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Use of Imaging in Axial Spondyloarthritis for Diagnosis and Assessment of Disease Remission in the Year 2022

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Abstract

Medical imaging remains the cornerstone of diagnostics and follow-up of axial spondyloarthritis (axSpA) patients. With the lack of specific biomarkers allowing monitoring of disease activity and progression, clinicians refer to imaging modalities for accurate evaluation of the axSpA burden. Technological advances and increasing availability of modern imaging techniques such as MRI have enabled faster diagnosis of the disease, hence dramatically changed the diagnostic delay and improved the prognosis and functional outcomes for axSpA patients.

Active sacroiliitis as visualized by MRI has been widely accepted as a diagnostic tool, and definitions of inflammatory and structural lesions within the axial skeleton have been developed. Recently, it has been acknowledged that bone marrow edema, suggestive of sacroiliitis, is a common finding among non-SpA patients, and could be attributed to mechanical loading or accumulate with age in healthy individuals. Therefore, it is crucial to distinguish between true pathological and concealing imaging findings, not only for diagnostic but also for disease remission purposes. New imaging modalities, aimed for in vivo visualization of specific molecular processes, could be employed to cross-validate findings from techniques used in daily clinical practice. This review critically evaluates the use of different imaging modalities for diagnosis and assessment of disease remission in axSpA in the year 2022.

Keywords Axial spondyloarthritis · Diagnosis · Remission · Conventional radiography · Magnetic resonance imaging · Computed tomography

Introduction

Spondyloarthritis (SpA), one of the most prevalent chronic rheumatic diseases, is characterized by a triad of joint inflammation, bone destruction, and new bone formation. The current clinical approach to SpA is driven by the predominant symptom and thus depends on whether inflammation primarily affects the sacroiliac joints and/or spine (axial SpA, axSpA) or peripheral joints and entheses (peripheral SpA, pSpA) [1, 2]. Since the early days of what is currently referred to as the SpA concept, imaging has been of key importance, as evidenced by the prerequisite to fulfill the radiological criterion of the 1984 modified New York (mNY) criteria to classify ankylosing spondylitis (AS), the prototype of axSpA [3]. In the subsequent decades, with increasing availability and utilization of magnetic resonance imaging (MRI), it was recognized that MRI features of sacroiliitis preceded radiographic changes, allowing earlier identification of axSpA patients. As a consequence, the 2009 Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA included an imaging arm incorporating radiographic sacroiliitis or MRI findings compatible with active sacroiliitis.

Although imaging is pivotal for diagnosis and follow-up of patients with suspected or confirmed axSpA, it should be emphasized that a clinical approach prevails in the daily management of these patients [4]. In particular, an international task force defined the treatment target of SpA as remission/inactive disease or alternatively low disease activity, as there is evidence supporting the association between high disease activity and radiographic progression, whereas remission halts structural progression [5, 6]. Clinical remission is

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defined as "the absence of clinical and laboratory evidence of significant disease," with the AS disease activity score (ASDAS) being the preferred outcome measure to assess disease activity [7]. Importantly, treat-to-target (T2T) recommendations refer to clinical remission/inactive disease and do not allude to imaging outcomes for the assessment of disease activity. Nevertheless, recently conducted clinical trials have defined the concept of "imaging remission" using different MRI scoring systems.

This review will discuss state-of-the-art imaging modalities and recent advances in the application of these techniques for the diagnosis and classification of adult axSpA patients. We will additionally highlight the role of imaging in defining disease remission. Application of imaging modalities for diagnosis, classification, and assessment of disease remission is summarized in Table 1.

Conventional Radiographs (X-rays)

Conventional radiographs (X-rays) of the sacroiliac joints (SIJ) and spine remain the cornerstone for diagnosis and monitoring of structural changes in axSpA patients [8]. X-rays only visualize bony structures and may therefore reveal bone destruction (e.g., erosions) and new bone formation (e.g., sclerosis, syndesmophytes). Sacroiliac alterations are collectively appraised in a semi-quantitative score which reflects the level of joint damage ("sacroiliitis"), ranging from grade 0 (no abnormalities) to grade 4 (complete ankylosis) for each SIJ separately. Radiographic sacroiliitis is defined as bilateral ≥ grade 2 or unilateral grades 3 to 4 sacroiliitis and determines the radiological criterion of the mNY criteria for the diagnosis of AS [3]. Patients with suggestive symptoms of inflammatory back pain who do not show definite

Table 1 Recommended application of different imaging modalities for the diagnosis, classification, and assessment of disease remission in axSpA

Imaging modality	Anatomical area	Diagnosis	Classification	Disease remission
CR	SIJ	Yes: radiographic sacroiliitis	Yes: radiological criterion of the modified New York criteria for AS	No: CR shows no inflammatory activity
	Spine	No	No	No: CR shows no inflammatory activity
MRI	SIJ	Yes: inflammatory and structural lesions; not mandatory but recommended if X-rays are negative or primary choice in young patients/short symptom duration	Yes: active inflammatory lesions according to the ASAS definition of a positive MRI; structural lesions not included	No: various definitions proposed, but remission is currently a clinical concept
	Spine	No: isolated spinal inflammation is rare in patients with suspected axSpA	No	No: various definitions proposed, but remission is currently a clinical concept
CT	SIJ (standard or low dose)	Yes/no: only structural lesions, superior to CR and equivalent to T1-weighted MRI, but no validated definition of CT- sacroiliitis	No	No: CT shows no inflammatory activity
	Spine (low dose)	No	No	No: CT shows no inflammatory activity
DECT	SIJ	Yes/no: may be an alternative for MRI in case of contra-indications	No	Not studied
Scintigraphy	SIJ, spine	No	No	Not studied
Immuno-scintigraphy	SIJ, spine	Yes/no: only in experimental settings	No	Not studied
PET-CT	SIJ, spine	No: not used in clinical practice because of high radiation dose	No	Not studied
SPECT	SIJ, spine	No	No	Not studied

