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Update of Imaging in the diagnosis and management of axial spondyloarthritis

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Abstract

Imaging of the spine and sacroiliac joints has acquired a central role in the diagnosis and classification of axial spondyloarthritis (axSpA) at the earliest phases of the disease. New definitions of specific imaging lesions, particularly in magnetic resonance imaging (MRI), have been recently updated and revised by the ASAS MRI working group to reach a standardized understanding and diagnosis of axSpA among rheumatologists. Recognizing the misleading pitfalls of MRI lesions and differential diagnosis also represents an essential issue in clinical practice to avoid false-positive findings and establish the diagnosis of axSpA with careful regard to the clinical context, clinical signs, and biological tests.

This review summarizes the current evidence on the different imaging modalities of the sacroiliac joints and the spine with their application in the clinical setting of SpA, their main pitfalls as well as a highlight on the newest emerging imaging techniques.

Keywords: imaging, axial spondyloarthritis, diagnosis, management.

I. Introduction

Imaging of the sacroiliac joints (SIJ) and the spine has gained a pivotal role in clinical practice for the recognition of early axial spondyloarthritis as no unique reliable serological marker is available. Even though radiography is still the first imaging tool used to capture structural damage suggestive of sacroiliitis, magnetic resonance imaging (MRI) is a more accurate tool and has become a major asset in the early diagnosis of spondyloarthritis (SpA) and a surrogate marker for prognosis and monitoring of disease activity in trials[1,2].

Over the past decade, understanding the natural development of different lesion types of the spine has increased significantly, and analyzing MRI lesions over time has been of great value in the interpretation of pathophysiological mechanisms [3,4]. It has become clear that inflammatory lesions are visualized on MRI long before structural lesions are detected on conventional radiography[5]. On MRI scans, bone marrow edema (BME)/osteitis in subchondral bone is still considered to be indicative of active inflammation of the sacroiliac joints (SIJ) in early and later stages of axial SpA (axSpA)[6] and an anchor element of the Assessment in SpondyloArthritis international Society (ASAS) classification criteria of axSpA [7]. In contrast, erosions and ankylosis indicate structural damage, which may occur relatively early in disease. The clear presence of BME/osteitis on MRI scans is detectable in early stages before structural damage is seen on radiography and computed tomography (CT) [8].

Nevertheless, for clinicians, the challenge remains in the proper interpretation of imaging findings and more specifically what really constitutes a “positive MRI”[9]. Recent comparative studies on athletes, pregnant women, and chronic low back pain patients [10–12] have raised awareness of the multiple misleading pitfalls and controversies that can occur in the evaluation of imaging with an emphasis on the ability to differentiate mechanical stress changes from pathological MRI lesions in SpA patients.

In 2015, the EULAR task force presented recommendations for the use of imaging modalities in SpA in clinical practice [13]. However, since 2015, new evidence has become available with data on specificity and sensitivity of MRI imaging findings in SpA, an updated consensus for MRI lesion definitions[14], improvement in MRI techniques and sequences for better imaging

performance[6] as well as the emergence of new imaging tools such as whole-body MRI and 18F-fluoride PET-CT [1,15].

This review provides a comprehensive overview of the different imaging tools with updated standardized protocols and thresholds in the diagnosis of axSpA of the SIJ and the spine as well as a highlight on the newest imaging modalities for axSpA monitoring and management.

II. Imaging of the sacroiliac joints in axial spondyloarthritis

1. Conventional radiography of the sacroiliac joints

Conventional radiography (CR) of the sacroiliac joints is the first imaging modality for the assessment of a patient with clinical suspicion of axSpA, despite its low sensitivity, specificity, and reliability. Radiographic structural changes are sclerosis, erosions, pseudo-widening, bony bridges, or ankylosis. The 1984 modified New York classification criteria [16] incorporate a radiographic grading system used to assess structural lesions. The radiographic criterion for classification of ankylosing spondylitis is met if there is bilateral sacroiliitis grade ≥II or unilateral sacroiliitis grade III or IV. A single view of the SIJ is recommended. This may be an anteroposterior (AP) view showing both the pelvis and the hip joints or a modified view in which the x-ray tube is angulated 30° to 35° cephalad (Ferguson view) [17,18]. Additional oblique views to reduce structural overlap result in more radiation and do not enhance diagnostic accuracy [19].

2. Computed tomography of the sacroiliac joints

Computed tomography (CT) has superior sensitivity and specificity compared to CR in the visualization of subtle bone erosions, sclerosis, and ankylosis at the SIJ, posterior elements of the spine, and costovertebral joints [20]. Even though CT results in an increased amount of radiation compared to CR, it can be useful in patients with negative CR and unable to undergo MRI [13] or when there are equivocal MRI abnormalities [21]. However, it does not detect inflammatory lesions in early axSpA before structural damage occurs.

Low- dose CT (ldCT)has emerged recently as an alternative to conventional CT in the imaging of the SIJ and spine. LdCT of the SIJ had a superior diagnostic accuracy to SIJ radiography with similar mean radiation exposure (0.51 mSv compared with 0.52 mSv respectively) [22]. However, it is still unknown whether ldCT would have higher sensitivity and specificity than conventional full dose CT for the detection of structural lesions and quantification of syndesmophytes [22]. Studies with abdominal CT scans done for another medical reason in patients with ankylosing spondylitis, have shown the possibility to detect SIJ abnormalities related to sacroiliitis with good sensitivity (Se: 0.71) and excellent specificity (Spe: 1) compared to SIJ CT [22].

3. Magnetic resonance imaging of the sacroiliac joints

MRI of the SIJ is the best tool for the evaluation of early inflammatory lesions. This examination should include T1-weighted (T1W) and fluid sensitive sequences such as T2-weighted fat-suppressed (T2-FS), T2-weighted Dixon, and short-tau inversion recovery (STIR). For sacroiliitis, intravenous gadolinium contrast-enhanced imaging (such as T1-FS post-Gd) is not recommended by EULAR [13] as it has not been shown to increase diagnostic accuracy and it is costly. However, in doubtful cases, it can be used for differential diagnosis.

3.1. ASAS definition for a positive MRI

In 2009, ASAS defined a positive MRI i.e., active sacroiliitis, as “highly suggestive of spondyloarthritis” if BME was seen in the same SIJ quadrant on at least two consecutive slices of an MRI scan or if there was more than one BME lesion present on a single slice [6,23]. In 2016, the ASAS MRI working group updated the definition of a positive MRI adding that BME observed on STIR or T2-FS or osteitis on T1-FS post-Gd must be clearly present in a typical anatomical location in the subchondral bone marrow and the appearance should be highly suggestive of SpA [6]. In particular, the importance of contextual interpretation of both fat-suppressed and T1W scans was emphasized. This definition was designated for classification purposes rather than for axSpA diagnosis. In the absence of BME, the other inflammatory or structural MRI lesions were not considered sufficient to define “active sacroiliitis on MRI” [6].

3.2. MRI Scoring system

The extent of BME can be quantified according to the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system [24]**.** Semicoronal slices are assessed on fat-suppressed scans from anterior to posterior. The six with the most severe inflammation are selected and each SIJ is divided into 4 quadrants: the upper and lower sacrum and the upper and lower ilium. Each quadrant is assigned a score of 1 for the presence of BME or 0 for the absence of BME. Each SIJ on each slice is scored for the presence of "deep" lesions (a homogeneous, unequivocal increase in signal extending ≥1 cm from the articular surface) or "intense" lesions (high signal compared to sacral blood vessels). Scoring for 6 consecutive slices leads to a maximum score of 48 for BME, 12 for intensity, 12 for depth, and 72 in total [24].

3.3. Recommended MRI sequences for sacroiliac joints

Simultaneous evaluation of T1W and fat-suppressed sequences (STIR, T2-FS) MRI sequences of the SIJ is recommended as the appropriate scanning protocol for axSpA diagnosis by the European Society of Musculoskeletal Radiology (ESSR) Arthritis Subcommittee[25]. The SIJ should be visualized in two perpendicular planes: oblique coronal (parallel to the posterior surface of the S2 vertebral body) and oblique axial (perpendicular to the oblique coronal slice) [25].

The T1W sequence detects the signal from fat (hyperintense signal on T1W) that contrasts with the cortical bone (hypointense signal on T1W). Hence, T1W is used to evaluate structural damage, mostly bone erosion [2]. As for fluid sensitive sequences, T2-FS sequences have suggested higher detection of BME compared to PD-STIR in the SIMACT study [26]. MRI can perceive various lesions indicating active inflammation/signs of disease activity (typically BME/osteitis) or structural damage (bone erosion, fat lesion, sclerosis, backfill, and new bone formation/ankylosis). Their standardized definitions were recently revised and validated by the ASAS MRI-working group [14,25]. New MRI lesions seen in axSpA were recently described such as joint space fluid or fat metaplasia in an erosion cavity (described in **Figure 1 and 2**) [14].

