

# Cartilage Imaging in Osteoarthritis

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## Abstract

Osteoarthritis (OA) is the most common joint disease in the United States. The prevalence of OA is rising due to an aging population and increasing rates of obesity. Magnetic resonance imaging (MRI) allows an incomparable noninvasive assessment of all joint structures. Irreversible and progressive degradation of the articular cartilage remains the hallmark feature of OA. To date, attempts at developing disease-modifying drugs or biomechanical interventions for treating OA have proven unsuccessful. MRI-based cartilage imaging techniques have continued to advance, however, and will likely play a central role in the development of these joint preservation methods of the future. In this narrative review, we describe clinical MR image acquisition and assessment of cartilage. We discuss the semiquantitative cartilage scoring methods used in research. Lastly, we review the quantitative MRI techniques that allow assessment of changes in the biochemical composition of cartilage, even before the morphological changes are evident.

## Keywords

- ▶ cartilage
- ▶ MRI
- ▶ quantitative
- ▶ semiquantitative

Osteoarthritis (OA) is the most common joint disease in the United States, and its prevalence is rising due to an aging population and increasing rates of obesity.<sup>1,2</sup> Irreversible and progressive degradation of the articular cartilage remains the fundamental feature of OA pathophysiology. Conventional radiography is considered the reference standard for imaging of OA; however, joint space narrowing (JSN) on radiography provides an indirect measure of cartilage loss and is not sensitive to progression of the disease.<sup>3–5</sup> Radiography-based JSN is nonetheless commonly used as the imaging outcome measure to establish the effectiveness of disease-modifying osteoarthritis drugs (DMOADs).<sup>6</sup> The use of radiographic JSN as an outcome measure may partly explain why attempts at developing DMOADs and behavioral therapy for OA have proven unsuccessful, despite promising preclinical research.<sup>7</sup>

Regulatory agencies including the U.S. Food and Drug Administration (FDA) are increasingly recommending imaging beyond radiography to assess early onset of abnormalities in OA.<sup>8</sup> The multiplanar, multiparametric capabilities of magnetic resonance imaging (MRI) and its excellent soft tissue contrast allow unparalleled evaluation of all joint structures including cartilage. Hence MRI-based outcome measures are ideal for

assessment of cartilage degradation in OA. In addition to the routine clinical MRI, advanced research techniques have been developed to assess the biochemical composition of cartilage in the earliest stages of OA. These include relaxometry measurements (T2, T2\*, and T1ρ mapping), sodium imaging, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), glycosaminoglycan specific chemical exchange saturation transfer (gagCEST), and diffusion tensor imaging (DTI). These compositional MRI techniques serve as quantitative, reproducible, and objective end points for OA research that will likely be introduced to clinical radiology practice in the near future.

In this narrative review, we describe the standard clinical imaging of cartilage in OA. We discuss semiquantitative scoring systems for the assessment of cartilage that serve as important outcome measures in research. Lastly, we highlight advanced compositional MRI techniques that allow the detection of early articular cartilage degradation.

## Cartilage Microarchitecture

Understanding the imaging of chondral degeneration in OA requires an understanding of the basic ultrastructure of the articular cartilage. It is composed of primarily fluid (70–80%) and extracellular matrix (ECM), both of which are essential

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for its normal function.<sup>9</sup> The ECM is a network of collagen fibrils and proteoglycan molecules, with the proteoglycan consisting of negatively charged glycosaminoglycan (GAGs) attached to the protein core.<sup>9</sup> The negative charge attracts and holds water within articular cartilage while cations such as sodium ( $\text{Na}^+$ ) counter the negative charge of GAGs. The redistribution of water within the ECM provides the known biomechanical properties of cartilage, that is, its ability to deal with tensile and compressive loads.<sup>10</sup> In OA, proteoglycan loss and disorganization and/or loss of the collagen fiber network lead to impaired ability of the articular cartilage to deal with these loads and results in progressive, irreversible breakdown.<sup>11</sup>

