Emerging quantitative MR imaging biomarkers in inflammatory arthritides

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Abstract

Structured abstract (as per journal requirement)

**Purpose:** To review quantitative magnetic resonance imaging (qMRI) methods for imaging inflammation in connective tissues and the skeleton in inflammatory arthritis. This review is designed for a broad audience including radiologists, imaging technologists, rheumatologists and other healthcare professionals.

**Methods:** We discuss the use of qMRI for imaging skeletal inflammation from both technical and clinical perspectives. We consider how qMRI can be targeted to specific aspects of the pathological process in synovium, cartilage, bone, tendons and entheses. Evidence for the various techniques from studies of both adults and children with inflammatory arthritis is reviewed and critically appraised.

**Results:** qMRI has the potential to objectively identify, characterize and quantify inflammation of the connective tissues and skeleton in both adult and pediatric patients. Measurements of tissue properties derived using qMRI methods can serve as imaging biomarkers, which are potentially more reproducible and informative than conventional MRI methods. Several qMRI methods are nearing transition into clinical practice and may inform diagnosis and treatment decisions, with the potential to improve patient outcomes.

**Conclusions:** qMRI enables specific assessment of inflammation in synovium, cartilage, bone, tendons and entheses, and can facilitate a more consistent, personalized approach to diagnosis, characterisation and monitoring of disease.
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Quantitative magnetic resonance imaging (qMRI) has the potential to image and quantify disease processes in the inflammatory arthritides in both adult and pediatric patients. Measurements of tissue properties derived using qMRI methods serve as imaging biomarkers and can facilitate a more personalized approach to diagnosis, characterisation and monitoring of diseases. Some qMRI methods are nearing transition into clinical practice and are likely to inform diagnosis and treatment decisions, with ultimate impact on patient outcome.

In this paper we review qMRI methods for imaging skeletal inflammation and arthritis from both technical and clinical perspectives, and focus on imaging of synovium, cartilage, bone, tendons and entheses. We have considered how qMRI techniques can be targeted to specific tissue pathophysiological processes.

This review is designed for a broad audience including radiologists, imaging technologists, rheumatologists and other healthcare professionals.
Keywords:
MRI, quantification, arthritis, osteitis, cartilage, synovium
Abbreviations used in this review

ADC = apparent diffusion coefficient
Anti-TNF = anti-tumour necrosis factor
AI = artificial intelligence
AIF = arterial input function
BMD = bone mineral density
CSE-MRI = Chemical shift-encoded MRI, or also DIXON MRI
DCE-MRI = dynamic contrast-enhanced MRI
dGEMRIC = delayed gadolinium-enhanced MRI of cartilage
DKI = diffusion kurtosis imaging
DWI = diffusion weighted imaging
EES = extracellular space
FF = fat fraction
GAG = glycosaminoglycan
GBCA = gadolinium based contrast agent
IVIM = intravoxel incoherent motion
MCP = metacarpophalangeal
MRI = magnetic resonance imaging
MTX = methotrexate
PDFF = proton density fat fraction
QIB = quantitative imaging biomarker
qMRI = quantitative MRI
QSM = chemical shift-corrected quantitative susceptibility mapping
RA = rheumatoid arthritis
ROI = region of interest
SpA = spondyloarthritis
UTE = ultra-short echo time
ZTE = zero echo time
Introduction

The inflammatory arthritides are a broad group of diseases characterised by inflammation of the joints, bones and soft tissues. These diseases result from immune-mediated activation of inflammatory cells and mediators, causing pain, swelling, stiffness and ultimately tissue damage. There have been dramatic improvements in clinical outcome for the inflammatory arthritides[1,2], largely due to the development and clinical introduction of ‘biologic’ drugs [3,4]. These are complex endogenous molecules that mimic or change the function of the immune system. However, they are expensive and can have serious side effects such as immunosuppression. Not all patients respond to biologic drugs and there are primary and secondary treatment failures. Further, biologics target only inflammatory processes and not the pathways of bone formation [5,6]. Consequently, there is a clinical need for improved treatments and improved methods for diagnosing, characterizing and monitoring disease, thus supporting more personalised care.

Magnetic resonance imaging (MRI) has emerged as a safe and noninvasive method for evaluating the diverse aspects of the inflammatory process. Recently, quantitative MRI (qMRI) methods have been developed for the measurement of particular physical tissue characteristics, such as cellularity, diffusion, perfusion and fat content, in cartilage, synovium and bone. These characteristics are estimated by acquiring a series of measurements that are sensitized to the properties of the tissues, and then fitting these measurements to a pre-defined model. The ability of qMRI techniques to measure specific tissue characteristics (potentially independent of the hardware and software used to acquire the images) qualifies these measurements to be used as quantitative imaging biomarkers (QIBs) [7]. Sullivan et al. define a QIB as ‘an objectively measured imaged characteristic derived from an in vivo image as an indicator of normal biologic processes, pathological processes, or response to a therapeutic intervention’ [7].