3.4. Diagnostic utility of MRI lesions

Altogether, defining a reference standard in imaging for axSpA remains a real challenge. A recent systematic review on MRI diagnostic performance reported an increased specificity when other lesions such as erosion and fat lesion were associated with BME[27]. In five studies, SIJ erosions

revealed good specificity but poor to moderate sensitivity with a higher sensitivity of erosions in AS than in non-radiographic axSpA [27]. As for the utility of SIJ fat lesion, four studies have shown a low to moderate sensitivity (0.15-0.70) but moderate to high specificity (0.72-0.95) for the diagnosis of axSpA with increased specificity in AS than in non-radiographic axSpA [27]. Concerning the other MRI lesions reported in three studies including ankylosis, sclerosis, capsulitis, fluid signal (**Figure 1 and 2**), backfill and vacuum phenomenon (presence of gas in the joint space associated with degenerative diseases) have demonstrated limited diagnostic performance [27,28].

3.5 Prognostic value

It is increasingly acknowledged today that MRI has prognostic value in the prediction of radiographic damage in SpA [29]. In the DESIR cohort study, BME on the SIJ-MRI was identified as a predisposing factor for progression to radiographic sacroiliitis 5 years later [30]. Further, the association of SIJ-BME with other parameters such as HLAB27 positivity and elevated C-reactive protein (CRP), increased the likelihood of progression from non-radiographic to radiographic axSpA from 1.2% to 18.4% [30]. Also, a recent histopathological analysis of 193 SIJ biopsies of patients with axSpA showed that the presence at baseline of cartilage pannus/granulation tissue invasion and endochondral ossification were both risk factors for progression to radiographic sacroiliitis [31].

III. Imaging of the spine in axial spondyloarthritis

Spinal changes may be clinically relevant for diagnosing axSpA because they usually represent more advanced stages of the disease. However, because only a limited proportion of the patients with axSpA were reported to have spinal changes without distinct SIJ changes, the involvement of the spine has not been part of any classification criteria for axSpA so far [32].

1. Conventional radiographs of the spine

Conventional radiographs (CRs) of the spine are usually the first imaging modality ordered for the assessment of a patient with low back pain of any cause in clinical practice.

1.1- Sensitivity

In the early phases of the disease, CR have low sensitivity to detect axSpA lesions which makes them of very limited utility for early diagnosis. Instead, they are used to evaluate other differential diagnoses.

In more advanced phases of the disease, the radiographic abnormalities in the spine can be categorized into osteo-destructive (erosions of the vertebral corner and the vertebral endplate) and hyperproliferative (enthesophytes, vertebral squaring, disc calcifications, spondylophytes, syndesmophytes, bony bridging, vertebral ankylosis) pathologic changes. These may rarely be evident without the involvement of the SIJ; therefore, the inclusion of routine radiography of the spine in diagnostic evaluation is not useful [3].

The time required for structural lesions of the spine to develop is still unknown, with significant individual variability among patients [33]. Globally, such structural changes have been reported to be present in more than 50% of patients within the first 16 years of AS [34].

1.2- Specificity

Syndesmophytes are typical axSpA lesions characterized by their characteristic vertical growth, which may lead to bridging phenomena in the pre-discal region between the intervertebral disc and the anterior longitudinal ligament [35]. However, they may be confused with spondylophytes, which are of degenerative etiology but can also be found in patients with axSpA, particularly in those with longer disease duration.

1.3- Prognostic value

The presence of syndesmophytes at baseline is a poor prognostic marker as it is associated with the development of additional syndesmophytes and structural progression in prospective cohorts[33]. In patients with early axSpA in the DESIR cohort, radiographic progression in the

spine at 5 years was evident in 42% of patients who had a syndesmophyte at the start of the study compared with 4% of patients without baseline syndesmophytes in this cohort [36]. Therefore, the presence of a syndesmophyte at baseline, or during follow-up, may be a factor in the decision of stepping up therapy towards biologics, particularly in patients who have failed NSAIDs.

In addition to inflammatory spinal changes, structural changes on CR may also play an important role in the evaluation of medical interventions because the effects of NSAIDs or biologic agents on new bone formation are relevant in clinical studies on patients with axSpA.

1.4- Scoring

The first described scoring method for assessing radiographic progression in the spine in patients with axSpA was the Stoke Ankylosing Spondylitis Spine Scoring (SASSS)[37] followed by the Bath Ankylosing Spondylitis Radiology Index (BASRI)[38]. Comparisons of the scoring methods have confirmed that the modified SASSS (mSASSS) method is the most valid, feasible, and responsive plain radiographic scoring method[39].

In the mSASSS method[40], lateral radiographs of the cervical and lumbar spine are evaluated. A score of 1 is assigned to any vertebral corner erosion, squaring of the vertebral body, or vertebral corner sclerosis, a score of 2 is assigned to a vertebral corner syndesmophyte and a score of 3 is assigned to a vertebral corner with intervertebral ankylosis present. The total score for the 12 anterior vertebral corners including each cervical and lumbar spinal segment, therefore, ranges from 0 to 36. Spinal radiographs are typically scored from at least two-time points at least 2 years apart. Several studies of axSpA cohorts have shown that the average mSASSS progression is 1 unit per year when radiographs are read in known time sequence and 1 unit every 2 years when read blinded to the time sequence [41,42]. A 2-year follow-up is required before changes can be reliably detected with this method and so detecting disease modification in the 12–16 week time frame of placebo-controlled trials is not possible. A working group has also developed a calibration module for mSASSS that includes standardized definitions and methodology for scoring; its use led to improved reliability of the mSASSS method [43]. A modification of the mSASSS method to include the lowest four thoracic vertebral corners (lower edge of T10 to upper

edge of T12) has also been attempted with the aim of improving its sensitivity to change, given the high frequency of spinal lesions at the thoracolumbar junction on MRI [44]. However, this modification did not improve the sensitivity to change of the mSASSS method when used to assess either patients with well-established SpA or patients with early axSpA (that is, patients from the DESIR cohort). The lower thoracic spine is often difficult to visualize owing to beam collimation for the lumbar spine combined with lumbar lordosis, which results in poor reliability in detecting change.

A further modification of the mSASSS method included the addition of the cervical facet joints [45]. Compared with the original mSASSS method, this modified mSASSS method detected more patients with definite damage at baseline (61% versus 57%) and more patients with definite progression after 4 years (55% versus 48%).

1.5- Limitations

The visibility of the C7–T1 (the cervicothoracic junction) and the L5–S1 (the lumbosacral joint) spinal segments is often poor and visualizing the thoracic spine is not possible because of overlapping soft and bony structures. Correct interpretation may be additionally limited due to scoliosis or kyphosis. Also, lateral CRs only show an over projection of the medial and lateral part of a vertebra, and the posterior corners on the lateral view of the CR cannot be assessed reliably. Moreover, CR are associated with irradiation, which may be a limitation, especially in juvenile forms of axSpA.

1.6- Diagnostic utility

CRs are the gold standard for the assessment and quantification of structural spinal changes, and thus are useful to assess the course of the disease and the damage that has already occurred.

2. Low-dose CT of the spine

Low-dose CT (ldCT) has also been described for the spine. Complete assessment of the spine is possible using an effective radiation dose of 4 mSv as compared with 8 mSv for assessment of

the thoracic and lumbar spine[46]. This imaging modality has been employed to quantify the structural progression of axSpA in research but is not yet recommended for diagnostic evaluation. In 50 patients with AS in the Sensitive Imaging in Ankylosing Spondylitis cohort, lateral cervical, and lumbar spine CR and whole spine ldCT were obtained at baseline and 2 years. LdCT, covering the whole spine, detected nearly five times more new or growing syndesmophytes compared with CR, most being found in the thoracic spine. The biggest advantages of ldCT were the ability to analyze the thoracic spine and the opportunity to analyze the growth of syndesmophytes in any plane, correcting for spinal curvatures, particularly at the posterior rim. Discrimination between treatments and testing if a shorter interval for ldCT can pick up sufficient change remain to be evaluated.