### Clinical MRI of Cartilage

An in-plane resolution of 0.3 mm resolves the earliest stage of morphological cartilage degeneration, that is, fraying of the articular surface.<sup>12</sup> Optimal evaluation of cartilage morphology on standard clinical MRI, therefore, requires high signal-to-noise ratio (SNR) and a high spatial resolution, both of which are advantages of higher field strength magnets ( $\geq 1.5\text{ T}$ , with dedicated extremity coils). A recent systemic review and meta-analysis comparing 1.5-T and 3-T MRI for detection of morphological cartilage lesions found both field strength magnets to offer high diagnostic accuracy; however, the 3-T MRI had greater accuracy than the 1.5 T.<sup>13</sup> In 2017, the FDA approved the first 7-T MRI system for clinical diagnostic imaging of the extremities. A comparison of routine clinical knee MRI performed at 3 T and 7 T found diagnostic confidence of radiologists for cartilage defects to be higher with 7 T.<sup>14</sup>

In addition to adequate SNR and spatial resolution, detection of cartilage pathology requires optimal cartilage–synovial fluid contrast. The International Cartilage Repair Society (ICRS) protocol for imaging of cartilage includes two-dimensional (2D) fast spin-echo (FSE) or turbo spin-echo (TSE) pulse

sequences to obtain fat-suppressed proton-density-weighted, T2-weighted, or intermediate-weighted images.<sup>15</sup> These sequences provide excellent tissue contrast allowing detection of cartilage lesions with high accuracy; however, they require acquisition in multiple planes. **►Fig. 1** shows fat-suppressed proton-density images of the patellofemoral compartment cartilage in a healthy volunteer (**►Fig. 1a**) and in a patient with advanced osteoarthritis (**►Fig. 1b**). Isotropic sequences (3D FSE or TSE) obviate the need for multiplanar acquisition, greatly reducing acquisition time.<sup>16</sup> Isotropic imaging suffers from blurring and lower tissue contrast compared with 2D sequences; however, the diagnostic accuracy of isotropic FSE for cartilage morphology was shown to be similar to 2D FSE at 3 T.<sup>17</sup>

Cartilage-sensitive techniques based on gradient spin-echo (GRE) such as 3D spoiled gradient recalled echo produce images with cartilage signal more intense than the surrounding tissues, which renders them insensitive to subtle cartilage lesions and of limited utility in clinical imaging.<sup>18</sup> These techniques were used successfully for quantitative assessment of cartilage thickness and volume in research studies.<sup>19–21</sup>

### Semiquantitative Assessment of Cartilage

Semiquantitative scoring systems for cartilage including the Outerbridge (1961)<sup>22</sup> and Noyes and Stabler (1989)<sup>23</sup> classifications were originally developed for grading the appearance and quantity of cartilage via direct evaluation during surgery. The ICRS classification, a 9-point scale, succeeded these initial scoring systems<sup>24</sup> and provided a more comprehensive and detailed assessment of articular cartilage pathology. All of these classifications have been adapted for assessment of joint cartilage on MRI,<sup>25–27</sup> primarily for research.

As the use of MRI for OA was researched and increased, dedicated MRI-based semiquantitative classifications for whole-organ assessment of joints, most commonly the knee joint, were developed and validated. In the next section, we



**Fig. 1** Sagittal fat-suppressed proton-density images of the patellofemoral compartment cartilage in (a) a healthy volunteer and (b) a patient with advanced osteoarthritis (OA). The healthy volunteer has normal patellar and femoral trochlear cartilage thickness and signal density. The patient with OA demonstrates full-thickness cartilage loss overlying the patella (yellow arrow) and overlying the femoral trochlea (red arrow), with associated subchondral bone marrow edema.

briefly describe a select few of these systems that are most likely to be encountered in the published literature.