Importantly, the QIB framework enables rigorous evaluation and/or validation of imaging methods, and there is now a substantial body of literature that can guide the validation process [7–10]. Statistical approaches for measuring the accuracy, precision (including repeatability and reproducibility), biological validity and ultimately clinical utility of candidate QIBs are well-described, meaning that each of these parameters can be assessed within a standardized framework [7–10]. QIB measurements can be compared between scanners, between different hospitals and across time points, and therefore offer greater objectivity than image assessment using conventional MRI. This can reduce the subjectivity associated with conventional MRI assessment and visual scoring approaches commonly used in research [7,11,12]. Further, the use of numeric data in qMRI maps can support automation and machine learning approaches to image analysis [13,14].
The aim of this review is to summarise the current progress in qMRI research applied to inflammation, to discuss how qMRI methods can be used to assess particular tissue processes, and to consider directions for future development of quantitative imaging biomarkers.

**Pathological Considerations**

Acute inflammation is the initial response to a harmful stimulus, characterised by movement of plasma and blood cells (leucocytes, particularly granulocytes) into the injured tissue. Acute inflammation increases capillary permeability and blood flow, enabling the movement of plasma fluid, which contains fibrin and immunoglobulins, into the tissue. Increased tissue fluid causes an expansion of the extracellular space and may result in swelling (oedema) of the tissue. In bone where the rigid structure prevents tissue deformity, oedema manifests as a change in the proportional size of each compartment, rather than increased overall tissue size. Vascular stasis can occur and this allows chemical mediators and inflammatory cells to accumulate and respond to the inflammatory insult. Leucocytes migrate into tissue via extravasation and these cells perpetuate inflammatory cascades.

Chronic inflammation is the result of a continued response against a persistent insult. In inflammatory arthritides, the ‘insult’ is loss of tolerance for self-antigens present in the soft tissues. In the chronic phase, the cardinal signs of active inflammation are reduced (but may persist to some extent) and tissue remodeling and fibrosis are initiated. The ultimate result of chronic inflammation varies depending on the disease and anatomical site, but in rheumatic diseases damage to cartilage and the adjacent bone is common. This damage can result in structural lesions that are visible on imaging such as erosions, joint ankylosis and alterations in the structure of subchondral bone.

In rheumatoid arthritis (RA), the prototypic inflammatory arthritis, inflammation typically starts in the synovium, where the activation of inflammatory cells leads to swelling and congestion. Once initiated, the immune response can become chronic, and inflammation becomes amplified in the synovium, resulting in the formation of granulation tissue (pannus), where there is extensive angiogenesis and enzyme production. This causes damage to the adjacent cartilage and bone. In other inflammatory arthritides such as spondyloarthritis (SpA), inflammation may be directed directly against cartilage causing secondary damage to the adjacent bone and soft tissues. The ultimate aim of imaging is to detect and characterize both the active inflammatory process and the structural damage, and to use this information for diagnosis, disease monitoring, prognostication and for guiding treatment.
Quantitative MRI techniques used in musculoskeletal imaging

**Diffusion weighted imaging**

Diffusion-weighted imaging (DWI) is used to quantify the freedom of water diffusion in tissue. Images are sensitized to diffusion through the addition of motion-sensitizing gradients to a spin echo acquisition; this causes signal loss from moving spins but not from those that are stationary [15–17]. Following acquisition of images with multiple diffusion weightings (b-values [18]), a signal model is fitted to the acquired data, allowing estimation of the diffusion coefficient for the tissue [15–17]. The diffusion coefficient gives an indication of the freedom with which water molecules diffuse. Tissue diffusion is typically estimated using a simple monoexponential model with a single ‘apparent’ diffusion coefficient (ADC). ADC measurements provide a useful ‘summary’ measure of tissue diffusion, but there has also been interest in the use of more sophisticated models of diffusion attenuation that can separate the contribution of different tissue characteristics. The intravoxel incoherent motion (IVIM) model, initially proposed by LeBihan, can capture both tissue diffusion and a rapid early diffusion component that is believed to be due to tissue perfusion [19–22], whilst diffusion kurtosis imaging (DKI) provides an alternative approach to capturing microstructural complexity [23,24].

The limitations of DWI include relatively low spatial resolution and signal-to-noise ratio. The reproducibility of ADC measurements between different scanners [25–27] and within patients [28] is also relatively poor. Improvements in reproducibility might be achieved by protocol standardization, use of normalized ADC values and use of ADC change over time as outcome measure [26]. ADC measurements may be contaminated by fat in the bone marrow: since fat has a much lower ADC than water, this artificially lowers marrow ADC [29]. Variations in the quality of fat suppression can therefore introduce variability into the measured ADC. Several methods for removing the effect of unsuppressed fat have been proposed, relying on Dixon-like methodology [30,31] which is discussed in more detail later (see Fat-Water MRI). Skeletal maturity also affects ADC measurements of bone marrow [32], but this problem could be addressed by using normal bone as a reference tissue, or by using segmentation methods which account for the variable composition of background marrow.