3. Magnetic resonance imaging of the spine

3.1- Sensitivity

Spine MRI is considered the most sensitive method for the detection of inflammatory lesions related to axSpA [47,48]. It can be used for the identification and quantification of active spinal lesions, where it has proved superior compared with other imaging techniques. Typical findings of disease activity when using spinal MRI in patients with axSpA are spondylitis, inflammation of the facet joints, and (aseptic) spondylodiscitis. Also, the lateral parts of the vertebral bodies and facet joint region should be assessed with the spinal images, because they are frequently affected in AS, and preferentially involved early in the course of the disease [49,50].

Spinal MRI can also be used as a response tool for biological treatment, and a possible predictor of response to therapy. In an MRI study from patients with active AS treated with tumor necrosis factor inhibitors (TNFi) who participated in randomized controlled trials, the likelihood ratio (LR) for the achievement of BASDAI 50 was increased in patients with widespread inflammation of the spine as per a Berlin MRI spine score >11 (LR 6.7) [51].

T1-weighted (T1W) MRI has also been successfully used to assess structural changes [52]. However, a significant inter-reader variability is noted, especially among less experienced readers.

3.2- Specificity

Similar to the SIJ, BME of spinal structures is not exclusive to axSpA but may also occur in other diseases. The most important differential diagnoses are degenerative/mechanical lesions, blood vessels, and hemangioma, fractures, metastases, or bacterial inflammation[3]. Degenerative lesions in the spine are common, even in young patients who have had a short duration of symptoms and can include vertebral corner inflammatory and fat lesions. On the other hand, inflammation in the costovertebral joints has a high specificity (>90%) for the diagnosis of axSpA but sensitivity is inadequate (<20%)[53,54].

3.3- Prognostic value

Several prospective studies have examined the link between inflammation at a vertebral corner and the subsequent formation of new bone as detected on radiography [55–58]. Evidence from these studies suggests that the vertebral corners where inflammation transforms into fat metaplasia are more likely to be associated with new bone formation. Biopsies were obtained from 21 patients with AS and 18 patients with degenerative disc diseases during planned surgery from vertebral edges where MRI signals of fatty lesions (FL) were detected [59]. FL corresponded to the presence of adipocytes, resulting in a change of cellular homeostasis towards the diminution of osteoclasts in the bone marrow of patients with AS. Consequently, the reparative response to inflammation, and not inflammation itself, might be the primary factor that predicts ankylosis. The presence of such MRI lesions in the SIJ joints and spine are may be a relevant factor when deciding whether to intensify treatment with the addition of a biologic drug, especially in young patients with active disease despite NSAID therapy.

3.4- Definition of a positive spine MRI lesion

The recommended approach for imaging of the spine in patients with axSpA is a T1W and a fat-suppressed MRI scan in the sagittal plane[25]. Fat-suppressed MRI scans can detect axSpA features such as spinal inflammatory lesions in the bone marrow of vertebral corners, adjacent to vertebral endplates, at costovertebral, facet, and costotransverse joints and in spinous

processes, as well as in soft tissues at the entheses. Fat metaplasia might be seen in the bone marrow at the same locations on T1W scans.

The ASAS/OMERACT MRI working group has provided a consensus definition for MRI findings of the spine indicative of axSpA[48]. This consensus statement concludes that inflammation in three or more anterior or posterior vertebral corners on at least two consecutive sagittal slices should be regarded as highly suggestive of axSpA, particularly in patients of younger age when degenerative changes are less frequently expected. In general, several studies demonstrated that lower thresholds for the number of inflammatory lesions resulted in reasonable sensitivity but poor specificity; increasing the threshold improved specificity but worsened sensitivity [53,60–62].

Regarding structural changes, fat metaplasia at several vertebral corners may also be indicative of axSpA. Detection of fat metaplasia at vertebral corners, particularly if present at several sites, increases the likelihood of axSpA, especially in younger patients, and is also associated with future radiographic progression at the affected vertebral corners [57].

Characteristic lesions in the spine of patients with axSpA as depicted by MRI are shown in Figure 3.

3.5- MRI scoring systems

Two methods of spinal inflammation assessment using fat-suppressed MRI scans have been widely used in clinical trials over the past several years[63,64]. Both methods score BME in the vertebral bodies on sagittal scans according to disco-vertebral units (DVU), each unit being delineated by two horizontal lines across the middle of the adjacent vertebrae.

The Berlin method scores the degree of BME according to the percentage volume of the DVU affected with BME (scoring range 0–3 per DVU). The SPARCC method divides the DVU into quadrants and records the presence or absence of BME on three consecutive sagittal slices and adds a weighting for intensity and depth of BME (scoring range 0–18 per DVU). Both the Berlin and SPARCC methods were able to discriminate between active therapy and placebo at 12–16 weeks in clinical trials of both AS and nr-axSpA [65–71].

A third method, the Canada–Denmark score, assesses the presence or absence of inflammation in vertebral bodies as well as the lateral and posterior segments of the spine[72]. As this anatomy-based method can also score structural lesions in the spine, in addition to BME, analysis of associations between different lesions on MRI is possible. Such analysis might further scrutinize the effects of potential disease-modifying therapies at different stages in the evolution of lesions from inflammation, to fat metaplasia, to new bone formation.

3.6- Diagnostic utility

Spinal MRI adds little incremental value to sacroiliac joint assessment alone in the diagnostic evaluation of patients with axSpA. In a Swiss–Canadian study of two cohorts (A and B, which together comprised 130 patients with undiagnosed back pain and a suspected diagnosis of axSpA, and 20 healthy individuals), sacroiliac joint and spine MRI assessments were conducted independently 6 months apart[73]. Of the patients with clinically suspected nr-axSpA who were negative for axSpA on sacroiliac joint MRI, 15.8% and 24.2% of those in cohorts A and B, respectively, were categorized as having axSpA following global evaluation of the combined MRI scans. However, of the patients with nonspecific back pain, 26.8% and 11.4% of those in cohorts A and B, respectively, and 17.5% of the healthy volunteers who were negative for axSpA on sacroiliac joint MRI, were falsely recategorized as having SpA by the combined MRI analysis. Also, data from the SPACE cohort[60], showed that the ASAS definition of a positive spine MRI did not have any useful diagnostic utility. The presence of inflammation in at least five corner lesions had a specificity of ~95% and a sensitivity of 14%. The presence of five corner lesions with fat metaplasia performed equally well as a cut-off in the SPACE cohort study. However, when these cut-offs were assessed in 541 and 650 patients with chronic back pain from the SPACE and DESIR cohorts, respectively, only 1% and 2% of patients without radiographic or MRI-detected sacroiliitis had at least five inflammatory and/or fat metaplasia corner lesions in the spine[74].

In general, spinal MRI may enhance the diagnostic sensitivity for axSpA by 15-20% in patients presenting with undiagnosed back pain where the MRI of the SIJ is considered equivocal or normal[73]. However, this is associated with a similar increase in false-positive diagnoses and a decline in specificity because vertebral corner BME and fat metaplasia can be observed in healthy

individuals and those with nonspecific back pain and degenerative disorders. Consequently, routine MRI of the spine and SIJ is not recommended.

Data from the DESIR cohort has shown that MRI inflammation is more frequently observed in spinal segments that are symptomatic[75]. However, a later Dutch study from 2016 investigated spinal imaging findings together with localization of pain in patients from the SPACE cohort and found that spinal pain correlated significantly with imaging findings of degenerative lesions and that axSpA spinal lesions were not associated with pain[76].

Therefore, spinal MRI could be considered in addition to the assessment of the SIJ in certain clinical settings such as in patients with IBP with high clinical suspicion of axSpA, with a substantial component of pain in the interscapular region and where a major treatment decision is pending. In established axSpA, spine MRI may have a role in the differential diagnosis of exacerbations of axial symptomatology in patients with previously stable symptoms. It may support the decision whether these symptoms reflect the failure of therapy or an alternate source of pain such as degenerative or prolapsed disc pain. Whether spinal MRI has a role in tailoring a treat-to-target strategy and prevention of structural damage remains to be confirmed [77].