### Whole-Organ Magnetic Resonance Imaging Score

The Osteoarthritis Initiative (OAI) and the Multicenter Osteoarthritis Study (MOST) are two of the largest multicenter and longitudinal studies of OA that included MRI acquisition in addition to expansive clinical data for the study of OA.<sup>28–33</sup> The Whole-Organ Magnetic Resonance Imaging Score (WORMS) is the most commonly used scoring system in knee OA research and was used as an outcome measure in the OAI and MOST. The WORMS assesses 14 features in the knee joint that include articular cartilage integrity, subchondral bone marrow abnormality, cruciate ligament, and meniscal integrity among other features.<sup>34</sup> Cartilage is graded on an 8-point scale in 14 subregions subdivided by anatomical landmarks. Cartilage grades in the different subregions are frequently summed to provide composite or global cartilage scores (► Fig. 2).

### Boston-Leeds Osteoarthritis Knee Score

Concerns about the responsiveness of WORMS and the validity of summation of subregional WORMS cartilage measurements led to the development of the Boston-Leeds Osteoarthritis Knee Score (BLOKS).<sup>35</sup> The BLOKS evaluates cartilage in nine subregions of the knee. BLOKS I cartilage score, the more commonly used of the two-part cartilage scoring component of BLOKS, assesses cartilage on a 4-point scale. It assigns separate scores for (1) the areal extent of any

cartilage loss in each subregion, and (2) the percentage of subregion surface area that has a full-thickness loss (► Fig. 2).

### MRI Osteoarthritis Knee Score

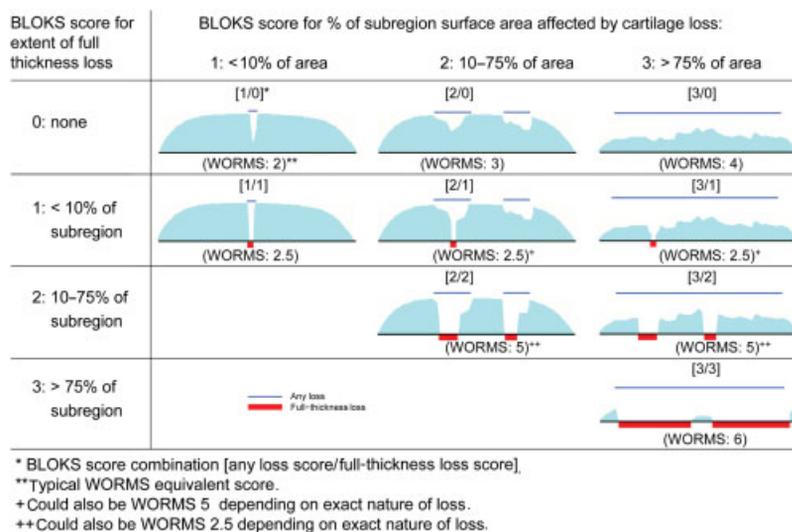
Both WORMS and BLOKS have limitations, highlighted in a two-part study comparing these methods.<sup>36,37</sup> As a result, the MRI Osteoarthritis Knee Score (MOAKS) was derived from both the BLOKS and WORMS to improve whole-organ assessment of the knee.<sup>38</sup> MOAKS grades cartilage in the same 14 subregions of the knee as are graded in WORMS, but it uses the grading scale used in the BLOKS “cartilage I” score (► Fig. 1).

### Knee Osteoarthritis Scoring System

The Knee Osteoarthritis Scoring System<sup>39</sup> is another whole-organ grading system focused on the knee that grades cartilage in nine subregions. It assigns separate 4-point scores for the depth of the cartilage and osseous components of an osteochondral defect. It also assigns a separate 4-point score for the surface extent of an osteochondral defect estimated by its maximal diameter. A focal cartilaginous defect is well defined with an acute angle between the defect and surrounding cartilage. A diffuse defect has an obtuse angle between the normal and thinned cartilage.

