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The impact of MRI on the clinical management of inflammatory arthritides

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Abstract In the past two decades, MRI has gained a major role in research and clinical management of patients with inflammatory arthritides, particularly in spondyloarthritis (SpA), rheumatoid arthritis (RA), and osteoarthritis (OA). MRI is regarded as the most sensitive imaging modality for detecting early SpA in young patients with inflammatory back pain and normal radiographs of the sacroiliac joints. The recently published Assessment of SpondyloArthritis International Society classification criteria for axial SpA include for the first time a positive MRI demonstrating sacroiliitis as an imaging criterion indicative of SpA together with at least one clinical feature of SpA. Recent data show that systematic assessment of sacroiliitis displayed on MRI has much greater diagnostic utility than previously reported and highlight the diagnostic relevance of structural lesions. In RA, MRI has predictive value for the development of disease in new onset undifferentiated arthritis, and MR pathology at disease onset is a highly significant predictor of radiographic erosions. Consequently MRI has been credited with an important role in the new ACR/EULAR 2010 classification criteria for RA. In OA, bone marrow edema (BME) and synovitis may serve as biomarkers in interventional trials. Treatment interventions targeting BME and synovitis observed on MRI in inflammatory arthritides may have a disease-modifying effect as these lesions are potentially reversible and have been shown to be associated with structural progression. Research should focus on the prognostic significance of MRI lesions in larger cohorts and whether adding MRI to routine care improves clinical and radiographic outcome in patients with inflammatory arthritides.

Keywords Spondyloarthritis · Ankylosing spondylitis · Inflammatory back pain · Rheumatoid arthritis · Osteoarthritis · Magnetic resonance imaging · Clinical management

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Introduction

The introduction of magnetic resonance imaging (MRI) to the field of medicine [1, 2], which lead to the Nobel Prize, has revolutionized pathophysiologic concepts and clinical decision making in many areas of clinical research and daily practice. The past two decades have witnessed advances in knowledge in inflammatory rheumatology

disorders by adopting MRI both for research and routine practice. These achievements may well represent just the first step of ongoing progress in the evaluation of inflammatory arthritides by MRI.

Several properties of MRI render this imaging modality particularly attractive for assessing inflammatory arthritides. The capability of visualizing both soft tissues and bone by tomographic imaging with high spatial and contrast resolution allows assessment of all structures involved in the disease process. Moreover, its noninvasive technique and its lack of ionizing radiation makes MRI an ideal imaging tool for monitoring disease outcome and following patients after treatment interventions. Current limitations preventing a more widespread use of MRI are costs and regionally limited availability. However, these expenses have to be weighed against the treatment costs of expensive biologic agents and the indirect costs incurred by delayed diagnosis or by complications resulting from an undiagnosed inflammatory condition.

The goal of this article is to review the contributions of MRI to research and clinical management in axial spondyloarthritis (SpA), rheumatoid arthritis (RA), and osteoarthritis (OA), which are the three most common inflammatory conditions in rheumatology. A focus will be on active lesions represented by bone marrow edema (BME; also termed bone marrow lesion, BML) and synovitis. These MRI signs of disease activity are potentially modifiable by treatment. There is growing evidence that these lesions are associated both with pain and with structural progression in inflammatory arthritides, and interventions targeting BME and synovitis may show a disease-modifying effect. BME and synovitis may also serve as biomarkers in interventional trials. At present, histopathology data from areas of BME displayed by MRI are limited. It is interesting that the uniform appearance of BME in typical subchondral locations displayed by MRI in inflammatory arthritides seems to reflect different histopathological findings. In RA, where the quality of perioperative correlation studies between BME on MRI and histopathology is highest, predominantly active cellular infiltrates with a variety of cytokine signatures have been found [3, 4]. Scarce data in SpA from vertebral facet joints removed during spinal extension surgery and from biopsies of the sacroiliac joint (SIJ) showed predominantly mononuclear cell infiltrates with only partial correlation with BME seen on preoperative MRI [5, 6]. In contrast, bone specimens in OA obtained from patients with advanced disease undergoing joint replacement surgery demonstrated mainly nonspecific findings such as bone marrow fibrosis or bone remodeling, whereas edema in the bone marrow and cellular infiltrates were rare findings [7–10].

MRI has a key role in clinical research in SpA, RA, and OA. Where the technique is available, MRI has also gained an important position in daily routine for early diagnosis of SpA. This is reflected by the inclusion of MRI as an imaging criterion in the recently published Assessment of SpondyloArthritis (ASAS) International Society classification criteria for axial spondyloarthritis [11]. In RA, the present data don't yet justify a recommendation for routine use of MRI in daily practice; however recent data have confirmed the high predictive value of MRI for structural progression, and the recent recommendations address the use of imaging modalities in the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria for RA [12]. In particular, the use of MRI is recommended in selected patients in daily routine [13, 14]. MRI in OA is mainly restricted to clinical research, although suspicion of a differential diagnosis may require the occasional use of MRI in routine care of patients [15].

MRI for axial spondyloarthritis

MRI in axial SpA—major component of new classification criteria

The spectrum of SpA comprises the related disorders ankylosing spondylitis (AS), psoriatic arthritis, enteropathic SpA associated with Crohn's disease and ulcerative colitis, reactive arthritis, juvenile SpA, and undifferentiated SpA. Imaging plays a major role in predominantly axial forms of SpA, which are less accessible to clinical examination than peripheral SpA. While sacroiliitis remains the hallmark for the diagnosis of SpA, disability usually results from inflammation of the spine with progressive axial ossification [16].

Advances in the field of SpA over the past few years include the application of MRI as a major diagnostic tool and the introduction of antitumour necrosis factor alpha (anti-TNFα) therapy [17]. Until recently, diagnosis after clinical assessment relied primarily on radiographs demonstrating sacroiliitis according to the modified New York criteria [18]. While this approach continues to play a major role in clinical practice, it has been shown that several years may elapse before sacroiliitis becomes apparent on radiographs [19], during which time patients may experience significant symptoms and impairment of quality of life comparable to those with established disease [20]. Moreover, patients with early SpA may respond to treatment with anti-TNFα agents, which may be even more effective than in those with established disease [21, 22]. MRI abnormalities may precede radiographic changes by several years [23].

The major relevance of MRI in recognition of early SpA is reflected by the new axial SpA classification criteria

developed by the ASAS [11]. For the first time, imaging is included as a major criterion that may be either radiographic (as defined by the modified New York criteria [18]) or MRI evidence of sacroiliitis, which allows classification of patients with preradiographic disease. A companion expert consensus statement by the ASAS/OMERACT working group defined a positive MRI of the SIJ based solely on active inflammatory lesions [24]. It requires subchondral or periarticular BME on STIR sequence or osteitis on contrast-enhanced T1-weighted (T1W) sequence highly suggestive of sacroiliitis; BME needs to be present in at least two lesions on a single SIJ slice or must be observed on two consecutive slices if only one lesion is present.

Apart from the major role of MRI in recognition of clinically suspected, yet radiographically unconfirmed early SpA, MRI may be used to assess patients with established SpA unresponsive to standard treatment or to evaluate response to therapeutic interventions. Moreover, there is growing evidence that inflammatory spinal lesions detected by MRI may be predictive of new syndesmophyte formation.

The spectrum of MRI lesions in sacroiliitis

Several groups have recently reported descriptions of active and structural abnormalities in the SIJ that are usually based on the combined information from both T1W and STIR sequences. Active lesions include subchondral, ligamentous, sacrotuberous, and capsular edema as well as synovitis, capsulitis, joint space inflammation, and ligamentous enthesitis. Structural lesions include fat infiltration, erosion, bone sclerosis, and ankylosis. The histopathology of bone marrow signal abnormalities in SpA is poorly characterized. Histology findings of interstitial, predominantly mononuclear cell infiltrates from CT-guided biopsies of the SIJ [6] and bone tissue from zygoapophyseal joints removed during spinal extension surgery [5] showed a moderate correlation with bone marrow inflammatory lesions on dynamic MRI or on STIR sequences. Moreover, MRI detected only about half of the inflammatory lesions evident on histopathology. Though MRI can reveal diverse lesions, there have been only a few attempts to achieve standardized and validated definitions.