4. Bone density testing

It has been established that patients with axSpA have an increased risk of osteoporosis and fractures [78,79]. Persistent systemic inflammation might be one of the etiologic factors responsible for bone loss, which is most frequently measured by using dual-energy X-ray absorptiometry (DXA) [79]. In the DESIR cohort, bone loss at the lumbar spine and hip was observed in half of the patients with early axSpA over 5 years. Intriguingly, MRI inflammation at baseline was not correlated to this bone loss. On the other hand, another interesting observation is that TNF-inhibitors can increase BMD at the lumbar spine and total hip in patients with AS [80]. Yet, the effect of TNF-inhibitors on bone density is still unclear. Besides, it has been raised whether the alteration of BMD at the lumbar spine is linked to regional bone metabolism at the vertebral corners. To address this hypothesis, a study has investigated the correlation between bone activity at the vertebral corners and bodies using ^{18}F-fluoro-deoxyglucose positron emission

tomography (^{18}F-FDG PET) and BMD at each vertebral level from L1 to L4 [81]. A positive correlation was found between 18F-fluoride SUVmax uptake at the vertebral corners and conventional BMD of the lumbar vertebra (γ= 0.402, p = 0.005); however, the correlation was not significant between vertebral bodies uptake and conventional BMD [81]. These findings suggest that BMD at the lumbar spine is affected by the osteoblastic activity at the vertebral corner. Therefore, a cautious interpretation of BMD on DXA should be undertaken in patients with axSpA.

IV. Clinical application of imaging in diagnosis and monitoring in axial spondyloarthritis

1. Clinical application of imaging in the diagnosis of axSpA

Detection and definition of patients with early axSpA, when treatment may be more effective, remains a continuous challenge. Diagnosis is often made years after symptoms develop [82] when radiographic damage is first noted.

1.1- Clinical application of conventional radiography of the pelvis in the diagnosis of axSpA

Pelvic radiography remains the cornerstone of the diagnostic evaluation of axSpA in clinical settings. In general, conventional radiographs of the SI joints are recommended by EULAR as the first imaging method to diagnose sacroiliitis as part of axial SpA [13]. They should be particularly considered in patients of less than 45 years of age with chronic back and/or buttock pain who present with symptoms suggesting an inflammatory basis to the symptomatology. The presence of SpA-related features such as iritis, psoriasis, and colitis and/or a family history of SpA should prompt the consideration of this diagnosis and evaluation by pelvic radiography.

An AP view of the SIJ is sufficient and additional views, such as dedicated oblique views, do not materially enhance the diagnostic utility. In Ferguson's view of the SIJ, the X-ray beam is projected

30-35° cranial centered to the mid-portion of the pelvis. In this view, the symphysis pubis overlaps the sacrum and does not obscure the SIJ. This may provide an enhanced view of the SIJ; however, the diagnostic utility of this view has not been formally demonstrated to be superior to the AP view[3].

Even when radiographs are used to make the diagnosis of axSpA, the agreement among readers is only fair to moderate[83,84]. Therefore, the rheumatologist and the radiologist must communicate together about the clinical context of a given case, to avoid under- or overdiagnosis of axSpA based on CR.

It is important to keep in mind that CR has limited value in the early stages of the disease, because of its poor sensitivity and specificity caused by its inability to detect inflammatory activity[85]. In case the pelvis radiography is normal in a symptomatic patient with a high clinical index of suspicion of axSpA, repeating the radiography within 5 years is not beneficial. Prospective studies of patients presenting with clinical features of SpA but without definite radiographic changes have shown that only 10-15% develop radiographic sacroiliitis after 2 years, approximately 40% develop after 5 years, and approximately 60% develop after 10 years[86–89]. A more appropriate next step would be to order a pelvic MRI, particularly if the patient is young with short symptom duration[13].

1.2- Clinical application of conventional radiography of the spine in the diagnosis of axSpA

Radiographic abnormalities in the spine without the involvement of the SIJ are infrequent; therefore, the inclusion of routine radiography of the spine in the diagnostic evaluation may not be useful. However, spine radiographs may be valuable in the early diagnostic phase of axSpA to rule-out differential diagnoses and, especially, to identify new bone formation (syndesmophyte) since this is a poor prognostic factor for future bone formation. In that case, treatment may be stepped up according to the patient's forecasted risk of structural progression, especially given the emergence of data suggesting that biotherapies may retard this progression [90].

1.3- Clinical application of SIJ MRI in the diagnosis of axSpA

MRI can detect SIJ abnormalities at a much earlier time point compared to CR, which has allowed for the identification of axSpA early in its disease course[91].

According to the 2015 EULAR recommendation[13], MRI of the SIJ is recommended if the diagnosis of axial SpA cannot be established based on clinical features and conventional radiography, and axSpA is still suspected. In certain cases, such as young patients and those with short symptom duration, MRI of the SI joints is an alternative first imaging method to the SIJ CR. On MRI, both active inflammatory lesions (primarily BME) and structural lesions (such as bone erosion, new bone formation, sclerosis, and fat lesion) should be considered. Although erosions are not included in the classification criteria, they may be seen in a substantial proportion of patients with nr-axSpA and can be detected on MRI of the SIJ before they are seen on radiography[92]. Also, the European Society of Musculoskeletal Radiology similarly advocated for the use of MRI when axSpA is suspected and radiographs are negative or equivocal [93]. Patients with nr-axSpA who have clinically active disease but who lack objective evidence of inflammation on SIJ MRI initially may benefit from subsequent retesting for inflammation to guide treatment. In a post hoc analysis of the randomized, double-blind ABILITY-1 study, 31% of patients without SIJ MRI inflammation at baseline subsequently developed inflammation after 12 weeks of placebo[94]. In addition to its diagnostic role, SIJ MRI also has a role in disease prognosis as inflammation and fat metaplasia might predict new bone formation in the spine. Moreover, the detection of inflammation in the sacroiliac joints on MRI is also helpful in selecting patients with nr-axSpA for treatment with a TNF inhibitor, whereas the absence of inflammation on MRI and a normal serum C-reactive protein concentration predicts failure of treatment.

1.4- Clinical application of spine MRI in the diagnosis of axSpA

Unlike the SIJ MRI, spine MRI is not recommended for the diagnosis of axSpA[13]. Spinal MRI may enhance the diagnostic sensitivity for axSpA by only 15-20% in patients presenting with undiagnosed back pain where the MRI of the SIJ is considered equivocal or normal. But it is associated with a similar increase in false-positive diagnoses and a decline in specificity because vertebral corner BME and fat metaplasia can be observed in healthy individuals and those with

nonspecific back pain and degenerative disorders[73]. Consequently, routine MRI of the spine and SIJ is not recommended. [74].

Fat lesions on MRI may be used to predict the development of new radiographic syndesmophytes, thus contributing to tailored therapy. These are factors to consider when deciding on the intensification of treatment to biologic agents, especially in young patients with active symptoms despite NSAID therapy. Also, extensive MRI inflammatory activity (BME), particularly in the spine, might be used as a predictor of good clinical response to anti-TNF-alpha treatment in axial SpA. Thus, MRI might aid in the decision for initiating TNFi therapy, in addition to clinical examination and CRP.

1.5- Clinical application of other imaging modalities in the diagnosis of axSpA

Imaging modalities, other than conventional radiography and MRI are generally not recommended in the diagnosis of axial SpA. CT may provide additional information on structural damage if conventional radiography is negative and MRI cannot be performed, in the case of a patient who is sufficiently symptomatic to warrant escalation to costly biological therapy but there is still diagnostic doubt. Scintigraphy and ultrasound are not recommended for the diagnosis of sacroiliitis as part of axial SpA [13]. A comparison of the advantages and limitations of the imaging techniques most widely used in the sacro-iliac and spine in axSpA is presented in Table 1.

2. Monitoring

Using imaging techniques to monitor disease activity and progression has been of recent interest in axSpA. To monitor structural progression, CR of the spine can be performed on a 2-year basis. CT, and more particularly ldCT, may also seem advantageous to follow-up the underlying structural damage with better performance than CR [1].

As for monitoring disease activity, MRI, rather than CR and CT -that only show structural lesions-, has been used in clinical trials and has shown a considerable reduction of inflammatory lesions

over time under biologic treatment [67,95–102]. Moreover, a significant correlation between clinical disease activity and inflammatory lesions on MRI was observed in the early phases of the disease. Data from the DESIR cohort including 167 early SpA patients (mean symptom duration <2 years), showed a significant correlation (in men but not in women) between SIJ inflammation on MRI and ASDAS (β = 2.4, 95% CI 1.13-3.69) after 2 years of follow-up[103]. In this study, an increase of one unit in ASDAS corresponded to a 2.4 unit increase in SIJ SPARCC score. However, in patients with longer symptom duration (> 5 years), the correlation is weaker [104–106]. More data are needed to understand whether we can rely on MRI to monitor disease activity and treatment response in clinical practice.

Overall, disease activity monitoring using imaging is still not yet endorsed; clinical monitoring using the Ankylosing Spondylitis Disease Activity (ASDAS) as the preferred disease activity outcome measure, has been recommended by the 2017 task-force for the treat-to-target strategy of axSpA management [107].