### Use of Semiquantitative Assessment Methods in Research

These classification schemes have been used extensively as outcome measures in research including in large multicenter trials such as the OAI and MOST. The following are select



**Fig. 2** Whole-organ magnetic resonance imaging score (WORMS) descriptions: 0 = normal thickness and signal; 1 = normal thickness but increased signal on T2-weighted images (not used in this study); 2.0 = partial-thickness focal defect < 1 cm in greatest width; 2.5 = full-thickness focal defect < 1 cm in greatest width; 3 = multiple areas of partial-thickness defects < 75% of region or a single partial-thickness defect wider than 1 cm but < 75% of the region; 4 = diffuse (> 75% of the region) partial-thickness loss; 5 = multiple areas of full-thickness loss < 75% of the region or a single full-thickness lesion wider than 1 cm but < 75% of the region; 6 = diffuse (> 75% of the region) full-thickness loss. Boston-Leeds Osteoarthritis Knee Score (BLOKS) descriptions: Size of any cartilage loss (including partial- and full-thickness loss) as a percentage of surface area as related to the size of each individual region: 0: none; 1: < 10% of region of cartilage surface area; 2: 10 to 75% of region of cartilage surface area; 3: > 75% of region of cartilage surface area; and percentage full-thickness cartilage loss of the region: 0: none; 1: < 10% of region of cartilage surface area; 2: 10 to 75% of region of cartilage surface area; 3: > 75% of region of cartilage surface area. Reproduced with permission from Lynch et al.<sup>36</sup>

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examples of studies of OA risk factors using semiquantitative assessment.

### Osteoarthritis and Physical Activity

The impact of physical activity on OA remains a controversial topic. Although some studies found exercise to be beneficial,<sup>40,41</sup> studies of patients from the OAI contradicted these findings. In particular, these studies of OAI patients reported that individuals who have risk factors for OA may suffer cartilage degeneration with high-intensity physical activity.<sup>29,42,43</sup> Even in asymptomatic individuals enrolled in the OAI, cartilage lesions were more common and more severe in the highly active subjects compared with the less active subjects.<sup>29,44</sup> In patients who have knee abnormalities at baseline, walking > 10,000 steps per day was associated with higher cartilage defect scores.<sup>45</sup> Physical activity involving frequent knee bending was also implicated in a higher prevalence of knee cartilage lesions and increased the progression of these lesions, particularly in the patellofemoral compartment.<sup>33</sup>

### Obesity

In obese adults, knee cartilage defects are associated with physical disability.<sup>46</sup> In the OAI cohort, obesity was associated with a higher prevalence and severity of knee cartilage lesions as well as with increased cartilage lesion progression over 3 years.<sup>32,47</sup> High body mass index was also associated with rapid tibiofemoral cartilage loss in patients enrolled in MOST who had or were at risk for OA.<sup>48</sup> Weight loss may help prevent development/progression of lesions and improve quality of life.<sup>49</sup>

### Injuries

In the OAI cohort, individuals with anterior cruciate ligament (ACL) abnormalities had a greater prevalence of cartilage lesions that were also more severe compared with individuals with a normal ACL.<sup>30</sup> Meniscal tears were also found to be associated with poor tibiofemoral cartilage scores, even in patients without OA.<sup>50</sup> Meniscal root tears are particularly implicated.<sup>51,52</sup> The presence of meniscal extrusion is also associated with the prevalence and severity of cartilage damage.<sup>53,54</sup>

### Alignment

Knee malalignment in either the valgus or varus direction affects the distribution of the load across the joint.<sup>55</sup> A large study examined 5,053 knees from the MOST and 5,953 knees from the OAI cohort using either WOMBS or BLOKS.<sup>56</sup> This study found valgus malalignment, particularly > 3 degrees, to be associated with an increased risk of cartilage defect progression in the lateral tibiofemoral compartment. In the MOST cohort, varus malalignment has, in contrast, been associated with incident cartilage damage in the medial compartment.<sup>57</sup>

## Compositional MRI Techniques for Assessment of Cartilage

Primarily used in research, these techniques allow detection of the earliest changes of cartilage degeneration in the ECM, well before the morphological cartilage defects are apparent. Thus, compositional imaging sequences have the potential to serve as quantitative imaging biomarkers of OA.

