Review

Progress in spondylarthritis

# Spondyloarthritis: lessons from imaging

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## Abstract

The advent of magnetic resonance imaging (MRI) and advanced sonographic techniques has led to a resurgence of interest in the role of imaging in the evaluation and management of spondyloarthritis. Radiography remains the cornerstone of diagnosis although MRI is more sensitive in early stages of the disease. Inflammatory changes in the sacroiliac joints and spine can now be reliably quantified and can also predict the subsequent development of radiographic changes in the corresponding locations. MRI-based scoring systems for inflammation are highly responsive, facilitating proof-of-concept studies of new therapies for spondyloarthritis. Assessment of chronic changes is much less reliable using MRI, while assessment using radiography lacks sensitivity to change. Assessment of disease modification therefore remains a principle challenge in the development of new therapies for ankylosing spondylitis. Ultrasound may be the preferred approach to the assessment of peripheral inflammation, especially enthesitis. Scintigraphy and computed tomography offer few advantages over MRI.

## Introduction

Spondyloarthritis (SpA) is a group of inflammatory disorders that primarily affect the sacroiliac joint (SIJ) structures of the spine, large peripheral joints, and entheses, that are associated with the *HLA-B27* gene. Most clinicians still use imaging primarily to evaluate structural abnormalities in the axial skeleton. Recent advances, however, now permit the object evaluation of inflammation and its sequelae in both the axial and peripheral skeleton. Five principle methods can be used to evaluate patients with SpA: plain radiography, computed tomography (CT), scintigraphy, ultrasound, and magnetic resonance imaging (MRI). The present review will address the key lessons learnt from studies evaluating each of these imaging modalities according to the following questions: What pathological feature is best shown by each method? What does each method tell us about the pathophysiology of disease? How does each method facilitate evaluation of patients presenting early in their disease course? What are the advantages and limitations of outcome assessment tools developed for each method?

Clarifying the answers to these questions constitutes a prerequisite to understanding how each modality may influence diagnostic and therapeutic decisions by the practicing clinician, how each modality may assist the clinician researcher in the assessment of prognostic factors and therapeutic interventions, and how the basic scientist might approach the examination of immunopathological events occurring early in disease.

## Plain radiography

### Radiography of the spine and sacroiliac joints

The cornerstone of diagnostic evaluation and classification of SpA is still plain radiography, even though there is growing recognition that radiographic changes occur late and may be preceded by a lengthy pre-radiographic stage where patients may have symptoms for many years. Radiography primarily detects abnormalities of bone and is particularly useful for evaluating erosions and ankylosis, but it may also detect more diffuse changes such as osteoporosis or sclerosis. The earliest feature of SpA is typically observed in the SIJs and is characterized by loss of distinctness of the subchondral bone in the iliac portion of the joint. Although inflammatory changes are not directly visualized, inflammation within bone marrow is implied when erosion of the calcified bony matrix is visible. A single anteroposterior pelvic radiograph is sufficient for evaluation of the SIJs, as shown in one study of 445 patients with SpA where oblique SIJ views and the anteroposterior pelvic view did not differ significantly regarding sensitivity for the diagnosis of sacroiliitis [1].

AS = ankylosing spondylitis; CT = computed tomography; MRI = magnetic resonance imaging; SASSS = Stoke Ankylosing Spondylitis Spine Score; SIJ = sacroiliac joint; SpA = spondyloarthritis; SPARCC = Spondyloarthritis Research Consortium of Canada; TNF = tumor necrosis factor.

The presence of radiographic sacroiliitis is a principle feature of the modified New York classification criteria for ankylosing spondylitis (AS), but these criteria lack sensitivity for diagnostic purposes [2]. One study of 88 patients with inflammatory back pain but with radiographically normal SIJs showed that only 36% had developed radiographic sacroiliitis after 5 years, and only 59% after 10 years [3]. Another study of 17 patients with inflammatory back pain of 3 to 14 months' duration and normal pelvic X-rays, however, showed that 11 (64.7%) patients had developed radiographic sacroiliitis after 1.5 to 2.5 years [4]. Potential reasons for this discrepancy may reflect differences in patient selection, the subjectivity of assessment of inflammatory back pain, and significant inter-individual variation in the interpretation of radiographic sacroiliitis, which does not improve with systematic training [5].