**Dynamic Contrast enhanced imaging**

Dynamic contrast-enhanced MRI (DCE-MRI) is a method for measuring tissue perfusion, relying on the acquisition of rapidly repeated images during intravenous administration of gadolinium-based contrast agent (GBCA) [33,34]. The changes in signal intensity over time are analysed to derive maps of specific ‘microvascular’ parameters. The most widely used model to calculate kinetic parameters from the
imaging data was described by Toft and colleagues [35]. In their model, a contrast agent is distributed between two compartments: the tissue and the blood plasma. The model incorporates three standard kinetic parameters: the volume transfer constant between plasma and extracellular space (Ktrans), the volume of the extracellular space (EES), and the flux rate constant between EES and plasma (Kep) [35]. From these parameters, measures of capillary wall permeability and tissue perfusion can be derived.

An essential input function for the Tofts model is the plasma concentration of contrast agent in the arterial system supplying the tissue of interest, known as the arterial input function (AIF). Many automated and non-automated methods are available to measure the AIF but obtaining reproducible results has been difficult with most methods [34,36,37]. An alternative approach to DCE-MRI is to analyse the shape of the signal intensity curves of contrast enhancement over time within the tissue of interest (Figure 1). This approach is often referred to as the descriptive or heuristic method, in which several distinct curve patterns are described (for example: a curve with a rapid enhancement pattern followed by a gradual contrast washout) [34,38]. A description of these curve patterns is often accompanied by measures derived from these curves such as the slope of the enhancement or the maximum enhancement [39].

**T1rho imaging**

T1rho (T1p) imaging is used to quantify the composition of cartilage. T1p is a time constant reflecting spin-lattice relaxation in the rotating frame, and is quantified using a dedicated relaxometry experiment. The magnetization is first flipped into the transverse plane by a 90°radiofrequency pulse. A long, low power radiofrequency pulse (the spin lock pulse) is then applied parallel to the magnetization. The magnetization nutates around the applied spin lock field, but undergoes relaxation (similar to longitudinal relaxation around the B0 field in the laboratory frame), with time constant T1p. T1p can be quantified by repeating the experiment with varying duration of the spin lock pulse, and then fitting the known signal model to the acquired data. T1p is related to both T1 and T2, and may approach either of these time constants depending on the specific conditions of the experiment. In collagen rich tissues such as cartilage, the main mechanisms contributing to T1p are from dipole-dipole interactions and chemical exchange, which inform of the macromolecular content and structure of the cartilage matrix (Figure 2). Importantly, the experiment can be designed to minimize the dipolar interactions and to emphasise exchange, thus extending the dynamic range of T1p compared to T2 and enabling the sequence to accurately detect changes in cartilage structure.

Technical limitations in T1p include measurement variability between different scanners and vendors [40]. T1p is susceptible to magic angle effects, and correct angulation of the tissue of interest to the
B0 field is important [41]. Patient-related factors including obesity and pre-scan exercise can also influence T1ρ values [42,43].

**Delayed gadolinium-enhanced MRI of cartilage**

Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is used to quantify the composition of cartilage, particularly with respect to glycosaminoglycans (GAGs). Following intravenously administered negatively-charged anionic contrast agent (Gd(DTPA)\(^2\)) (gadolinium diethylenetriamine-pentaacetic acid), contrast diffuses into cartilage in a dose-dependent manner, but uptake is inhibited by the presence of GAGs, which are negatively charged. Thus, uptake of contrast is inversely related to GAG density. In healthy cartilage, GAGs are abundant. In GAG-depleted joints, such as those affected by arthritis, the net charge of the cartilage matrix increases, and contrast uptake increases. T1 relaxation time can be used to calculate the remaining cartilage GAG concentration [44] expressed as the dGEMRIC index; a shorter dGEMRIC index indicates cartilage damage.

In clinical practice, there are limitations to the use of dGEMRIC. The delay between injection of the contrast agent and the time of optimal imaging is long, substantially prolonging standard imaging protocols. The optimal time interval for imaging is unknown and delays of between 30 and 120 minutes have been described [45,46] and it is likely that the interval influences the dGEMRIC index. Exercise probably accelerates cartilage uptake of contrast, but the size of this effect is unknown. Finally, there are no studies correlating the histopathological cartilage composition with dGEMRIC values in rheumatic diseases.