V. The misleading pitfalls and differential diagnosis of MRI imaging

1. Positive MRI by ASAS definition in non-SpA patients

Several studies have shown that healthy subjects and conditions other than axSpA can present with BME in the SIJ on MRI fulfilling the ASAS criteria for a positive MRI. It is notable that the current ASAS criteria for axSpA diagnosis have unequivocal limitations which may lead spuriously to false-positive diagnosis. Further, it provides important insights into the specificity of BME lesions that have been much debated recently. Since a wide majority of patients present at the rheumatology clinic with low back pain, the challenge remains in recognizing specific MRI features to distinguish axSpA from common LBP and other diseases.

One study has shown that among 1020 patients with chronic back pain from a spine center, 21% were falsely considered as having sacroiliitis according to the ASAS definition; of those 42% had only the minimum amount of BME required to fulfill the ASAS positive MRI [108]. This raises

concerns about MRI specificity because subchondral BME may be induced by different causes including mechanical stress. Thus, the high prevalence of common LBP which may lead to a high number of falsely diagnosed axSpA when relying too much on MRI. In the study of Winter et al, the prevalence and extent of SIJ MRI inflammation were compared between axSpA and non-axSpA subjects [10]. Although 91.5% of 47 axSpA patients had positive MRI for sacroiliitis according to the ASAS definition, 23.4% of the 47 healthy individuals without current or past back pain also had sacroiliitis with the same ASAS definition [10]. Similarly, 6.4% of 47 controls with chronic back pain, 12.5% of 24 runners, 57.1% of the 7 women with postpartum back pain, were also considered to have positive MRI by trained readers. However, high SPARCC scores ≥5 were rarely found in healthy subjects, runners, or patients with chronic back pain. BME lesions were more frequently located in the anterior or posterior lower iliac bone in healthy persons whereas extensive BME lesions (homogeneous and unequivocal increase in signal 1cm from the articular surface) were highly specific for axSpA [10]. A study by Weber et al. showed that 30-41% of young athletes met the ASAS definition of active sacroiliitis with BME in the SIJ affecting on average 3 to 4 SIJ quadrants mostly located in the posterior lower ilium and to a lesser extent in the anterior upper sacrum. However, bone erosion was absent [11]. Another study by Varkas et al evaluating mechanical stress on SIJ MRI has shown a high prevalence of BME lesions with a SPARCC score≥1(40.9%) observed in 22 healthy active young military recruits without back pain symptoms [12]. Around 23% of them displayed SIJ BME fulfilling the ASAS definition for sacroiliitis with a non-significant increase to 36.4% after 6 weeks of intensive physical training. These findings are consistent with the fact that SIJ BME seems to be mechanically induced or strain-induced and this highlights again the importance of interpreting MRI by referring to the clinical history and background. This also highlights the serious problems in using the current quantitative definition of an ASAS positive MRI i.e. BME affecting ≥2 SIJ quadrants, for diagnostic purposes [12].

2. Which MRI lesions are specific to axSpA?

Since MRI imaging has shown some lack in specificity when looking at only BME lesions, studies have been undertaken to find more specific MRI lesions and more appropriate thresholds. A retrospective study including 485 patients without rheumatologic diseases was interested in

studying the specificity of fat metaplasia which is described as a typical structural lesion for sacroiliitis, and considered to be at an intermediate stage between inflammation and new bone formation[109]. In this study, periarticular fat metaplasia at the SIJ which was defined as adjacent to the joint and graded semi-quantitatively regarding its extent, appeared to be very prevalent and its frequency increased with age: it was detected in 51% of patients <45 years and 94.4% of patients ≥75 years [109]. On the other hand, erosions were almost absent in age groups ≤45 years (3%) and also infrequent in patients >45 years, showing that erosions are a rather specific finding for axSpA [109].

In a recent prospective study, some MRI lesions seemed to be more specific for axSpA than others, contributing to differentiating axSpA patients from the other conditions included in the analysis: postpartum women, patients with disc herniation, cleaning staff, long-distance runners, and healthy men [110]. BME and fat metaplasia were present in all the groups studied with higher frequency and severity in axSpA patients followed by postpartum women with post-partum pain. At a higher cut-off, SPARCC BME ≥ 4 was only observed in axSpA (61%) and women with postpartum pain (30%) and none of the other groups (0%): patients with disc herniation, cleaning staff, long-distance runners, and healthy men. In healthy men, the SPARCC BME score never exceeded 2 (SPARC BME ≤2). Similarly, bone erosion was only seen in axSpA (61%) and women with postpartum pain (9%). At a higher cut-off ≥ 4, erosion was almost exclusively seen in axSpA (34% in axSpA vs 2% in women, with postpartum pain) and erosions were always absent in the other groups (SPARCC erosion <1) [110]. Women with postpartum pain seem to be the primary diagnostic challenge; however, backfill lesion and ankylosis were highly specific of axSpA (occurred in 37% and 32% respectively) and were not seen in women with postpartum pain. The cut-off of SIJ BME and erosions were much lower in patients with other types of mechanical stress (ie, runners) or healthy men. Overall, while fat lesions and low levels of BME were seen in other conditions than axSpA, high levels of BME, erosions, backfill lesions, and ankylosis were highly specific for the diagnosis axSpA.

Recognizing SpA lesions and pitfalls is a crucial step to ascertain the diagnosis with careful regard to the clinical context, clinical signs, and biological tests. The results indicate a need for further defining the requirements for a positive sacroiliitis on MRI, with alternative approaches to

overcome these limitations such as including the localization of the lesions in the SIJ [111], the combination of MRI inflammatory and structural lesions (e.g, BME with erosions), or better imaging techniques to detect highly specific lesions.

VI. Future potential imaging techniques

1. The magnetic resonance imaging VIBE technique

It has been argued that BME lesions might be not specific enough for a reliable axSpA diagnosis, therefore, improving the visualization of specific lesions such as erosions might be of high relevance to this issue. An improvement of MRI sensitivity can be achieved with the volumetric interpolated breath-hold examination (VIBE-MRI) which is a fast three-dimensional MR technique employing a spoiled gradient-echo sequence. This MRI technique, the so-called 3D-FLASH sequence with fat saturation, provides high contrast of the cartilage-bone interface with thinner slices leading to the detection of structural abnormalities at a higher resolution. In the SIMACT study, MRI-VIBE identified 16% more patients with erosions compared to the standard T1W-MRI. MRI-VIBE detected even more erosions than with ldCT used as a reference standard while there was no difference in patients with no erosions in ldCT [112]. This increases the sensitivity for erosions with VIBE-MRI (Se: 0.95[0.82-0.99]) without a decrease in specificity (Spe: 0.93 [0.85-0.98]). MRI-VIBE was better and more reliable in the detection of SIJ erosions without increasing the number of false-positive findings [112]. Similarly, another study has shown that significantly more erosions in the SIJ were detected by MRI-VIBE compared to T1W-MRI and CT [113], ascertaining again that this new technique can be promising and further research is needed to better define its diagnostic performance and limitations.

2. The Diffusion-weighted imaging

Diffusion-weighted imaging (DWI) is an MRI method relying on the apparent diffusion coefficient (ADC) which reflects the degree of movement of water molecules in tissue. In axSpA patients, BME reveals increased extracellular water in inflammatory regions and can yield a high signal on

DWI with an increased ADC. In the DWI technique, the region of interest where inflammation is suspected has to be drawn and the spatial resolution is not optimal[114]. Also, this method is not superior to fluid-sensitive conventional MRI sequences in its diagnostic performance [115,116]. Images with DWI are prone to variability between 2 different examinations and between different MRI platforms [2]. This is caused by the ADC and internal reference standard variability: the internal reference standard itself may vary with the patient's age and sex, whereas, ADC values can be reduced by the presence of fat lesion which may impact the diffusion of water at BME regions. Despite its limitations in spatial resolution and ADC variability between readers and MRI units, DWI has been used as an objective tool for diagnostic purposes, improving the specificity of sacroiliitis detection and for monitoring of response to therapy in trials [2,114], however, its additive value is still debated.

3. The Dixon methods

Other new MRI techniques, such as the modified Dixon and functional quantitative Gadolinium-chelate based contrast agents (GBCA)-enhanced dynamic MRI, are being explored in osteoarthritis and rheumatoid arthritis research [117]. Recently, the Dixon techniques have changed and improved. Now images of high-resolution high-contrast including water only and water-fat combined can be reconstructed in a single acquisition of nearly 2 minute-duration. The advantage of these techniques is that they are less subject to artifacts induced by field inhomogeneity in contrast to fat-suppressed sequences that can vary in mid and low field. They also have the ability to decrease technical variability and increase reproducibility between different MRI centers because of its adaptability independent of field strength [117]. A study including 107 patient with SpA has shown that there was no difference in diagnostic performance between the T2W Dixon and the standard protocol (T1W and fat-suppressed T2W sequence) with an area under the curve (AUC) of 0.73-0.75 versus 0.74-0.76 respectively and a higher interobserver agreements for BME and fat lesion on the Dixon sequence[118].