axSpA, axial spondyloarthritis; *AS*, ankylosing spondylitis; *ASAS*, Assessment of SpondyloArthritis international Society; *SIJ*, sacroiliac joints; *CR*, conventional radiography; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *DECT*, dual energy CT; *PET*, positron emission tomography; *SPECT*, single photon emission CT

radiographic sacroiliitis may be clinically diagnosed with axSpA, but this often requires objectivation of sacroiliitis on MRI. These patients are currently categorized as non-radiographic axSpA as opposed to radiographic axSpA, which was formerly known as AS [9]. Both have been considered as an early and advanced stage of the same disease, respectively, although structural SIJ progression from non-radiographic to radiographic axSpA is rather limited nowadays (approximately 5% over 5 years) [10–12]. The differentiation between non-radiographic and radiographic axSpA is therefore obsolete, not at least because disease burden and therapeutic responses were shown to be similar in both groups [13]. Both terms should thus be used for classification of patients with axSpA and not as separate diagnoses.

Unlike SIJ imaging, which is essential for making a formal diagnosis of AS, spinal radiographs may provide additional information but are not recommended in the diagnostic evaluation of axSpA. Although spinal structural damage in the absence of radiographic sacroiliitis is rare, spinal radiographs may reveal syndesmophytes both in radiographic and non-radiographic axSpA patients, being one of the strongest risk factors for development of new syndesmophytes during follow-up [14, 15]. Such radiographic progression is relevant as it correlates with limitations in spinal mobility and worse functional outcomes [16, 17], but a minimal interval of 2 years between consecutive images should be respected to detect a meaningful change [18]. To this end, several scoring methods have been developed that quantify spinal radiographic damage, among which the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) is the most sensitive, validated, and widely used method [19–21]. Although spinal radiographs may also be useful to detect complications of axSpA (e.g., osteoporotic fractures), their use is mainly restricted to a research setting.

The main disadvantage of conventional radiography in the clinical assessment of patients suspected for axSpA is its low sensitivity, especially in early disease. In fact, only structural damage of the SIJs and the spine can be detected, which is the consequence of prior inflammation and therefore a sign of long-standing or advanced disease [22]. The diagnostic delay up to several years in radiographic axSpA patients is thus mainly due to the relatively late appearance of definite radiographic sacroiliitis according to the mNY criteria. Other major challenges in the detection of radiographic sacroiliitis are projection artifacts, poor visibility, and especially the low intra- and inter-observer agreement [23]. To accommodate this problem, recent developments in the field of artificial intelligence (AI) resulted in deep learning algorithms for automated classification of SIJ radiographs. These methods look promising but require further validation in various clinical settings and refinement to enable not only classification but also automated grading of sacroiliitis [24]. Despite some major drawbacks, conventional radiography is simple, cheap, and easily accessible, and is therefore still widely used in clinical practice today, especially in countries with limited facilities. Importantly, both SIJ and spinal radiographs may provide clues for alternative causes of (inflammatory) back pain such as osteoarthritis, osteitis condensans ilii, or diffuse idiopathic skeletal hyperostosis. However, they are not suitable for assessment of disease remission in axSpA patients since they provide little to no information on inflammatory activity.

Magnetic Resonance Imaging

A large body of evidence supports the use of MRI for the diagnosis and monitoring of disease activity in axSpA patients. This relates to the simultaneous imaging of both inflammatory and structural lesions of the SIJs and the spine, using respectively a T2-weighted sequence sensitive for free water (e.g., short tau inversion recovery, STIR) and a T1-weighted sequence. In adults, the use of gadolinium contrast to detect active inflammatory lesions is discouraged, as it did not show added value for the diagnosis of axSpA [25].

Sacroiliac Joints

According to the European Alliance of Associations for Rheumatology (EULAR) and the European Society of Skeletal Radiology (ESSR), MRI of the SIJs is recommended in patients with suspected axSpA who do not show unequivocal radiographic sacroiliitis [8, 26]. In young patients or those with a short symptom duration, MRI should even be the primary imaging method. Indeed, it was shown in the late 1990s that inflammation of the SIJs may already be visible on MRI prior to the detection of structural changes on SIJ radiographs [22]. Sensitivity of MRI-SIJ for a diagnosis of axSpA ranges from 35 to 91%, depending on the clinical context [27]. In case of a negative MRI at the initial work-up of a patient with chronic back pain suspected for axSpA, the probability of a positive MRI after 3 months to 2 years is low (5–15%) and even negligible in female or HLA-B27-negative patients, suggesting that repeated MRI of the SIJs is only diagnostically useful in selected cases [28–31]. In this regard, cautious interpretation is warranted in patients under full dose of non-steroidal anti-inflammatory drugs (NSAIDs). This may in fact attenuate inflammatory MRI lesions in patients with established SpA, albeit that the impact on diagnostic investigations in patients with suspected axSpA has not been formally studied [32].