Bone marrow edema Active lesions can be observed on MRI within a few weeks of presentation of inflammatory back pain [25, 26]. Subchondral edema can be reliably detected on STIR sequences [27]. An online training module for systematic assessment of edema in the SIJ has been developed and validated by demonstrating increased reliability of detection after review of the module [28].

Do contrast-enhanced MRI sequences improve the detection of active SIJ lesions compared to STIR sequence alone? It has been reported that a T1W fat-suppressed sequence after administration of gadolinium contrast (T1WGd) may enhance diagnostic utility for detection of sacroiliitis as compared to the STIR sequence [29]. Although sensitivity for SpA was comparable at 65.7 and 62.9% for the STIR and T1WGd sequences, respectively, 24 and 13% were considered inconclusive, while disease was ruled out in 34 and 47 patients by STIR and T1WGd, respectively. Although the authors concluded that T1WGd had superior diagnostic capacity, this was a retrospective rather than a prospective inception cohort study, and the indication for performing the MRI was left to the discretion of the clinician. Because this may introduce significant bias, further comparative study is necessary in early inception SpA cohorts because contrast enhancement doubles the time required for the patient to lie still in the magnet as well as the costs of the procedure.

A study comparing STIR and gadolinium-enhanced T1W sequences to detect active bone marrow lesions in the SIJ of 40 SpA patients fulfilling the ESSG criteria (27 patients met the modified New York criteria) concluded that both sequences performed nearly equally well [30]. A previous report in 2005 did not show an advantage of contrast-enhanced T1W sequence over STIR sequence alone to detect spinal inflammation in 38 patients with AS [31].

Erosion Bone erosion has been defined as full-thickness loss of the dark appearance of either iliac or sacral cortical bone of the SIJ with loss of the adjacent marrow signal on T1SE images [32].

It has been suggested that so-called cartilage sequences, such as T2W gradient echo or fat-saturated T1W (T1W FS), may facilitate reliable detection of erosions. These directly demonstrate cartilage as a thin zone of intermediate to high signal intensity with an adjacent low signal intensity cortex and a sharply defined bone margin. Erosions are identified as high or intermediate signal defects in the hypointense cortical bone on these sequences. One study used both T1W and T1FS to identify erosions in the SIJ and showed good reliability for an erosion score based on the extent of involvement of the joint surface, although this study did not directly compare these two sequences as regards reliability of detection or diagnostic utility [32]. A recent report compared T1W FS with spin-echo, three-dimensional-fast low angle shot (3D-FLASH), and three-dimensional-double excitation in the steady-state (3D-DESS) sequences in a retrospective analysis of scans from 30 patients with suspected sacroiliitis and 9 healthy controls [33]. These sequences provide higher resolution, greater contrast, and lower partial volume effects in the assessment of the cartilage. A similar number of patients demonstrated bone and cartilage erosions for each of the sequences,

although erosion scores for bone and cartilage based on extent of involvement were significantly higher in 3D-DESS and 3D-FLASH than T1W FS images. The superiority of these sequences over T1W images in the reliable detection of SIJ erosions and their contribution to diagnostic utility requires further study.

Fat infiltration Fat infiltration is evident as bright signal on T1W scans and is often seen in healthy individuals in the SIJ. The fat infiltration observed in SpA patients often occurs adjacent to subchondral bone, may have a distinct border, and is seen in areas of ankylosis and adjacent to other lesions such as edema and sclerosis. It likely indicates prior inflammation though this has not been proven in prospective studies. It is unknown which, if any, of these characteristics contributes to diagnostic utility. A preliminary report from a controlled analysis of 64 individuals concluded that fat infiltration in the SIJ per se has high sensitivity but low specificity for SpA and that its diagnostic utility primarily reflected the presence of associated abnormalities, especially erosions [34].

Diagnostic utility of MRI in preradiographic sacroiliitis

The few studies that were reported over a decade ago demonstrated that MRI had sensitivity and specificity in the range of 54–95% and 83–100%, respectively, but most studies employed gadolinium enhancement with dynamic imaging and lacked age- and sex-matched controls [35–39]. This approach is not used in clinical practice because it is costly, requires prolonged scanning times, and is unreliable. The sum of this data has been incorporated into diagnostic algorithms where the presence of a positive MRI has been assigned a likelihood ratio (LR) of 9 for a diagnosis of SpA [40].

The necessity for standardization of methodology as an approach to knowledge transfer was elaborated in two recent reports by the MORPHO International MRI Group, which aimed at assessing diagnostic utility of MRI by sequences commonly used in clinical practice. MRI scans were assessed from patients with AS meeting modified New York criteria as well as patients with preradiographic SpA [41, 42]. In addition, scans were assessed from age- and sex-matched controls that included healthy individuals as well as those diagnosed with mechanical causes of back pain. The methodological approach was unique in not only implementing standardized definitions of active inflammatory and structural lesions of the SIJ but also a customized online data entry module based on a standardized approach to recording abnormalities in the SIJ (available at www.arthritisimaging.ca). The latter derived from the method developed by the Spondyloarthritis Research Consortium of Canada (SPARCC) for scoring inflammatory lesions in the SIJ [43]. This is based on the division of each SIJ into quadrants and then the assessment of active and structural lesions on a dichotomous basis in all SIJ quadrants of each semicoronal slice. This method has been standardized to assess tilted coronal slices from anterior to posterior, and such methodological details have been incorporated into an online training module that has been validated for reliability and sensitivity to change [44].

When readers were trained and calibrated to assess SIJ scans and record lesions in this manner, much greater diagnostic utility was evident than reported in earlier studies. In patients without radiographic sacroiliitis, mean sensitivity and specificity of MRI amongst five readers for the clinical diagnosis of SpA made by a rheumatologist was 51 and 97%, respectively (positive LR=26.0, negative LR=0.5). Diagnostic utility based solely on detection of BME as defined in the ASAS proposal enhanced sensitivity to 67% but reduced specificity to 88%. This was because a single BME lesion in the SIJ was observed in up to 27% of controls, and BME meeting the ASAS proposal for a positive MRI was recorded concordantly in 23% of mechanical back pain patients and 7% of healthy controls. On the other hand, erosions were recorded concordantly in only 4% of mechanical back pain patients and 2% of healthy controls, and so the inclusion of erosions in addition to BME further enhanced sensitivity to 81% but without changing specificity. Erosions were detected in half of the preradiographic SpA patients, which demonstrates that structural damage of the SIJ starts early in the disease course and contributes substantially to diagnostic utility (Fig. 1).

In a second report from the MORPHO group [42], the authors demonstrated that rheumatologists primarily base diagnostic decisions on the finding of BME on the STIR sequence, while experienced radiologists base decisions on information available from both the T1W and STIR sequences, emphasizing the importance of structural lesions. Moreover, diagnostic utility is enhanced when rheumatologist readers are trained to specifically recognize abnormalities on T1W MRI. This is not surprising because abnormalities may often be subtle on one sequence, and the combined information from both sequences may enhance confidence in diagnostic decision making. This observation is also important in pointing to a major unmet need in the continuing education of rheumatologists to achieve an informed dialogue with the radiologist.