Therefore, integrating the Dixon methods into MRI protocols can be promising in the field of spondyloarthritis.

4. *Positron emission tomography*

Positron emission tomography (PET) is a nuclear imaging technique that can be used as hybrid imaging when combined with CT or MRI for anatomical reference. Similarly to MRI, PET may be useful in the early diagnosis of axSpA since it may allow early detection of inflammatory changes even before structural damage occurs [119]. It can visualize and quantify disease activity at different targeted binding sites in the whole body (bone marrow, synovial tissue, ligament, and entheses) through the use of different specific tissue tracers.

4.1. PET tracers

Three PET tracers with different uptake mechanisms have been investigated in the SpA field. Two are inflammatory tracers: the ^{18}F-FDG (^{18}F-fluoro-deoxyglucose), a glucose analogue isotope that can visualize inflamed synovial tissue and the ^{11}C-PK11195, that binds to macrophage receptors. The ^{18}F-FDG seems to detect osteolytic lesions rather than osteoblastic lesions and may be less able to detect bone formation in axSpA with low or absent inflammation [120]. The third tracer, ^{18}F-Fluoride, is a bone tracer integrated into hydroxyapatite crystals and forming the mineral fluoro-apatite of the bone and seems to detect osteoblastic activity located mostly at active sites of bone formation in the axial skeleton [120].

4.2. Diagnostic performance of ^{18}F-Fluoride PET scan

In a pilot study on 10 patients with AS, both inflammatory tracers ^{18}F-FDG and ^{11}C-PK11195 did not show increased uptake on PET-CT scans whereas the ^{18}F-Fluoride bone tracer detected positive lesions in the spine and SIJ that matched with two-thirds of the MRI-BME lesions [120]. Thus, the ^{18}F-fluoride bone tracer seems to be more useful to evaluate disease activity in AS which is depicted by active bone formation rather than an inflammatory process [120].

Concerning inflammatory lesions in axSpA patients, a study showed a significant correlation between ^{18}F-Fluoride PET uptake in the SIJ and inflammation on MRI (ICC[IC95] = 0.61[0.26; 0.82]; p= 0.001), even if it was detected in only half of the patients [119]. Interestingly, ^{18}F- fluoride PET scans recognized twice as many as having sacroiliitis compared to MRI and CT scans suggesting that ^{18}F-fluoride PET may be a more sensitive technique to detect early lesions not yet visible on

MRI or CT scans [119]. Another study has shown a moderate correlation between ^{18}F-fluoride uptake on PET-MRI and BME in the SIJ (kappa= 0.64) and a poor correlation in the spine (kappa=0.25) [121]. Overall, the correlation between osteoblastic activity on PET and BME is still controversial, especially in the spine [119,122]. Concerning structural lesions, no correlation was found between ^{18}F-fluoride PET and the presence of erosions, ankylosis, and sclerosis visible on the SIJ CT scans [119]. These findings suggest that ^{18}F-fluoride PET can probably detect early bone remodeling before structural lesions become visible on CT or MRI. On biopsy, these ^{18}F-fluoride PET-positive lesions corresponded to non-mineralized-osteoid tissue which was absent in PET-negative lesions [123].

On the other hand, although disease activity outcome measures such as BASDAI, ASDAS, and BASFI have shown a good correlation with the number of ^{18}F-fluoride high uptake lesions on PET [124], there is still limited evidence for the use of PET scans for monitoring of disease activity in active AS patients. Still, the hybrid PET technique seems to be a promising tool for the early diagnosis of axSpA.

5. ***Bone scintigraphy and Single-Photon Emission Tomography***

Planar bone scintigraphy using a radionuclide tracer, the 99m-technetium methylene diphosphonate (99m-Tc MDP), has been extensively used to visualize sites with high bone turnover such as sacroiliitis but has shown to be of low diagnostic value in axSpA with poor correlation with MRI findings [15].

Compared to bone scintigraphy, 99m-Tc MDP single positron emission tomography (SPECT)/CT allows a more accurate anatomic localization in 3D and a more precise quantification of radionuclide tracer activity in the SIJ. A study has compared SPECT-CT to MRI for the diagnosis of sacroiliitis in 155 patients with SpA and has shown a sensitivity of 90% and specificity of 80% for SPECT-CT, with a diagnostic accuracy comparable to that of MRI [125]. More studies are awaited to delineate the role of 99m-Tc MDP SPECT-CT imaging as an alternative imaging modality for SpA diagnosis in patient with a contraindication to MRI.

6. Immunoscintigraphy

Immunoscintigraphy is a recent technique combining scintigraphy with the injection of a radiolabelled tracer, such as 99m-technetium labeled certolizumab pegol (99m-Tc CZP), which was evaluated in a pilot study [126]. A good correlation was found in 7 axSpA patients between the tracer uptake on immunoscintigraphy and BME on MRI within the same SIJ quadrant. Also, there was excellent agreement between deep BME lesions on SIJ-MRI and clear tracer uptake (score 2) assessed by SPECT (r spearman= 0.986 ($p<0.00$) and 0.956 ($p<0.00$) for left and right SIJ respectively) [126]. It has not been fully elucidated whether this immunoscintigraphic procedure using monoclonal anti-cytokine antibodies, can possibly be used to determine the underlying cytokine that drive the inflammatory process observed in BME lesions. The present observations with CZP provide insight into the possibility of a future individualized biologic treatment approach.

7. Whole body-MRI

Whole-body magnetic resonance imaging (WBMRI) can assess simultaneously both axial and peripheral joints/entheses in the same examination. Validated scoring methods are now developed to quantify the overall inflammatory load in SpA patients [127]. Although correlations with clinical evaluations have been poor[128,129], WBMRI showed a significant decline of inflammation following TNFi treatment [130,131] in parallel with a significant decrease in disease activity outcome measures in SpA [132]. While its prognostic value is still unclear, WBMRI is a promising tool for SpA evaluation and monitoring.

8. Dual-Energy Computed Tomography

Dual-Energy Computed Tomography (DECT) is a new technique using dual-source spiral CT scanners with the same radiation dose as standard CT and involves the acquisition of images

simultaneously at 2 energy levels (classically, tube voltages at 80 and 140 kV) corresponding to elements with a high atomic number or, as most of the human body tissues, to low atomic numbers. DECT has been used in gout (for the evaluation of urate deposition), calcium pyrophosphate deposition disease (CPPD), rheumatoid arthritis, and psoriatic arthritis[114]. Based on the x-ray absorption values, DECT with the virtual non-calcium (VNCa) technique, can visualize and quantify on a color-coded map the different components of bone marrow: yellow bone marrow/fat in blue color, BME/ water in green color. In a study on 47 SpA patients, DECT has been used to detect sacroiliitis/BME in the SIJ with good sensitivity (87% and 93% for readers 1 and 2) and specificity (94% and 91% for readers 1 and 2); MRI was the reference standard for BME [133]. Thus, DECT may be an alternative emerging technique for BME detection especially in SpA patients with contraindication to MRI.

VII. Summary

Imaging and especially MRI is a key asset for the early recognition of clinically suspected axSpA as well as for monitoring, prognosticating patients with confirmed axSpA. While CT performs better for structural changes, MRI is the best imaging tool to visualize inflammation at the earliest disease stages. A consensus-based update of standardized definitions for MRI lesions of the SIJ were recently updated by the ASAS MRI working group to improve agreement between physicians and enhance research initiatives. However, because of the mechanical stress on the pelvic area (i.e. post-partum women), limitations and pitfalls of the different imaging modalities mostly need to be considered when diagnosing axSpA. Further studies are awaited to better define specific MRI lesions and cut-offs that could be integrated in a new ASAS definition of a positive MRI in SpA. Also, improving imaging performance and incorporating the newest imaging modalities into the clinical practice is a real challenge.

VIII. Practice points

- MRI is the best imaging modality to diagnose axSpA at the earliest stages of the disease.
- Recognizing limitation and pitfalls of MRI imaging is a crucial step to ascertain the diagnosis with careful regard to the clinical context, clinical signs, and biological tests.
- Athletes, women with post-partum pain, patients with chronic back pain and even healthy subjects can present BME in the SIJ on MRI fulfilling falsely the ASAS criteria for a positive MRI.
- Localization of the lesions in the SIJ, higher cut-off for BME lesions, and detection of highly specific MRI lesions constitute alternative approaches to overcome these limitations for axSpA diagnosis.