**T2 relaxation time mapping**

The presence of water in cartilage is dependent on the content and orientation of proteoglycans; T2 relaxation time mapping utilizes this principle to study (amongst others) the zonal orientation of articular cartilage. In T2 mapping, T2 images with different echo times are acquired and, in the simplest case, a monoexponential single model is fit to the data, enabling simple extraction of the relaxation constant T2 for each pixel [47].

An intrinsic limitation of T2 mapping is that T2 measurements can vary depending on the sequence used to acquire the data [48]. A number of complex approaches including the use of extended phase graph modelling have been developed to correct for confounding factors such as the presence of stimulated echoes [49]. Additionally, similar to T1ρ, the angulation of the cartilage towards the main magnetic B0 field influences T2 relaxation time values [50] and loading conditions (exercise, obesity) might influence T2 relaxation values [51,52]. High image resolution is essential for correct delineation of the areas of interest within the different cartilage layers.

**Fat-Water MRI**
Chemical shift-encoded MRI (CSE-MRI or Dixon MRI) utilises the fact that protons in fat and water molecules resonate at slightly different frequencies, depending on variations in the local magnetic field experienced. The Larmor frequency for hydrogen is said to be modified or shifted depending on the degree of shielding of the electronic nucleus, which differs between fat and water molecules. Since the MR signal from a voxel containing fat and water is sampled at multiple predetermined time points, the signal can be separated into water and fat components (producing water and fat only images) [53]. The fat fraction (FF) is simply the proportion of the total signal (S) arising from fat [i.e. FF = \( \frac{S_{\text{fat}}}{S_{\text{water}}+S_{\text{fat}}} \)]. Using modern techniques, it is also possible to eliminate the effect of confounding factors such as T2* and the spectral complexity of fat, which would otherwise bias the FF measurement, thus enabling more accurate quantification [54]. Once relaxation and the spectral complexity of fat have been accounted for, the calculated FF value can be referred to as a proton density fat fraction (PDFF), since it theoretically eliminates these confounds and gives an estimate of the density of fat in the tissue which is independent of the scanner and acquisition parameters used to acquire the data.

**Ultra-short echo time and zero echo time**

The tissue components of bones, tendons and entheses are densely packed, causing the MRI signal to decay rapidly. Consequently, alternative methods are needed to image these tissues. Two methods – ultra-short echo time (UTE) and zero echo time (ZTE) - have been developed for capturing the rapidly decaying transverse magnetization of these tissues [55,56]. UTE uses a short radiofrequency excitation pulse with very early read-out gradients; thus tissues with short T2 relaxation times contribute to image signal and contrast.

Limitations of UTE include magic angle effects that can interfere with qualitative and quantitative imaging, especially when tendons or entheses have a multidirectional orientation, preventing the positioning of tendons in an appropriate ‘fiber-to-field’ angle. In this respect, the Achilles tendon with its unidirectional fiber orientation is well suited to UTE imaging. Another technical issue is eddy currents, which cause image artefacts. Newer protocols such as the 3D-UTE-Cones [57] reduce susceptibility from eddy currents and may require less user input. Despite these issues, UTE/ZTE methods offer a unique opportunity to study these tissues, and provide an alternative window into the inflammatory process.
Imaging of Synovium

Autoimmune mediated inflammation of the synovial membrane is the hallmark of many of the inflammatory arthritides. Normal synovial membrane has two layers (the subintimal and intimal layer) both comprising a zone of a few cells. After exogenous or endogenous stimulation, the synovial membrane is invaded by inflammatory cells and pro-inflammatory mediators. Consequently, the subintimal and intimal layer thicken due to hyperplasia and hypertrophy of the original synovial lineage cells and the influx of the mononuclear cells. Angiogenesis in the synovial membrane completes the acute inflammatory response. Several quantitative MR techniques can image the cellular and vascular changes in the synovium.

Quantifying Synovial Perfusion

DCE imaging can provide a measure of synovial perfusion. Studies of synovial perfusion in inflammatory arthritis have shown that, amongst others, the rate of enhancement and maximum enhancement of contrast influx correlate with histological grades of synovitis ([58–60]. A detailed review of the use of DCE-MRI in inflammatory arthritis has been published recently [34].

Synovial Diffusivity Measurement

Studies using DWI in inflammatory arthritis have focused on the differences between diffusivity in synovium and effusion, and between acute and chronic inflammation. Free fluid within a joint effusion typically shows unrestricted diffusion, with high ADC values. Several studies have found that the ADC of synovium in adult or pediatric patients with arthritis is lower than in effusions [61–64]. In these studies ADC of synovium is typically less than 2 x 10⁻³ mm²/s [61,62,64], whereas ADC of effusions was greater than 2 x 10⁻³ mm²/s. These studies suggest that ADC values can distinguish synovium from effusion (Figure 3).

