Osteoarthritis (OA) is a debilitating disease that reflects a complex interplay of biochemical, biomechanical, metabolic and genetic factors, which are often triggered by injury, and mediated by inflammation, catabolic cytokines and enzymes. An unmet clinical need is the lack of reliable methods that are able to probe the pathogenesis of early OA when disease-rectifying therapies may be most effective. Non-invasive quantitative magnetic resonance imaging (qMRI) techniques have shown potential for characterizing the structural, biochemical and mechanical changes that occur with cartilage degeneration. In this paper, we review the background in articular cartilage and OA as it pertains to conventional MRI and qMRI techniques. We then discuss how conventional MRI and qMRI techniques are used in clinical and research environments to evaluate biochemical and mechanical changes associated with degeneration. Some qMRI techniques allow for the use of relaxometry values as indirect biomarkers for cartilage components. Direct characterization of mechanical behaviour of cartilage is possible via other specialized qMRI techniques. The combination of these qMRI techniques has the potential to fully characterize the biochemical and biomechanical states that represent the initial changes associated with cartilage degeneration. Additionally, knowledge of *in vivo* cartilage biochemistry and mechanical behaviour in healthy subjects and across a spectrum of osteoarthritic patients could lead to improvements in the detection, management and treatment of OA.

1. Introduction

There is an unmet clinical need for reliable methods that are able to probe the pathogenesis of the earliest stages of osteoarthritis (OA), a debilitating disease of multifactorial etiology [1], when disease-rectifying therapies may be most effective. Non-invasive quantitative magnetic resonance imaging (qMRI) techniques have shown potential for characterizing the changes that occur with cartilage damage and disease [2]. In this review, we address the use and efficacy of MRI techniques in evaluating articular cartilage and OA, with a strong emphasis on qMRI techniques used to quantify the structural, biochemical and mechanical properties of both normal and damaged or diseased articular cartilage. With further refinement of qMRI, a combination of qMRI techniques has the potential to fully characterize the biochemical and biomechanical changes that occur with cartilage damage. We will therefore conclude this review by presenting engineering design criteria that can guide the use of qMRI for the identification of cartilage damage, the diagnosis of early OA and the monitoring of the progression of cartilage degeneration.

2. Articular cartilage and changes with osteoarthritis

Articular cartilage covers the ends of bones in the moving joints of the body, acting as a low-friction bearing and dissipating loads in the normal joint [3]. The primary biochemical components of articular cartilage—water, collagen and proteoglycans [3]—vary with depth and subsequently influence the mechanical behaviour of the tissue [4], creating differences in material properties and...
swelling pressure through the thickness of cartilage [5,6]. Cartilage affected by trauma or disease can progress from pre-clinical, pre-radiographic, to radiographic damage (figure 1). Notably, the progression of OA is characterized by the structural, biochemical and mechanical changes that typically progress from the superficial zone to the middle and deep zones of cartilage [7]. Because depth-dependent biochemical and mechanical properties deteriorate with cartilage damage or disease, changes in both the mechanical environment in the joint [8] and biochemical structure of the collagen matrix [9] are observed with degeneration.

Medical imaging strategies have advanced to meet the need to visualize and characterize normal and damaged cartilage (figure 1). Radiography is the most common of non-invasive imaging modalities but is restricted to visualization of radio-opaque tissues such as bone [10]. Despite the ability to identify morphological changes in hard tissues and to measure joint space narrowing [10], radiography is not sensitive enough to detect earlier soft tissue changes [11]. Arthroscopy allows for a visual examination of the surfaces of the joint and therefore is capable of recognizing earlier stages of cartilage damage [12]. Although used to confirm an OA diagnosis [12], arthroscopy remains invasive and therefore inappropriate for longitudinal studies. MRI, on the other hand, is a non-invasive technique that is already used clinically to assess tissue damage and cartilage degeneration [13]. Unlike arthroscopy and radiography, MRI can provide a three-dimensional visualization through the volume of cartilage, whereas radiography cannot depict cartilage, and arthroscopy provides observations on and near the tissue surface (figure 2). MRI-based grading systems for chondral lesions can take into account the thickening or thinning of cartilage, changes in contour of the articular surface, increased fibrillation, and even changes in signal intensity [61] and correlate well with the anatomical loss of cartilage [61] and correlate well with the anatomical loss of cartilage [61] and correlate well with the anatomical loss of cartilage [61] and correlate well with the anatomical loss of cartilage [61] and correlate well with the anatomical loss of cartilage [61] and correlate well with the anatomical loss of cartilage [61]. However, these grading schemes are affected by the magnet strength [63] and the choice of imaging technique and parameters [63,64]. Given the limitations and semi-quantitative nature of grading schemes, qMRI techniques could provide more objective and potentially more consistent characterization of cartilage damage. 'Quantitative MRI' is used herein as an umbrella term to include the myriad of MRI techniques that enable an objective quantification of anatomical or physiological measures.
4. Magnetic resonance imaging to quantify structural changes with osteoarthritis

