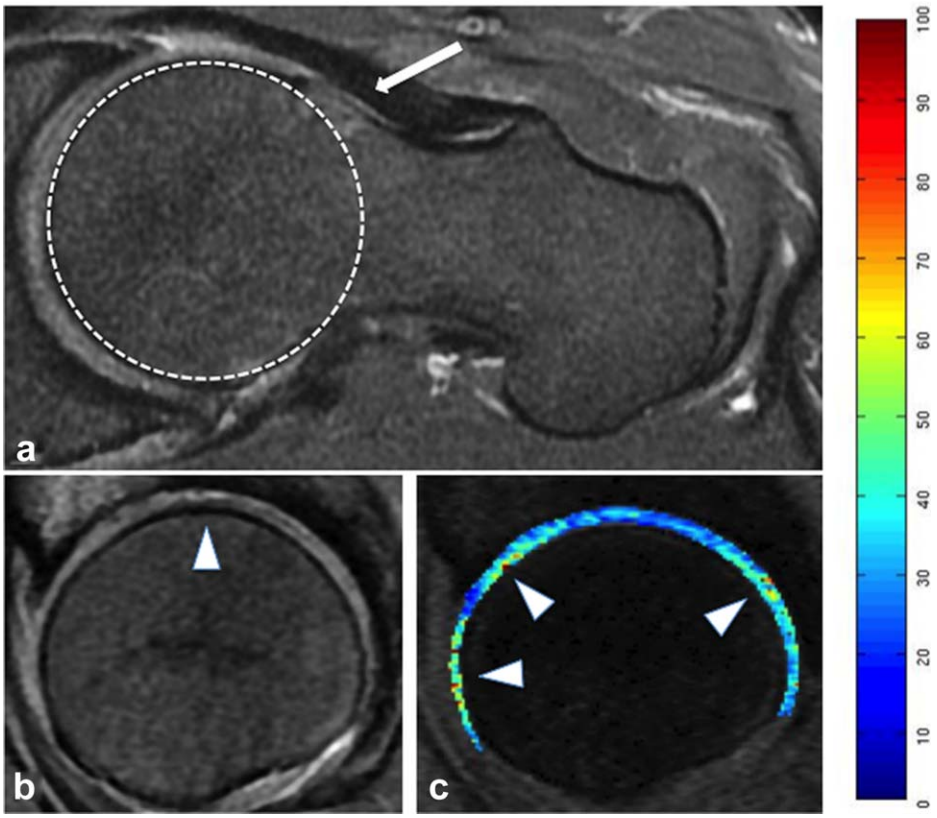

FIGURE 6: T1ρ imaging of the left hip in a patient with CAM type femoro-acetabular impingement. Oblique transverse intermediate-weighted fat-saturated 2D fast spin-echo sequence of the left hip demonstrates an osseous bump of the anterior femoral head-neck junction (A; white arrow). Sagittal plane (B) shows thinning and defects (white arrowhead) of the femoral and acetabular cartilage. Compositional T1ρ color map, obtained in the sagittal plane of the left hip of the same patient (C), shows more extensive cartilage abnormalities with elevated T1ρ values in the anterior, anterior-superior and posterior-superior aspect (white arrowheads) of the acetabular and femoral cartilage, indicating cartilage loss with focus in the anterior-superior margin. (Image courtesy Dr. Richard B. Souza, Department of Physical Therapy & Rehabilitation Science, University of California at San Francisco; Dr. Michael Samaan and Matt Tanaka, MS, Department of Radiology and Biomedical Imaging, University of California at San Francisco)

impressive case of a patient with left sided hip dysplasia with a lower dGEMRIC index compared with the unaffected right hip, although both hips appear, except for the inadequate coverage of the left femoral head, morphologically normal.

SODIUM IMAGING

TECHNIQUE AND CONCEPT. Glycosaminoglycan side chains of the proteoglycans are negatively charged, attracting cations such as Na + in the cartilaginous interstitial matrix. Based on the Donnan theory, the fixed charge density, which is correlated with the glycosaminoglycan concentration, can be estimated using the sodium content.[97] This, however, requires dedicated sodium MRI, which suffers from inherent low signal-to-noise-ratio due to (1) low concentrations in vivo (<300 mM of ^{23}Na versus 50 M of 1H in healthy cartilage), (2) a four times lower gyromagnetic ratio (11.262 MHz/T of ^{23}Na versus 42.575 MHz/T for 1H), and (3) the ultra-short T2 and T2* relaxation times (short T2 and T2* component less than 2 ms, and long T2 and T2* component less than 15 ms).[49] Thus, it is challenging to acquire in vivo sodium MR images with adequate SNR and spatial resolution in a clinically reasonable scan time. Higher static magnetic field strengths, dedicated coils, and optimal pulse sequences are essential for in vivo sodium