MRI for recognition of spinal inflammation

A set of definitions for active and structural lesions in the central, lateral, and posterior compartment of the spine has been reported by the Canada-Denmark MRI International Working Group, and reference images depicting these

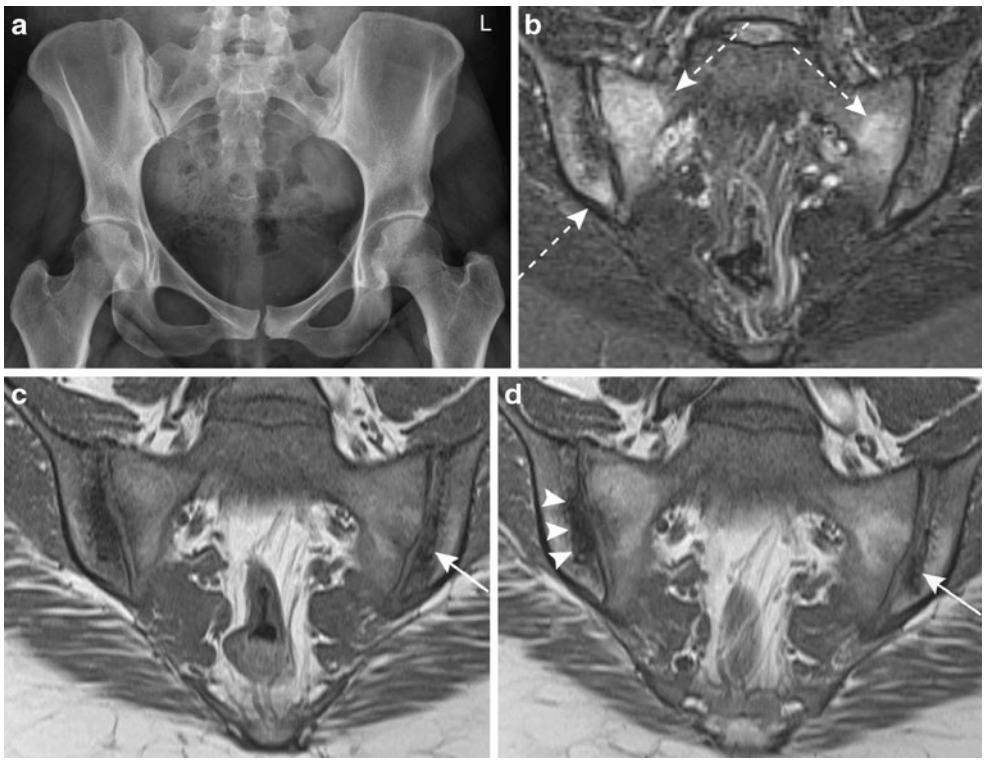

Fig. 1 MRI to confirm a diagnosis of preradiographic spondyloarthritis. A 27-year-old, HLA-B27-negative female patient with inflammatory back pain since 19 months. **a** Pelvic radiograph. The radiographic modified New York criteria are not met. **b** MRI of the sacroiliac joints, STIR sequence. Bone marrow edema shows in the sacral portion of both sacroiliac joints and in the right distal ilium (*broken arrows*). **c** MRI of the sacroiliac joints, T1SE sequence. A small erosion is seen in the distal iliac part of the left sacroiliac joint (*solid arrow*). **d** MRI of the sacroiliac joints 9 months later, T1SE sequence. The erosive process in the distal iliac portion of the left sacroiliac joint is demarcated more clearly (*solid arrow*). The right iliac joint part shows decreased signal intensity with small bright areas (*arrowheads*). This may represent bone sclerosis with areas of fat infiltration or metaplastic tissue. The overlaying cortical bone seems preserved

lesions are available at www.arthritisdoctor.ca [45, 46]. Good to very good interobserver reliability was reported for most of these lesion definitions [47, 48].

One study of WBMRI that included patients with preradiographic SpA and age- and sex-matched controls assessed the diagnostic utility of active spinal inflammatory lesions and showed that the presence of two or more vertebral corner BME lesions had optimal diagnostic utility for SpA (sensitivity 69% and specificity 94%, respectively), especially when located in the thoracic spine [49]. A single vertebral corner BME lesion was observed in up to 26% of healthy controls aged 45 years or less, which is a relevant finding for routine practice to avoid misclassification of healthy individuals as having SpA on the basis of an isolated or doubtful corner inflammatory lesion, particularly if seen in the vicinity of a degenerating disc. Another study focused on the diagnostic utility of vertebral corner BME lesions and of vertebral corner fat lesions separately and concluded that a cut-off of three or more BME lesions and of five or more fat lesions provided optimal diagnostic utility [50, 51]. However, the heterogeneous control group was not age- and sex-matched, the patients had long-standing AS, the influence of spinal location of lesions on diagnostic utility was not assessed and the study design was retrospective. There is a need for more data from systematic studies in a younger population with SpA and age- and sex-matched controls before conclusions on the diagnostic utility of structural spinal lesions can be drawn.

Routine scanning protocols of the spine may not include the lateral segments of the thoracic spine where lesions may be observed at sites such as the costo-vertebral and costo-transverse joints. This is particularly relevant in the presence of even a slight degree of scoliosis, which occurs in about 70% of individuals. When scanning the spine of a patient suspected as having SpA, the number of sagittal slices should be increased to ensure that also the lateral spinal segments are depicted. A systematic analysis in patients with established AS showed that inflammatory lesions were more frequent in lateral versus central segments in the thoracic spine [52]. In one study where the diagnostic utility of active spinal lesions was assessed in early SpA, the presence of active lesions in the lateral segments had very high specificity for SpA but lacked sensitivity [49]. Furthermore a recent study demonstrated

inflammatory lesions also in the posterior spinal elements in a majority of AS patients indicating that scrutiny of posterior spinal structures is essential [53].

During the last few years, multichannel and multicoil technology has been introduced into clinical MR scanners. This whole body (WB) MRI method, which provides comprehensive assessment of systemic disorders, allows the scanning of the SIJ, the entire spine, the anterior chest wall, and the shoulder and pelvic girdle within 30 min without repositioning the patient. Scanning the entire spine in one single examination is more convenient for the patient and less time consuming than separate imaging of the upper and lower halves of the spine by conventional MRI. Imaging of the lower extremities is an additional option that may be relevant for some patients with concomitant peripheral enthesitis, but this has to be weighed against an additional examination time of 20 min. WB MRI of the SIJ and spine has been shown to correlate well and demonstrate comparable reliability to conventional MRI for the detection of active inflammatory lesions in patients with established AS [54, 55]. However, it depicts the SIJ in the coronal plane rather than the tilted coronal plane used in conventional MRI so that the images do not focus on the cartilaginous portion of the joint. It therefore requires further assessment of diagnostic utility compared to conventional imaging in early SpA.

MRI to assess patients with established axial SpA unresponsive to standard treatment or to monitor response to therapy

Patients with established axial SpA may have both inflammatory and mechanical sources of back pain, and it may be difficult to distinguish between these on clinical grounds. In this setting, MRI may be useful to confirm active inflammatory features of SpA and as an objective measure of disease activity before initiating long-term treatment with expensive TNFα inhibitors. There is evidence that widespread inflammation in the spine displayed by MRI may be predictive of a favorable clinical response to anti-TNFα treatment [56]. Response to treatment with anti-TNFα agents may be even more pronounced in very early disease that is detected only by MRI than in patients with established radiographic disease [21, 22]. Several scoring systems to assess SIJ and spinal inflammation have been developed for clinical research to objectively monitor response to treatment. As an example, the SPARCC indices were used to assess disease activity in both the SIJ and spine in a recent randomized controlled trial of adalimumab in active AS. They were shown to be reliable and highly discriminatory between treatment groups [27]. Persisting back pain in AS patients despite anti-TNFα treatment may be due to physical deconditioning after longstanding disease or unrelated mechanical causes and not attributable to failure of the biologic agent. An MRI documenting an improvement in axial inflammation may influence decision making towards physiotherapy rather than switching to another anti-TNFα agent.

A combination of MR and high resolution CT with multiplanar reconstruction showed the best sensitivity to detect transspinal fractures in an ankylosed spine [57, 58] (Fig. 2). These serious fractures through intervertebral syndesmophytes, the former disc, and the posterior spinal elements carry a substantial risk of spinal cord injury [59] and are very difficult to locate by standard radiography in most instances.

Emerging role of MRI to predict spinal ossification

Three recent studies concluded that inflammatory spinal lesions detected by MRI are predictive of new syndesmophytes as shown on spinal radiographs 24 months later, although the association with progression differed among studies [60–62]. New syndesmophytes developed significantly more frequently in vertebral corners with inflammation than in those without inflammation seen on baseline MRI. Interestingly, vertebral corner inflammation that resolved upon treatment with anti-TNFα agents was more strongly associated with new syndesmophyte formation [62]. However, vertebral corners that appeared normal on MRI also developed new bone formation. Further research in larger cohorts is needed to determine the prognostic significance of spinal inflammation on MRI and whether progression can be modified by treatment with biologics, especially if therapy starts early in the disease course.

