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MRI and non-cartilaginous structures in knee osteoarthritis

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Summary

Magnetic resonance imaging (MRI) provides a sensitive tool for examining all the structures involved in the osteoarthritis (OA) process. While much of the MRI literature previously focussed on cartilage, there is increasing research on whole-organ evaluation and including features such as synovitis, bone marrow edema, and meniscal and ligamentous pathology. The aim of this session at the Outcome Measures in Rheumatology Clinical Trials (OMERACT)–Osteoarthritis Research Society International (OARSI) Workshop for Consensus in Osteoarthritis Imaging was to describe the current MRI methods for identifying and quantifying non-cartilaginous structures and review their associations with both OA symptoms and structural progression. Although there is much experience in measuring synovitis (derived from the rheumatoid arthritis literature), only one study has reported an association of MRI-detected synovitis and effusions with OA pain. Bone marrow edema lesions, which may represent areas of trabecular remodelling, have been associated with pain and compartment-specific structural deterioration. MRI studies have confirmed the frequency and importance of meniscal damage in progressive cartilage loss, but not related such damage to symptoms. Osteophytes have been associated with cartilage loss and malalignment to the side of the osteophyte. Ligament damage, including anterior cruciate ligament tears, has been found more commonly than expected in painful OA knees. Improvements in quantitative and semi-quantitative assessments of non-cartilage features will greatly assist understanding of the OA process and its response to therapy.

Key words: Osteoarthritis, Knee, MRI, Synovium, Subchondral bone, Ligaments, Menisci.

Osteoarthritis (OA) is the commonest joint disease and is strongly associated with aging. It is now accepted that the OA process involves the whole joint organ including the synovium, subchondral bone, menisci and ligaments[1]. A number of presentations on non-cartilaginous knee structures in OA were therefore included in the Outcome Measures in Rheumatology Clinical Trials (OMERACT)–Osteoarthritis Research Society International (OARSI) Workshop for Consensus in Osteoarthritis Imaging. This review will summarize these presentations by focusing on the magnetic resonance imaging (MRI)-derived information relevant to each structure in OA and where possible the available information on quantitating abnormalities of these structures using MRI.

Much of the data relating to these non-cartilaginous structures are recent, as prior to MRI most of these structures were not visualised; furthermore, even the MRI OA studies have largely focussed on cartilage. Of course, specific structural abnormalities do not occur in isolation but rather as part of a complex inter-related biochemical and biomechanical structure. With that complexity in mind, whole-organ MRI evaluation will also be discussed.

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Synovitis and effusions

The importance of inflammation in OA is well recognised[2]. Although synovitis in OA appears to be secondary, synovial abnormalities are present in early OA and are seen with increased frequency with increasing severity of chondropathy[3–5]. Publications involving MRI measurement of the synovium in OA are few[6–12]. However, there is a large quantity of literature on quantification of rheumatoid arthritis (RA) synovitis (systematically reviewed in Ref.[13]) and there is no reason to believe that using MRI to detect synovitis in RA will be a different process from detection in OA, except as histological inflammatory studies would suggest, in quantitative measure.

Synovitis is probably best assessed with MRI using the intravenous, paramagnetic-enhancing agent gadolinium (Fig. 1)[9], although modern non-gadolinium sequences for delineating synovitis (including fat suppression and pulsed saturation transfer sequences) can be optimised to assess synovium[7,14]. Synovial hypertrophy detected by both gadolinium and non-gadolinium sequences has been correlated with microscopic synovial inflammation[7,9]. The decision to

