# The Future of Imaging in Axial Spondyloarthritis

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**KEYWORDS**

• Axial spondyloarthritis • Imaging • MRI • Conventional radiography
• Immunoscintigraphy • Low-dose CT

**KEY POINTS**

- MRI and conventional radiography are recommended imaging techniques in axial spondyloarthritis (axSpA) but are not the only options for diagnosing patients with axSpA.
- Studies report a minimal effect on the performance of the Assessment of Spondyloarthritis International Society classification criteria when adding structural MRI–sacroiliac (MRI-SI) lesions or spinal MRI lesions to the definition of a positive MRI.
- Despite several disadvantages, nuclear imaging methods should not be ruled out in the individual diagnostic process and evaluation of patients with axSpA.
- Taking into account the limited and contradicting data currently available, further investigation on the morphology and location of MRI-SI lesions is needed to distinguish MRI lesions in patients with axSpA from spondyloarthritis-like lesions.

## THE CURRENT POSITION OF IMAGING IN AXIAL SPONDYLOARTHRITIS

With the lack of an appropriate gold standard and the absence of a pathognomonic feature, the recognition and diagnosis of axial spondyloarthritis (axSpA), especially in the early stages, is still a time-consuming process. AxSpA is considered to have a heterogeneous clinical presentation. In daily practice, patients suspected to have axSpA therefore often go through an extensive diagnostic work-up involving clinical assessment, laboratory tests, and imaging to identify illustrative features so that a diagnosis can be made. There are 2 important imaging techniques used for diagnostic purpose in axSpA. For late diagnosis, conventional radiography is often used. Patients with axSpA with severe disease, ankylosing spondylitis (AS), are characterized by the presence and development of syndesmophytes and radiographic sacroiliitis. Spinal structural damage is measured most accurately with the modified Stoke Ankylosis Spondylitis Spine Score (mSASSS), whereas the modified New York (mNY) criteria are preferred to assess radiographic sacroiliitis.[1] For early recognition of axSpA, MRI is the main tool. Unlike conventional radiography, MRI can visualize inflammation and

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Rheum Dis Clin N Am 46 (2020) 297–309
https://doi.org/10.1016/j.rdc.2020.01.005
rheumatic.theclinics.com

is therefore used in addition to identify patients with axSpA in an early stage. Rheumatologists worldwide prefer imaging, especially MRI, rather than human leukocyte antigen (HLA) B27 testing in the diagnostic process.[2,3] Although imaging results play an important role in the diagnostic considerations of rheumatologists and increase the confidence in a diagnosis regardless of a positive or negative imaging outcome, physicians do not explicitly find imaging crucial in the diagnostic process of axSpA.[4,5] Besides the involvement in the diagnostic process, imaging is used for the classification of axSpA. In the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA, the importance of imaging is evident because there is a clear role for radiography and MRI. Unlike in the diagnostic process, imaging in these criteria is limited to sacroiliitis, which can either refer to radiographic sacroiliitis, according to the mNY criteria, or to the presence of inflammation on MRI of the sacroiliac (SI) joints (MRI-SI); that is, a positive MRI-SI according to the ASAS definition.[6] Following this definition, a positive MRI-SI shows 1 or more inflammatory lesion highly suggestive of axSpA and visible on 2 or more consecutive slices, or more inflammatory lesions on the same slice. The sole presence of synovitis, capsulitis, or enthesitis is insufficient for a positive MRI-SI.[7,8] For diagnosis as well as classification of axSpA, MRI and radiography are the imaging techniques most commonly used, which is reflected in the European League Against Rheumatism (EULAR) recommendations for the use of imaging in axSpA.[9] Therefore the focus here is on radiography and MRI.

## CHALLENGES AND AREAS OF DEVELOPMENT

With the development of the ASAS classification criteria, and therewith the official introduction of MRI in classifying patients with axSpA, there has been substantial improvement in the understanding and early recognition of axSpA. However, there are still areas that need attention, and several unmet needs remain.