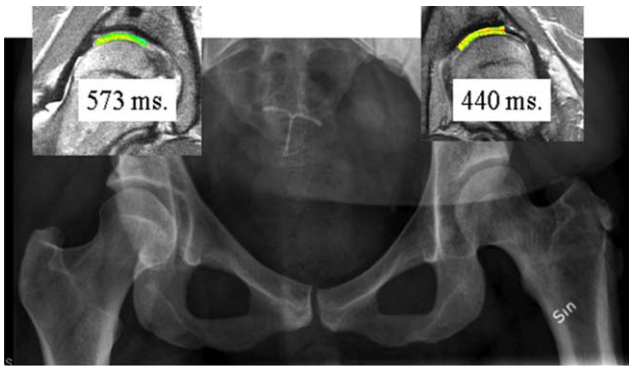

FIGURE 7: Radiograph of the pelvis and dGEMRIC maps of a 20-year old woman with left sided hip pain and radiographic dysplasia with a low CE (center edge) angle. No radiographic evidence of osteoarthritis with normal joint space and no osteophytes; signs of previous left proximal femur surgery. The left hip shows a diffusely lower dGEMRIC index (440 ms) compared with the unaffected right hip (573 ms) consistent with lower glycosaminoglycan content and pre-radiographic degenerative cartilage changes (Image courtesy Dr. Carl Johan Tiderius, Department of Orthopedics, Skane University Hospital, Lund University, Sweden).

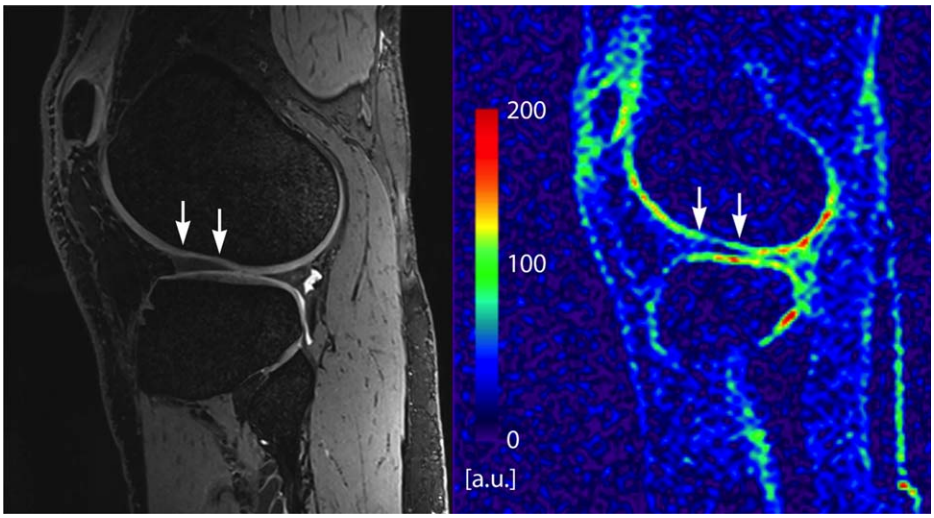

FIGURE 8: Sodium image of a 26-year-old female athlete with a traumatic injury of the knee. Sodium image in the sagittal plane of a 26-year-old female athlete 6 months after traumatic injury (ACL-tear, tear of the medial collateral ligament and horizontal tear of the posterior horn of the medial meniscus) examined on a 7T MRI system. Incipient cartilage defect grade I in the weight-bearing femoral cartilage, barely visible on sagittal morphological T2-DESS image (left, arrows), showing reduced sodium signal in the sodium image (right, arrows). (Image courtesy Dr. Markus Schreiner, Univ.-Prof. Dr. Siegfried Trattnig and Dr. Vladimir Mlynarik, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria)

MRI. Using optimized techniques, at 3T or 7T, images can be acquired approximately within 15–30 min with a reasonable SNR and spatial resolution.

REQUIREMENTS FOR IMAGING BIOMARKERS. A limited number of studies have been performed to validate sodium imaging. For example, Wheaton et al demonstrated in a pig model with MRI at 4T that sodium MRI can be used to measure in vivo changes of proteoglycans.[98] Also, it was shown that sodium MRI at 3T was reproducible with CVs for within-subject variation of 2% for healthy volunteers and 3.6% for OA subjects.[99] Madelin et al found RMS CVs in the range of 7.5–13.6% at 3T and 7T.[100] However, other requirements for imaging biomarkers such as diagnosing OA are not met. Also there is limited information on how disease burden is measured with Sodium MRI and whether quantitative measures obtained from sodium MRI can predict OA or other joint diseases.