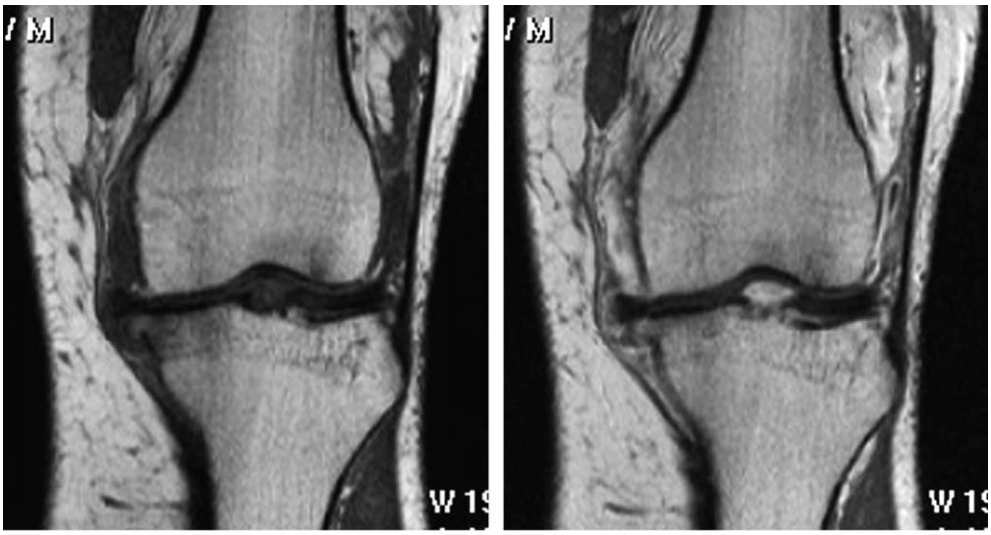

Fig. 1. T1-weighted coronal images of an osteoarthritic knee before and after gadolinium demonstrating enhancing synovium (image courtesy of Dr A. Grainger, Leeds UK).

use gadolinium has implications for the subject, duration of scan and selection of sequences. Preliminary information from a gadolinium vs no-gadolinium scoring exercise conducted using semi-quantitative scoring of metacarpophalangeal and wrist joints in RA, using T1 coronal and axial sequences with T2 Short Tau Inversion Recovery (STIR) sequences, demonstrated that moderate to good agreement on synovitis scores could be achieved[15]. A study comparing non-gadolinium MR sequences – including proton-density (PD), T2-weighted spin echo and fast spin echo (FSE) images with fat saturation – with arthroscopy in the detection of knee synovitis demonstrated high sensitivity, specificity and accuracy for the MRI sequences[16].

Quantification of synovitis may be achieved using either estimations of volume or assessing the characteristics of gadolinium signal using dynamic-enhanced MRI (DEMRI) techniques. Volume may be assessed semi-quantitatively and in a recent study of 35 OA knees, semi-quantitative scores (graded 0–3) at four sites (medial and lateral parapatellar recesses, intercondylar notch and suprapatella pouch) correlated well with detailed volumetric assessments[17]. Hill *et al.*[12] used scoring of presence or absence of synovial hypertrophy at three sites in the knee (infrapatella fat pad, intercondylar space and anterior horn of lateral meniscus) of 150 OA subjects; this study demonstrated that this synovial volume measurement was associated with pain. Peterfy *et al.*[18] have described a whole-organ semi-quantitative OA knee scoring system (the WORMS score) and work is presented elsewhere in these Workshop proceedings on assessing the psychometric properties of this score. The relevant WORMS subscale scores global knee synovitis and effusion (without distinguishing the two) on a 0–3 scale. Recently Loeuille *et al.*[5] evaluated synovial hypertrophy at five sites in the knee using a 4-point scale and correlated this with arthroscopic synovial scores.

Using post-gadolinium scans, synovial volume may be estimated using a somewhat laborious manual outline or using semi-automated methods that involve subtraction and enhancement thresholding and require post-gadolinium images[8,9,19,20]. Although manual volume studies probably represent the 'gold standard', automated methods have been correlated with these methods[8]. A number of different image analysis software packages are available for performing volume calculations. When doing these synovial volume studies there are a number of sources of variability including where to set the threshold above which pixels of a certain intensity will be analysed[8]. Reports on the reliability of these methods in knee studies are few, but in one study evaluating the efficacy of intraarticular steroids in the knee, the measured change was demonstrated to be greater than the smallest detectable difference (i.e., the difference beyond measurement error)[21].

DEMRI enables the study of pharmacokinetic and pharmacodynamic parameters, such as initial rate of enhancement and maximum enhancement[22–24]. The sources of variability include acquisition (injection dose, rate, route, hydration of patient, cardiac output), and analysis (curved fitting, calculation of parameters and selection of region of interest). These dynamic studies have been correlated with histology, although there is better correlation when large synovial areas such as the whole knee, have been evaluated[22,23].

Joint effusion is best detected on fat-suppressed PD or T2-weighted FSE sequences. The volume of joint effusions can also be calculated using semi-automated volume analysis[9] and have been demonstrated responsive to change in inflammatory knee arthritis treated with intra-articular corticosteroids[21]. A recent study in OA patients with and without knee pain (referred to above for semi-quantitative assessment of synovial hypertrophy) also studied effusions and popliteal cysts, both graded 0–3 on T2-weighted axial and sagittal sequences, and found both abnormalities common[12]. Moderate or large effusions were more common in those subjects with pain than in those without pain.