In a recent consensus-based update from the ASAS MRI Working Group, several standardized MRI lesion definitions were revised, and new definitions were developed and validated to describe the spectrum of inflammatory lesions (namely subchondral bone marrow edema or osteitis, capsulitis, enthesitis, joint space enhancement — formerly known as synovitis, and joint space fluid) and structural lesions (namely

erosions, fat metaplasia, sclerosis, fat metaplasia in an erosion cavity or backfill, non-bridging bone bud, and ankylosis) that can be seen on MRI of the SIJs in axSpA patients [33]. Active sacroiliitis, characterized by the presence of subchondral bone marrow edema on MRI of the SIJs, is still considered to be the hallmark feature of axSpA and is therefore included in the imaging arm of the 2009 ASAS classification criteria, besides radiographic sacroiliitis. This feature, however, only determines classification and is therefore not strictly necessary for the diagnosis of axSpA. The definition of active sacroiliitis ("a positive MRI") has repeatedly been reviewed and is currently formulated as "bone marrow edema on a T2-weigthed sequence (or bone marrow contrast enhancement on a T1-weigthed sequence post-Gd), … clearly present and located in a typical anatomical area (subchondral bone), with an appearance highly suggestive of SpA." [34] The criterion "highly suggestive of SpA" was initially clarified as bone marrow edema representing an inflammatory lesion on at least two consecutive slices or more than one inflammatory lesion present on a single slice, although this quantitative aspect was less emphasized in the updated definition [34, 35]. Other inflammatory signs such as capsulitis or enthesitis are not included in the definition due to their low prevalence, although these could certainly contribute to making a diagnosis of axSpA [36]. The inter-observer agreement for detection of inflammatory lesions on MRI of the SIJs was found to be acceptable and at least more reliable than the definition of radiographic sacroiliitis according to the mNY criteria [37, 38]. Nevertheless, in recent years it became clear that bone marrow edema, and secondarily the definition of active sacroiliitis on MRI, is less specific for axSpA than initially anticipated. Numerous studies have reported a substantial prevalence of bone marrow edema in healthy individuals [39, 40], non-specific back pain patients [41], recreational and professional sportsmen [42], military recruits [43], and postpartum women [44], which is generally attributed to mechanical loading [45]. The location, morphology, and anatomical distribution of these lesions might be helpful in distinguishing inflammatory from non-inflammatory bone marrow edema, with e.g. bilateral lesions and deep lesions (extending ≥ 1 cm from the articular surface) being more indicative for axSpA [40, 46] while a predilection for the posterior lower ilium was observed in athletes and healthy individuals [40, 42]. In addition, certain thresholds have been proposed to increase the diagnostic utility. Bone marrow edema in ≥ 2 SIJ quadrants, which was shown to be most consistent with the quantitative component of the ASAS definition for a positive MRI, has erroneously been used as a diagnostic criterion, although intended for classification purposes [47]. Contrary to this consensus-based criterion, a data-driven approach showed that bone marrow edema in ≥ 3 or ≥ 4 SIJ quadrants had higher specificity for axSpA (respectively 89% and 92%) with similar sensitivity compared to a cut-off of ≥ 2 SIJ quadrants (sensitivity 80%) [48]. More recently, the ASAS MRI working group established cut-off values of bone marrow edema in ≥ 4 SIJ quadrants at any location or in the same location on ≥ 3 consecutive slices to be optimal in terms of high positive predictive value for the diagnosis of axSpA [49]. Lastly, AI-based models are emerging as unbiased tools for the automated prediction of inflammation on a quadrant-, image-, or patient-level, with potential applications in screening and quantitative assessment of MRI-SIJs. Using a semi-automated algorithm, Kucybala et al. achieved an AUC of 0.87–0.88, sensitivity of 75–80%, and specificity of 86–88% compared to human experts [50]. It is expected that additional optimization, including automated detection and segmentation of ilium/sacrum, will pave the way towards fully automated inflammation prediction.

The focus of current research is put on the accurate detection and the diagnostic value of structural lesions on MRI of the SIJs. There is ongoing debate as to whether including structural lesions in the definition of a positive MRI would improve classification, but current evidence has not yet proven sufficient to merit a change of the definition [51]. Nevertheless, structural SIJ lesions are embedded in the contextual interpretation of suspected inflammatory lesions, according to the definition. Beyond classification, a thorough evaluation of structural lesions, and especially their concomitant presence (e.g., fat metaplasia adjacent to an erosion) and association with signs of inflammation, may enhance diagnostic accuracy [52–54]. Structural lesions could additionally be observed in the absence of bone marrow edema in axSpA patients [55]. Because of the good overall agreement between MRI- and X-ray-detected "chronic" sacroiliitis, structural lesions on MRI of the SIJs have been suggested to replace the role of radiographic sacroiliitis in the ASAS classification criteria for axSpA [56].