Plain radiography of the spine may show loss of bone cortex at the corner of the vertebral body, giving the appearance of an erosion, while reparative phenomena include squaring, sclerosis, syndesmophytes, and, ultimately, complete ankylosis. Destructive changes at the vertebral endplate appear radiographically as spondylodiscitis. Facet joint abnormalities are typically seen as joint space narrowing and ankylosis, erosion being much less common. Radiography lacks sensitivity, so that only 5 to 10% of patients with longstanding AS have at least one erosion and only a minority of patients have syndesmophytes extending over multiple vertebrae. Progression of radiographic change is slow and only 40% of patients will demonstrate changes after 2 years, particularly those whose baseline radiographs already show the presence of syndesmophytes [6]. Progression was evident in 44% of patients with syndesmophytes and/or ankylosis at baseline versus 19% of patients without such changes [7]. Spinal mobility measures correlate with radiographic abnormalities, particularly with increasing level of abnormality, although they cannot be used to substitute for radiographs due to low sensitivity and/or specificity [8].

### Radiographic scoring methods for detection of chronic lesions in the spine

Several methods have been described to systematically score abnormalities in the spine. The Bath Ankylosing Spondylitis Radiology Index is a global grading of the lateral cervical spine, the anterior and lateral lumbar spine combined, and the SIJs – with a scoring range from 0 to 12 [9]. The index suffers from ceiling effects, poor reproducibility, and inadequate sensitivity to change, with only 20% of patients demonstrating change after 2 years. The Stoke Ankylosing Spondylitis Spine Score (SASSS) assesses abnormalities in the anterior and posterior corners of each lumbar vertebra [10]. This score also suffers from poor reliability and lack of sensitivity to change. In the modified SASSS, the anterior corners of the cervical and lumbar vertebrae are assessed and the scoring range is 0 to 72. A comparison of these three scoring methods showed that no method reliably detected change over 1 year and that only the modified SASSS reliably detected change over 2 years [6]. The ability of the modified SASSS to discriminate between treatment groups has been demonstrated in a trial comparing two strategies of nonsteroidal anti-inflammatory drugs, where it was shown that the group of patients who received continuous nonsteroidal anti-inflammatory drug therapy ($n = 111$) had less progression than the group receiving discontinuous therapy ($n = 104$) [11].

There are both conceptual and methodological limitations to the modified SASSS scoring method. The score assesses both destructive changes (that is, erosions) as well as reparative changes (that is, sclerosis, syndesmophytes, ankylosis), and this may not be ideal for the evaluation of all therapies. Since higher scores are assigned to new bone formation, this method is primarily useful for patients with longstanding disease and it may not be a sensitive approach in studies evaluating early disease. Some features such as erosions and sclerosis are very infrequent, while others such as squaring are not reliability detected [12]. The thoracic spine is not assessed due to overlapping structures despite frequent involvement in disease, and even though attempts have been made to assess radiographic abnormalities in this segment, reliability has been inadequate. Radiographic progression over 2 years is minimal, and is even less when observers are blinded to the time point as recommended for clinical trials. This minimal progression precludes placebo-controlled trials and necessitates treatment groups of several hundred patients to ensure sufficient power to detect even modest treatment group differences. Moreover, training does not appear to improve reliability of change scores [12]. There is, therefore, a major need for more responsive tools for assessment of structural damage.

## Radiography of peripheral structures

Radiographic changes in peripheral SpA occur primarily in the hip joint and entheses. A recent study of the Achilles tendon insertion provides evidence to support the possibility that erosion and new bone formation occur independently because erosive changes are typically observed at the posterior calcaneum superior to the tendon insertion while new bone formation occurs at the insertion of the tendon [13]. Erosive changes are very uncommon in the hip joint, where concentric narrowing is observed in about 5 to 10% of patients, particularly those with juvenile onset SpA.