IX. Research agenda

- Future perspectives are directed toward more advanced MRI techniques such as VIBE-MRI technique or the Dixon methods that improve imaging performances with a better visualization of structural damage, less technical variability and more reproducibility between institutions.
- While more studies are awaited to prove their diagnostic utility, newest imaging modalities such as the 18F-Fluoride PET scan, DECT, 99m-Tc SPECT-CT, whole body-MRI may be promising tools in the field of spondyloarthritis possibly for further defining a positive sacroiliitis and for disease monitoring on treatment.
- Immunoscintigraphy using monoclonal anti-cytokine antibodies, such as certolizumab pegol, may potentially delineate a future individualized biologic treatment approach.
- Improving imaging performance and integrating the newest imaging modalities into clinical practice are now the current challenge.

X. Conflict of interest/ disclosure:

Walter P. Maksymowych is Chief Medical Officer of CARE Arthritis Limited.

KA, XB, NZ: no conflict of interest.

XI. Funding:

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XII. Tables and Figures

Figure 1. Active inflammatory lesions on MRI images of the sacroiliac joints in patients with axial spondyloarthritis, as defined by the ASAS MRI working group [14,23]. All images have been acquired in the semicoronal orientation. ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; STIR, short tau inversion recovery; T1W, T1-weighted. Images obtained from https://www.carearthritis.com/mriportal/mriopencourse/ with permission.

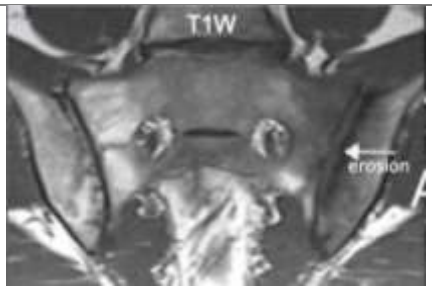
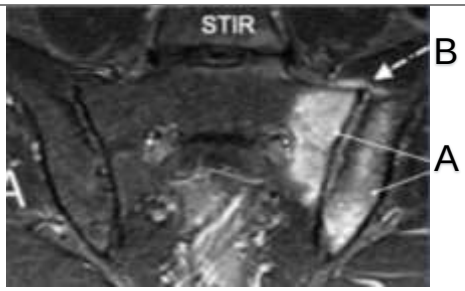
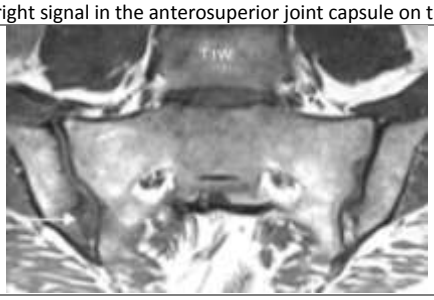
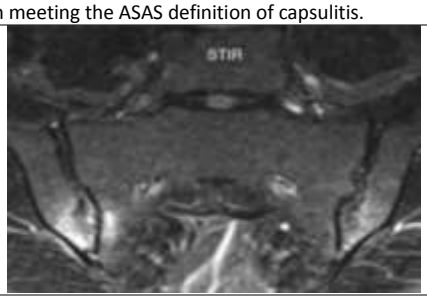
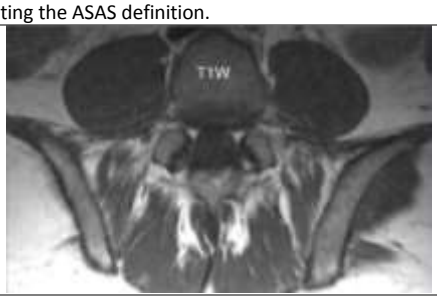
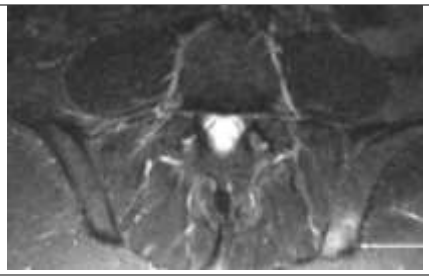
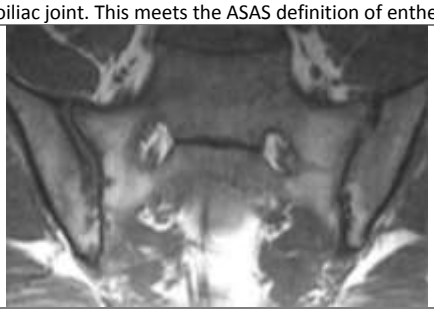
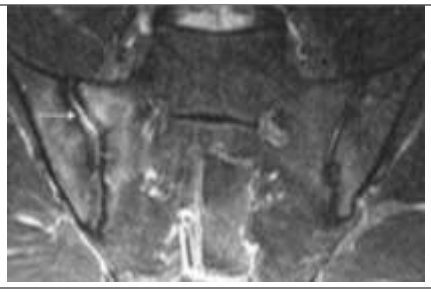
Active lesion	MRI Image in T1W	MRI image in STIR
A- Bone Marrow Edema (BME) or osteitis **B- Capsulitis**		
	A- MRI scans of a 42-year-old man with a 1-year history of inflammatory back pain, a single episode of acute anterior uveitis, HLA-B27 positivity and a CRP level of 67.5 mg/L. Extensive BME in the left iliac and sacral subchondral bone marrow is depicted as bright signal on the STIR MRI scan meeting the ASAS definition of a positive MRI. B- Bright signal in the anterosuperior joint capsule on the STIR scan meeting the ASAS definition of capsulitis.	
C- Inflammation at the site of erosion		
	MRI scans of a 35-year-old man with a 5-year history of inflammatory back pain, lack of response to NSAID therapy, HLA-B27 positivity and a CRP level of 6.8 mg/L. The arrow on the T1W scan points to erosion of the right iliac bone. There is bright signal in the cavity of the erosion on the STIR scan, indicating that there is inflammation within the erosion cavity meeting the ASAS definition.	
D- Enthesitis		
	The arrow on the STIR scan points to bright signal in the bone marrow of the left iliac bone several slices posterior to the sacroiliac joint. This meets the ASAS definition of enthesitis.	
E- Joint space fluid		
	MRI scan of a 33-year-old man with a 2-year history of inflammatory back pain, HLA-B27 positive and a CRP level of 18.6 mg/L. The arrow on the STIR scan points to bright signal, with intensity comparable to vascular signal, in the right sacroiliac joint space. This meets the ASAS definition of joint fluid.	

Figure 2. Structural lesions on MRI images of the sacroiliac joints in patients with axial spondyloarthritis, as defined by the ASAS MRI working group [14,23]**..** All images have been acquired in the semicoronal orientation. ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; STIR, short tau inversion recovery; T1W, T1-weighted. Images obtained from https://www.carearthritis.com/mriportal/mriopencourse/ with permission.