Standard MRI techniques can be easily extended to assess the changes in cartilage thickness, surface area and volume before and during, or before and after, load [17–20]. Such measures are sensitive enough to delineate changes in volume and surface area with early radiographic damage [22]. MRI can visualize local cartilage changes that have yet to manifest as the global joint space narrowing that can be detected by radiograph, including swelling that occurs with pre-radiographic damage [21] and localized thinning and loss of cartilage [23]. However, these measurements of thickness and volume change are nominal and may mask any depth-dependent changes in cartilage (figures 2b and 3c). Additionally, measurements of cartilage thickness and surface area are limited by the spatial resolution of imaging [68], the segmentation of regions of interest [63] and the registration of images taken at different time points [63].

5. Magnetic resonance imaging to quantify mechanical changes with osteoarthritis

Because tissue properties and the mechanical environment of the joint change with progressive cartilage damage [8], non-invasive methods to evaluate the biomechanics of normal and damaged cartilage are necessary. Degeneration proceeds from the superficial to deep zone [7], and the zonal structure of cartilage affects its mechanics [69]. Therefore, depth-dependent characterization of cartilage mechanics is desirable (figure 3b). A direct non-invasive visualization of biomechanics considers the in situ loading environment [70] and the complex, depth-dependent mechanical behaviour of the tissue [66,71].

MRI techniques that can measure the internal deformation of articular cartilage can be used to visualize heterogeneous mechanical behaviour and also locate abnormal responses to applied loads. Cartilage deformation by tag registration imposes lines of interest onto cartilage and tracks these during the cyclic compression of cartilage [67,72], but requires interpolation to determine depth-dependent responses to load. In terms of pixel-by-pixel mechanical characterization, displacement-sensitive stimulated-echo acquisition mode (STEAM) has measured deformations and strains in articular cartilage [73]. MR elastography [74] can determine the shear properties of articular cartilage [25] and measure changes that occur with enzymatic degradation [24]. Displacement encoding by stimulated echoes can be synchronized to cyclic loading [66,75] for the measurement of displacements under applied loading with MRI (dualMRI) in any MRI-visible biomaterial (figure 3b). DualMRI has been used to determine heterogeneous, depth-dependent displacements and strains in cartilage explants [66] and intact cadaveric joints [70].

The qMRI techniques that are currently available to evaluate material properties or mechanical behaviour in cartilage remain limited. While relatively easy to implement, techniques that compute nominal changes in cartilage thickness or volume do not provide depth-dependent nor regionally specific information. For techniques that require interpolation to track tissue deformation, the size of the tissue of interest limits the number of nodes or taglines that can be registered using interpolation-based techniques. STEAM is constrained by long imaging times and low resolution, which becomes a major limitation with thinner tissues such as articular
cartilage. Propagating high-frequency shear [24,25] or compression [73] waves indirectly to tissue within intact joints for MR elastography and STEAM, respectively, is technically difficult and requires additional equipment (i.e. high-frequency actuators). A low-frequency loading device that is compatible with both the tissue of interest and the MRI system is also necessary for dualMRI [66,75]. Finally, although dualMRI has shown promise for measuring mechanical behaviour in intact joints, this technique remains to be implemented on clinical MRI systems, where lower resolution and longer imaging times may be expected. Because several of these techniques to quantify cartilage mechanical behaviour are currently limited to ex vivo use, there remains untapped potential for these techniques to identify and monitor cartilage damage.