### *Reliability of Reading Assessments*

The interobserver and intraobserver reliability for imaging in axSpA has been a constant topic of discussion. In particular, the agreement on radiographic sacroiliitis is considered low and does not seem to improve with education or training.[10,11] The agreement on sacroiliitis on MRI according to the ASAS definition shows more potential (kappa = 0.73) but still 7.9% of patients with inflammatory back pain change classification criteria fulfillment solely based on different imaging assessment between readers.[12] When focusing on spinal lesions, there is a disappointing agreement between local and central (calibrated) readers in both radiographs (kappa = 0.26) as well as MRI scans (kappa = 0.27), in which local observers overestimate spinal lesions on imaging in the context of axSpA. The agreement between central readers seems to be good (kappa = 0.79) for radiographic spinal lesions, moderate (kappa = 0.58) for inflammation, and poor (kappa = 0.19) for syndesmophytes on MRI of the spine.[13,14] These data support the use of radiographic and MRI consensus scores determined by calibrated central readers rather than local readers, with the notion that spinal structural MRI lesions are also challenging for calibrated readers. For clinical trials and cohort studies, using central reader scores is an appropriate choice; however, obtaining central reader scores to use in daily practice seems less feasible.

### *Differentiation Between Axial Spondyloarthritis Lesions and Spondyloarthritis-like Lesions*

A recent rapidly developing field of interest is focusing on the presence of MRI lesions found in the population at large that have similar characteristics to axSpA MRI lesions.

Alarmingly, several studies report on SpA-like bone marrow edema (BME) on MRI-SI in study populations of postpartum women,[15,16] runners,[16] military recruits,[17] athletes,[18] and in healthy people.[19,20] The ASAS definition of positive MRI-SI was met in a substantial percentage of patients throughout these studies. In addition, 1 study also reported an extremely high presence of inflammatory MRI-spine lesions (in 88.6% of male and 84.6% of female subjects) in healthy subjects.[20] The reason for frequently reported BME on MRI in healthy individuals is not known. A potential explanation is that it can be caused by mechanical stress. However, this is not certain, because conflicting data have been published on inflammation caused by mechanical involvement in axSpA.[17,21]

Now that it is evident that inflammatory SpA-like lesions are present in healthy people, the obvious question is: how can the axSpA be separated from the SpA-like lesions? Weber and colleagues[18] suggest that the location of BME lesions can be a distinctive feature. They found the posterior lower iliac bone to be the most affected SI joint region in athletes. In contrast, another study compared patients with chronic back pain to patients with axSpA, and found the lower posterior iliac region to be the most affected area with BME in patients with axSpA. The upper anterior sacral region was the most affected area for BME in the non-SpA patient group.[22] Another characteristic that should be evaluated to a larger extent is extensive inflammatory MRI lesions. According to de Winter and colleagues,[16] the extensiveness of BME MRI-SI lesions may contribute to the distinction between patients with axSpA and healthy persons, because deep (extensive) lesions are reported almost exclusively in patients with axSpA.

Final conclusions cannot be drawn yet, but these studies on possible background noise findings and the typical characteristics show an interesting area for gaining insights on MRI lesions representative for axSpA.

### *Defining a Positive MRI Scan*

Another recurring topic of discussion is the comprehensiveness of the current definition of a positive MRI scan, as mentioned in the ASAS classification criteria for axSpA. There is some evidence that the structural MRI-SI abnormalities of fatty lesions and erosions may contribute to the usefulness of MRI in axSpA classification, although this is not the case for sclerosis and ankylosis.[23] Cutoffs of greater than or equal to 3 erosions, greater than or equal to 3 fatty lesions, and greater than or equal to 5 erosions and/or fatty lesions were found to be specific for axSpA ($\geq$95% specificity).[24] These cutoffs were subsequently used to assess the impact of structural MRI-SI lesions on the classification of patients with axSpA. Investigators concluded that adding structural MRI-SI lesions to the definition of sacroiliitis on imaging as well as replacing radiographic sacroiliitis by structural MRI-SI lesions has little impact on the classification of patients with axSpA. Most patients change from one subcategory to another but most (80.6%–95.5%, depending on the reader) do not change fulfillment of the ASAS classification criteria.[25]