Studies comparing inflamed synovium to non-inflamed synovium are contradictory. Li et al. [63] reported decreasing ADC values with higher grades of inflammation, while Barendregt et al. described higher ADC values in inflamed synovium as compared to non-inflamed synovium[65]. However, the number of patients with synovial inflammation is low in both studies (17 and 31 respectively[63,65]), and larger studies may help characterize inflamed synovium as compared to normal synovium. It could be hypothesized that during acute inflammation, the synovium would have different diffusion properties compared to chronic inflammation. In the chronic inflammatory phase, fibrin deposits in the synovium would reduce water diffusion. Potentially studies correlating ADC with synovial histopathology could help understand the mechanisms affecting synovial ADC.
Imaging of Cartilage

Cartilage damage is a key feature of inflammatory joint disorders and is caused by pannus invasion and presence of cytokines and proteases in the synovial fluid [66]. Cartilage consists of chondrocytes, collagen and extra-cellular matrix, which contains water, proteoglycans, glycoproteins and lipids. Inflammatory mediators and enzymes affect proteoglycans and collagen; severe degradation of normal proteoglycan and collagen structure and depletion of these molecules occurs after inflammatory stimuli [67]. Conventional MRI can reveal cartilage thinning, fissures and erosion/ulceration, resulting from accumulated microstructural damage to the cartilage matrix. However, early microstructural cartilage damage cannot be visualized on conventional MRI. Other MR tools that can identify early cartilage damage have been developed, but these are not commonly used in clinical practice.

T1rho (ρ) Imaging of Cartilage

In 2012, a study of T1rho in five patients with severe and long-standing RA who underwent total knee arthroplasty showed lower T1ρ values in macroscopically normal than in macroscopically abnormal cartilage [68]. In another study, healthy controls without knee symptoms were compared to patients with RA [69]. Patients with RA demonstrated higher T1ρ values in the majority of assessed articular surfaces.

Two studies in RA patients have assessed T1p during treatment, and found conflicting results. The first study included 17 symptomatic RA patients and performed MRI of knee cartilage before and 1 year after the start of biological treatment [70]. This study showed that although clinical scores improved after 1 year of treatment, no significant changes in T1ρ values were found in the articular cartilage of the knee [70].

In contrast, in a second study, the radiocarpal cartilage of 9 patients undergoing treatment with methotrexate (MTX) was imaged. Six patients with moderate to severe disease activity started with concomitant anti-tumour necrosis factor (TNF) therapy and 3 patients with low disease activity remained on MTX only [71]. MRI was repeated in all patients after 3 months. After 3 months, good clinical treatment response (as assessed by the EULAR criteria[72]) was observed in 2 patients (both in the MTX+anti-TNF group) and this was associated with declining T1p values (Figure 2), whilst patients with an absent or moderate treatment response showed increasing T1p values compared to baseline.

Overall, the evidence for use of cartilage T1ρ to assess treatment response in RA patients is currently inconclusive, and further research in this area is required.
**dGEMRIC imaging**

Several authors have studied the use of the dGEMRIC index in patients with RA. Healthy controls have a shorter dGEMRIC index than RA patients [46,73–75]. dGEMRIC indices are lower in patients with long-standing RA compared to recently diagnosed RA [76], indicating the presence of progressive cartilage damage. Metacarpophalangeal joints (MCPs) with the most severe inflammation (highest RAMRIS synovitis score) had lower dGEMRIC indices compared to less severely inflamed MCPs in RA [77,78].

Two small studies investigated changes in dGEMRIC values over time in patients starting treatment. The dGEMRIC index of knee femoral cartilage decreased over time in 7 chronic RA patients started on infliximab but simultaneously taking other regimens (prednisone, azathioprine, MTX) [46]. In a study of 28 patients with early RA who started MTX [78], dGEMRIC indices of MCP 2 and 3 did not significantly change on three sequential MRI scans acquired over 6 months, but the differences in dGEMRIC values between the most severely inflamed MCPs and the less severely inflamed MCPs seemed to decline [78].

**T2 relaxation time mapping**

An initial study demonstrated increased T2 relaxation time of knee cartilage in children suffering with JIA compared to healthy controls [79]. In an adult cohort, nine patients with RA and gonarthritis were found to have higher T2 values than healthy volunteers in the articular cartilage of the knee, except for the cartilage of the patella and lateral tibial plateau [69]. In a recent study in patients with RA, T2 mapping showed that cartilage T2 values of pooled MCP 2 and MCP 3 articular cartilage were significantly higher in patients who had anti-citrullinated protein antibodies as opposed to patients without these antibodies [80], and longer disease duration resulted in higher T2 relaxation time in the articular cartilage. These studies all indicate that the T2 relaxation time is increased in patients with current or previous inflammation, presumably due to an increase in the proportion of ‘damaged’ proteoglycans.