Table 1. Summary of quantitative MRI techniques commonly used for articular cartilage research. Most of these techniques are discussed in this review or, in the case of sodium imaging, in a previous review [14]. MRE, magnetic resonance elastography; dualMRI, displacements under applied loading with magnetic resonance imaging; $T_2$, spin–spin (transverse) relaxation time; dGEMRIC, delayed gadolinium-enhanced magnetic resonance imaging of cartilage; $T_{1r}$, spin–lattice (longitudinal) relaxation time in the rotating frame.

<table>
<thead>
<tr>
<th>MRI technique</th>
<th>used in vivo?</th>
<th>biochemical assessment</th>
<th>biomechanical assessment</th>
<th>clinical (OA) assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>standard MRI</td>
<td>yes</td>
<td>assessment of water content based on signal intensity [15,16]</td>
<td>measurement of changes in thickness [17–19], surface area [17] and volume [18,20] under various load conditions</td>
<td>changes in volume and surface area seen in cartilage with pre-radiographic (pre-clinical) [21] and radiographic (clinical) damage [22,23]</td>
</tr>
<tr>
<td>MRE</td>
<td>no</td>
<td>none</td>
<td>measurement of shear modulus in response to high-frequency shear waves [24,25]</td>
<td>not yet shown</td>
</tr>
<tr>
<td>dualMRI</td>
<td>no, translation in progress</td>
<td>none</td>
<td>measurement of displacement and strain in response to an exogenous load</td>
<td>not yet shown</td>
</tr>
<tr>
<td>$T_2$ mapping</td>
<td>yes</td>
<td>correlation with collagen content [26–28] and fibril alignment [29,30]</td>
<td>correlation with material properties and mechanical behaviour found ex vivo [27,31,32]</td>
<td>correlation with various clinical measures of cartilage damage [33–40]</td>
</tr>
<tr>
<td>dGEMRIC</td>
<td>yes</td>
<td>directly related to GAG content [41,42]; correlation with proteoglycan and collagen content [27]</td>
<td>correlation with material properties and mechanical behaviour found ex vivo [27,31,32]</td>
<td>correlations with clinical measures of degeneration [43–45]; significant differences with radiographic damage [46–48]; sensitivity to pre-radiographic damage [49]</td>
</tr>
<tr>
<td>$T_{1r}$ mapping</td>
<td>yes, limited</td>
<td>correlation with proteoglycan content [14,28,50–52]</td>
<td>correlation with aggregate modulus and hydraulic permeability [14,52]</td>
<td>sensitivity to pre-radiographic [53,54] and radiographic damage [54–56]; correlation with clinical measures of degeneration [57]</td>
</tr>
<tr>
<td>sodium MRI</td>
<td>yes, limited</td>
<td>directly related to GAG content [14]</td>
<td>not reported</td>
<td>feasible for assessment of cartilage damage [58] and repair quality [59]</td>
</tr>
</tbody>
</table>

6. Magnetic resonance imaging to quantify biochemical changes with osteoarthritis

Because pre-clinical cartilage damage is characterized by biochemical changes that are not macroscopically evident, qMRI techniques that can be correlated to macromolecular concentration or ultrastructure have potential for identifying early cartilage damage. Cartilage composition and biochemistry have strong influences on the relaxation time constants defined by $T_1$ and $T_2$ [76], which vary with depth and region in articular cartilage. Sodium MRI also holds potential for localized characterization of in vivo cartilage biochemistry and damage, as previously discussed in depth by another review [14]. We focus herein on mapping $T_2$, delayed gadolinium (Gd)-enhanced MRI of cartilage (dGEMRIC) and
longitudinal relaxation time in a rotating frame ($T_{1r}$) in cartilage. This review does not discuss some proton-based qMRI techniques used for biochemical characterization, including magnetization transfer, ‘magic angle’ imaging, diffusion imaging and chemical exchange saturation transfer, because these are not as well developed or are more difficult to implement clinically. For the interested reader, most of these techniques are covered well by a previous review [77].