At the time of developing the ASAS criteria, spinal MRI lesions were discarded for inclusion in the definition of a positive MRI because of limited evidence on the added value of these lesions in the classification of axSpA. Recently a study was published tackling this query. Ez-Zaitouni and colleagues[26] showed that, in patients with chronic back pain (SPACE cohort) and inflammatory back pain (DESIR cohort) with symptom onset less than 3 years, including positive MRI-spine as an imaging feature in the ASAS axSpA classification criteria yields few newly classified patients. Also, the number of patients with positive MRI-spine but negative MRI-SI was 1% and 7%, respectively. This finding is in line with previously published data in patients with longstanding disease.[27]

The definitions of MRI-SI lesions have recently been updated by the ASAS,[28] but no changes have been made to the classification criteria. Literature on the added utility of spinal MRI and structural MRI-SI lesions is present but is too limited to be a basis for radical changes in the definition of positive MRI. The few studies that investigate the added value of either structural MRI-SI or spinal MRI lesions show only marginal impact when added to the criteria. These findings all argue in favor of keeping the current definition of a positive MRI scan in the ASAS classification criteria.

### *The Natural Course of Disease*

Until now there has not been a full understanding of the pathologic pathway of axSpA, but it is proposed that inflammation precedes structural damage. Inflammation on MRI-SI at baseline is highly predictive of radiographic SI progression after 5 years in HLA-B27-positive (odds ratio [OR], 5.4; 95% confidence interval [CI], 3.3–8.9) and HLA-B27–negative patients (OR, 2.2; 95% CI, 1.0–4.5).[29] This group also reported that, in 5 years, inflammation in 1 SI quadrant leads to sclerosis (OR, 1.7; 95% CI, 1.0–3.2), erosions (OR, 2.0; 95% CI, 1.5–2.5), or fatty lesions (OR, 1.7; 95% CI, 1.2–2.5) in the same quadrant.[30] In the spine, this association is less clear-cut; vertebral corner inflammation and fat deposition on MRI slightly increases the chance of new syndesmophyte forming at the same level but does not predict growth of existing syndesmophytes over 2 years. Nevertheless, most new syndesmophytes developed without preceding inflammation.[31,32]

These findings emphasize the pathophysiologic implications of inflammation in axSpA. They also suggest the presence of noninflammatory pathways, especially in the spine. However, the natural progression of lesions over a longer period remains unknown. Cohort studies that could offer insights currently exist, but longer follow-up is the key factor so it will take some time before there are answers.

### *Is There a Role for Posterior Elements?*

Lesions in the posterior structures of the spine (pedicles, facet joints, spinous and transverse processes, and soft tissue) are often overlooked but may be of clinical significance because inflammation of the facet joints may lead to longer disease duration, higher disease activity, and functional impairment. In addition, it is suggested that the development of syndesmophytes is preceded by facet joint ankylosis.[33–35] So, do posterior elements of the spine play a role in the diagnostic process of axSpA? The number of studies investigating this topic is limited. A study group showed that including radiographic damage of the cervical facet joints in the assessment of spinal structural damage increases the sensitivity of the mSASSS method in patients with AS on anti-tumor necrosis factor (TNF) treatment, without introducing more measurement errors.[36] When focusing on MRI inflammation in the posterior elements, a high percentage (87.5%) of patients with AS with greater than or equal to 1 inflammatory posterior element lesion anywhere in the spine has been reported. The extent of inflammatory lesions was slightly lower in the posterior elements (6.7 $\pm$ 5.3 spinal levels) compared with inflammation in the vertebral body (8.4 $\pm$ 6.7 spinal levels) but still evidently present.[37] In line with those findings, another study reported inflammatory lesions in the posterior elements in patients with AS but to a lesser extent (3.7 $\pm$ 5.3), likely because the investigators only took facet joints into account.[38] Although studies show the presence of posterior inflammatory lesions in patients with axSpA, they also show a concordant presence with BME in the vertebra in AS,[39] nonradiographic axSpA,[39,40] and HLA-B27–positive patients with SpA.[41] However, all these studies lack a control group. Studies reporting on the added value of

posterior element inflammation in early axSpA recognition including a proper control group (eg, patients with non-specific back pain) have yet to be performed.