Interestingly, in a longitudinal analysis of children with JIA, T2 values of the anterior non-weight bearing distal femur were shown to increase over time despite improvements in clinical assessment of disease activity [81]. It was concluded that deterioration of the articular cartilage continued, and that T2 mapping could provide information distinct from that provided by conventional clinical assessment [81]. Unfortunately, no healthy children were assessed in this study and the increase in T2 values over time might have been influenced not only by JIA but also by normal maturation of the cartilage.
**Imaging of Osteitis**

Although osteitis may be seen as a secondary phenomenon in inflammatory disease, it is a central focus of imaging methods that aim to diagnose, stratify and monitor inflammation. The characteristic imaging finding in osteitis is “bone marrow oedema”, showing hyperintensity on T2-weighted, fat suppressed images (typically short-tau inversion recovery images), hypointensity on T1-weighted imaging and enhancement with GBCA. These imaging features are probably due to the presence of an inflammatory exudate in tissue, causing increased extracellular fluid and increased numbers of inflammatory cells. Unfortunately, these conventional imaging methods do not correlate specifically to pathological processes and their interpretation is subjective, relying on the expertise and opinion of the observer. qMRI has several potential advantages including more objective and precise assessment of pathology, and an improved ability to monitor change over time.

**Measuring Diffusivity in Oedematous Marrow**

In the bone marrow, the presence of an inflammatory exudate causes expansion of the extracellular space, and an increase in the proportion of extracellular water molecules. These extracellular water molecules inhabit a freer, less hindered diffusion environment than intracellular molecules and consequently the ADC increases (Figure 4). Thus, ADC measurements offer a means to determine the presence and severity of the exudate, reflecting disease activity.

Initial studies of the sacroiliac joint in SpA showed that ADC measurements were increased in areas of bone marrow oedema compared to controls with mechanical back pain [82,83]. Subsequently, it was shown that ADC values reduce after time in patients treated with infliximab, demonstrating biological validity of ADC as a biomarker [84].

DWI had good discriminatory performance for differentiating patients with active inflammation from those without, with potential to inform on treatment response [85]. It has also been shown that ADC measurements can monitor response in young patients with spondyloarthritis [86]. A recent prospective study assessing the utility of ADC as a marker of disease activity in discovertebral lesions showed that a normalised maximum ADC measurement was associated with increased disease activity, functional impairment and functional global assessment [87]. There is also evidence that ADC measurements are higher in inflammatory lesions than inflammatory ‘Modic’ changes, potentially offering a means to differentiate between these entities [88].

There has been some reluctance to use DWI, and quantitative imaging in general, on the grounds that the process of placing regions of interest (ROIs) is subjective [89]. However, several suggestions have the potential to resolve these issues [90]. Automated methods for ROI placement using histographic
analysis to 'target' the inflamed parts of the ADC distribution may improve the sensitivity of this biomarker for active inflammation [91].

As ADC is essentially a 'summary' measure of tissue diffusion, there has been interest in the use of more sophisticated models of diffusion attenuation such as IVIM and DKI [19–22]. DKI aims to capture the microstructural complexity in marrow and preliminary data suggest potential improvements in diagnostic performance [92]. Preliminary data also suggest that IVIM offers a better description of the signal in both normal and inflamed marrow than the monoexponential ADC model or kurtosis, suggesting that this model deserves further investigation (Figure 5) [93].

**Quantifying Fat in the Marrow**

CSE-MRI/PDFF imaging can quantify bone marrow fat fraction, reflecting bone inflammation. A strength of PDFF as a biomarker is its reproducibility across scanners and vendors [94,95]. It can also quantify both active and chronic inflammation, facilitating more detailed assessment of the heterogenous nature of inflammation.

CSE-MRI imaging in young patients with spondyloarthritis has shown that PDFF measurements are significantly reduced in areas of bone marrow oedema compared to normal marrow (which has a PDFF of around 50%), and significantly increased in areas of fat metaplasia (thought to reflect previous inflammation) (Figure 6) [96]. PDFF measurements may also be useful as a biomarker of structural damage [97], and can distinguish patients with 'inactive' sacroilitis from healthy controls [98]. Histogramic measurements can be used to quantify changes in PDFF and could enable a more sensitive and specific assessment of qMRI maps in clinical practice [91].

CSE-MRI may also be used to correct for the effects of chemical shift where it would otherwise confound measurements of tissue properties. For example, chemical shift-corrected quantitative susceptibility mapping (QSM) has shown some promising results in the quantification of bone mineral density (BMD) in phantoms (see below) [99]. CSE-MRI methods can be combined with techniques for T2-mapping, enabling a specific measurement of the T2 of the water resonance alone without contamination from the T2 of fat [100]. This approach has shown promise in muscle [101].

