

New Bone Formation in Axial Spondyloarthritis: A Review

Knochenneubildung bei axialer Spondyloarthritis: eine Übersichtsarbeit



Authors

Sevtap Tugce Ulas^{1, 2}, Dominik Deppe¹, Katharina Ziegeler¹, Torsten Diekhoff^{1, 2}

Affiliations

- 1 Department of Radiology (Campus Charité Mitte), Charité Universitätsmedizin Berlin, Germany
- 2 Charité – Universitätsmedizin, Berlin Institute of Health at Charite, Berlin, Germany

Key words

axial spondyloarthritis, imaging, new bone formation

received 27.06.2023

accepted 06.09.2023

published online 2023

Bibliography

Fortschr Röntgenstr

DOI 10.1055/a-2193-1970

ISSN 1438-9029

© 2023. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Dr. Sevtap Tugce Ulas

Department of Radiology (Campus Charité Mitte), Charité
Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin,
Germany

Tel.: +49/30/4 50 62 70 44

sevtap-tugce.ulas@charite.de

ABSTRACT

Background Axial spondyloarthritis (axSpA) is a chronic inflammatory disease primarily affecting the sacroiliac joints (SIJs) and the spine. Imaging plays a crucial role in the diagnosis of axSpA, with magnetic resonance imaging (MRI) and radiography being the primary modalities used in clinical practice. New bone formation occurs in both the spine (non-bridging and bridging syndesmophytes, transdiscal ankylosis, and ankylosis of small joints and posterior elements) and the SIJs (backfill and ankylosis). New bone formation indicates advanced axSpA.

Method This review explores the role of imaging in the diagnosis and monitoring of axSpA, focusing on the significance of new bone formation, and provides an overview of the characteristic imaging findings of new bone formation in axSpA in each imaging modality.

Conclusion Imaging methods, such as X-ray, MRI, and CT, have different diagnostic accuracies for detecting structural lesions and new bone formation. Each modality has its strengths and weaknesses, and the choice depends on the specific clinical context. Imaging is crucial for the diagnosis and monitoring of axSpA, particularly for the detection of new bone formation. Different imaging techniques provide valuable information about disease progression and treatment response. Understanding the significance of new bone formation and its detection using imaging modalities is essential for the accurate diagnosis and effective management of patients with axSpA.

Key Points:

- New bone formation is a hallmark feature of advanced axial spondyloarthritis.
- New bone formation occurs both in the spine and in the sacroiliac joints.
- Differentiation of new bone formation in axial spondyloarthritis from that in other conditions such as diffuse idiopathic skeletal hyperostosis and from osteophytes is essential.
- Imaging methods, such as X-ray, MRI, and CT, have different diagnostic accuracies for detecting new bone formation.

ZUSAMMENFASSUNG

Hintergrund Die axiale Spondyloarthritis (axSpA) ist eine chronisch entzündliche Erkrankung, die vor allem das Sakroiliakgelenk (SIG) und die Wirbelsäule betrifft. Die Bildgebung spielt bei der Diagnose der axSpA eine entscheidende Rolle, wobei MRT und Röntgenuntersuchung die wichtigsten Untersuchungsmethoden in der klinischen Praxis sind. Knochenneubildung tritt sowohl an der Wirbelsäule (nicht brückenbildende und brückenbildende Syndesmophyten, transdiskale Ankylose und Ankylose der kleinen Gelenke und der hinteren Elemente) als auch am Sakroiliakgelenk (Backfill und Anky-

lose) auf. Das Vorhandensein von Knochenneubildung weist auf fortgeschrittene Stadien der axSpA hin.

Methode In dieser Übersichtsarbeit wird die Rolle der Bildgebung bei der Diagnose und Überwachung der axSpA untersucht, wobei der Schwerpunkt auf der Bedeutung der Knochenneubildung liegt, und es wird ein Überblick über die charakteristischen Bildgebungsbefunde der Knochenneubildung bei axSpA in den jeweiligen Bildgebungsmodalitäten gegeben.

Schlussfolgerung Bildgebende Verfahren wie Röntgen, MRT und CT haben unterschiedliche diagnostische Genauigkeiten bei der Erkennung struktureller Läsionen und Knochenneubildung. Jede Modalität hat ihre Stärken und Schwächen, und die Wahl hängt vom jeweiligen klinischen Kontext ab. Die Bildgebung ist für die Diagnose und Überwachung der axSpA von entscheidender Bedeutung, insbesondere für den Nachweis von Knochenneubildung. Verschiedene bildgebende Verfahren liefern wertvolle Informationen über das Fortschreiten der Krankheit und das Ansprechen auf die Behandlung. Das Verständnis der Bedeutung der Knochenneubildung und ihrer Erkennung durch bildgebende Verfahren ist für eine genaue Diagnose und eine wirksame Behandlung der axSpA unerlässlich.