With the complex anatomy of the facet joints, it is difficult to properly display damage in these structures. In addition, it is extremely challenging to evaluate the thoracic facet joints on plain radiographs because of overprojection of other structures such as the costotransverse and costovertebral joints. The advantage of MRI is that anatomic structures are visualized throughout the whole structure and therefore a three-dimensional image can be made. However, to our knowledge, there have not been any studies related to axSpA reporting on structural MRI lesions in the posterior elements. A reason may be that with MRI it is also difficult to accurately evaluate posterior elements, because they are only visible on 1 or 2 slices in the sagittal plane (the recommended MRI-spine scan protocol for axSpA lesions). For reasons mentioned earlier, it is likely that the involvement of structural damage of the facet joints in axSpA is currently underrated, but this may change in the near future. Recently there have been a few studies using computed tomography (CT) imaging techniques for assessing facet joint lesions. Tan and colleagues[42] showed 51 out 55 patients with AS with greater than or equal to 1 facet joint fusion on thoracolumbar CT scans. However, as with inflammatory lesions in the posterior elements and the vertebral body, ankylosis of the facet joints is often seen concordant with syndesmophytes in the vertebra; in 89.9% of the patients there is overlap. Another (low-dose) CT study including patients with AS with greater than or equal to 1 syndesmophyte on conventional radiographs covered the whole spine (C2 to S1) and found lesions in the cervical (means of 2.3–2.0), thoracic (means of 5.9–6.8), and lumbar (means of 1.0–1.8) segments assessed by 2 readers independently.[43] In the same cohort, the reliability of state and changes scores was measured and found to be good in all segments excluding the lumbar spine, where, in general, limited progression was seen. This study showed that low-dose CT is an appropriate imaging technique to evaluate progression of facet joint ankylosis in patients with AS.[44] Although the diagnostic utility of facet joint ankylosis in axSpA is still unclear, it is positive to have identified an imaging technique that depicts facet ankylosis well.

For lesions in the posterior elements, it seems that MRI best shows inflammation, whereas CT is promising for structural lesions. However, research on the precise involvement of these lesions is limited and studies with control groups are missing. Therefore, no conclusive verdict can be given on the utility of posterior element lesions in axSpA.

## OUT OF THE COMFORT ZONE

Radiography and MRI are currently the preferred imaging techniques in axSpA.[9] Nonetheless, other techniques can be used to diagnose axSpA. Looking beyond the 2 common imaging techniques, there are alternative options that could counter the disadvantages of conventional radiography and/or MRI. Dual-energy CT scanning is discussed earlier in Min Chen and colleagues' article, "Emerging Imaging Techniques in Spondyloarthritis: Dual-Energy CT and New MRI Sequences," in this issue, as well as several new MRI sequences, other than the short-tau inversion recovery and T1-weighted sequences that are generally used in axSpA for MRI assessment. Therefore, these techniques are not repeated here. In addition, ultrasonography is not discussed further because this technique is useful for depicting small, peripheral joints but is not preferred for the joints involved in axSpA. The focus here is on the additional value of different nuclear imaging techniques to diagnose patients with axSpA.