6.1. $T_2$ mapping

$T_2$ mapping has been used to evaluate cartilage in healthy and damaged states (figure 3c). $T_2$ has been strongly correlated with collagen content [26,27,78,79], with collagen degradation resulting in increased $T_2$ [28], and with collagen alignment [29,30]. Most studies have also found that the effect of proteoglycans on $T_2$ is negligible [26,28,50,78,80]. $T_2$ varies through the depth of articular cartilage, reflecting the depth-dependent content and structure of the collagen matrix (figure 3c), with $T_2$ increasing from deep to superficial tangential zones [26,29,30,33,81]. $T_2$-weighted images can also been used to assess water content in cartilage [15,16]. Because changes in water content, collagen content and collagen alignment affect $T_2$ values, mapping $T_2$ can identify areas of damaged or degenerated cartilage. $T_2$ has been found to increase with cartilage damage [33,34], morphologic changes [35,36], the presence of pain and defects [37,38] and clinical scores of joint pain and function [39], although one study

Figure 3. Quantitative MRI techniques can be used to evaluate the structural, mechanical and biochemical characteristics of normal and damaged cartilage. Although these images are taken of a cartilage explant from a patient for total knee arthroplasty, they permit a comparison of qMRI techniques discussed in this review. (a) Thickness and volumetric changes can be measured by comparing cartilage before and during externally applied cyclic compression. (b) Mechanical behaviour (i.e. displacements and strains) under physiologically relevant rates of cyclic loading can be characterized by using displacement-encoded MRI. (c) Correlations to biochemical changes with cartilage damage can be made using $T_1$, $T_2$ and $T_{1r}$ mapping and analysis. Images of a 25.6 x 25.6 mm$^2$ volume and 0.1 x 0.1 x 1.0 mm$^3$ voxel size were taken with a 14T Bruker Avance 600 (Ettlingen, Germany) under the following parameters: (a) fast spin echo, echo and repetition time (TE/TR) = 8.84/1000 ms; (b) displacement encoding with stimulated echoes acquired with true fast imaging with steady-state precession, encoding gradient area = 2.13 mm$^2$, TE = 1.85/3.7 ms, flip angle = 25°; (c) fast spin echo, $T_1$: TE/TR = 8.84/[100,250,500,1000,2000,4000] ms; $T_2$: TE/TR = [10,30,50,70,90]/1000 ms; $T_{1r}$: TE/TR = 8.92/2000 ms, spin-lock frequency = 500 Hz, spin-lock durations = [10,30,50,70,90] ms. (Online version in colour.)
found no correlation between $T_2$ and OA grade in cartilage with radiographic damage [82]. Changes in $T_2$ values have also been found to be more sensitive to longitudinal changes in cartilage than MRI-based morphological grading schemes [40]. Focal increases in $T_2$ values relative to surrounding cartilage are associated with loss of matrix integrity [81], cartilage lesions [83] and damage to the underlying bone [84]. While focal increases in $T_2$ are characteristic of degenerated cartilage [85], overall increases in $T_2$ can occur with normal ageing [46,86]. $T_2$ patterns also differ between normal cartilage and cartilage with pre-radiographic and radiographic damage [87]. Patients with elevated risk factors for OA exhibit greater $T_2$ values and heterogeneity than controls with similar pre-radiographic cartilage damage, possibly indicating a higher degree of extracellular matrix breakdown [88].

$T_2$ mapping can indicate changes associated with cartilage damage, but the interpretation of these changes must consider the limitations of this technique. Although an evaluation of variations in $T_2$ values can be helpful in identifying cartilage degeneration, some of these variations also exist in normal cartilage of young patients [89]. There may also be little distinction in $T_2$ values within the spectrum of pre-radiographic to radiographic cartilage damage [34,90]. In addition to being affected by the angle at which cartilage is positioned with respect to the main magnetic field [55], $T_2$ values are sensitive to the type of radiofrequency coil [91], the choice of pulse sequence and sequence parameters [92], the joint position during imaging [93] and the type of equation used to fit data [94].