## Computed tomography

As for plain radiography, observations with CT are restricted to abnormalities of cancellous or cortical bone. The primary advantage of CT over radiography is the ability to detect erosions at an earlier stage, and limited studies with small numbers of patients have shown greater sensitivity and specificity in the diagnosis of sacroiliitis. A recent retrospective study of 910 patients with back pain indicated that agreement between the methods was only fair and sacroiliitis was reported twice as frequently with CT (25%) as with plain

radiography (11%) [14]. The use of CT is primarily limited by the higher dose of radiation – although some have proposed the use of discontiguous slices, which may substantially reduce the radiation dose [15]. Limited comparative studies with MRI indicate that the latter imaging modality is more sensitive for detecting sacroiliitis [16]. The use of CT must at present be regarded as limited to the diagnostic evaluation of inflammatory back pain where plain radiography shows normal SIJs and access to MRI is limited.

## Isotopic imaging

Scintigraphy relies upon abnormal uptake of radio tracer in areas of increased bone turnover. The technique therefore has only an indirect and limited relationship to inflammation. Several studies have evaluated quantitative scanning of the SIJs, applying cutoff values to distinguish patients from control individuals. Sensitivity ranged from 29 to 40% while specificity was less than 80% [17-19]. A systematic review of scintigraphy of the SIJs concluded that this modality had limited diagnostic utility in early SpA [20]. A prospective study comparing scintigraphy with MRI of the SIJs in 21 patients with inflammatory back pain but with normal plain radiographs showed that while 20 patients had MRI features of inflammation, only 10 patients had abnormal tracer uptake on scintigraphy [21]. Unilateral abnormalities similarly have low diagnostic utility in early disease.

## Ultrasound

Ultrasound shows considerable promise in SpA as a tool for the assessment of peripheral inflammation, especially enthesitis. Several reports indicate the value of this technique in the detection of subclinical enthesitis, particularly when power Doppler is used to detect abnormalities in the entheseal vascular supply. It has been shown that virtually all patients with SpA have enthesitis by ultrasound, which is much more sensitive than clinical examination – where a much lower frequency (14%) of enthesitis and substantial discrepancy with ultrasound findings is observed.

One study of 2,952 entheses from 164 patients with SpA (AS = 104 patients, undifferentiated SpA = 30 patients, psoriatic arthritis = 21 patients, inflammatory bowel disease arthritis = 6 patients, reactive arthritis = 3 patients), 64 control individuals (34 with mechanical back pain) and 30 individuals with rheumatoid arthritis using power Doppler ultrasound showed that enthesitis was particularly common at the Achilles (79%) and plantar facia (74%) insertion into the calcaneum [22]. The distribution of affected enthesis did not vary amongst SpA subtypes or whether inflammation was predominately axial or peripheral.

A sonographic enthesitis index has been developed that scores enthesitis around the knee and heel [23]. Inter-observer reliability was modest and no correlation with clinical measures of disease activity or severity was apparent. Limited comparative study suggests that ultrasound may be superior to MRI in detecting the early signs of peripheral enthesitis [24,25].

## Magnetic resonance imaging

The introduction of this modality in SpA constitutes the principle advance in imaging over the past two decades. The primary advantage of MRI is its ability to visualize soft tissue inflammation and inflammatory lesions within bone in three dimensions. Clinicians are often confused by the technical details and the multitude of sequences used in MRI. Most abnormalities can be detected using a combination of T1-weighted images, which detect the bright signal from fat, and the short tau inversion recovery sequence, which suppresses the signal from marrow fat and allows the detection of free water that may be associated with inflammatory lesions in bone marrow. Bone is dark with both sequences. Contrast enhancement after intravenous administration of gadolinium is an additional approach to the detection of inflammation. Accumulation of gadolinium occurs at sites of increased vascularity and capillary permeability. This approach, however, is costly, requires that the patient lie within the magnet for up to 1 hour, and appears to offer few advantages over the short tau inversion recovery sequence for assessment of the spine [26].