MRI in daily routine for patients suspected to have axial SpA

Patients presenting with clinical features of SpA with equivocal radiographs should be further investigated using T1W and STIR MRI of the SIJ scanned in the tilted coronal orientation as the principal diagnostic tool, especially if they are B27-positive [63]. There are presently no data supporting the routine evaluation of the spine in addition to the SIJ in the absence of symptoms in the spine and/or chest wall. In that setting the radiologist should be alerted to the requirement for an imaging protocol that ensures visualization of lateral segments (available at www.arthritisdoctor.ca). The finding of unequivocal BME and erosions in the SIJ carries a high probability for SpA. In addition, the presence of active spinal inflammatory lesions, especially in the thoracic spine and in the lateral segments, substantially increases the likelihood of SpA.

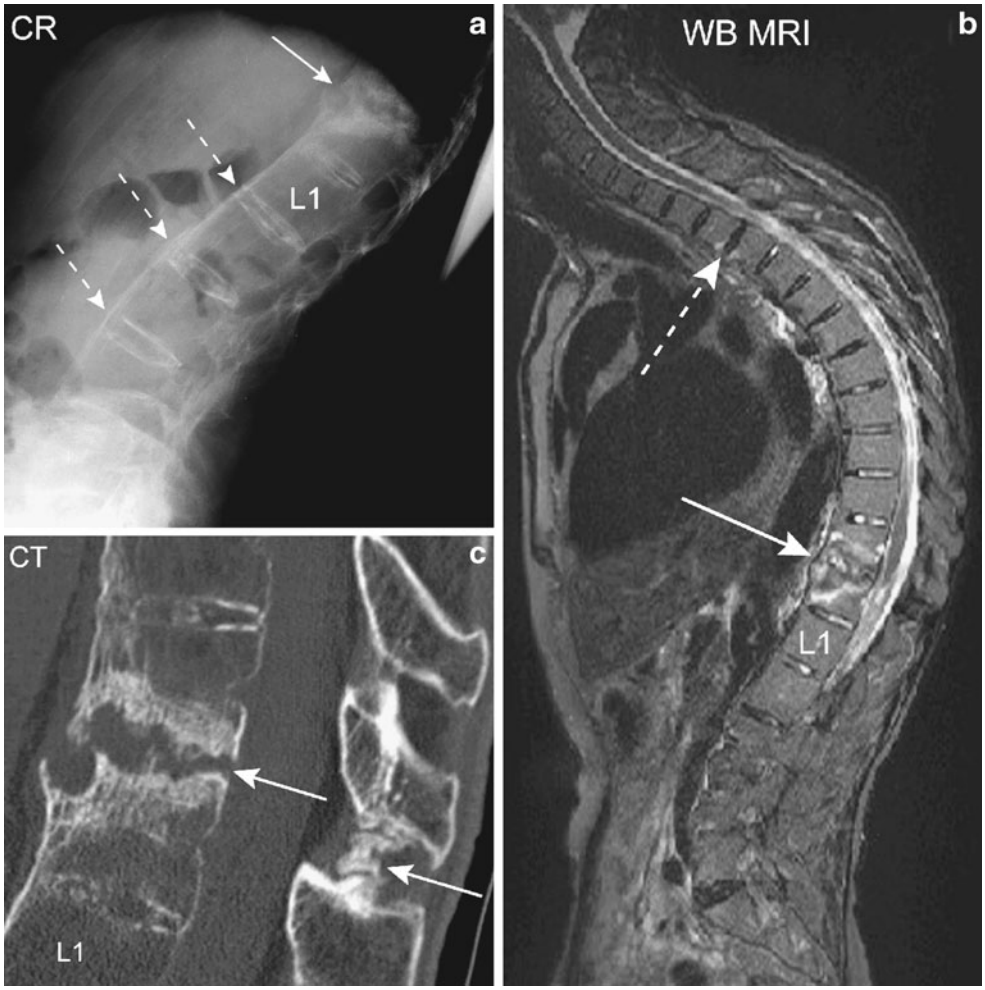

Fig. 2 Transspinal fracture in a patient with longstanding ankylosing spondylitis and fusion of the thoracolumbar segment. A 57-year-old male patient with HLA-B27-positive ankylosing spondylitis. The thoracolumbar spine was completely ankylosed after a disease duration of 32 years. The patient complained about increasing back pain since 3 years without recalling an initiating event. The reason for referring the patient was the question whether TNFα-inhibitor therapy should be started due to persistent flare of ankylosing spondylitis. **a** Conventional radiography of the thoracolumbar spine. Syndesmophyte bridging of all lumbar levels (*broken arrows*). Advanced degenerative bony changes on level Th 11 / Th 12 (*solid arrow*). **b** Whole body MRI of the spine, STIR sequence. Active inflammation with bone marrow edema in adjacent anterior vertebral corners Th 2 and Th 3 (*broken arrow*). Polymorph increased signal intensity on level Th 11 / Th 12 (*solid arrow*). **c** CT of the thoracolumbar spine. Old transspinal fracture through syndesmophytes, vertebral disc, and posterior elements of the spine (*solid arrows*) with marked secondary degenerative changes

MRI in rheumatoid arthritis

The spectrum of MRI lesions in RA and their histopathologic correlation

MRI allows assessment of all the structures involved in RA, i.e., synovial membrane, tendons and tendon sheaths, intra- and extraarticular fluid collections, cartilage, bone, and ligaments. MRI has been shown to be more sensitive than clinical examination and radiographs for detection of inflammatory and destructive joint changes in early RA (Fig. 3). MRI and histopathological signs of synovial inflammation are closely correlated [64–66]; in a study of metacarpophalangeal (MCP) joints in patients with early and with established RA, miniarthroscopy confirmed the presence of bone pathology in all joints with MRI bone erosions and histologic and macroscopic synovitis in all joints with MRI synovitis [67]. MRI BME represents inflammatory infiltrates in the bone marrow, i.e., osteitis, as demonstrated by comparison with histological samples obtained at surgery in RA patients [3, 4]. Whereas erosions reflect bone damage that has already occurred, BME appears to represent the link between joint inflammation and bone destruction.

A high level of agreement for detection of bone erosions in wrist and MCP joints in RA patients (concordance at 77–90% of sites) between MRI and computed tomography (CT), the gold standard reference for detection of bony