### *Bone Scintigraphy*

With this technique, the radionuclide technetium-99m (Tc-99m) is chemically attached to a ligand that is preferentially taken up by bone. The tracer uptake is increased in areas with a high bone turnover, such as inflamed sites, which makes it possible to visualize, for example, inflammation in the SI joints. Several decades ago, the results of studies using bone scintigraphy to identify sacroiliitis were promising. However, in 2008, an systematic literature review on the performance of scintigraphy concluded there was very low diagnostic value for this imaging technique axSpA.[45] In 2010 Song and colleagues[46] reported a moderate performance (sensitivity 64.9%/specificity 50.5%) of conventional bone scintigraphy using Tc-99m labeled methylene diphosphate in 207 chronic back pain patients. Instead of using MRI as an external standard as previous studies did, this study more accurately used the diagnosis of the rheumatologist (axSpA or no axSpA) to test the performance of scintigraphy scanning. Interestingly, when reporting on isolated unilateral sacroiliitis, specificity increased to 92.8% because false-positive rates decreased enormously. However, sensitivity decreased to 24.7%, which also showed the diminished diagnostic value of scintigraphy in axSpA. More recently, there have been some studies using anti–TNF alpha antibodies with radionuclides as a tracer in scintigraphy scanning. These studies report some use for scintigraphy in axSpA, but the scintigraphy never outperforms the MRI.[47,48] In a follow-up report, Carron and colleagues[49] found a strong correlation between tracer uptake on the immunoscintigraphy with Tc-99m–radiolabeled certolizumab and BME on MRI-SI in the same quadrant in patients with axSpA. There was a high correlation between tracer uptake and deep inflammatory MRI lesions (extended $\geq$1 cm from the articular surface of the SI joints into the bone, defined according to the SPARCC definition). This correlation was not found with so-called intense lesions. Although the number of patients in this study was limited, this finding has potential interest and touches on a reoccurring topic of the possible relevance of extensive (deep) inflammatory lesions in patients with axSpA.

There is limited added value in using bone scintigraphy the as imaging method in diagnosing patients with axSpA. Although immunoscintigraphy, using labeled monoclonal antibodies, does not outperform MRI this technique may provide more insight into the pathophysiologic course of disease at different stages. Moreover, in daily practice, finding the correct diagnosis and treatment requires an individualized approach and conventional scintigraphy or immunoscintigraphy can play a role in this process. Nevertheless, the high radiation burden is a disadvantage that should carefully be taken into account when considering this imaging technique.

### *$^{18}$F-Fluorodeoxyglucose PET/Computed Tomography*

Another nuclear imaging method that is, of interest to present abnormal bone activity is $^{18}$F-fluorodeoxyglucose (FDG) PET/CT. The diagnostic potential of PET imaging has been investigated in several studies. The concordance between inflammatory MRI-SI lesions and tracer uptake on $^{18}$F-FDG-PET/CT scans was good, but there was no full overlap within the same quadrant in patients with either radiographic or nonradiographic axSpA.[50,51] The correlation between PET imaging and structural lesions is less straightforward. Strobel and colleagues[52] showed a low sensitivity of PET in patients with AS with sacroiliitis grade 2 or 3. Other studies reported poor agreements with erosions, sclerosis, and ankylosis on MRI-SI of patients with active SpA.[53,54] Nevertheless, not all structural MRI-SI lesions were badly correlated with tracer uptake on FDG-PET/CT scans. Particularly areas with both inflammatory as well as fatty lesions, but also areas with less inflammatory activity but where bone turnover is

more prominent, such as areas with (postinflammatory) fatty lesions, correlate well with tracer uptake.[55,56] A better association between tracer uptake and BME and/or fatty lesions compared with only BME lesions was seen in both SI and spine; however, it is more explicit in the spine, with an increase in percentage agreement of 26.3%.[54] High levels of tracer uptake are therefore reported in areas with high BME MRI lesions as well as areas with low BME but high fatty MRI lesions, and lower levels of tracer uptake are reported in areas with more established MRI lesions (eg, erosions). Therefore, it can be suggested that FDG-PET/CT reflects areas with osteoblastic activity rather than pure inflammation in patients with axSpA. If this is the case, FDG-PET/CT scans might preferably be chosen for monitoring the course of disease because FDG-PET/CT scans can give a meaningful contribution to the prediction of structural damage. However, the credibility of that theory has yet to be proved. Proper studies on the utility of FDG-PET/CT scans are still missing because most studies currently available have a small study population and lack a control group. As with scintigraphy, PET/CT scans also have a very high radiation dose, which is a major disadvantage and makes both techniques less appropriate for daily care.