### 6.2. $T_1$ mapping and delayed gadolinium-enhanced magnetic resonance imaging of cartilage

The dGEMRIC technique measures $T_1$, in the presence of Gd to quantify glycosaminoglycan (GAG) content directly [95,96]. Gd is a paramagnetic element that shortens the local $T_1$ [97]. In dGEMRIC, $T_1$ is mapped before and after gadopentate (Gd-DTPA$^2$) distributes into joint tissues, with preference for less negatively charged regions [95]. Because the GAG side chains in proteoglycans are highly negatively charged, Gd-DTPA$^2$ accumulates in cartilage in proportion to the GAG content. The longitudinal relaxation rates ($R_1 = 1/T_1$) are measured before and after Gd contrast, and the change in relaxation rates ($\Delta R_1$) is linearly related to the Gd-DTPA$^2$ concentration and therefore the GAG content [41]. There is a strong inverse correlation between $T_1$ after Gd-DTPA$^2$ contrast ($T_{1,Gd}$) and $\Delta R_1$ [98], so researchers sometimes measure only $T_{1,Gd}$, the so-called dGEMRIC index, to monitor changes in degenerating cartilage. However, measurement of $\Delta R_1$ is still required to calculate GAG content directly [41,42]. Nonetheless, $T_{1,Gd}$ has been correlated with proteoglycan content [27,79,99]. $T_{1,Gd}$ also varies depending on the region of cartilage [31,49] and is higher in load-bearing cartilage compared with non-contact regions [100].

Some studies have used dGEMRIC to compute GAG content in healthy cartilage [31] and cartilage with pre-radiographic damage [49]. Overall, $T_{1,Gd}$ is lower with pre-radiographic damage [47] and with radiographic cartilage damage and OA [43,46,48] when compared with healthy joints. $T_{1,Gd}$ also correlates with radiographic scores of OA [43,44], joint alignment [43,45,101] and measures of joint pain [45]. Additionally, dGEMRIC has been shown to be sensitive to pre-radiographic damage [49]. Tissues without radiographic damage exhibit a large range of dGEMRIC indices [43], indicating that dGEMRIC could distinguish levels of pre-radiographic and perhaps even pre-clinical damage.

Although dGEMRIC has been validated for the direct measurement of GAG content, there are several limitations to this technique. Because $T_1$ without contrast enhancement varies by depth and region [102], using $T_{1,Gd}$ rather than $\Delta R_1$ as measure of depth-dependent GAG content may be biased by the existing $T_1$ values. Similarly, the application of a static load has also been shown to decrease the $T_{1,Gd}$ values observed [100], possibly because $T_1$ is altered with water exudation during static compression. Because the joint is imaged after the administration of a contrast agent, a consistent protocol is necessary, especially in vivo [96,103]. Timing is crucial to capturing MRI signal at the peak of contrast agent concentration within the joint and penetration into the cartilage [49], especially because contrast agent penetration can vary with depth [104]. In addition, the spatial and temporal distribution of contrast agent is different between intravenous and intra-articular injection [42,105]. Because of these limitations, some researchers are focusing on another option for visualizing proteoglycan content with qMRI—$T_{1p}$ mapping.

### 6.3. $T_{1p}$ mapping

$T_{1p}$ mapping is accomplished through spin-lock MRI, in which the magnetization is prepared with spin-lock pulses, which generate an applied magnetic field, over a specified spin-lock time and prior to standard image acquisition. The time constant at which the spin-locked magnetization relaxes with respect to the applied magnetic field in the rotating frame is defined as $T_{1p}$, which, like other relaxation mechanisms, is affected by interactions within the chemical environment.

$T_{1p}$ is affected by both water and proteoglycan content in articular cartilage [28,50,51,106], although another study also shows that $T_{1p}$ is influenced by collagen content [107]. Other studies have shown only a moderate correlation with proteoglycan content with no correlation with collagen content [55] nor water content [108]. Additionally, a recent study found that $T_{1p}$ and GAG content can be correlated in the deeper zones but not in the upper half of cartilage [109]. While the exact contributions of water, proteoglycans and collagen to $T_{1p}$ have yet to be determined [110], proteoglycan depletion does result in an increase in $T_{1p}$ [50,51,106,111]. Additionally, studies have shown that $T_{1p}$ tends to reflect depth-dependent trends in $T_1$ [33], with the highest $T_{1p}$ values at the superficial tangential zone and decreasing values reaching a minimum at either the middle zone [28,51] or the deep zone [33,110]. Although the exact relationship of $T_{1p}$ to proteoglycan or other biochemical content in articular cartilage remains unclear [55,107], $T_{1p}$ mapping is gaining momentum as a viable technique for imaging of cartilage biochemistry.