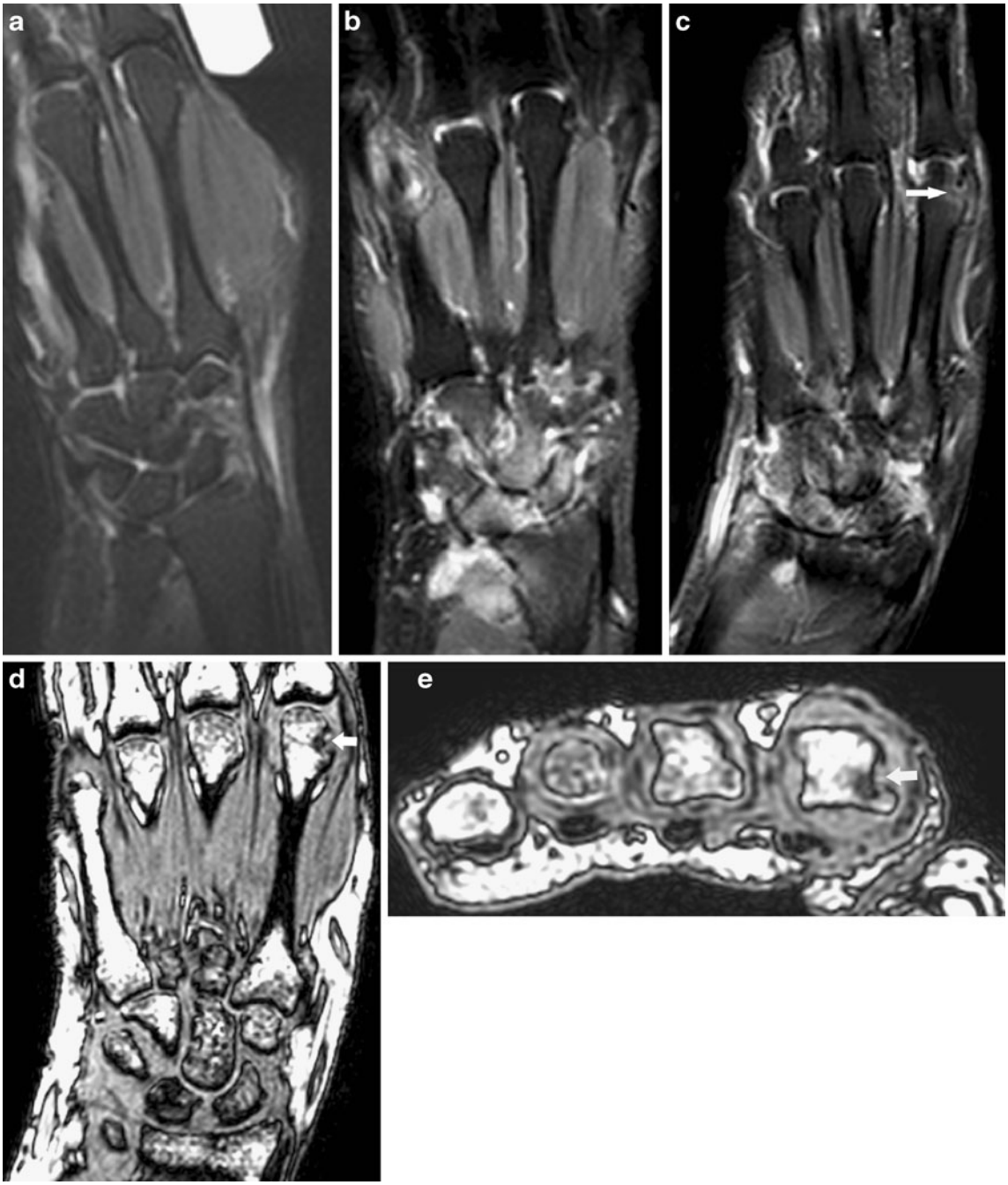

Fig. 3 MRI findings in patients with early rheumatoid arthritis. **a**–**c** Coronal STIR sequence of the wrist and metacarpophalangeal joints of three different patients with early rheumatoid arthritis. **a** shows no bone marrow edema, **b** bone marrow edema (high signal intensity) in many wrist bones, but not in the metacarpophalangeal joints, whereas **c** shows bone marrow edema in various wrist bones as well as in the second metacarpophalangeal joint (*arrow*). **d** Coronal T1SE sequence and **e** axial T1SE sequence of the same patient as illustrated in **c**. These images show bone erosion, confirmed in two planes, in the second metacarpal head (*arrow*). Courtesy Susanne J. Pedersen, MD, Copenhagen

destruction, documents that MRI erosions represent true bone damage [68–71].

The majority of MRI studies in RA investigated knee, wrist, or finger joints. Reports on other peripheral joints are few and not essentially different. Although only one formal comparison with follow-up of other joints exists, MRI of unilateral MCP and wrist joints are most commonly recommended for MRI follow-up of RA patients, whereas MRI of other joints is only to be obtained if specifically clinically indicated.

Compared with radiography, MRI offers clear advantages but also has disadvantages due to increased cost and

lower availability. However, MRI costs represent only a fraction of the total expense incurred in the management of RA patients when the costs of biological RA treatment or the indirect costs of sick leave/early retirement are considered. Dedicated extremity MRI units are increasingly used and offer improved patient comfort at lower cost than conventional MRI units [72–80]. The better of the dedicated low-field MRI units provide similar information on erosions and synovitis as conventional high-field MRI devices [75, 76]. However, performance characteristics of different machines differ widely [81], emphasizing the need for careful testing of the individual machines.

Optimal MRI assessment of synovitis requires use of intravenous gadolinium contrast media, while assessment of BME and erosion does not [82]. Thus, for assessment of synovitis, BME, and erosions, a pre- and post-contrast T1-weighted sequence in two planes plus a T2-weighted fat-saturated or short tau inversion recovery (STIR) sequence is recommended [83] (Fig. 4).

Monitoring disease activity and structural damage

To be valuable for monitoring joint inflammation and destruction, a measure must be reproducible and sensitive to change [84]. MRI allows quantitative measurement of the early contrast augmentation ("enhancement") rate after intravenous injection of gadolinium, which reflects the degree of synovitis, the measurement of synovial volume, as well as less detailed (qualitative: presence/absence; semiquantitative: scoring) evaluation of synovitis and bone erosions. In observational studies and randomized clinical trials, semiquantitative scoring has been the most frequently used approach. The OMERACT (Outcome Measures in Rheumatology) RA MRI scoring system (RAMRIS) involves semiquantitative assessment of synovitis, bone erosions, and BME in RA finger and wrist joints [83]. This method was developed and validated through iterative multicenter studies under OMERACT and EULAR banners [83, 85–88]. Consensus MRI definitions of important joint pathologies and a "core set" of basic MRI sequences were also suggested [83].

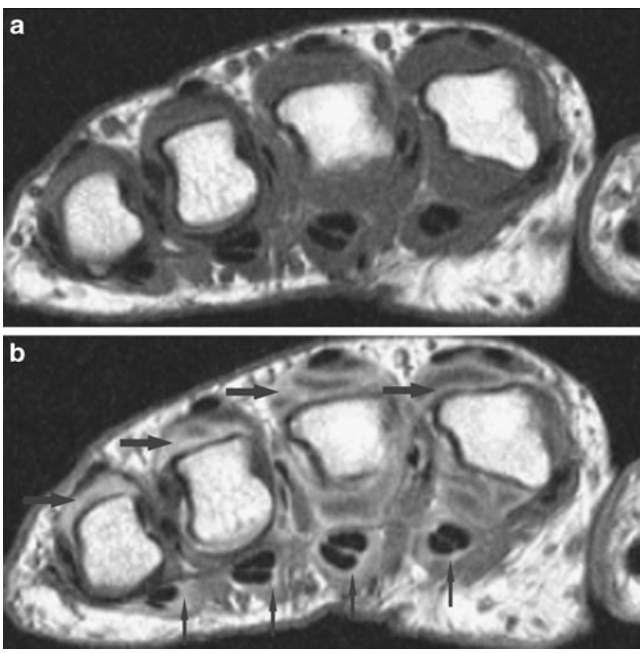

Fig. 4 MRI to detect (teno-)synovitis in a patient with early rheumatoid arthritis. Axial T1SE sequence of the second to fifth metacarpophalangeal joints in a patient with early rheumatoid arthritis before (**a**) and after (**b**) intravenous contrast agent injection. Severe synovitis is seen in all metacarpophalangeal joints (*horizontal arrows*). Flexor tendon tenosynovitis is also noted, particularly at the second and third finger (*vertical arrows*). Courtesy Susanne J. Pedersen, MD, Copenhagen

The OMERACT erosion scores are closely correlated with erosion volumes estimated by MRI and CT [69, 70]. Using the RAMRIS, very good intrareader reliability, good interreader reliability, and a high level of sensitivity to change have been reported, demonstrating that the OMERACT RAMRIS system, after proper training and calibration of readers, is suitable for monitoring joint inflammation and destruction in RA [89, 90]. A EULAR-OMERACT RA MRI reference image atlas has been developed, providing an easy-to-use tool for standardized RAMRIS scoring of MR images for RA activity and damage by comparison with reference images [91]. Scoring systems for tenosynovitis [92] and joint space narrowing [93] may be used in addition to the OMERACT scoring system.

The OMERACT synovitis score is sensitive to change over weeks as well as months, and MRI, as assessed according to the OMERACT system, is increasingly used in trials of biologic agents [71, 94–100]. Haavardsholm et al. reported that a combined score of synovitis, tenosynovitis, and BME was more sensitive than conventional biomarkers and clinical measures as well as the individual MRI parameters [101].

Quantitative methods of synovitis (synovial membrane volumes and post-contrast enhancement rates), which in knee joints have been shown to be closely related with histopathological synovitis [64–66] and to be sensitive to change [65, 102], have only been used sparsely in clinical trials, probably due to them being laborious (particularly the measurement of synovial volume) and/or having limited reproducibility with multicenter use (particularly early enhancement rates by dynamic MRI). However, recent software improvements, providing more automated methods, potentially increase assessment speed and reproducibility [103–107]. This encourages the reappraisal of the usefulness of such quantitative methods.

Several studies have demonstrated that MRI is more sensitive than radiography for monitoring erosive progres-

sion in individual joint regions [108–111]. RAMRIS scoring of unilateral wrist and MCP joints is more sensitive to change than Sharp/van der Heijde radiography scoring of bilateral hands, wrist joints, and forefeet [112].