### *Low-Dose Computed Tomography*

In 2015, a EULAR taskforce published recommendations for the use of imaging in axSpA. By these recommendations, conventional radiography and MRI are endorsed. Other imaging techniques are generally not recommended, with the exception of CT. With the conventional CT imaging technique, it is not possible to visualize inflammatory signs in addition to joint destruction. However, this technique may provide a contribution to the visualization of structural damage under conditions in which the radiographs are negative, it is not possible to perform MRI, and there is still a valid suspicion of axSpA.[9] Although recommended by EULAR, the value of MRI in detecting structural lesions is still under debate, and some literature even suggests CT instead of MRI as the gold standard to evaluate structural damage in SI joints.[57,58] Literature also shows that CT is much more sensitive than MRI for the detection and 2-year change in scores of syndesmophytes.[59] In addition, CT imaging proves to be more sensitive in detecting syndesmophytes than conventional radiography, which at the moment is still the recommended method to identify and assess syndesmophytes in patients with axSpA. The superiority of CT was most explicit in the detection of already existing syndesmophytes that grew over time, but CT also detected more new syndesmophytes.[60,61]

The argument that CT imaging comes with inherent risk factors because it has a high radiation exposure has been refuted with the development of the low-dose CT (ldCT) imaging technique in axSpA. With ldCT, the exposure to radiation is similar to that of radiography with the advantage of properly displaying three-dimensional structures such as the SI joints. However, it is understandable that MRI is given preference in clinical practice and classification of axSpA, because it is impossible to visualize either inflammatory or fatty lesions with conventional and low-dose CT.

## SUMMARY

This article focuses mainly on the role of imaging for diagnostic and classification purposes. Besides these, imaging can be used to monitor disease and can play a part in predicting treatment response. The next article in this issue concentrates on these topics.

Several unmet needs and challenges with the common goal to increase the understanding and improve the recognition of axSpA have been discussed. There are

difficulties in obtaining high agreement for readers assessing conventional radiography or MRI lesions typical of axSpA. In addition, SpA-like lesions are frequently recorded in healthy people. A part of the answer to how to overcome these difficulties may lie in the morphology of lesions, because deep MRI-SI lesions seem to be characteristic for axSpA. This area of research needs further exploration. Although there is a belief that the current definition of a positive MRI scan would improve when extended, studies investigating this all report that adding either structural MRI-SI lesions or spinal MRI lesions seems to yield a minimal effect on the utility of the ASAS classification criteria. Perhaps involving the posterior elements could give additional value to the classification and even the diagnosis of axSpA as well as the further understanding of the course of disease. Current literature cannot give a conclusive answer yet; however, it shows that this is a relevant field for future research.

Conventional radiography and MRI are the endorsed imaging techniques in axSpA. In addition to these techniques, this article discusses several studies using nuclear imaging techniques. The current studies on scintigraphy and FDG-PET/CT imaging techniques have limitations that must be taken into account. Most studies have small sample sizes and often miss a valid control group to test the performance of these techniques. The techniques themselves also have disadvantages. First, these techniques come with a high radiation burden. These methods are invasive because there is an administration of tracer into the body. Patients often experience this as unpleasant. Second, it is time consuming because it may take 1 hour to several hours for the body to take up the tracer. There is also a limitation in the assessment of the lesions. There are standardized scoring approaches for inflammation or structural damage on neither the scintigraphy nor the FDG-PET scan. The scoring methods are often semiquantitative and never validated, which makes the comparison with lesion scores on conventional radiographs or MRI ambivalent. This problem in contrast with the ldCT imaging technique, which has a low radiation dose and for which 2 scoring methods have been proved valid.[60,62] Despite several disadvantages, nuclear imaging methods should not be ruled out in the individual diagnostic process and evaluation of patients with axSpA. Especially for patients with medical implants or other nonremovable bodily metal and patients who may not be able to undergo an MRI examination safely for other reasons, these alternative imaging techniques can be used.

In addition, MRI and conventional radiography are powerful imaging techniques but are not the sole means of diagnosing patients with axSpA. Diagnosing a patient with axSpA is about recognizing patterns, a process in which the rheumatologist should acquire a clear view of the probability of the disease. This view is only obtained when taking imaging, as well as the patient's medical history, results from physical examination and laboratory tests into consideration.

## DISCLOSURE

The author has nothing to disclose.

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