Erosions and fat metaplasia are the most relevant structural lesions in axSpA patients, especially in early disease, while ankylosis is primarily seen in patients with advanced disease. Erosions were previously considered to be highly specific for axSpA [52]. However, Renson et al. very recently reported the progressive occurrence of structural lesions in healthy subjects in relation to age, with up to 40% of subjects aged ≥ 40 having erosions on MRI of the SIJs [39]. In contrast, the moderate specificity of fat metaplasia and sclerosis is not a new finding; its frequent occurrence in non-SpA populations has previously been acknowledged by multiple authors [57–59]. Fat metaplasia adjacent to other structural lesions is however very uncommon in non-axSpA patients, and some morphological features (e.g., distinct border, homogeneity, and depth > 5 mm) were also shown to be of certain diagnostic value [53, 60]. In analogy to inflammatory lesions, several thresholds for structural lesions have been suggested to increase diagnostic confidence. Weber et al. reported erosions in ≥ 2 SIJ quadrants to be highly specific for SpA (97%), while de Hooge et al. suggested that ≥ 3 erosions, ≥ 3 fat lesions,

or ≥ 5 of these in any combination, each lesion being present on ≥ 2 consecutive slices, being optimal to ensure > 95% specificity [48, 61]. According to the ASAS MRI working group, optimal cut-offs were any one of ≥ 3 quadrants with erosion or ≥ 5 with fat lesions, erosion at the same location for ≥ 2 consecutive slices, fat lesions at the same location for ≥ 3 consecutive slices, or presence of a deep fat lesion [49]. The latest progress in this field, although still preliminary and awaiting validation, is the development of composite structural damage scores, based on different weights for erosion, backfill, and ankylosis [62]. Importantly, all authors conclude that a combination of quantitative criteria for inflammatory and structural lesions (most often erosions) outperform individual lesion-based criteria, which most closely reflects the global assessment of an MRI-SIJ in the diagnostic evaluation for axSpA.

The reliability of erosion detection on MRI of the SIJs varies considerably and is complicated by its heterogenous appearance, different definitions and the impact of varying MRI acquisition parameters (e.g., choice of contrast-rich sequences or slice thickness) [63, 64]. Several alternative MRI sequences were therefore recently developed, primarily aiming for a more accurate assessment of erosions compared to routine T1-weighted MRI. Three-dimensional (3D) volumetric interpolated breath-hold examination (VIBE) has received most attention in recent years, as it was found to be more sensitive for detection of SIJ erosions compared to T1-weighted MRI [65, 66]. However, slice thickness also determined its performance [67]. Few studies explored other 3D MRI sequences such 3D fast low-angle shot (FLASH), 3D double excitation in the steady-state (DESS), and 3D water selective balanced steady-state free precession sequence (b-WS-SSFP) in their ability to delineate cartilaginous defects of SIJs, given their high intrinsic contrast between cartilage and cortical bone and high spatial resolution [68, 69]. Another recent development is the generation of "radiograph-like" and "CT-like" images from axial 3D T1-weighted multiple gradient echo (T1w-MGE) MRI, using a deep learning-based method, in order to improve the visualization of osseous structures. Using conventional CT as reference standard, *synthetic CT* of the SIJs has shown better diagnostic performance for detection of structural lesions in patients with suspected sacroiliitis compared to routine T1-weighted MRI [70]. Representative images of the SIJs created by the *synthetic CT* algorithm are shown in Fig. 1 (own data). Although promising, these novel techniques collectively require further validation as the question remains how detected lesions should be quantified and interpreted. The differentiation from physiological variants indeed becomes more difficult when smaller structural lesions compatible with erosions can be detected, with subsequent impact on its diagnostic performance. Additional acquisition time, costs and availability also need to be considered prior to incorporating these techniques in daily clinical practice.

Spine

A variety of inflammatory and structural lesions can be seen on MRI of the spine in axSpA patients, as defined by the ASAS MRI working group. Inflammatory lesions include anterior/posterior spondylitis (corner inflammatory lesions or *Romanus* lesions), spondylodiscitis (*Andersson* lesion), costovertebral or facet joint arthritis, and enthesitis of spinal ligaments, while structural lesions are defined as fatty depositions, erosions, syndesmophytes, or ankylosis [71]. A cut-off of ≥ 2 or ≥ 3 corner inflammatory lesions and ≥ 6 corner fatty lesions has been proposed to define a positive MRI spine for spondylitis, but these thresholds failed to show clinical relevance for the diagnosis of axSpA, i.e., only poor to moderate sensitivity [71, 72]. Inflammatory and fatty corner lesions are also commonly observed in healthy subjects, particularly with increasing age [59]. In addition, the assessment of all lesion types suffers from poor to moderate inter-reader agreement [73]. Importantly, radiographs are still superior to MRI when it comes to detection of morphologic cervical and lumbar vertebral changes (i.e., erosions and syndesmophytes), while MRI is the preferred method to assess the thoracic spine [74, 75].

In a diagnostic context, the incremental value of spinal MRI besides MRI of the SIJs is very limited; only 1% of suspected axSpA patients show suggestive inflammatory

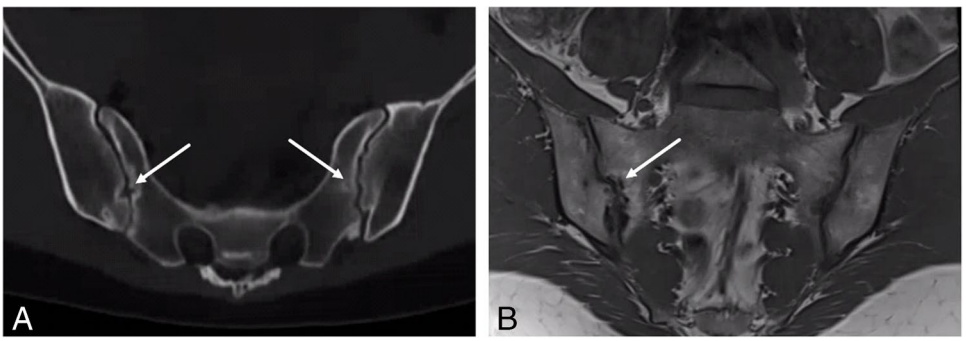

Fig. 1 MRI imaging of the sacroiliac joints of a 30-year-old female patient diagnosed with axial spondyloarthritis. **A** Synthetic CT algorithm, **B** T1-weighted sequence

or structural spinal lesions in the absence SIJ abnormalities [76, 77]. Spinal MRI is therefore not generally recommended in the diagnostic work-up of axSpA [8].