### MRI of the sacroiliac joints

Magnetic resonance images of the SIJs are obtained in the semicoronal orientation along the long axis of the sacral bone to allow visualization of the cartilaginous portion of the joint, which is convex shaped with the apex facing antero-inferiorly. The diagnostic utility of MRI has been the subject of recent investigation. Abnormalities evident in early disease include capsulitis, synovitis, and subchondral bone marrow inflammation, particularly in the postero-inferior region of the SIJs [27]. Sensitivity has varied from 54 to 95% and specificity from 83 to 100% in studies of pre-radiographic SpA, although only small numbers of patients with nonspecific back pain were included [21,27-31].

One group used dynamic imaging with gadolinium augmentation to compare patients with inflammatory back pain ($n = 36$) according to the European Spondyloarthropathy Study Group criteria but with normal pelvic X-rays and patients with established AS ($n = 36$) with those patients who had mechanical causes for low back pain ($n = 53$). MRI had sensitivity of 83% and specificity of 93% for clinically defined inflammatory back pain [30]. In another cohort of 68 patients with inflammatory back pain of whom 57 and 14 patients fulfilled European Spondyloarthropathy Study Group and modified New York criteria, respectively, and who had less than 2 years duration of symptoms, inflammation of the SIJs could be detected by MRI in only about one-third of the patients [32]. The discrepancy in these reports highlights the challenges to the evaluation of sensitivity and specificity of imaging modalities in patients with early SpA because the gold standard for diagnosis is radiographic sacroiliitis, which

means that such evaluations must be prospective to allow time for radiographic abnormalities to appear. In addition, sensitivity and specificity will be determined by the criteria used to select patients considered to have inflammatory back pain. The percentage of patients with MRI abnormalities increases as patients satisfy more clinical classification criteria [32].

A recent report examined the predictive validity of MRI for radiographic sacroiliitis 8 years after baseline assessment in patients with inflammatory back pain but normal pelvic X-rays. The degree of bone marrow edema was highly predictive of radiographic appearances of sacroiliitis [33]. Further study requires that investigators apply standardized definitions of MRI abnormalities in sufficiently large numbers of well-characterized patients followed for a sufficient duration of time.

*Validation of MRI abnormalities in the sacroiliac joints*

Validation of the early MRI abnormalities in the SIJs has been indirect. A correlation has been demonstrated between the degree of gadolinium augmentation and disease activity determined by clinical parameters in patients who received CT-guided intraarticular injections with corticosteroid [34]. Direct CT-guided biopsy of the SIJs also demonstrated significant correlations with histological grade of inflammation [35].

*Scoring methods for lesions detected by MRI in the sacroiliac joints*

Several methods for quantifying disease activity on MRI in the SIJs have been proposed, although only one approach has been clearly validated as having the ability to discriminate between treatment groups in a placebo-controlled randomized study that assessed adalimumab in nonsteroidal anti-inflammatory drug-refractory AS [36,37]. The primary MRI feature that is scored is the extent of bone marrow edema in the synovial portion of the joint. The methods differ in that scoring is based either on a global scheme that focuses on the single image displaying the worst abnormalities or a more detailed method that scores several consecutive semicoronal images depicting the synovial portion of the SIJ (Spondyloarthritis Research Consortium of Canada (SPARCC) scoring method). A multireader exercise evaluating the different scoring methods for reliability and sensitivity to change according to the requirements of the Outcome Measures in Rheumatology filter showed that the more detailed SPARCC method was more reliable and sensitive to change [36].

A training module has been developed that can be viewed online to promote the standardization of the approach to scoring by the application of explicit rules based on anatomical landmarks and standardized definitions relevant to inflammation [38]. There has been limited development of methods for scoring chronic changes in the SIJs. One method scores sclerosis and erosions at eight sites and also the joint space width [16]. Inter-reader reliability of this method was moderate to poor. It is presently unclear what advantages MRI offers over plain imaging or CT in the evaluation of chronic change.