The superior sensitivity to change and discriminatory ability of MRI compared to radiography has been demonstrated in randomized controlled clinical trials (RCTs) [94, 113, 114]. Quinn et al. demonstrated a significantly lower erosion progression rate by MRI, but not by the Sharp/van der Heijde radiography method, in 12 early RA patients treated with methotrexate plus infliximab compared to 12 patients receiving methotrexate alone [94]. This was the first study to verify that the use of MRI in RCTs allows shorter observation periods and/or fewer patients for discriminating between different therapies concerning reduction of structural joint damage. This has been confirmed by subsequent studies [113, 115]. A recent large study of 318 methotrexate-naïve patients demonstrated that inhibition of erosive progression by biological therapy compared to placebo can be demonstrated by MRI using half the patients and half the follow-up time of radiography [116]. These latter data reinforce the superior sensitivity of MRI as compared to radiography assessment for measuring change owing to erosive damage.

Diagnostic utility of MRI in undifferentiated peripheral arthritis

A number of relatively small studies (≤50 patients per study) provided ambiguous results regarding the differential diagnostic value of MRI [117–121]. Recently, data from two large follow-up studies of undifferentiated arthritis have allowed a more thorough investigation of the utility of MRI to diagnose RA [122, 123]. Tamai et al. investigated 129 patients with nonclassifiable arthritis despite routine examination, including C-reactive protein and biochemical tests, and developed a prediction model containing anti-cyclic citrullinated peptide (anti-CCP) and/or IgM rheumatoid factors (RF), MRI-proven symmetric synovitis, and MRI-proven BME and/or bone erosion. Of patients positive for more than two of these variables, 71.3% developed RA within 1 year (specificity 75.9% and sensitivity 68.0%, respectively). Presence of BME had a positive predictive value of 86.1% for subsequent development of RA [122].

In a study of 116 patients with early undifferentiated arthritis, Duer-Jensen et al. documented that MRI BME in metatarsophalangeal (MTP) and wrist joints is an independent predictor of future RA in patients with early undifferentiated arthritis. A prediction model, including clinical hand arthritis, morning stiffness, positive RF, and MRI BME score in MTP and wrist joints correctly identified the development of RA or non-RA in 82% of patients [123].

Two systematic literature reviews have been published recently [124, 125], but too early to include the study by Duer-Jensen et al. [123]. The former study states that widespread use of MRI for diagnosing RA is scientifically not justified, because the sensitivity and specificity of MRI findings for RA differ substantially among studies, depending upon the criteria applied. However, the authors emphasize that the diagnostic performance of MRI was better when lower quality studies or studies in RA patients with longer disease duration were excluded [124]. A systematic literature review by Machado et al. concludes that BME and combined synovitis and erosion pattern seem useful in predicting development of RA from undifferentiated peripheral arthritis. The difference in conclusions seems partly explained by whether poor-quality studies are included [124] or not included [125] in the systematic literature review.

A new role for MRI has recently been added. Due to the limited sensitivity of the ACR 1987 classification criteria for RA in early disease, new criteria have been developed and recently reported, the ACR/EULAR 2010 criteria [12]. Classification as definite RA is based on the presence of definite clinical synovitis (swelling at clinical examination) in one or more joints, absence of an alternative diagnosis that explains the synovitis, and achievement of a total score ≥6 (range 0–10) from the individual scores in four domains: number/site of involved joints (range 0–5), serologic abnormality (range 0–3), elevated acute-phase response (range 0–1), and symptom duration (range 0–1) [12]. MRI and ultrasound may be used to detect joint inflammation and to count joints in the "joint involvement" domain of the new RA classification criteria [13, 14].

In summary, two large studies document an independent predictive value of MRI for the development of RA, implying a diagnostic utility when used in combination with clinical parameters. Furthermore, MRI and ultrasound have an important role in the recent ACR/EULAR 2010 classification criteria for RA. Thus, MRI could be used in routine clinical practice for confirming an early diagnosis of RA made on clinical grounds.

Prognostication

Various studies have reported that MRI pathology (synovitis, bone erosions or, most often, BME) of the wrist and MCP joints at disease onset in early RA predicts radiographic erosions [108, 126–134]. Some looked at the short-term predictive value of MRI after 1 year [108, 126, 128, 130, 131], whereas other studies had 2 [128, 132], 3 [134], 5 [133], 6 [127], or 10 years [129] of follow-up. All studies found MRI to be a highly significant predictor of radiographic erosions.

With the exception of two early RA cohorts [131, 132], all MRI studies in RA did not include anti-CCP or take into

account other potential prognostic markers such as smoking or shared epitope carriage. Haavardsholm et al. [131] reported BME and male gender (but not anti-CCP) to be independent predictors of radiographic progression after 1 year in a single-center cohort of 84 patients treated according to standard clinical practice. A study by Hetland et al. was the first clinical trial with a standardized treatment protocol that investigated the predictive value of a variety of potential prognostic markers including both imaging modalities MRI and conventional radiography, immunologic (anti-CCP, IgM RF, and IgA RF), environmental (smoking, educational level), genetic (shared epitope), and disease activity markers [132]. The main finding was that in this comprehensive model, MRI BME at presentation was the strongest independent predictor of radiographic progression 2 years later in early RA patients as determined in both multivariate linear and logistic regression analyses. Three-year [135] and 5-year [133] follow-up studies in the two respective cohorts have documented that MRI BME is also a predictor of long-term radiographic progression. A recent systematic literature review, not incorporating the latest data, reports that when studies of all qualities are included in the analysis, the sensitivity and specificity of MRI findings for predicting erosive progression are so variable that the authors do not recommend clinical use of MRI for this purpose. However, they also note that BME was predictive of erosions if only the highest quality data were included in the analysis [124].

A relation between baseline MRI findings and long-term functional disability has only been documented in one study [136]. Data from the same cohort revealed that extensive MRI BME and erosions at the wrist in early rheumatoid arthritis predicted tendon dysfunction and impaired hand function [137]. Furthermore, a high baseline MRI tendinopathy score was predictive of tendon rupture at 6 years (odds ratio 1.52) [138]. Further studies are required to determine the clinical relevance of these findings.

Another issue of high clinical importance is whether MRI is useful in patients in clinical remission to predict the disease course. Residual synovitis on MRI is frequent in patients in clinical remission [139, 140]. The impact of subclinical imaging findings has been studied by Brown and coworkers [141]. Seventeen controls and 102 RA patients on conventional treatment judged to be in remission by their treating rheumatologists underwent clinical, laboratory, functional, and quality of life assessments during a 12-month period. Radiographs of hands and feet, and MRI and ultrasound of unilateral hand and wrist were performed at baseline and after 12 months. Despite clinical remission, 19% of patients experienced progression in radiographic joint damage during the study period. Baseline ultrasound synovial hypertrophy, ultrasound power Doppler signal and MRI synovitis scores in individual joints were significantly associated with progressive radiographic damage. The study encourages further exploration of MRI and ultrasound for predicting the disease course and for evaluating disease status, including defining what constitutes true disease remission.

MRI in osteoarthritis

MRI has become the imaging modality of choice to assess active and structural joint lesions in OA. The main focus of interest for MRI in OA is clinical research whereas routine use of MRI for the evaluation of patients with OA in daily practice is not justified by currently available data [15]. In clinical practice, MRI for OA may be ordered to exclude relevant conditions in the differential diagnosis such as avascular osteonecrosis or perhaps to assess the extent of structural lesions prior to joint replacement surgery. An emerging indication for daily routine is preradiographic OA where early subtle joint pathology can be detected by MRI long before structural changes are seen on radiography. Research using MRI in OA has focused on the knee joint because this large joint allows good discrimination of anatomical structures, has a relatively thick articular cartilage compared to other joints, and because the prevalence of knee OA in the population is high [142].

Semiquantitative multi-feature whole-joint assessment systems in knee OA

Whole joint MRI evaluation methods reflect the concept of knee OA as a multifactorial disorder of the whole synovial joint organ resulting in changes in structure and function. MRI captures many features of soft tissue, cartilage, and bone that are relevant to clinical manifestations, functional impairment, or pathophysiology of OA. These articular features include bone marrow lesions (BML), joint effusion, synovitis, and bursitis that represent active lesions as well as structural features such as articular cartilage degeneration, subchondral bone attrition and cysts, osteophytes, meniscal, cruciate and collateral ligament integrity, and intraarticular loose bodies.