MRI for Assessment of Remission

Several scoring methods have been developed that aim to quantify the level of inflammation on MRI of the SIJs and the spine as a proxy for disease activity (e.g., the SpondyloArthritis Research Consortium of Canada (SPARCC) index) [78]. Because these scores objectify inflammation, it is not surprising that they correlate better with ASDAS status and change scores compared to outcomes that are exclusively patient reported such as Bath AS Disease Activity Index (BASDAI) and ASAS response criteria [79, 80]. Multiple clinical trials demonstrated efficacy of tumor necrosis factor inhibitors (TNFi), interleukin-17 inhibitors (IL-17i) and recently Janus Kinase inhibitors (JAKi) in active radiographic and/or non-radiographic axSpA through a significant and sustained reduction of SIJ and spinal inflammation scores parallel to improvements in clinical outcomes [81–83]. Notwithstanding, there is no consensus on a standardized definition of MRI remission in axSpA, thus several trials have defined it differently. In the EMBARK trial, MRI remission of the SIJs and the spine was defined as a SPARCC MRI SIJ score ≤ 2 and SPARCC MRI spinal 6-discovertebral unit (6-DVU) score ≤ 3, respectively [81]. In the RAPID-axSpA trial, remission thresholds were SPARCC MRI SIJ score < 2 for the SIJs (validated) and Berlin modified ASspi-MRI-a ≤ 2 for the spine (unvalidated) [82], while the ABILITY-1 trial used more stringent cutoffs: a SPARCC score < 2 for the SIJs, spine, or both [83]. Besides remission criteria based on axial MRI inflammation indices, criteria for peripheral joints and entheses (inflammation index ≤ 2) as well as a comprehensive index defining whole-body MRI remission have been established in axSpA [84]. However, in addition to its ambiguous definition, MRI remission shows no strong correlation with clinical remission [85]. Similarly, a dissociation between clinical responses and changes in MRI inflammation scores, especially in patients with longer disease duration, suggests that inflammation is not the only cause of symptoms in axSpA [86]. Noteworthy, the background noise of inflammatory lesions on MRI in the healthy population is not negligible. Recently, an age-related increase in inflammatory lesions on MRI of the SIJs was reported in healthy subjects. The finding that 13.9% (20–29 years old), 25.8% (30–39 years old), and 35.7% (40–49 years old) of healthy individuals showed bone marrow edema suggestive of axSpA should be kept in mind when defining "imaging remission" in an axSpA population [39] (Table 2). Figure 2 represents findings from MRI of the SIJs of healthy individuals compared to axSpA patients, from a study published in 2022 by Renson et al. (reprinted with permission). Ultimately, treatment targets in axSpA are still based on clinical outcomes as it remains an open question whether imaging outcomes, in particular MRI remission, relate to structural progression and long-term functional outcomes. A consensus on the timing and frequency of repeated MRI to monitor disease activity is also lacking and currently depends on the clinical context.

Computed Tomography

Low-Dose CT

Standard CT images enable visualization of structural abnormalities in the SIJs and the spine. For complicated anatomical structures such as the SIJ, it permits multi-planar assessment of the synovial joint space and the ligamentous compartment, resulting in greater sensitivity for detection of SIJ lesions compared to two-dimensional radiographs [87]. Relative to T1-weighted MRI, CT was found to be equivalent or even superior for detecting signs of SIJ destruction [68,

Table 2 Inflammatory and structural MRI lesions of the sacroiliac joints in healthy subjects (adapted from Renson et al., Arthritis Rheum, 2022) [39]

	All age categories ($n=95$)		20–29 years ($n=36$)		30–39 years ($n=31$)		40–49 years ($n=28$)	
	N (%)	Median** (IQR)	*N* (%)	Median** (IQR)	*N* (%)	Median** (IQR)	*N* (%)	Median** (IQR)
Active sacroiliitis (ASAS definition)	11 (11.6)	-	1 (2.8)	-	5 (16.1)	-	5 (17.9)	-
SPARCC index > 0	23 (24.2)	2.0 (1.00–4.50)	5 (13.9)	1.0 (0.75–2.00)	8 (25.8)	3.3 (1.13–6.00)	10 (35.7)	2.3 (1.00–5.25)
Erosions*	19 (20.0)	2.0 (0.50–4.50)	5 (13.9)	0.5 (0.50–0.75)	3 (9.7)	5.5 (-)	11 (39.3)	2.0 (1.50–3.50)
Fat metaplasia*	13 (13.7)	2.0 (1.00–3.50)	3 (8.3)	1.0 (-)	6 (19.3)	2.5 (1.00–3.25)	4 (14.3)	3.3 (1.13–10.25)
Sclerosis*	2 (2.1)	1.8 (-)	1 (2.8)	3.0 (-)	0	-	1 (3.6)	1.0 (-)
Partial ankylosis*	1 (1.1)	9 (-)	0	-	1 (3.2)	9 (-)	0	-