Subchondral bone

The subchondral bone has long been recognised as important in terms of the pain and progression of OA[25]. MRI has provided some novel insights into the role of bone in

OA. The commonest bone abnormality described in OA is 'bone marrow edema' (BME), a term uniquely associated with MRI and initially reported in 1988[26]. As will be discussed below, edema does not appear to be a major constituent of this abnormality and 'bone marrow lesion' may be a more appropriate term. It refers to ill-defined areas typically visualised as intermediate to high signal on fat-suppressed T2W or STIR images (Fig. 2). Bone edema on MRI has also been described in other conditions including inflammatory arthritis, osteomyelitis and enthesitis; it has also been commonly observed after joint trauma[27].

Two studies have looked at validity issues concerning BME by examining histologic associations in OA knee. Zanetti *et al.*[28] compared MRI tibial plateau abnormalities in 16 OA knees with appropriately co-ordinated histologic specimens at joint replacement (a cohort with severe OA). True edema was seen in only a very small percentage of biopsies, and indeed abnormal tissue was only demonstrated in approximately half of the MRI BME areas. The commonest abnormalities were bone marrow necrosis, fibrosis and abnormal remodelled trabeculae; such findings are similar to those found in avascular necrosis and after bone trauma. Similarly Bergman *et al.*[29] demonstrated that bone marrow fibrosis was the commonest finding in areas corresponding to subchondral BME in nine subjects with OA.

Information about BME in OA is slowly accumulating. In a study of 47 subjects with chronic knee pain, some with radiographic OA, an increase and decease in size of lesions over 2 years was reported[30]. In a 377 OA painful OA knee cohort (mean age 63, 76% women), 82% of patients had BME (30a). In 71% of patients these lesions did not change in size over 3 months, with 19% having increased lesions. The same study demonstrated that reduced BME size was associated with a reduction in cartilage degradation as measured by urinary excretion of crosslinking telopeptide of type II collagen[31]. In another large OA knee study, medial BME lesions were associated with higher medial bone mineral density, and similar findings were demonstrated for the lateral compartment, supporting the concept that these lesions reflect increased loading of the joint[32].

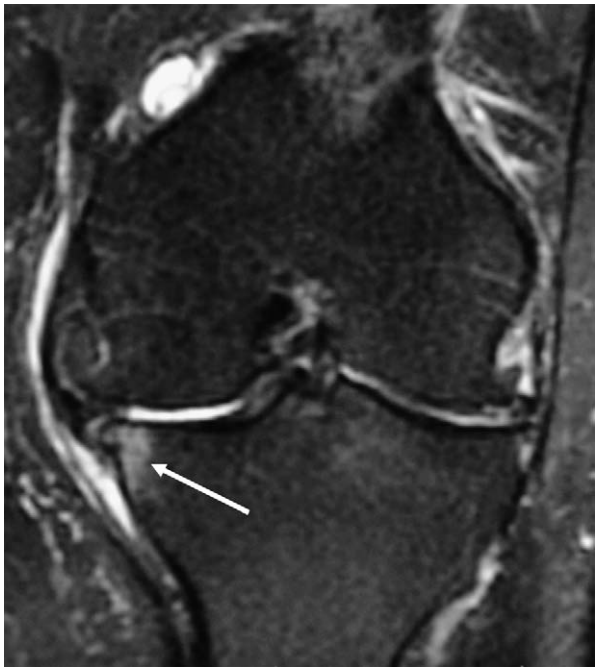

Fig. 2. Coronal STIR knee image demonstrating bone marrow edema (white arrow) of the medial tibial plateau involving osteophyte (image courtesy of Dr A. Grainger, Leeds, UK).

There are a number of MRI publications evaluating symptoms and BME. Lotke *et al.*[33] described three types of subchondral bone lesions in 41 painful subjects with painful knee OA and found that persistence of pain was predominantly associated with the largest lesions. Felson *et al.*[34] imaged a cohort of 401 subjects with radiographic OA knee, including 50 subjects without pain. They reported that BME was present in 77.5% and 30% of the painful and painless groups, respectively, but more impressively demonstrated that large lesions (graded semi-quantitatively on a 0–3 scale) were largely predominant in the painful knees (35.9% painful group vs 2% painless group, $P < 0.001$). There was no association with pain severity. Sowers *et al.*[35] have presented data on 120 women aged 30–55, with and without radiographic OA or pain. They found that BME frequency was similar in both painful and painless OA, but that BME lesions greater than 1 cm (found more commonly in knees with advanced cartilage loss) were more frequent in the painful OA group. Link *et al.*[36] in a smaller cohort of 50 OA knees again demonstrated an association of BME with cartilage loss, but did not demonstrate an association with pain; however, this cohort did not include a comparator group without pain.