**MRI of the spine**

The spine is typically imaged in the sagittal orientation and is scanned in two segments, C1 to T10 and T10 to S2, which allows visualization of the entire spine within a reasonable time frame of 20 to 25 minutes in which patients have to lie still within the magnet. This results in a large field of view, however, so the cervical vertebrae are not that well visualized. Characteristic abnormalities observed on fat-suppressed images include increased marrow signal in the anterior and posterior corners of the vertebrae and noncorner high-marrow signal within the vertebral bone marrow adjacent to the vertebral end plate. The former corresponds to the Romanus lesion observed histopathologically, while the latter reflects an inflammatory spondylodiscitis. It is likely that these lesions resolve through a process that includes fat replacement since it is not unusual to see increased signal on T1-weighted images reflecting increased fat content at vertebral corners surrounded by areas of increased short tau inversion recovery sequence marrow signal. Neither inflammatory lesions nor fat infiltration are visible on plain radiography. Unlike plain radiography, erosions – particularly those affecting the end plate – are seen in the majority of patients when using MRI [39].

A variety of lesions are frequently present in the lateral and posterior segments of the spine, including inflammatory lesions in the costo-vertebral and costo-transverse joints, the pedicles, facet joints, and ligamentary insertions at spinous processes. Systematic evaluation shows that these are at least as frequent as lesions occurring in the anterior portion of the spine but may be overlooked by radiologists because imaging and evaluation of the spine is typically focused on central sagittal slices, which are more relevant to neurological and orthopedic indications for MRI [40,41]. Minor degrees of scoliosis are very common and conventional imaging in the sagittal orientation may not depict the lateral structures on both sides of the spinal canal. Similarly, fat replacement in the costo-vertebral joints is often overlooked during diagnostic evaluation because its significance as a postinflammatory feature is not appreciated.

The sensitivity and specificity of these lesions for SpA has yet to be systematically addressed. One report that included patients with established AS and inflammatory back pain but no radiographic abnormalities and healthy age-matched and sex-matched control individuals showed that about one-third of healthy control individuals will have one inflammatory lesion at a vertebral corner, although the presence of at least two such inflammatory lesions is highly sensitive and specific for SpA [42]. Further work is required that includes age-matched and sex-matched patients with nonspecific back pain.

*Validation of MRI lesions in the spine*

Validation of MRI lesions is compromised by their inaccessibility to biopsy and by the lack of prospective data addressing their association with the development of radiographic changes. Several reports have described correlations between changes in acute MRI lesions and changes in either self-reported pain and stiffness or C-reactive protein in AS patients receiving anti-TNF therapies [37,43,44]. One report described a moderate correlation between the presence of acute MRI lesions and histopathological scores for inflammation in facet joints obtained at the time of corrective surgery for severe kyphosis [45]. This latter study also underlined the lack of sensitivity of MRI, however, with only three out of eight patients with histopathological inflammation demonstrating lesions visible on MRI.

Several reports have recently addressed the association between acute lesions on MRI and the development of radiographic ankylosis on prospective follow-up. The reports have been consistent in demonstrating development of new syndesmophytes on radiography after 2 years of follow-up where a baseline MRI demonstrated an acute lesion at the corresponding vertebral corner [46-48]. New syndesmophytes still developed, however, from vertebral corners where baseline MRI was normal. It should be emphasized that sensitivity of MRI in relation to histopathological abnormalities is limited and the baseline MRI represents only a snapshot of the evolution of change from an acute to a chronic lesion. It is, for instance, possible that an MRI may look completely normal after the acute lesion has resolved and prior to the development of more chronic changes such as fat replacement and new bone formation.