*Median values refer to the number of quadrants with the respective structural lesion. **Median values are those in subjects displaying one or more of the respective lesion. *ASAS*, Assessment of SpondyloArthritis international Society; *SPARCC*, Spondyloarthritis Research Consortium of Canada

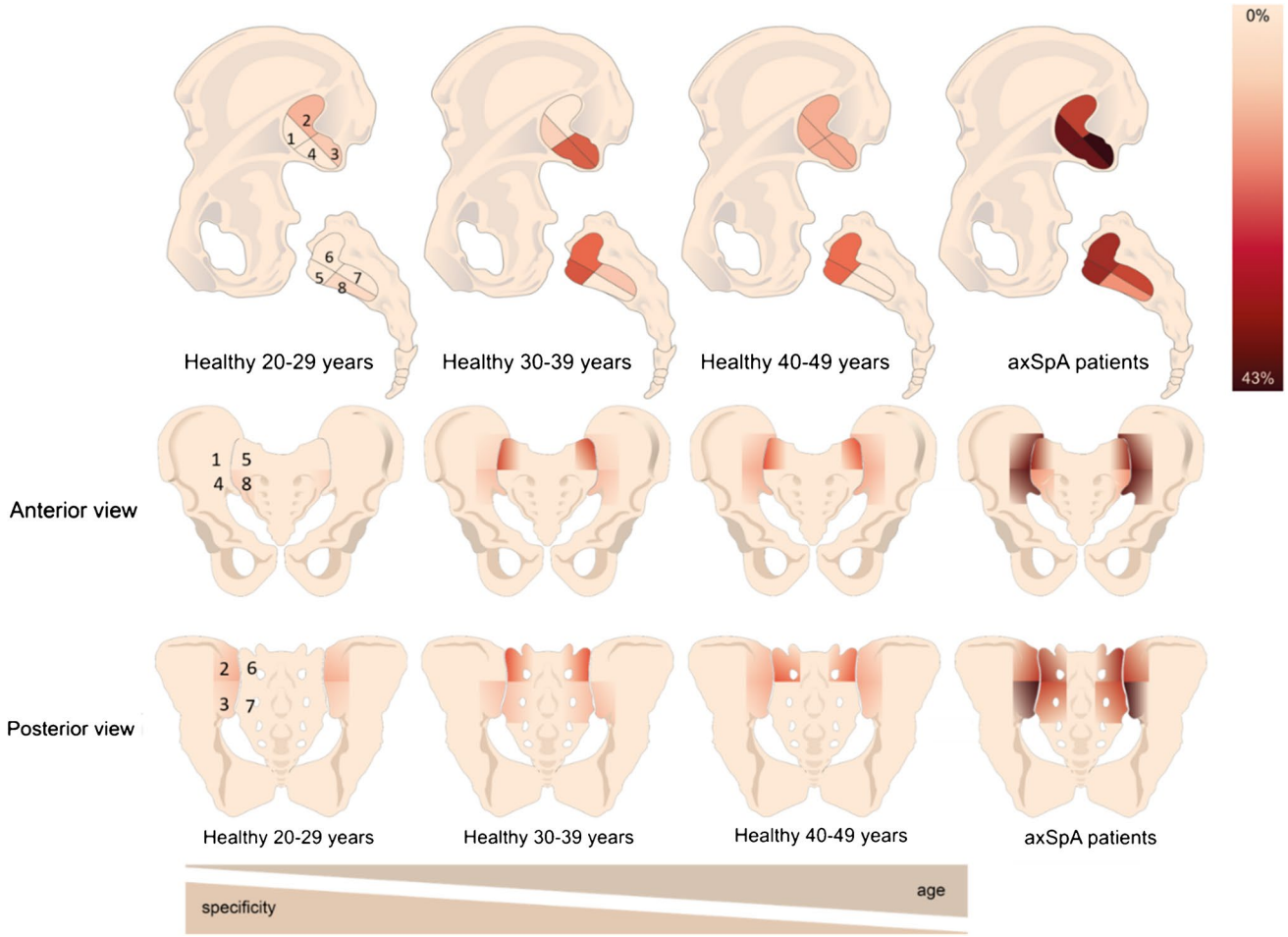

Fig. 2 The prevalence of structural lesions on MRI of the sacroiliac joints of healthy, asymptomatic subjects compared to axSpA patients. Heatmaps (both sagittal and frontal view) of the percentage of healthy, asymptomatic subjects ($n=95$) with bone marrow edema on MRI at the different quadrants of the sacroiliac joints compared to axial spondyloarthritis (axSpA) patients of the Belgian inflammatory arthritis and spondylitis cohort (Be-GIANT, $n=86$). (1) = anterior superior ilium; (2) = posterior superior ilium; (3) = posterior inferior ilium; (4) = anterior inferior; ilium; (5) = anterior superior sacrum; (6) = posterior superior sacrum; (7) = posterior inferior sacrum; (8) = anterior inferior sacrum. Reprinted with permission from Renson T, de Hooge M, De Craemer A-S, et al. Progressive increase in sacroiliac joint and spinal MRI lesions in healthy individuals in relation to age. Arthritis and Rheumatology