Several semiquantitative whole joint scoring systems have been proposed: the Whole Organ Magnetic Resonance Imaging Score (WORMS) [143], the Knee Osteoarthritis Scoring System (KOSS) [144], the Boston-Leeds Osteoarthritis Knee Score (BLOKS) [145], and the system proposed by Biswal and colleagues [146]. The scoring modules apply different subregional divisions for the femur and the tibial plateau. None of them uses contrast-enhanced MRI. To date no single whole-joint scoring method has gained widespread acceptance as a standard reference for clinical research. A comparison between these scoring

systems regarding construct validity is limited by the absence of histopathological data while assessment of discriminatory capacity is limited by the absence of therapeutic modalities that have major treatment effects.

In a cross-sectional study of 115 knees with radiographic OA at high risk of cartilage loss, the WORMS and BLOKS scoring systems performed similarly for prevalence and severity of cartilage loss, bone marrow lesions, and meniscal damage [147]. A comparison of 1.0 Tesla extremity MRI versus large-bore 1.5 Tesla MRI using the WORMS system showed moderate (weighted kappa for effusion and synovitis 0.53 and 0.54, respectively) to substantial agreement (0.75 and 0.71 for cartilage and BME, respectively) between the two techniques [148].

Quantitative measurement methods have also been developed to assess cartilage integrity in knee OA. These systems are less observer-dependent and may better detect small changes in the cartilage structure over large areas compared to semiquantitative methods. However, quantitative measurement requires specialized software and time-consuming segmentation between different articular structures by trained operators [142].

Bone marrow lesions and synovitis

MRI signs of disease activity such as BML and synovitis/joint effusion are particularly interesting as they are potentially modifiable by treatment [149]. Interventions targeting BML and synovitis may not only result in symptomatic improvement but may have a potential for disease modification as active MRI lesions are associated with both knee pain and progression of structural damage. It is possible that osteochondral fracture and subsequent osteonecrosis may develop in some cases as a consequence of weakening of inflamed bone rather than the inflammation developing as a response to the injury or necrosis.

Bone marrow lesions BML appear on T2-weighted sequences as ill-defined areas of increased signal intensity (Figs. 5 and 6). The pathophysiology of BML is poorly understood. Histology of BML in knee and hip joint tissue removed at total joint replacement surgery in patients with advanced OA showed predominantly nonspecific findings such as bone marrow fibrosis and necrosis or trabecular microfractures, but only sparse interstitial edema [7–10]. These histopathol-

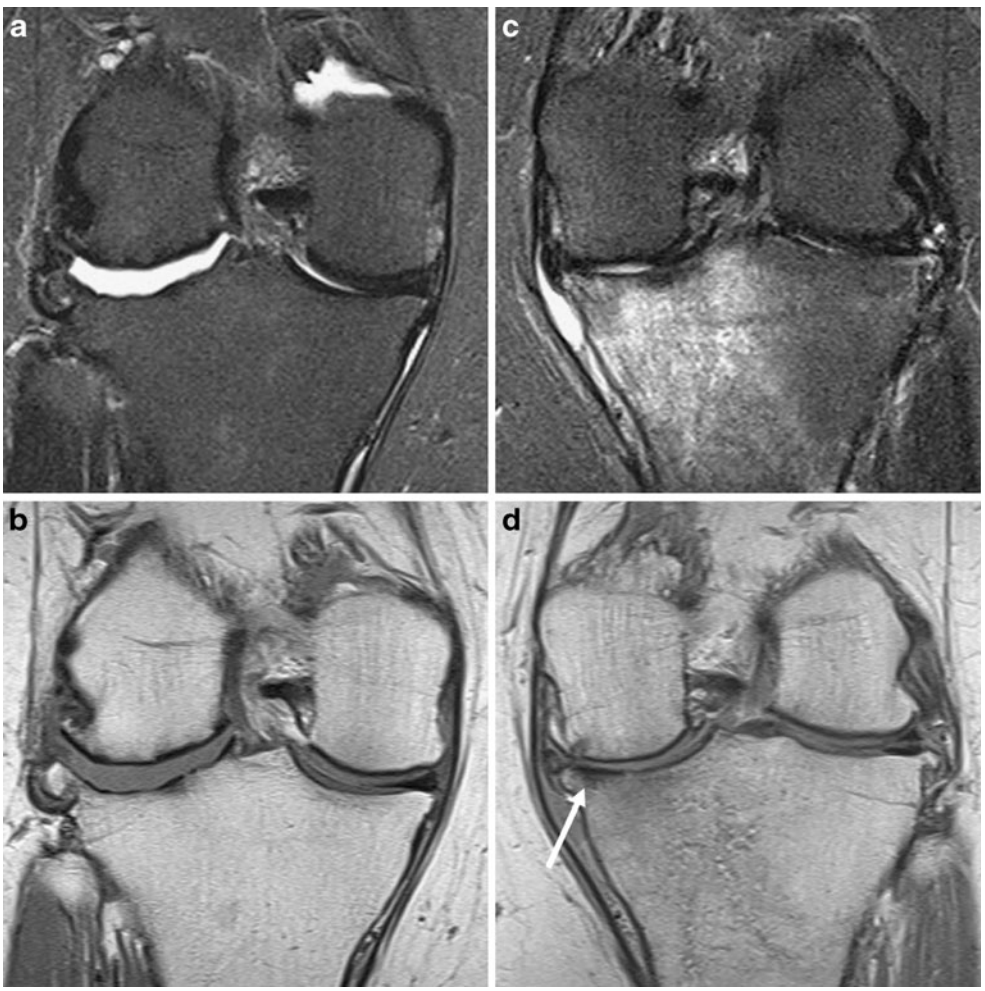

Fig. 5 Discrepancy between severity of hyaline cartilage damage and presence of bone marrow lesions. Bilateral knee MRI (right knee **a** and **b**, left knee **c** and **d**) with short tau inversion recovery (STIR) and proton density (PD) images. A 60-year-old woman with bilateral knee pain and instability. Right knee symptoms have been present for longer, and on the left side, symptoms have deteriorated recently. Bilateral knee osteoarthritis is severe. On the right side (**a** and **b**), this is associated with remodeling of the articular surfaces and subchondral sclerosis. No edema or cyst formation is present. On the left, extensive bone marrow lesion (**c**) is present with a focal area of diminished signal seen adjacent to the tibial plateau (*arrow* in **d**). This presumably represents a sclerotic response to more focal stress/hyaline cartilage damage