Radiographic cartilage damage has been correlated with elevated $T_{1p}$ values [34,55,56]. $T_{1p}$ mapping has been shown to be comparable to arthroscopy in detecting pre-radiographic damage after trauma [112]. $T_{1p}$ measures are also more sensitive and have a larger dynamic range than $T_2$ mapping [34,56,57]. Because of the improved sensitivity of $T_{1p}$ values in distinguishing levels of cartilage damage [34,57], $T_{1p}$ showed significant differences between healthy controls and OA patients with pre-radiographic and radiographic cartilage damage [53,54], with $T_{1p}$ differences being more significant than differences in $T_2$ [53]. $T_{1p}$ but not $T_2$ was found to be elevated in patients about to undergo
anterior cruciate ligament surgery [113], showing that $T_{1p}$ may be more sensitive at revealing cartilage damage.

$T_{1p}$ values also correlate with various clinical scores for radiographic cartilage damage [57] and measures of joint pain and function [39]. $T_{1p}$ in patients with pre-radiographic cartilage damage was higher than controls, with regional comparisons providing the best correspondence between $T_{1p}$ and arthscopic OA grade [114]. $T_{1p}$ is also significantly higher in cartilage with radiographic damage in specific regions of cartilage but not globally [115]. Therefore, $T_{1p}$ mapping shows promise for the detection of localized cartilage damage and for use in longitudinal studies [34,53,116].

As with other qMRI techniques, $T_{1p}$ mapping is not without its limitations. $T_{1p}$ values are affected by the orientation of the cartilage to the main magnetic field during imaging [55]. The spin-lock sequences required for $T_{1p}$ mapping impart higher amounts of radiofrequency energy compared with most standard MRI sequences [117]. Additionally, these sequences remain limited in availability both at the research and at the clinical level. Despite studies that indicate a correlation between $T_{1p}$ and proteoglycan content, a study comparing multiple MRI-based biomarker measures could not find a correlation between $T_{1p}$ and dGEMRIC index [118], a known indicator of GAG content. Additionally, the authors are aware of no studies that directly compare both dGEMRIC and $T_{1p}$, with ‘gold standard’ biochemical or histological measurements of proteoglycan content in the same cartilage, leaving unanswered the question of whether $T_{1p}$ is comparable to or better than dGEMRIC for the measurement of proteoglycan content. Further research is required on the factors that contribute to $T_{1p}$ values and the exact nature of $T_{1p}$ changes with cartilage damage.

### 7. Designing towards individual diagnosis

The ability to monitor the morphological, biomechanical and biochemical characteristics of cartilage through the spectrum of cartilage health and damage is key to the early diagnosis of OA and the development and evaluation of clinical interventions. In this review, we have presented various qMRI methods by which structural, biochemical and mechanical characteristics of normal and degenerated cartilage can be imaged. Information that MRI can provide about cartilage structure, biochemistry and mechanics is unique to this imaging modality and, with further development and refinement of MRI techniques [77], MRI will become invaluable in diagnosing and monitoring cartilage damage. Continued advancement of these qMRI techniques requires a careful understanding of the technical limitations of these techniques, including the overarching limitations that come through as themes in the current research.

#### 7.1. Current limitations of quantitative magnetic resonance imaging techniques

The evaluation of structural changes using qMRI, especially the measurements of nominal thickness or volume, highlights the fallacy of using bulk information to describe damage and other changes that often occur locally, either as focal injury due to trauma or as depth-dependent degeneration. Characterization of the local mechanics can be implemented using some of the techniques reviewed for the mechanical evaluation of cartilage degeneration. However, these techniques are often strongly influenced by the geometry of the tissue and the joint [71] and the overall external loading protocol (i.e. frequency, magnitude). Additionally, because the mechanical behaviour can only be evaluated in the tissues that are experiencing a load, researchers must be careful in how they apply results found in loaded areas to any conclusions about the unloaded tissues. Lastly, the use of qMRI to evaluate mechanical changes in articular cartilage remains underdeveloped, especially in vivo, compared with qMRI techniques designed to measure biochemical changes.