88]. Despite substantial inter-reader reliability, CT has not yet been extensively validated for the diagnosis of axSpA [89]. This is partly due to the absence of a consensus definition of sacroiliitis on CT, although the New York criteria, developed for plain radiography, have been uncritically adopted in many studies. It was shown that only erosions, especially in the middle and dorsal joint portion, and diffuse inhomogeneous sclerosis correlated well with a clinical diagnosis of axSpA [90–92]. In addition, CT lacks information on inflammatory lesions and is accompanied by a relatively high radiation dose, contrary to MRI. Nevertheless, this argument has been refuted with the introduction of low-dose CT imaging, which has the advantage of properly displaying a three-dimensional structure such as the SIJ, while exposing patients to a radiation dose of approximately 0.5–1 mSv, which is similar to or even lower than conventional SIJ radiographs [93]. Low-dose CT may serve as an appropriate alternative for conventional radiography to assess structural changes of the SIJ, given its higher sensitivity for detection of erosions and joint space changes including ankylosis [94]. Moreover, a recent study confirmed that low-dose CT comes with similar sensitivity and higher specificity for the diagnosis of axSpA compared to T1-weighted MRI [95]. The latest progress in this field is the development of ultra-low-dose CT using tin filtration (radiation exposure of 0.11 mSv), which equally showed better overall diagnostic performance for sacroiliitis than conventional radiography [96].

Dual Energy CT

The inability of standard CT imaging to depict bone marrow edema restricts its use for the diagnosis, assessment of

disease activity or treatment response in axSpA patients. Dual energy CT (DECT) might however respond to this shortcoming. DECT simultaneously acquires two CT imaging sets at different tube voltages, followed by subtraction of calcium in the trabecular bone using postprocessing software. The resulting virtual non-calcium CT images enable visualization of increased water content (edema), which has recently been evaluated in axSpA. Using MRI as a reference standard, DECT showed a sensitivity of 81–93% and specificity of 91–94% for detection of bone marrow edema, therefore providing a valuable diagnostic option in patients with contra-indications for MRI [97, 98].

Molecular Imaging

The ground-braking discovery that bone is a metabolically active tissue has opened a new chapter in skeletal imaging. It allowed for the development of highly sensitive techniques based on the detection of signal from radioactive tracers albeit coupled to pharmaceuticals, accumulating in the areas of increased metabolic activity. A vast range of the available radiopharmaceuticals and different acquisition modalities enable non-invasive visualization, characterization, and quantification of molecular processes at inflammatory lesions in the bone tissue of SpA patients.

Bone Scintigraphy

Bone scintigraphy is the most established skeletal nuclear medicine imaging method. Methyl diphosphonate labeled with Technetium-99 m (^{99m}Tc) is injected intravenously and absorbed by the bone tissue [99]. While normal bone absorption of the radiopharmaceutical does not exceed 40%, it increases significantly in hyper-metabolic states making it a sensitive tool for the diagnosis of early and radiologically occult bone pathologies. However, accelerated bone turnover and hence increased uptake of the radionuclide are not always indicative of the underlying pathology. Increased tracer uptake has been described in joint pathologies traditionally perceived as non-inflammatory, such as osteoarthritis [100]. This decreases the value of bone scintigraphy as a diagnostic tool in inflammatory conditions such as SpA. Although early reports on the use of bone scintigraphy in detecting sacroiliitis were promising [101–103], more recent studies have suggested that clear separation of active inflammatory AS from controls is difficult [104–106]. In a study comparing different imaging modalities for the detection of early signs of SIJ inflammation, MRI revealed twice as many cases of sacroiliitis as bone scintigraphy [107]. Quantitative SIJ scintigraphy was shown to have no discriminative value in distinguishing axSpA patients and control individuals complaining of inflammatory back pain [108]. A systematic review of the diagnostic value of scintigraphy for the assessment of sacroiliitis concluded that the method's sensitivity does not exceed 53% in AS patients [109]. Attempts to increase the sensitivity and specificity of planar bone scintigraphy in inflammatory arthritides have been made, by including results of bone scintigraphy in algorithms accounting for laboratory parameters such as C-reactive protein (CRP) levels [110], but the method remains of little clinical application.

Immunoscintigraphy

Several inflammatory pathways involved in the pathogenesis of SpA have been identified and successfully targeted with biological and small molecules including TNFi, IL-17i, and JAKi [111, 112]. The emergence of these medications has opened new opportunities for scintigraphy-based imaging: highly specific in vivo visualization of inflammatory processes and the possibility to predict response to treatment. Uptake and distribution of radiolabeled TNFi have been studied in different inflammatory arthritides, namely rheumatoid arthritis [113–115], psoriatic arthritis [115, 116], and axSpA [117]. These studies proved the expected value of immunoscintigraphy in visualizing active TNF-driven inflammation in both peripheral and axial joints, as well as the entheses. Radiotracer uptake correlated with clinical evaluation of the affected joints and traditional imaging [117]. In the light of the challenges associated with MRI-SIJ evaluation, immunoscintigraphy could provide a valuable alternative in the diagnostic algorithms of early axSpA. Importantly, response to treatment with TNFi was also shown to match the accumulation of the radiotracer [115], but the prognostic value of a negative immunoscintigraphic image in the prediction of therapeutic response or in the light of imaging remission, remains to be evaluated. Radiolabeling of biological drugs other than TNFi has not yet been explored in imaging of SpA. It could offer interesting insights into the mechanisms of the disease with regard to the involvement of distinct immune pathways at different anatomical sites affected by SpA, and at different stages of the disease (non-radiographic vs radiographic axSpA).