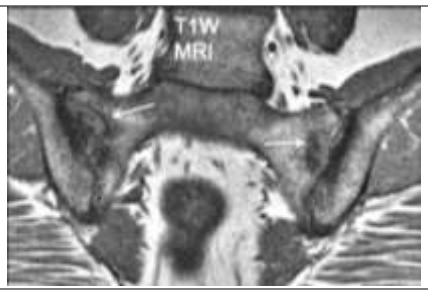
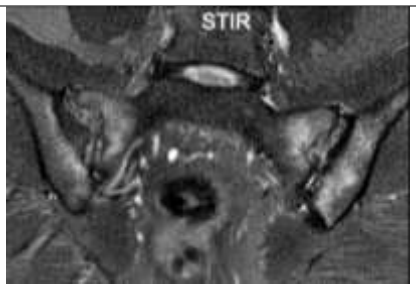
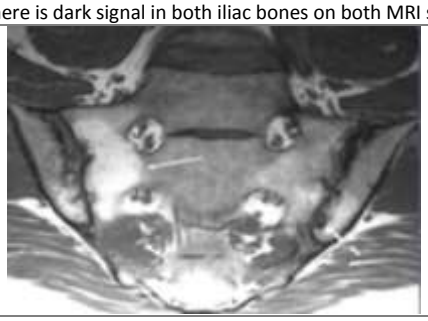
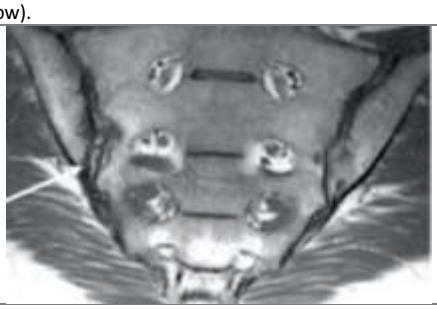
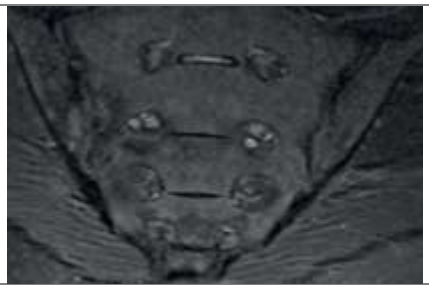
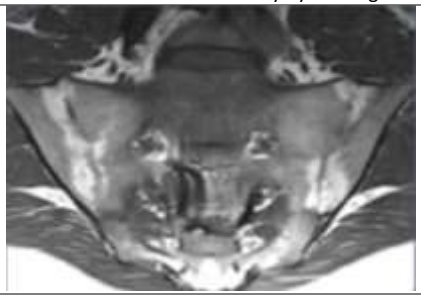
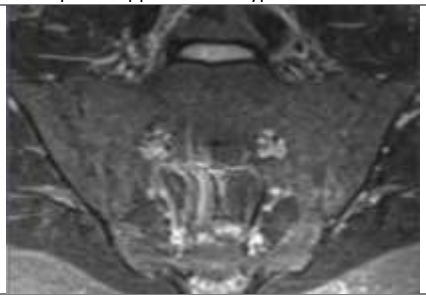
Structural lesion	MRI Image in T1W	MRI image in STIR
A- Erosion **B- Subchondral sclerosis**		
	A- MRI scans from a 39-year-old man with a 4-year history of inflammatory back pain unresponsive to NSAID therapy, HLA-B27 positivity and a CRP level of 18.8 mg/L. The arrows on the T1W scan point to large sacral erosions with loss of cortical bone and adjacent marrow matrix meeting the ASAS definition for erosion. B- There is dark signal in both iliac bones on both MRI sequences meeting the ASAS definition for bone sclerosis.	
C- Fat lesion or fat metaplasia		
	MRI scan of a 32-yearold man with a 3-year history of inflammatory back pain, Crohn's colitis controlled with TNF inhibitor therapy, HLA-B27 negativity and a CRP level of 3.5 mg/L. The arrow points to a region of homogeneously increased signal in the right sacral bone marrow on the T1W scan that has a distinct border and is adjacent to subchondral bone and erosion of the right sacral cortex. This appearance meets the ASAS definition for fat metaplasia related to SpA. There are smaller areas of fat metaplasia in both lower iliac bones adjacent to areas of erosion, especially the left iliac cortex (arrow).	
D- Fat metaplasia in the erosion cavity, known as "backfill"		
	MRI images of the sacroiliac joints of a patient after anti-TNF therapy. Bright signal in the joint space (arrow) at the site of previous erosion bordered laterally by an irregular dark band. This composite appearance is typical of backfill.	
E- Non-bridging bone bud **F- Ankylosis**		
	MRI scans of a 54-year-old woman with a 23-year history of inflammatory back pain responsive to NSAID therapy, HLA-B27 positivity and a CRP level of 4.2 mg/L. The T1W scan demonstrates several regions of both sacroiliac joints where there is continuity of bright marrow signal from ilium to sacrum across the joint space meeting the ASAS definition for ankylosis.	

Figure 3. Characteristic lesions in the spine of patients with axial spondyloarthritis as depicted by MRI. Images obtained from https://www.carearthritis.com/mriportal/mriopencourse/ with permission.

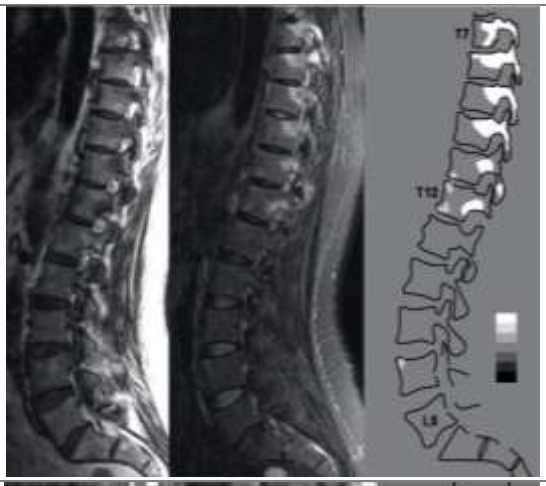
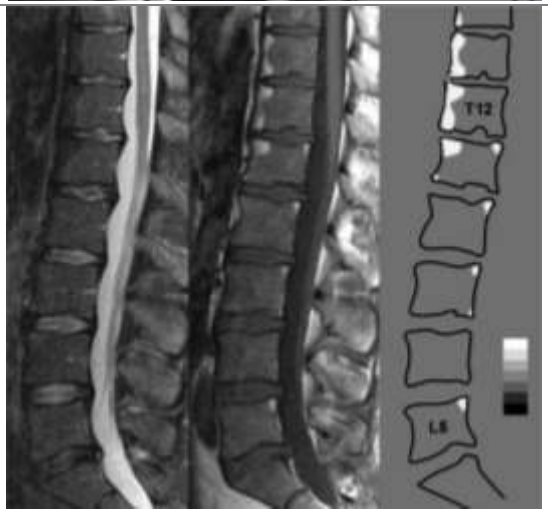
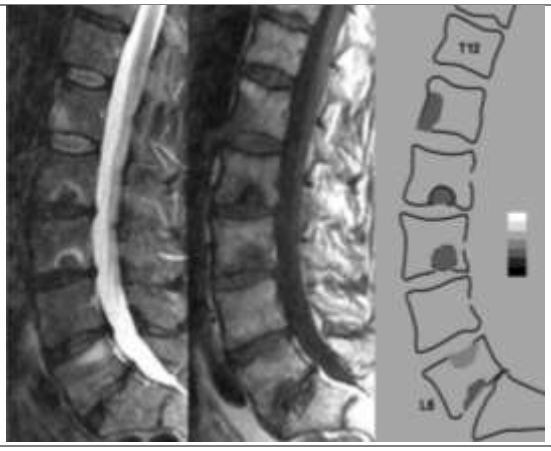
Spine lesions in axial spondyloarthritis depicted by MRI	Example
Bone Marrow Edema Multiple foci of inflammation are identified in the lateral aspects of 6 consecutive thoracic vertebrae (T7-T12). At T7/8, intense edema is present in the facet processes. At all six levels in this case, some or all of the edema is due to costovertebral inflammation. Faint anterior corner inflammatory lesions are present at T11 (inferior), T12 (superior and inferior) and L4 (superior).	
Fat infiltration Multiple focal fat lesions of bone marrow are present at many vertebral body corners, anteriorly and posteriorly.	
Anterior ankylosis T11/12 subtle ankylosis is present with bright signal in bridging bony spurs – at the threshold for detection.	
Spine Erosion An anterior Corner bone erosion (COBE) is present at the L1 inferior endplate on the T1 image. The STIR image shows increased signal indicating active inflammation at this corner. There is a large central non-corner bone erosion (NOBE) at the L2 inferior endplate [on the STIR image a non-corner inflammatory lesion with a dimorphic appearance is seen], at the L3 inferior endplate, L5 superior endplate and the L5 inferior endplate.	

Table 1. Overview of the imaging techniques used in the sacro-iliac and spine in axial spondyloarthritis , with comparison of their advantages (pros) and limitations (cons)

	Pros	Cons	Radiation	Cost	Availability
Conventional radiography	Current gold standard for the assessment and quantification of structural lesions Prognostic value for disease progression	Low reliability, sensitivity and specificity Inflammatory lesions not visualized Thoracic spine not visualized Lateral and posterior elements of spine not visualized	+	+	+++
Low dose computed tomography	Imaging of the whole spine with visualization of the thoracic spine, and lateral and posterior elements	Inflammatory lesions not visualized Lack of data regarding sensitivity and specificity for structural lesions Lack of data on sensitivity to changel	+	++	+++
Magnetic resonance imaging	Best method for detecting inflammatory lesions Differential diagnosis during spinal pain flares Selection of responders to therapy Prediction of structural progression based on fat metaplasia	Specificity Minimal added value of spinal MRI over SIJ MRI for axSpA diagnosis	-	+++	++ (depending on regions and settings)

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