Despite the potential for use as identifiers of biochemical changes in cartilage, current qMRI techniques that characterize biochemistry in normal and damaged cartilage cannot offer a complete picture of cartilage damage either. These various quantities (i.e. $T_{1p}$, T2, dGEMRIC index) do not necessarily correlate well with each other [33,118]. As mentioned previously, $T_2$ and $T_{1p}$ cannot be attributed to single biochemical factors [107]. Values for $T_2$, $T_{1,Gd}$ and $T_{1p}$ even in normal cartilage, differ in the literature and can be dependent on pulse sequence [92], the strength of the static magnetic field [32,119] and the radiofrequency coil [91]. A number of studies have shown that loading history [93,120–122] and joint alignment [93,123] can also affect some of these qMRI measures. Additionally, despite correlations that show a difference in these qMRI measures between normal and damaged cartilage, there may be a lack of sensitivity in distinguishing the levels of clinical damage [37,90,124,125]. Finally, among the studies examined herein, even studies that have shown a significant difference in $T_2$, dGEMRIC or $T_{1p}$ values between normal cartilage and varying degrees of cartilage damage require anywhere from just two to four samples [57] to 95 samples [36] per group, depending on the specific study [33,49,55].

Comprehensive knowledge of the biochemical and biomechanical changes that occur with OA may require a combination of various qMRI techniques. While this knowledge is tremendously useful on a basic science level, the application of these qMRI techniques to the identification and monitoring of cartilage damage in individual patients for the early diagnosis and treatment of OA would be more clinically significant. As the variability in research results demonstrates, qMRI techniques lack the ability of arthroscopy to positively identify the presence and extent of cartilage damage (figure 1). Research towards a non-invasive imaging technique to identify and monitor cartilage damage would therefore benefit from a shift in the research paradigm towards the ability to make these individualized diagnoses.

#### 7.2. Shifting the paradigm towards diagnosis of osteoarthritis in individuals

A significant thrust in much of the qMRI literature is towards the correlation of various qMRI values to biochemical content, typically determined in explants through histology [14,26–30,41,42,50–52,107], and to pain score or OA grade [39,43,44,48,54,56,57,90,126]. A number of groups have applied qMRI techniques to evaluate the differences between cartilage in normal subjects and patients with higher OA risk [43–45,67,101]. These studies typically use healthy, asymptomatic subjects as external controls for OA or at-risk patients. However, if qMRI is to be used effectively as a diagnostic tool, these techniques must be refined so that internal controls can be used to assess whether an individual demonstrates sufficient structural, biochemical or mechanical damage to be
classified as having early OA and require clinical intervention. Additionally, early biochemical and biomechanical changes with cartilage damage may be better identified using a combination of qMRI techniques [127].

Only a handful of qMRI studies have compared diseased or damaged tissue to normal tissue within the same patient, or used a normalization factor to delineate between healthy and diseased or damaged cartilage. One group has used $T_2$ normalized by the $T_2$ values and distribution of healthy cartilage, although even normalized values could not distinguish significantly between mild and severe radiographic damage [90]. Another group assessed cartilage damage within patients by comparing dGEMRIC values normalized by the overall $T_1$ of cartilage in a patient [128]. Another recent study found that the $T_2$ of proximal tibiofemoral cartilage does not vary significantly with increasing radiographic OA grade [124] and could therefore be used as a control or normalization value in future studies. Further research into similar regions that can be used as a control for $T_1p$ is needed, as well as for qMRI techniques designed for mechanical characterization of cartilage. Research that focuses on the use of controlled or normalized comparisons that are internal to individual patients will propel the use of qMRI techniques for individualized healthcare throughout the spectrum of cartilage health and damage.

8. Conclusions

In conclusion, qMRI has proved to be a very powerful tool for researchers to examine the structural, biochemical and mechanical changes that occur through the spectrum of cartilage damage and disease. However, as the various qMRI technologies continue to mature, the research community should refine its focus on the use of these techniques as sensitive tools for the diagnosis of the pre-clinical and pre-radio-graphic cartilage damage that leads to OA and for the longitudinal study of the progression of both cartilage damage and repair. In particular, based on both the successes and gaps in the research reviewed herein, the following engineering design criteria should help guide the progress towards clinical application of non-invasive qMRI techniques towards the diagnosis and assessment of articular cartilage damage: (i) adequate precision to detect both location- and depth-dependent changes in cartilage, (ii) sensitivity to the structural, mechanical and biochemical changes that correspond to currently pre-clinical levels of cartilage damage, and (iii) robust internal controls and comparisons that enable diagnosis of cartilage damage in individual patients.

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