Positron Emission Tomography

PET imaging is based on detection of pairs of photons emitted from intravenously administered radiopharmaceuticals. Radioisotopes release two positrons (positively charged electrons), which in a process called annihilation with electrons, release two photons moving in opposite directions. These are detected and multiplied to create 3-dimensional functional images [118]. PET imaging is frequently combined with CT for accurate anatomical mapping of functional readouts. In the context of axSpA, it

allows to visualize structural changes in the axial skeleton. The most commonly used radiopharmaceutical is fluorine-18 [^{18}F] fluorodeoxyglucose (FDG), accumulating at sites of increased metabolic activity. While this property is usually employed in cancer diagnostics, [^{18}F]FDG PET/CT has been evaluated as a tool for the diagnosis of enthesitis, spondylodiscitis and sacroiliitis in SpA patients [119–122]. [^{18}F]FDG PET/CT successfully detected axial enthesitis in SpA patients, with sensitivity reported to be greater than MRI [119]. A study from a different group confirmed the observation that highest uptake values are localized in the tendons and soft tissue of the clinically affected joints of SpA patients [121]. However, with regard to the diagnosis of bone pathology in SpA, [^{18}F]FDG PET/CT has been shown to be of little value. Low correlation with standard imaging techniques and inconsistent results have been reported [123]. In a study comparing the uptake of different PET tracers in AS patients, [^{18}F]FDG accumulation was concluded to be more representative of osteolysis and [^{18}F]Fluoride to reflect osteoblastic activity and new bone formation, suggesting it is a more suitable radiopharmaceutical for the assessment of axSpA [124]. How this discrepancy relates to the established relationship between persisting inflammation and bone remodeling remains to be investigated [125]. The authors of this study further examined biopsies from [^{18}F]Fluoride PET-positive lesions of AS patients. Histological analysis confirmed local osteoid formation [126]. Interestingly, they have shown that [^{18}F] Fluoride uptake at affected sites decreases rapidly after treatment with TNFi, suggesting that PET imaging could help evaluate response to treatment [126].

Another radiopharmaceutical explored in PET imaging of axSpA is [^{18}F]-sodium fluoride (NaF). The tracer accumulates at both osteolytic lesions and sites of osteoblastic activity, where the compound gets absorbed into the hydroxyapatite matrix to form fluoroapatite [127]. It has been reported to distinguish between patients with AS fulfilling the ASAS criteria and control individuals with inflammatory back pain [128]. In patients with AS, higher uptake values were observed at sites of active spinal inflammation as assessed by MRI and at syndesmophytes [129]. A different group observed twice as many positive [^{18}F]-NaF PET scans as pathological findings on MRI or CT scans in a group of axSpA patients, indicating higher sensitivity of the technique and its potential to reflect the dynamics of the inflammatory process [130]. [^{18}F]-NaF PET scan has also been shown to predict response to treatment with TNFi [131].

One caveat to the promising reports on the usefulness of PET imaging in diagnosis of axSpA and assessment of therapy response is that no standardized protocols for the assessment of PET scans in SpA exist and that these studies have been performed on a small number of patients. A unified scoring system is required before the technique can find its application in clinical practice. A high radiation exposure, cost, and availability are further limiting the use of PET/CT in everyday clinical practice.

Single Photon Emission Computed Tomography

Another imaging modality using the emission of gamma rays is SPECT. In this technique, however, gamma radiation is emitted directly by the administered radiolabeled pharmaceutical. Radionuclides emitting gamma rays include widely available Indium-111 (^{111}In) and ^{99m}Tc. In comparison to radionuclides used in PET imaging, these are characterized by a longer half-life, increasing the availability and affordability of SPECT. A gamma camera acquires two-dimensional images from multiple angles, which are then reconstructed into a three-dimensional visualization [132]. Rapid technological advances in SPECT, including the use of multiple pinhole collimators, allow high-resolution imaging. Slice-by-slice three-dimensional analysis of tracer uptake significantly increases imaging sensitivity, especially in anatomical regions difficult to visualize, such as the SIJ. Complexity and anatomical variability of the SIJ could be the major causes of low accuracy of standard bone scintigraphy and plain radiographs; SPECT imaging overcomes this difficulty. It has been suggested in a study of 46 patients with chronic low back pain that SPECT with calculated indices of uptakes could detect sacroiliitis with a sensitivity and specificity of 80% and 97%, respectively [133]. A study involving 20 patients diagnosed with early SpA according to the Amor criteria confirmed these results [134]. SPECT was reported to visualize active sacroiliitis and structural SpA lesions in accordance with MRI [135]. However, higher tracer uptake has also been reported in patients with sacroiliac dysfunction, pointing towards metabolic disturbances in inflamed joint tissue, irrespective of the mechanism of inflammation [136, 137]. For the time being, SPECT remains an exploratory imaging modality in SpA.

Concluding Remarks

Recent years brought important advances in the imaging techniques available for the diagnosis and follow-up of axSpA patients. MRI is currently the most established tool for visualization of active inflammation at sites affected by axSpA, though modern algorithms allow precise detection of bone erosions too. With increased sensitivity of medical imaging, questions on the specificity of the detected lesions arise. Numerous studies report on the prevalence of inflammatory or structural lesions in healthy, asymptomatic individuals, pointing out the need for defining physiological findings on MRI. As no strong correlation between clinical remission and remission on MRI exists, consistent

definitions and protocols need to be developed in order to employ it in the follow-up workflow of axSpA patients. New imaging modalities, aimed for in vivo visualization of specific molecular processes, could be employed to cross-validate findings from techniques used in daily clinical practice.

Declarations

Competing Interests The authors declare no competing interests.

Informed Consent MR images were acquired with the patient's informed consent.

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