Higher field strength magnets (3 T and 7 T) are particularly useful for compositional imaging, even more so than for clinical imaging of cartilage. These MR units afford higher SNR with resultant greater spatial resolution and shorter MRI acquisition times.<sup>58</sup> Additionally, many biologically relevant nuclei in addition to <sup>1</sup>H, such as sodium and phosphorous, occur in relatively low concentrations and warrant high field strength magnets to allow signal acquisition. Among numerous challenges, impediments to routine use of higher field strength MRI include increasing inhomogeneity, changes in relaxation times,<sup>59</sup> increased sensitivity to susceptibility effects (decreased  $T_2^*$ ),<sup>60</sup> and increase in chemical shift artifact in the frequency-encode direction.<sup>61</sup>

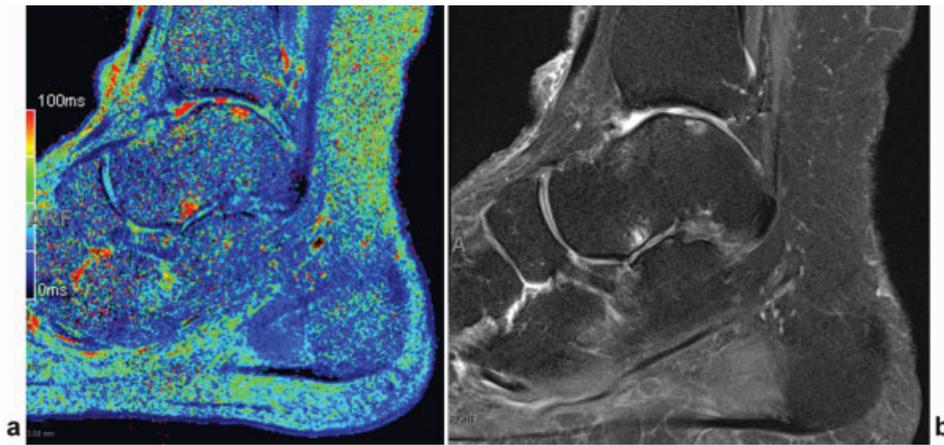
### T<sub>2</sub> Mapping and T<sub>2</sub>\* Mapping

T<sub>2</sub> mapping was obtained as part of the knee MRI acquisition protocol in the OAI and was the most widely studied of all compositional imaging techniques.<sup>62</sup> T<sub>2</sub> measurements reflect dephasing in the transverse plane after application of a radiofrequency (RF) pulse. These measurements were found to be associated with cartilage water content and reflect an indirect measure of the ECM collagen content.<sup>63</sup> Lamellar analysis of cartilage found these measurements to be higher in the superficial layers of cartilage than in the deep layers.<sup>64</sup> Higher T<sub>2</sub> values were shown to predict the development of cartilage lesions.<sup>65</sup> At our institutions, a few select surgeons request T<sub>2</sub> mapping as part of the preoperative MRI to identify problem areas in the cartilage before performing arthroscopy (► Fig. 3). T<sub>2</sub> mapping can discriminate between repaired knee cartilage and adjacent healthy cartilage,<sup>66–68</sup> and it may be particularly helpful in assessing the maturation of reparative cartilage.<sup>69</sup>

T<sub>2</sub>\* mapping measures transverse-plane dephasing using multiecho GRE techniques. These sequences have a shorter acquisition time but are also more vulnerable to local field inhomogeneity.<sup>70,71</sup> Both T<sub>2</sub> and T<sub>2</sub>\* are affected by the magic angle effect; that is, the values increase as the angle between collagen fibers and B<sub>0</sub> approaches 55 degrees.