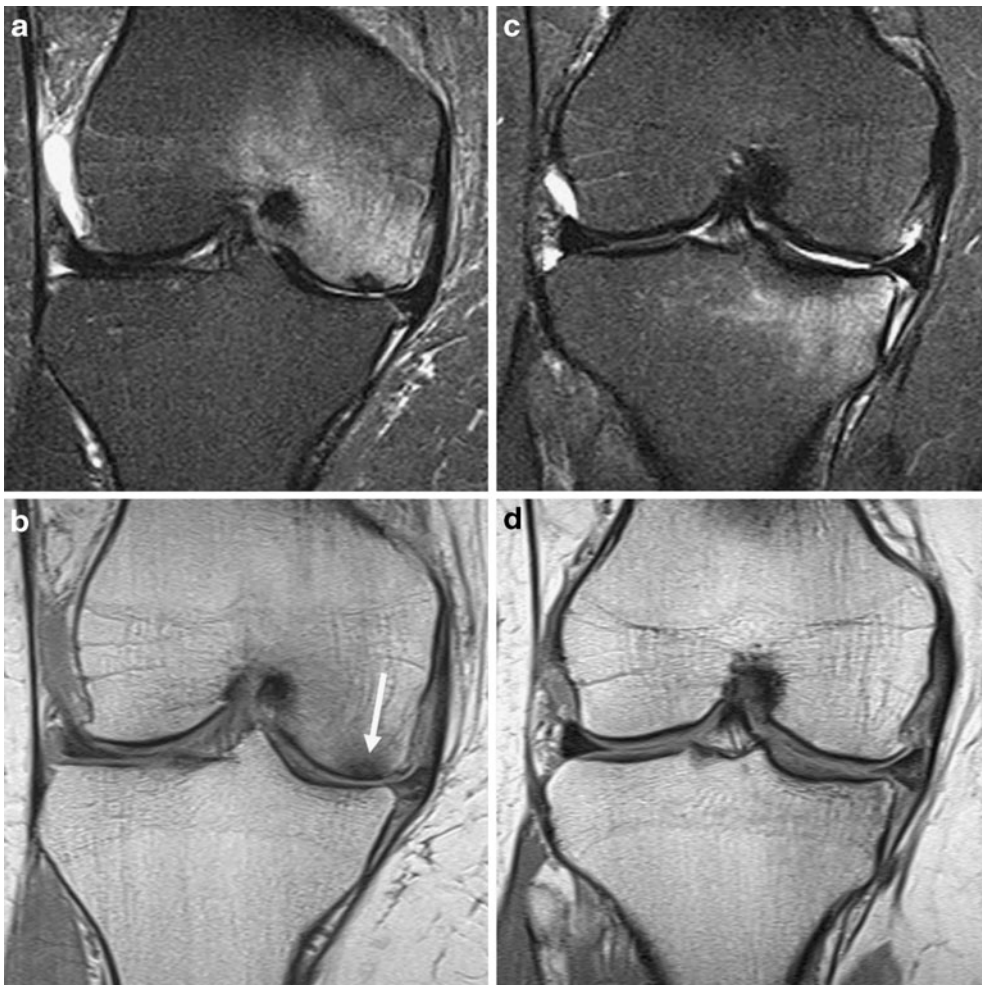

Fig. 6 Unpredictability of presence and distribution of bone marrow lesions in osteoarthritis. Right knee MRI in two patients (patient 1 **a** and **b**; patient 2 **c** and **d**) with STIR and PD images. Two 60-year-old women with right knee pain and instability with recent onset of symptoms with near-normal weight-bearing radiographs 8 weeks previously (preserved joint space with tiny osteophytes only). Both patients had tears of the root attachment of the posterior horn of the medial meniscus (not shown) and some medial extrusion of the body of the meniscus. Cartilage loss is a little worse in the first patient, and an extensive bone marrow lesion in the femoral condyle is associated with a focal area of low signal in the subchondral bone without loss of integrity of the articular contour (*arrow* in **b**). This likely represents occult osteochondral injury without any substantial area of necrosis. The second patient has an extensive bone marrow lesion in the tibial plateau (**c**). Although the association of an overweight middle-aged female with meniscal root or radial tear and rapid deterioration of osteoarthritis is well established, the exact distribution of bone marrow signal change, speed of progression, and the presence of co-existent osteonecrosis are unpredictable

ogy findings in OA suggest that BML seen on MRI reflects metaplastic fibrovascular tissue in the bone marrow together with trabecular remodeling. However, most BML fluctuate in size over time, which may be observed after only a few months suggesting that BML reflect more active histopathological changes than structural remodeling [150–155]. In one of these reports, fluctuations in BML scores over 3 months were positively correlated with changes in urinary C-terminal crosslinking telopeptide of type II collagen, a biomarker reflecting cartilage turnover [150].

A cross-sectional study of patients with knee OA found a strong association between BML and pain [156]. Amongst patients with pain, 77.5% showed BML on MRI, while these lesions were detected in only 30% of patients without pain. In 2007, the same working group reported the results of a 15 month follow-up study [157]. An increase in BML volume was observed in 49.1% of patients with painful knee OA as opposed to only 26.8% of OA patients without knee pain. Among patients with no BML at baseline, the development of new BML was more common in painful knees than in control knees (32.4 versus 10.8%). A recently published self-matched case-control study in patients with knee OA showed that changes in BML extent and synovitis were associated with fluctuations in knee pain; improvement of BML, but not of synovitis or effusion, was associated with a decreased risk of knee pain [158].

However, a recent systematic literature review evaluating the association between active and structural MR findings and pain in patients with knee OA concluded that the level of evidence for a positive association between either BML or synovitis/effusion and pain is only moderate [159]. The odds ratio for having pain when BML was present ranged from 2.0 to 5.0 and for synovitis/effusion from 3.2 to 10.0.

In patients with radiographic knee OA, many studies consistently showed an association of BML with cartilage loss and OA progression [151, 154, 160–163], even in patients with minimal baseline cartilage damage [164]. Absence of BML was associated with a decreased risk of cartilage loss [154]. The risk for structural progression in the medial and lateral compartment was increased more than sixfold when medial or lateral BML were present (adjusted odds ratio 6.5 with medial BME present and 6.1 with lateral BML present) [160]. Varus or valgus limb malalignment is a confounder in the assessment of the relationship between BML and structural progression [151, 160]. A recent report showed that meniscal pathology also increases the risk of incident or enlarging BML over a period of 30 months [165] and may not be an independent predictor of structural progression.

A prospective cohort study in 271 healthy community-based adults with no clinical knee OA showed incident BML developing over the 2 year study period in 14% [153]. Incident BML were associated with knee pain (odds ratio 4.2) and with increased BMI. Of the BML present at baseline, 46% completely resolved. In a prospective cohort of 148 healthy women in middle age with no knee pain and no clinical knee OA, large BML were associated with progression of tibiofemoral cartilage defects [166]. These data suggest that the relationship between BML and cartilage loss is similar in knees with established OA and in knees without clinical knee OA or pain.

Synovitis The optimal MRI evaluation of synovitis in knee OA requires contrast enhancement. Synovial enhancement by the contrast agent provides superior image quality for the assessment of synovial volume and differentiates synovitis from joint effusion by increased vascular perfusion and capillary permeability of the synovium [167]. Synovitis scores obtained by contrast-enhanced MRI showed good correlation with arthroscopic and microscopic synovitis scores [168]. Studies using nonenhanced MRI showed inconsistent results regarding an association between synovitis and knee pain. A recent report showed that synovitis detected by contrast-enhanced MRI had a strong association (adjusted odds ratio 9.2) with at least moderate severity of knee pain as assessed by the Western Ontario and McMaster Osteoarthritis Index pain scale [169]. A comprehensive whole-knee joint synovitis scoring system has been proposed recently, which showed a high reliability based on contrast-enhanced MRI [170]. Interventional studies assessing intraarticular corticosteroids or NSAIDs and paracetamol demonstrated associations between decreased synovitis and reduction of pain in patients with knee OA [171, 172]. Several semiquantitative and quantitative contrast-enhanced MRI assessment systems using different subregional approaches have been proposed to quantify synovitis [65, 167, 173–175].

Future directions

Future research in axial SpA should focus on further prospective assessment of the utility of structural lesions in more diverse settings and larger cohorts of patients suspected of having early SpA. It is also important for clinicians to know to what degree imaging of the spine contributes to diagnostic utility over and above assessment of the SIJ, which might in turn argue in favor of the use of WB MRI over conventional imaging. Finally, it is important to understand the prognostic significance of lesions observed on MRI and to what degree and which features portend an unfavorable radiographic outcome.

In addition to the documented utility for risk stratification for erosive progression in early RA and for early diagnosis of RA, other areas where MRI may be clinically important are emerging. Important research areas include whether adding MRI to routine clinical examination will improve clinical and radiographic outcome in RA patients. In particular, it is important to understand the prognostic significance of MRI findings in those patients achieving clinical remission with respect to the subsequent course of erosive progression, functional impairment, and disease activity. Technical advances, including the possibility of achieving overall assessment of the disease load by WB MRI and the potential clinical and scientific utility of improved cartilage assessment, e.g., by 3 T MRI, should be evaluated.

Research in OA should evaluate treatment interventions targeting BML and synovitis. These MRI signs of disease activity are potentially reversible, and there is some evidence that their improvement may also preserve joint integrity. Before using MRI for OA in daily routine, we need data that address whether a diagnosis of preradiographic OA by MR, which may facilitate early intervention, translates into a more favorable clinical outcome.

MRI is a very promising imaging modality not only for our understanding of the pathophysiology of axial SpA, RA, and OA and for confirming an early diagnosis before radiographic lesions appear, but also for monitoring disease upon treatment due to its noninvasive technique, lack of ionizing radiation, and its superior spatial and contrast resolution of all tissues involved in the disease process.

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