With respect to structural progression, normal (or negative) bone scintigraphy is predictive of little if any change in joint space width in OA knee at follow-up[37]. Studies have also demonstrated correlations between 'positive' scintigraphic findings and the MRI findings of BME[38,39]. With these data in mind, Felson *et al.*[40] reported data from a cohort of 256 subjects and comparing MRI-detected BME and OA progression as assessed by fluoroscopically positioned X-rays. They found strong associations of BME with progression in the same compartment (medial odds ratio (OR) 6.5, lateral OR 6.1), with some reduction in risk when alignment was considered (medial OR 5.6, lateral OR 2.8). The site-specific nature of this BME risk should be emphasised. This is also reflected in another study comparing medial compartment chondroscopic progression with MRI in 20 OA knees; this study demonstrated that lack of MR-detected subchondral bone abnormalities predicted no worsening of chondropathy[41].

The ever improving technology continues to offer new measurement possibilities. In a novel application using high resolution MR images and comparing normal and OA knees (with spatial resolution of $195 \times 195\ \mu m^2$), Beuf *et al.*[42] demonstrated reduced trabecular bone volume fraction and increased trabecular spacing in the distal femur, consistent with loss of trabecular bone. Novel techniques for quantitative analysis of joint surface size, incongruity and curvature have also recently been described[43]. Preliminary data were presented at the Workshop demonstrating semi-automated image analysis techniques that can measure BME and record its location using PD and T2-weighted or PD and intermediate-weighted fat suppressed SE images.

Menisci

Evaluation of the menisci has been one of the major uses of MRI in the knee over many years. It is seen as the best non-invasive test for assessing meniscal pathology and has demonstrated high sensitivity and specificity for both medial

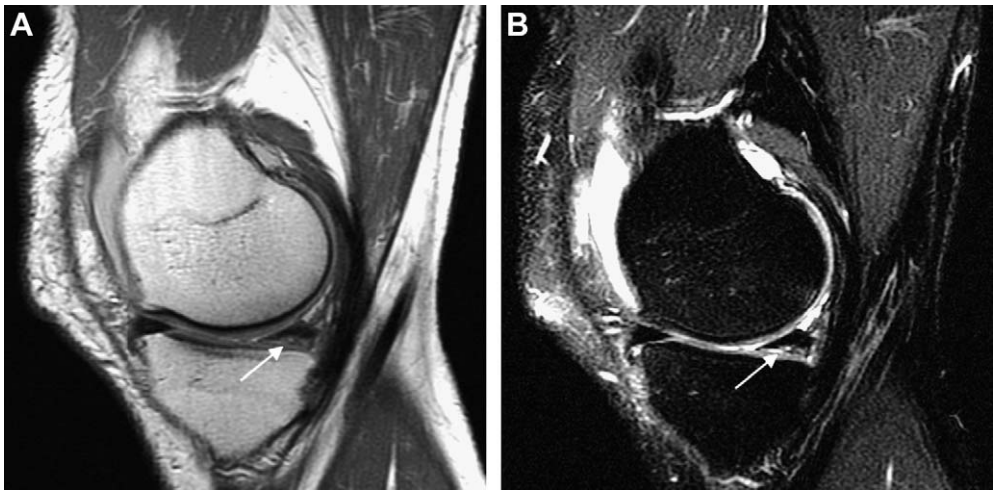

Fig. 3. Horizontal posterior horn medial meniscus tear (image courtesy of Dr G. Gold, USA).

(89% and 84%, respectively) and lateral (72% and 93%, respectively) tears[44]. Currently, sagittal PD (TE $<$ 20) FSE sequences are the standard for evaluating the menisci (Fig. 3), although 2–4% of tears may only be visualised in the coronal plane.