### T1ρ Mapping

T1ρ imaging is more challenging to acquire than T<sub>2</sub> mapping and therefore only performed at a few select academic institutions. The imaging is difficult to acquire due to B<sub>0</sub> and B<sub>1</sub> inhomogeneity, specialized RF pulse sequence requirements, and long acquisition times that may result in high specific absorption rates (SARs). The SNR gain at 7 T has been used, however, to show the feasibility of acquiring high-resolution T1ρ images (0.2 mm<sup>2</sup> in-plane resolution) in reasonable acquisition times



**Fig. 3** T2 mapping was performed as part of the clinical preoperative MRI protocol per the request of the referring orthopaedic surgeon. (a) Sagittal T2 color map is shown with the scale provided on the left; red represents highest T2 measurements; dark blue reflects the lowest T2 values. Focal high T2 values are seen within the central tibiotalar cartilage (yellow arrow) and with the subchondral talar dome (red arrow). (b) Sagittal fat-suppressed proton-density images in the same patient demonstrate that these findings correspond to full-thickness tibiotalar cartilage loss and subchondral bone marrow edema, respectively.

(< 30 minutes) and within SAR constraints.<sup>72</sup> T1 $\rho$  assesses the spin-lattice (T<sub>1</sub>) relaxation in the rotating frame<sup>73</sup> and is thought to reflect the proteoglycan content of the ECM.<sup>74</sup> T1 $\rho$  values are higher in patients with OA compared with healthy subjects.<sup>75</sup> T1 $\rho$  was also shown to predict morphological chondral wear.<sup>76</sup>

### Ultrashort Echo Time and Zero Echo Time Imaging

Like cortical bone, tendons, and menisci, the deep calcified part of cartilage contains a high fraction of components with “ultrashort” transverse relaxation times. This essentially equates to a post-RF pulse signal decay rate that is too rapid to allow signal acquisition.<sup>77</sup> Ultrashort echo time (UTE) and zero echo time use specialized acquisition and reconstruction techniques to capture these ultrashort components before signal decay. Although the application of techniques for imaging of cartilage is not common, UTE was shown to delineate the calcified deepest cartilage layer<sup>78</sup> and used to evaluate the integrity of this layer in osteochondral allografts.<sup>79</sup> UTE also enables T<sub>2</sub> and T<sub>2</sub>\* mapping of tissues with a high fraction of ultrashort components.<sup>80</sup>

### Delayed Gadolinium-Enhanced MRI of Cartilage

The dGEMRIC MRI is performed after intravenous injection of a gadolinium-based contrast with subsequent joint exercise and substantial time delay to allow diffusion of the contrast into the joint. Gadopentetate dimeglumine (Gd-DTPA<sup>2-</sup>), the MRI contrast, is an anion and repelled by the negatively charged GAGs, allowing this technique to map GAG content within the cartilage. Damaged cartilage with low GAG content will accumulate more Gd-DTPA<sup>2-</sup> and therefore have a shorter T<sub>1</sub> relaxation time. This technique was used in research to study a variety of topics including

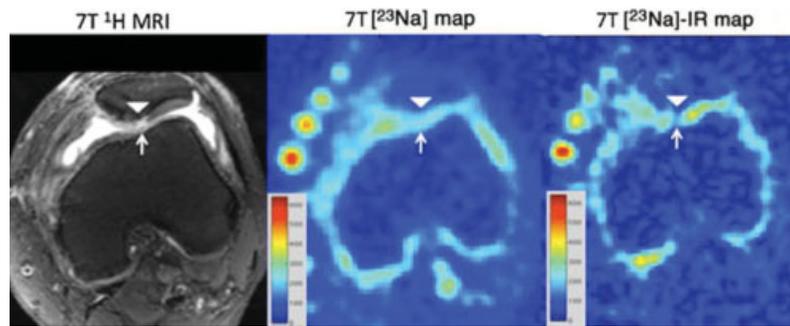
cartilage repair tissue,<sup>81,82</sup> effects of tibial osteotomy on cartilage,<sup>83</sup> inflammatory arthritis,<sup>84</sup> and the effects of chronic joint unloading.<sup>85</sup> The need for intravenous contrast is the main drawback of dGEMRIC; however, it does allow an indirect MR arthrogram to be obtained during the delay between injection and acquisition of dGEMRIC T<sub>1</sub> imaging. This may particularly be helpful in the morphological evaluation of the acetabular or glenoid labrum.