CLINICAL APPLICATION. Overall sodium MRI has limited clinical applicability as it requires dedicated coils and has limited SNR. Although researchers have performed imaging at 1.5T,[101] most studies have been performed at 3T or higher field strength[102,103] and focused on imaging of cartilage repair tissue and osteoarthritis. While sodium MRI has shown great promise, further hardware and software improvements are necessary to complete the translation of sodium MRI into a clinically feasible method for 3T systems.[103] To date, sodium MRI is a useful research tool if combined with high field imaging at 3T and 7T. Figure 8 shows a sodium MRI color map and the corresponding morphological MR image in a patient with traumatic knee injury and better visibility of the lesion in the sodium MRI.

Glycosaminoglycan Chemical Exchange Saturation Transfer

TECHNIQUE AND CONCEPT. Among the presented technologies, chemical exchange dependent saturation transfer (CEST) imaging is the newest compositional cartilage imaging technique.[104] In CEST experiments, exogenous or endogenous compounds containing either exchangeable protons or exchangeable molecules are selectively saturated and after transfer of this saturation upon chemical exchange to the bulk water, detected indirectly through the water signal with enhanced sensitivity.[49] To account for direct saturation of water and background magnetization transfer that is related to mechanisms other than chemical exchange, such as the nuclear Overhauser effect in cartilage,[105] two images are normally acquired in CEST experiments. One with a saturation pulse applied at the resonance frequency of interest ($-\delta$), and the other acquired with an equal frequency offset but applied on the other side of the bulk water peak (δ). The CEST effect is quantified as the difference of these two images.[105] In cartilage, CEST exploits the exchangeable protons, including NH, OH, and NH2 proton groups, on the glycosaminoglycan side chains of PG,[105,106] and was termed as gagCEST. Ling et al. showed that –OH at $\delta = -1.0$ ppm, where δ is the frequency offset relative to the water, among other labile protons, can be used to monitor glycosaminoglycan concentration in cartilage in vivo.[105] There are several limitations with this technique including sensitivity to pH changes, changes in hydration and collagen that may also change the exchange rate of –OH protons and to pulse sequence parameters which complicates multicenter studies.

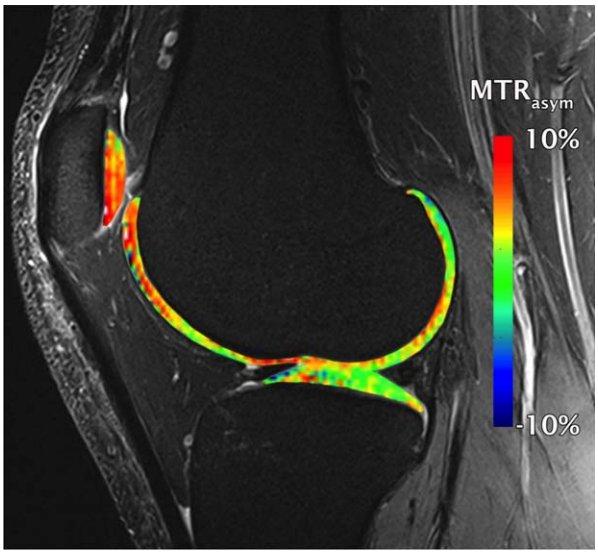

FIGURE 9: gagCEST imaging of the right knee of a 25-year-old healthy volunteer. A gagCEST color map in the sagittal plane of the right knee of a 25-year-old healthy male volunteer overlaid on an anatomic PD-weighted TSE image, both acquired at 7T. The femorotibial and patellofemoral is smoothly configured without any morphological visible cartilage defects. The overlaying gagCEST image map displays moderate (green and yellow) to high (red) values, indicating a high GAG level in the healthy cartilage matrix. (Image courtesy Dr. Markus Schreiner, Univ.-Prof. Dr. Siegfried Trattnig and Dr. Vladimir Mlynarik, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria)

REQUIREMENTS FOR IMAGING BIOMARKERS. Only a limited number of publications are available to date and there is no solid data on validation and reproducibility. Also data on measurement of disease burden, prediction of joint disease and monitoring of therapy are not yet available.