One of the common systems used for grading meniscal damage is based on the distribution of MRI signal intensity and its relation to the articular surface[45,46]. It employs a 0–3 scale where 0 is normal, 1 represents punctate signal intensity, 2 represents linear intrameniscal signal and 3 represents signal intensity extending to an articular surface. This system has been correlated with histological findings[46]. The WORMS score referred to above scores anterior, body and posterior horn segments of both menisci using sagittal and coronal sequences and a 0–4 scale where 0 is normal, 1 represents a minor radial or parrot-beak tear, 2 represents a non-displaced tear, 3 represents a displaced tear or partial resection and 4 represents complete maceration or resection[18].

Meniscal abnormalities are found commonly in OA. In a large cohort of 245 elderly subjects (aged 70–79) with 277 unilateral or bilateral OA knees, the prevalence of meniscal lesions was 83% in men and 73% in women[47]. The meniscal abnormalities were strongly associated with cartilage defects. Another large cohort from the same study and selected for normal knee radiographs again demonstrated a high prevalence of meniscal lesions (44% of males and 20% of females)[48]. The relevance of meniscal tears to patient symptoms was investigated in an MRI-based study that examined medial or lateral definite meniscal tears in 154 symptomatic OA patients[49]. Pain was not greater in those OA knees with a meniscal tear compared to those without.

Meniscectomy has long been associated with increased rates of symptomatic and radiographic OA[50]. Recent longitudinal studies employing MRI have confirmed that both meniscal tears and partial meniscectomy lead to increased rate of cartilage loss[51,52]. Using sagittal MRI of the knee positioned in extension and 45° of flexion, one study suggested that abnormal movement of the meniscus may also contribute to greater cartilage loss[53]. Meniscal extrusion is known to contribute, along with cartilage loss, to radiographic joint space narrowing[54] and increasing degree of subluxation has been correlated with the severity of joint space loss[55]. Meniscal damage and extrusion have also been identified as a factor (together with cartilage loss and bone attrition) associated with knee alignment[56].

Ligaments

The importance of the knee ligaments in the development of OA has been appreciated through studies of anterior cruciate ligament (ACL) ruptures and subsequent radiographic OA[57]. These risks seem increased with combined ligamentous injuries[58]. Furthermore, recent literature emphasising the influence of joint laxity and alignment on the risk of radiographic OA progression[1,59] heightens the importance of ligament evaluation.

PD and T2-weighted FSE or turbo spin echo sequences are commonly used for evaluating knee ligaments on MRI (Fig. 4), with sensitivity and specificity of 96% and 98%, respectively, for detecting ACL damage when compared with arthroscopy[60]. Sagittal sequences are most useful for ACL and posterior cruciate ligament evaluation, while coronal views are best for collateral ligaments. There are few MRI scoring methods published for evaluating ligaments in OA knee. One report of 10 OA patients used a notional grid to evaluate superficial and deep capsulo-ligamentous planes as well as the medial collateral ligament (MCL), all scored for no, weak and high signal intensity on coronal and axial sections[61]. Another study used a classification system based on ligamentous injury grading of 0–3 where 1 represents edema on one side of the ligament fibres, 2 represents edema on both sides and 3 represents edema with ligamentous disruption[62]. In this study of 30 patients with moderately severe radiographic OA knee compared with controls, MCL abnormalities were found in most patients but few controls. The WORMS method scores cruciate ligaments as normal or torn (0/1) and collateral ligaments as normal, thickened or torn (0, 1 or 2)[18]. In the large elderly OA knee cohort described above[47] the prevalence of any ligament tears was surprisingly high (27% in men and 30% in women) but again strongly associated with cartilage damage. In another large cohort of painful knee OA (mean age 67), complete ACL rupture was seen in 23% compared with 3% of age-matched, non-painful knees[63], suggesting that ACL rupture (for which subjects had poor recall) is more common in symptomatic OA knee.