### Sodium (<sup>23</sup>Na) Imaging

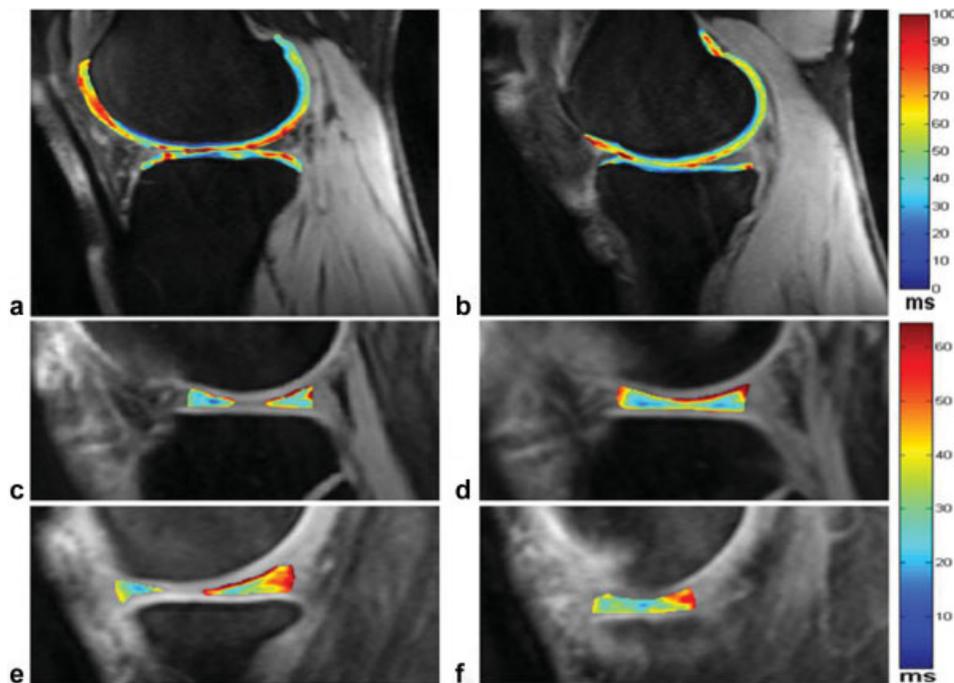
In contrast to Gd-DTPA<sup>2-</sup>, sodium (<sup>23</sup>Na<sup>+</sup>) is a naturally occurring cation (albeit in very low concentrations) that is attracted to and counteracts the negatively charged GAGs in the cartilage ECM. The distribution of <sup>23</sup>Na<sup>+</sup> can hence also be used to map the cartilage GAG content, with cartilage degeneration resulting in a lower concentration of <sup>23</sup>Na<sup>+</sup> ions.<sup>86</sup> Unsurprisingly, <sup>23</sup>Na imaging correlates well with dGEMRIC.<sup>87</sup> The low concentrations of <sup>23</sup>Na<sup>+</sup> in cartilage, however, make it difficult to elicit signal during MRI, resulting in noisy images and long acquisition times. The SNR gain at 7-T MRI is particularly useful for <sup>23</sup>Na imaging.<sup>88</sup> Because the Larmor frequency of <sup>23</sup>Na<sup>+</sup> differs from <sup>1</sup>H, specialized transmit-receive coils are also required to perform sodium imaging.<sup>89</sup> As with T<sub>2</sub> mapping, sodium imaging can discriminate between cartilage repair tissue and healthy cartilage, with lower sodium signal intensity in repair tissue compared with healthy cartilage reflecting a diminished GAG content<sup>90,91</sup> (– Fig. 4).