CLINICAL APPLICATION. Singh et al suggested that gagCEST does not lead to accurate quantification of glycosaminoglycan content in healthy or degenerated cartilage at 3T.[107] This may limit the clinical applicability of this technology to 7T MRI, which is a research tool and not clinically feasible. The number of clinical studies published to date is quite small and mostly limited to experiments at 7T in small patient cohorts. Figure 9 shows a gagCEST color map of the right knee in a 25-year-old healthy volunteer. One study looked at results 8 years after autologous osteochondral transplantation using a cross-sectional study design with gagCEST imaging at 7T and found a correlation between semi-quantitative cartilage repair scores and the CEST ratio [ρ = -0.749, 95% CI: (-0.944; -0.169)].[108]

In Vivo Diffusion MRI

TECHNIQUE AND CONCEPT. Both diffusion weighted and diffusion tensor imaging have been used to explore cartilage. Standard diffusion weighted imaging provides information on water mobility, which is restricted in the intact collagen network. Increased mobility of water is found if there is deterioration of the extracellular matrix[109] and apparent diffusion coefficients are increased in early degenerative disease of articular cartilage.[110]

Diffusion tensor imaging can also measure diffusion anisotropy of cartilage and has been shown to be sensitive to the proteoglycan content through the mean diffusivity

TABLE 1. Available Techniques for Compositional Cartilage Imaging

Technique	Concept	Joints	Spatial resolution	Clinical feasibility	Suited as Biomarkers
T2	Measures water content and collagen integrity	Knee, hip, hands	Adequate	High	++++
T2*	Measures water content and collagen integrity	Knee, hip, hands	Adequate	High	+++
T1ρ	Measures macromolecules, in particular glycosaminoglycans	Knee, hip, hands	Adequate	High	+++
dGEMRIC	Glycosaminoglycans	Knee, hip, hands	Adequate	Acceptable	++
Sodium	Glycosaminoglycans	Knee	Limited	Low with current technologies	+
gagCEST	Glycosaminoglycans	Knee	Limited	Low with current technologies	+
Diffusion MRI	Collagen integrity, glycosaminoglycans	Knee	Limited	Low with current technologies	+

and to the collagen architecture through the fractional anisotropy in cadaver studies.[111] Measurement of diffusion anisotropy also provides information on mechanical function of articular cartilage and on the transport of nutrients to the chondrocytes and for the removal of their metabolic waste product.[112] However, the acquisition of diffusion tensor imaging of articular cartilage in vivo is challenging due to the short T2 of articular cartilage (~40 ms at 3T) and the high resolution needed (0.5–0.7 mm in plane) to depict the cartilage anatomy.[112]

REQUIREMENTS FOR IMAGING BIOMARKERS. Using Safranin O stains with OARSI grades of human articular cartilage specimens as a standard of reference, one previous ex vivo study showed excellent performance of diffusion tensor imaging in the detection of cartilage damage (accuracy, 95%; 41 of 43 samples) and good performance in the grading of cartilage damage (accuracy, 74%; 32 of 43 samples).[113] An additional validation study was performed using arthroscopy as a standard of reference and found highly significant correlations between arthroscopic Outerbridge scores versus apparent diffusion coefficients and fractional anisotropy.[114] Reproducibility was also tested in two previous studies at 7T and 3T[115,116] and CVs of 2.9 and 6.5% were found for mean diffusivity and of 5.6 and 11.6% for fractional anisotropy; the better reproducibilities were found at 7T, which, however, is not feasible for clinical routine imaging, while at 3T CVs were higher. Several studies were also performed that demonstrated significant differences in mean diffusivity and fractional anisotropy in individuals with and without OA.[115–117] Limited information is available on prediction of osteoarthritis and monitoring of degenerative disease using diffusion tensor imaging.

CLINICAL APPLICATION. Previous clinical work on diffusion weighted imaging mostly focused on the assessment of cartilage repair tissue at the knee and ankle.[118–120] The number of clinical studies on diffusion tensor imaging is limited and has to date mostly focused on the knee joint investigating small numbers of subjects with and without degenerative joint disease.[115–117]

Major Limitations

Some of the major issues limiting widespread application of the compositional techniques to date are (i) limited standardization of these technologies across sites and vendors, (ii) time consuming cartilage segmentation required to analyze cartilage and (iii) no effective pharmacotherapies that would require monitoring therapy response and disease progression. Future research will need to address these issues before cartilage prestructural imaging techniques are applicable in clinical routine.

Conclusion and Summary

In this article, we reviewed current MRI techniques to quantify cartilage composition. We described the technologies but our main goal was to analyze their suitability as imaging biomarkers and to review clinical applications. To date, the best explored technique is T2 relaxation time mapping, with the largest body of literature, satisfactory validity and reproductivity, allowing the prediction of OA and monitoring of interventions. This is largely due to the OAI database a large multi-center study, which provides longitudinal data in several thousand subjects over 8 years. T1ρ is also a promising imaging biomarker, which was used in a recent multicenter study with good inter-site reproducibility.[25] Compared with T2, it allows similar and potentially improved prediction of cartilage loss and monitoring of interventions. Studies using dGEMRIC appear overall less rigorous and this technique requires Gd contrast application, with potential risks that are not completely understood. Sodium imaging, gagCEST and Diffusion MRI are promising techniques, but they require sophisticated and high field imaging, making them currently less well suited for larger scale clinical application.

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