**Quantifying Marrow Perfusion**

Using perfusion imaging, it may be possible to detect subtle derangements in tissue vasculature, and to separate these from the increase in extracellular water (which probably dominates the MR characteristics of the tissue). There have been some early studies investigating this issue in the marrow surrounding the sacroiliac joints. Perfusion parameters $K^{\text{trans}}$, $K^{\text{ep}}$, $V^*$, time to peak (TTP) and maximum concentration have been shown to differentiate between patients with active and inactive SpA stratified using clinical and biochemical criteria [102]. Potentially DCE-MRI could monitor changes in...
inflammation with biologic therapy [84]. An interesting possibility is that IVIM diffusion models may offer an alternative means to probe tissue diffusion. For example, the rapid diffusion parameter $D_f$, correlates with the maximum enhancement of tissue, arguing that this parameter reflects tissue perfusion [22]. However, more confirmatory data are needed.

**Measurement of Bone Formation and Loss**

The spondyloarthritides are characterised by changes in the bone structure and bone mineral density, both in the form of new bone formation (which contributes to joint fusion and the eventual development of the characteristic ‘bamboo spine’) and osteoporosis. Early new bone formation and bone loss can be subtle and difficult to detect using conventional sequences.

Measurement of $R_2^*$ - the rate of signal decay in a gradient echo sequence – is correlated with bone mineral density, and preliminary data have shown that $R_2^*$ measurements are reduced in areas of fat metaplasia, potentially providing a mechanism to monitor BMD (Figure 7) [96]. QSM can also detect changes in BMD in phantoms, although data from patients are equivocal [99]. $R_2^*$ mapping and QSM measurements rely on local dephasing produced by variations in the amount of mineral present in the tissue. An important technical consideration is that both methods can be confounded by variations in tissue fat content but this can be more easily corrected for with QSM [99].

An alternative approach to imaging bone mineral component is to use ultrashort echo time (UTE) and zero echo time (ZTE) imaging. UTE and ZTE methods can acquire signal from water molecules within the cortex and trabeculae themselves, and thus inform on the structure/porosity of bone [56,103–105].
**Imaging of Tendons and Entheses**

Tendons and entheses can be involved in the disease process in all inflammatory arthritides, however enthesal involvement is particularly common in SpA [106]. Tendons and entheses consist of tightly packed collagen fibers that connect connective tissues originating from the musculoskeletal apparatus (such as tendon, ligaments and fascia) to bone. Interstitial volume and water content are low in these tissues. Consequently, on conventional MRI, enthesal abnormalities are only seen when a significant disruption of the normal fibrillary structure is present, when water accumulates inside a tendon, or when a tendon thickens. These findings are considered as major abnormalities. Earlier signs of tendon and/or enthesis pathology are difficult to detect due to the very short T2 (1-2 ms) of normal entheses and tendons and are likely overlooked by conventional MRI (Figure 8). Consequently, imaging which captures echos early in the imaging experiment (such as UTE and ZTE), has been utilized for imaging these dense, collagen rich structures.

Preliminary data [107] indicated that UTE images of patients with psoriatic arthritis showed many enthesal abnormalities not captured on conventional T1-weighted and T2-weighted images. In a further study of 25 patients with SpA, abnormalities in the Achilles tendon were more commonly seen on contrast enhanced UTE and 3D spoiled gradient echo with a TE of 2 ms than on conventional MRI or ultrasound [108]. The authors also imaged 10 healthy controls and found abnormalities on MRI in only 1 patient (10%), while in the SpA group, up to 92% of patients demonstrated abnormalities on MRI. In another study, UTE was used as a technique to quantify enhancement in the enthesis [109]. Twenty-four symptomatic SpA-patients and 14 healthy controls underwent UTE (TE = 0.07 ms) before and after GdCA administration. Quantification was performed by calculating the relative contrast enhancement in a single-slice axial ROI of the Achilles tendon. Relative enhancement on the UTE images was higher in SpA patients as compared to controls.
Future Directions

One of the major goals for future research will be to translate qMRI techniques into clinical practice. Although many of these techniques are promising, the time taken to acquire the images and requirement for offline processing will need to be addressed before these methods can be widely implemented. Some of the faster techniques (e.g. diffusion and Dixon imaging) are relatively easy to implement and are being used in some centres. Accelerated acquisition and relaxometry techniques aiming to separate individual properties of tissue may help to overcome some of the technical challenges, and to increase the uptake of these methods. The methods will also need large-scale collaborative validation studies to demonstrate repeatability, reproducibility and clinical benefit. Furthermore, the clinical implementation of qMRI techniques will require the engagement of all members of multidisciplinary teams involved in patient care.