### Diffusion Tensor Imaging

The cartilage ultrastructure consists of a highly organized network of collagen that results in anisotropic diffusion of water. In cartilage, DTI can assess both proteoglycan content through mean apparent diffusion coefficient (ADC) and collagen microarchitecture through fractional anisotropy (FA). Both mean ADC and FA values were found to be able



**Fig. 4** Axial T2-weighted 7-T MR image (left panel) of the left knee, demonstrating a displaced osteochondral fragment reattachment (arrowhead) at the medial facet of the patella. Synovial fluid is seen within a full-thickness fissure (arrow). On the conventional  $^{23}\text{Na}$  map (middle panel), hyperintense signal is seen from synovial fluid within the fissure (arrow). On the  $^{23}\text{Na}$ -IR map (right panel), there is suppression of signal from synovial fluid within the fissure. The calibration phantoms containing 300 mM, 250 mM, 200 mM, and 150 mM are seen at the anterior aspect of the knee. The sodium images represent concentration maps with colored bars indicating range of  $[\text{Na}^+]$  in mM (red = 600 mM; blue = 0 mM). Reproduced with permission from Chang et al.<sup>91</sup>



**Fig. 5** Representative T1rho maps of cartilage in the (a) lateral and (b) medial compartments. T1rho maps of menisci in the (c, d) lateral and (e, f) medial compartments, respectively, obtained from a doubtful/minimal osteoarthritis patient. The color bars on the right show the T1rho values ranges, respectively. The different bar scale ranges can display the respective T1rho values distribution of cartilage and meniscus more effectively. Reproduced with permission from Wang et al.<sup>95</sup>

to discriminate cartilage in OA patients from healthy cartilage, with FA having higher specificity.<sup>92</sup> DTI was found to have high accuracy for detecting cartilage damage as well as for grading cartilage damage.<sup>93</sup>

### GAG Chemical Exchange Saturation Transfer Imaging

Water exists in two states within cartilage, either bound to macromolecules or in the free water state. Water protons bound to macromolecules have unique RF frequency that can be saturated using off-resonance RF pulses. The bound water pool then interacts with the free water pool resulting in partial saturation of the free water pool. This effect can be measured to estimate local macromolecule content.

With gagCEST, off-resonance RF saturation pulses are designed specifically to saturate exchangeable protons residing on the hydroxyl groups of cartilage GAGs (→ Fig. 5). This technique correlates well with  $^{23}\text{Na}^+$  imaging, and like  $^{23}\text{Na}^+$  imaging, it is optimally performed at ultrahigh field strength (7 T) magnets.<sup>94</sup>

### Conclusion

OA is the most prevalent joint disease in the United States with a tremendous socioeconomic burden. With efforts to develop a DMOAD for OA proving unsuccessful to date, it is clearly evident that imaging beyond radiography is needed for both clinical diagnoses of OA and for use as an outcome measure in OA research. MRI provides an unparalleled

assessment of articular cartilage and has aptly been incorporated into the major clinical studies of OA including the OAI and the MOST. For the purpose of quantifying data from such trials, MRI-based semiquantitative grading systems for OA have been developed. The most widely used of these classification schemes include the WOMBS and the BLOKS, with the MOAKS representing a hybrid of both these systems. In addition to the morphological evaluation, advanced MRI techniques have been developed to assess the biochemical composition of cartilage. These include relaxometry measurements (T2, T2\*, and T1ρ mapping), sodium imaging, dGEMRIC, gagCEST, and DTI. These techniques have the potential to serve both as imaging biomarkers for OA and as quantitative, reproducible, and objective end points for OA research.

#### Conflict of Interest

None declared.

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