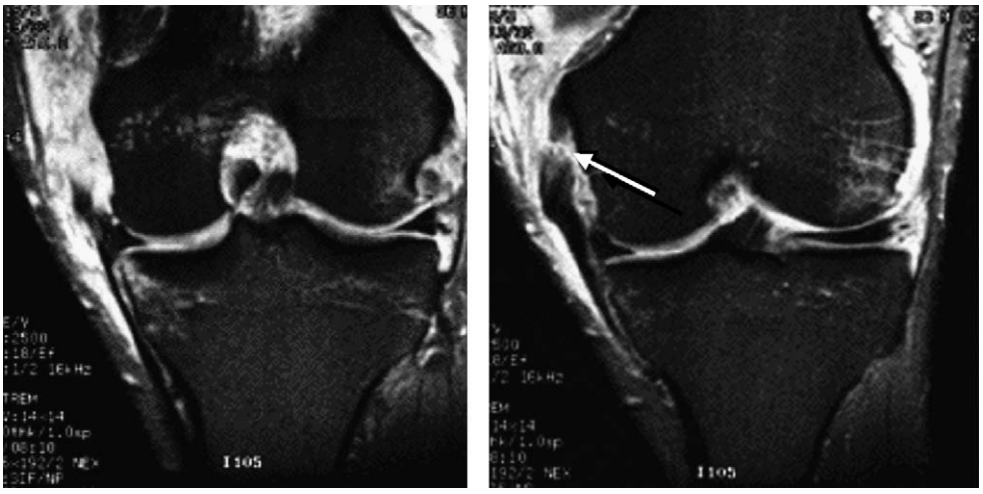

Fig. 4. Complete MCL tear (white arrow) (image courtesy of Dr G. Gold, CA, USA).

Osteophytes

Osteophytes are part of classic OA classifications and have been strongly associated with radiographic joint space narrowing and subchondral sclerosis[64]; they have also been associated with pain[65,66]. Recent studies have improved understanding of OA pathogenesis by demonstrating in tibiofemoral and patello-femoral joints that osteophytes are associated with cartilage defects in the affected joints[67,68]. The WORMS score grades osteophytes at multiple sites according to an 8-point scale[18]. The tomographic nature of MRI means that it is highly sensitive to the detection of osteophytes (Fig. 5) – in 445 knees with normal radiographs, osteophytes were detected (using the WORMS method) in 72% of men and 67% of women[48]. Recent data from a natural history study of painful OA knee have shown that large osteophytes do not increase the risk of radiographic OA progression, but are associated with malalignment to the side of the osteophyte[69].

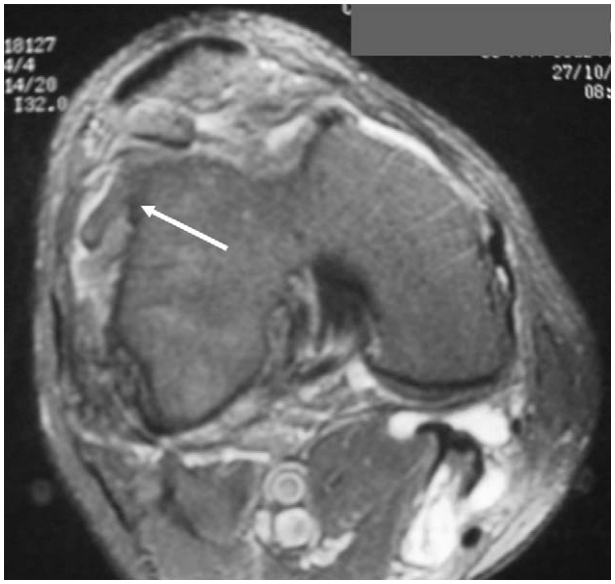

Fig. 5. Axial knee sequence demonstrating large femoral condyle osteophyte (white arrow) (image courtesy of Dr D. Louille, Nancy France).

Whole-organ evaluation

It seems appropriate, after reviewing the above, to have whole-organ evaluation as a desirable goal to understand more fully the pathogenesis of OA. There are a number of semi-quantitative whole-organ scoring systems currently under development[18,70,71] and these will require further data on their performance before interpretation of their application to clinical cohorts. Automated whole-organ assessment is achievable with recent MRI advances. Technology has been described that separates individual tissues using multispectral image analysis and information from different sequences that are co-registered, fused[72] and then segmented using a hierarchical statistical region growing algorithm based on local mean and variance[73]. Such algorithms have been evaluated for their ability to distinguish soft tissues and bone in animals and humans[73,74]. Further data from human OA studies are awaited.

Conclusion

The MRI evaluation of non-cartilage components of the OA joint is just starting to impact on our understanding of the OA process and importantly its relationship to both pain and structural progression. Work on the synovium can build on previous work in inflammatory arthritides and the utility of other dynamic perfusion parameters that have been used in cancer studies has not yet been tested. Semi-automated quantification of key features such as BME seems likely. Whole-organ evaluation is now possible, currently with semi-quantitative scoring systems. However, much more work is required on these imaging biomarkers to establish their validity, reliability, responsiveness and feasibility. This is a hugely exciting and rapidly moving field that must lead to improved patient therapies.

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