*Scoring methods for lesions detected by MRI in the spine*

The unique ability of MRI to depict inflammatory lesions throughout the spine has been used to develop scoring methodologies that allow quantitation of the extent of inflammation. Two primary approaches have been developed that are based on the assessment of a discovertebral unit, which represents the region between two imaginary lines drawn through the middle of two adjacent vertebrae. The first method, the ASspiMRI index, scores the severity of bone edema and erosions at each discovertebral unit in a single sagittal plane of view according to a zero to six scoring scheme, with higher values being assigned to the presence of erosions [43]. An adaptation of this method, the Berlin method, omits the scoring of erosions. The second method has been developed by SPARCC and differs from the other methods in that lesion are evaluated in three consecutive sagittal slices, which permits a three-dimensional quantitation of the extent of the lesion [49]. In addition, the discovertebral unit is divided into quadrants and bone edema is scored on a dichotomous basis according to its presence or absence. This scoring method was developed to discriminate between treatment groups in clinical trials, and further work showed that limiting the assessment to the six most severely affected discovertebral units was at least as reliable as assessment of all 23 discovertebral units and was even more discriminatory [44]. MRI is subject to artifacts, and a potential limitation of mandatory scoring of all 23 discovertebral units is that reliability and sensitivity to change may be impaired if such artifacts, which are typically small, are recorded as lesions.

A recent multireader exercise conducted under the auspices of Outcome Measures in Rheumatology concluded that each method discriminated adequately between anti-TNF and placebo treatment groups, although consistency and reliability was better with the SPARCC method, particularly when evaluated by neutral observers with limited experience in either method [50].

Systematic approaches to scoring chronic changes in the spine have been limited. One method has described an approach based on a discovertebral unit that scores sclerosis, squaring, syndesmophytes, and ankylosis in a manner resembling the modified SASSS [51]. The inter-reader reliability of this method was poor and a comparative study showed that this approach offered no advantages over plain imaging in the detection and scoring of chronic lesions.

### Whole body MRI

A recent advance in MRI has been the use of whole body multicoil systems and a moving table platform that allows scanning of adjacent anatomical regions without repositioning of the patient or the imaging coils. Fusion of the images obtained at each table position enables imaging of the entire body in a single head-to-toe scan in a relatively short period of time. This whole body MRI has the potential advantage that lesions in the axial skeleton, anterior chest wall, hip and shoulder girdles, peripheral joints, and entheses may be visualized on the same image. Recent reports show that reliability of detection is comparable with that of conventional MRI [52,53].

### MRI of peripheral structures

MRI of peripheral structures affected in SpA may have diagnostic utility by revealing characteristic abnormalities such as acromion enthesitis at the insertion of the deltoid muscle at the shoulder or peri-articular enthesitic lesions in early and undiagnosed knee synovitis, where a combination of enthesitis with bone marrow edema is much more likely to predict subsequent development of SpA as compared with rheumatoid arthritis [54,55]. Further studies have also shown that bone marrow edema at entheses is common in non-SpA-related conditions of the shoulder and heel, and it is the size of the lesion together with its association with bone erosion that has the highest specificity for SpA [56].

## Conclusions

Plain radiography continues to be the primary approach for the evaluation of SpA in routine practice. MRI is now established as the most sensitive imaging modality for the

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assessment of active inflammation. Ultrasound appears to be particularly useful in the assessment of peripheral enthesitis. There is increasing evidence that acute lesions on MRI also have predictive validity for radiographic abnormalities in both the SIJs and the spine, although it is still unclear to what degree MRI findings contribute information of diagnostic value for routine practice beyond clinical evaluation, assessment of response to nonsteroidal anti-inflammatory drugs, and *HLA-B27* gene and C-reactive protein analysis. Moreover, further work is required to clarify the sensitivity and specificity of MRI lesions. It remains unclear to what degree MRI may offer advantages over radiography for the assessment of chronic lesions. These additional studies will set the stage for addressing two of the most significant challenges in the field of SpA – namely, early diagnosis and early therapeutic intervention prior to the development of structural damage investigating the possibility of a window of opportunity in the approach to disease modification.

## Competing interests

The authors declare that they have no competing interests.

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