An interesting new development is the use of qMRI to image immune cell function and metabolism at inflamed sites. There has been preclinical research demonstrating that inflammatory cells can be magnetically labelled and tracked in vivo, with promising results in rodent models of inflammation [110,111]. Hyperpolarised MRI can potentially be used to detect inflammation-induced hypoxia: rats with a model of inflammatory arthritis have been injected with 13C-pyruvate and an increase in labelled 13C-labelled pyruvate and in the lactate pyruvate ratio in inflamed tissue has been shown [112]. Given the recent advances in oncological imaging, where hyperpolarised MRI has been used to image small numbers of human subjects, it seems possible that this method could be applied to inflammatory diseases.

Recent, rapid advances in artificial intelligence (AI) are an important development [14,113]. Although extensive training and refinement of AI algorithms is required before it can be incorporated into research and clinical practice, we expect that AI will ultimately facilitate automated assessment and scoring of quantitative images. Training of these algorithms may require large, international collaborations to acquire datasets of sufficient size. Also, a coordinated effort is needed to ensure that methods are implemented in a consistent, transparent fashion between different centres, particularly where the vendors of MRI scanners may vary.

An outstanding clinical problem is differentiating between diseases which are primarily inflammatory and those where inflammation is secondary to another insult. 'Bone marrow oedema' has been used as a descriptive term for bone marrow signals changes for many years; despite evidence that this lesion is highly heterogenous, it remains poorly characterised in clinical practice. Similarly, synovial inflammation in inflammatory arthritis might be difficult to differentiate from synovial inflammation.
resulting from biomechanical damage. qMRI techniques may facilitate more detailed phenotyping of these changes and help differentiate inflammatory from non-inflammatory causes of arthritis.

Summary

There have been significant advances in recent years in the imaging and quantification of inflammation of the musculoskeletal system. Acute and chronic inflammation in cartilage, synovium, bone marrow and tendons can be measured with qMRI and these detailed quantitative imaging biomarkers can potentially impact patient care. Improvements in imaging technology have been paralleled by newer drugs, particularly biologic therapies. The challenge is to marry these developments and to produce imaging biomarkers, which are clinically practical, biologically relevant, and enable us to tailor our treatments to patients in the clinic.
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Figure Legends

Figure 1 – DCE-derived time intensity curve shape maps of two patients with JIA. The first patient demonstrated active synovial inflammation and the DCE MRI of this patient shows an increased number and percentage of TIC-4 shapes as compared to the second patient, who has no synovial inflammation on MRI. (From Hemke 2014, European Radiology[114])

Figure 2 – T1rho of radiocarpal cartilage in an RA patient. The baseline pre-treatment image shows higher T1rho values in the cartilage as compared to the follow-up image, 3 months later. This was a patient with a good clinical response to a treatment regimen of MTX and anti-TNF. (Image from Ku 2016, J Magn Reson Imaging[71])

Figure 3 – DWI and ADC in active gonarthritis. DWI with b-value 800 s/mm² (a) and ADC50/800 map (b) of a 15-year old patient with arthritis of the knee demonstrating higher ADC in effusion as compared to synovium. The post-contrast image (c) shows synovial uptake of contrast agent, note the similarities of delineation of the synovium between the diffusion-derived images and the post-contrast image. (Image from Li 2019, World J Pediatr. 2019[63])

Figure 4 – ADC mapping in a patient with sacroiliitis. A conventional STIR image is shown in (a); the corresponding ADC map is shown in (b). The arrows indicate areas of bone marrow oedema, corresponding to the high signal on the STIR image. (c,d) show ADC histograms derived from subchondral bone in a patient with sacroiliitis and a control respectively; (c) demonstrates the rightward shift in ADC values in the inflamed subject.

Figure 5 – Diffusion-weighted signal in normal and inflamed marrow. Signal intensity is shown on a log scale on the y axis, b-value is shown on the x-axis. The datapoints are shown as triangles and the error bars indicate the standard deviation. The IVIM model (blue) provides the best description of the data at the lower b-values; the other models cannot capture the early ‘perfusion’ component of the IVIM signal.

Figure 6 – Image of osteitis with chemical shift-encoded MRI. Fat fraction maps are shown on the top row (a,b,c) and the corresponding histograms are below (d,e,f). In the inflamed case (b,e), areas of bone marrow oedema produce reduced fat fraction measurements. In areas of fat metaplasia (c,f), fat fraction measurements are increased.

Figure 7 – Fat fraction and R2* maps showing fat metaplasia. The arrow shows an area of fat metaplasia (a post-inflammatory lesion characterised by increased marrow lipid content), with increased fat fraction measurements (a) and reduced R2* measurements (b).
Figure 8 – UTE imaging of the Achilles tendon. UTE images of a healthy volunteer (a, b) and a patient with psoriatic arthritis (c, d) show the increase in signal and visibility of the tendon structure with lower echo times. Note the heterogeneously increased signal in the posterior half of the Achilles tendon in the patient on the 32 us image. On the conventional T1-FSE image (e) the tendon abnormalities seem less extensive. (Image from Chen 2018 [57]).