Kernaussagen:

- Knochenneubildung ist kennzeichnende Veränderung bei meist fortgeschrittener axialer Spondyloarthritis.
- Knochenneubildung kommt sowohl an der Wirbelsäule als auch am Sakroiliakgelenk vor.
- Die Unterscheidung zwischen Knochenneubildung bei axialer Spondyloarthritis und anderen Differenzialdiagnosen, wie der diffusen idiopathischen skeletalen Hyperostosis, sowie degenerativ bedingten Spondylophyten ist essenziell.
- Bildgebende Verfahren wie Röntgen, MRT und CT haben unterschiedliche diagnostische Genauigkeiten bei der Darstellung von Knochenneubildung.

Zitierweise

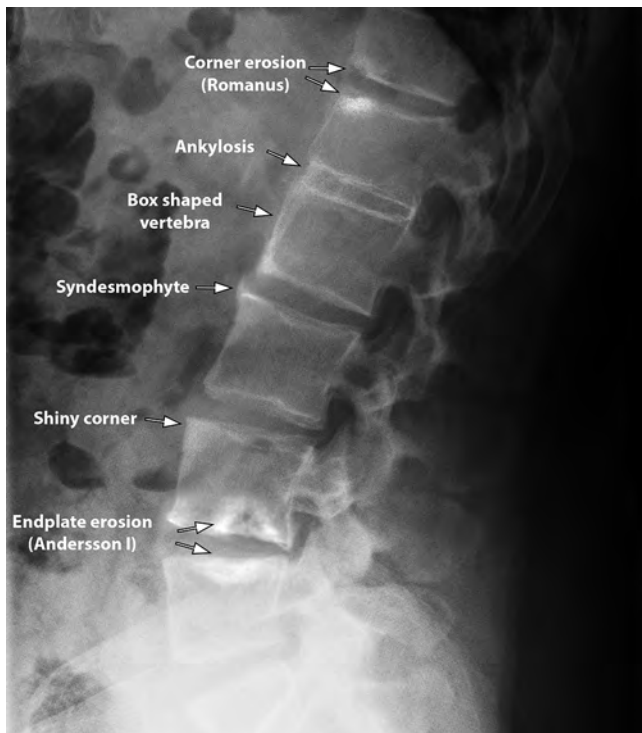
- Ulas S, Deppe D, Ziegeler K et al. New Bone Formation in Axial Spondyloarthritis: A Review. *Fortschr Röntgenstr* 2023; DOI 10.1055/a-2193-1970

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease with preferable involvement of the sacroiliac joints (SIJs) and the spine. Its incidence in Caucasians in European countries is estimated to be approximately 0.5 % to 2 % [1, 2]. The disease often occurs in early adulthood with symptom onset typically before 45 years of age [3]. The leading early symptoms are (lower) back pain, stiffness, and fatigue while loss of function occurs in the later stages of the disease [4]. One form of axSpA is ankylosing spondylitis (formerly known as Morbus Bechterew), which is characterized by the presence of structural lesions in the SIJs and the spine. Most people will experience back pain, even at a younger age, but only a few individuals with back pain actually have axSpA. In most patients, back pain is due to degenerative conditions, or no specific source of the pain can be determined. More specific back pain definitions might help identify individuals with axSpA. Such definitions include chronic back pain lasting 12 weeks or longer or inflammatory back pain, which is characterized by additional factors such as worsening at night and good response to non-steroidal antirheumatic drugs (NSAIDs) [5]. Other factors that can contribute to the diagnosis include human leucocyte antigen B27 (HLA-B27) positivity, moderately elevated C-reactive protein and comorbidities such as uveitis, psoriasis, or inflammatory bowel disease. However, few are more specific than the presence or absence of imaging findings in the context of axSpA [6].

Role of imaging for axSpA

Before the introduction of magnetic resonance imaging (MRI) and the development of the Assessment of Spondyloarthritis international Society (ASAS) classification criteria, the diagnosis of axSpA relied on radiography and the depiction of structural SIJ damage [7]. Structural changes seen on radiographs characterize advanced disease and include narrowing of the joint space and partial or complete ankylosis. For this reason, the focus of various guidelines is to develop the most evidence-based and feasible recommendation for early diagnosis to minimize diagnostic delay. There is consensus that imaging in patients with axSpA is essential for the diagnosis and management of the disease [8]. To this end, it is desirable to initiate treatment before the occurrence of irreversible structural changes, which are associated with chronic pain and permanent functional impairment. Therefore, bone marrow edema (BME) on MRI was proposed as an early and pre-structural imaging sign [9]. However, BME is not restricted to axSpA or inflammatory diseases. It may also be seen on imaging in traumatic or degenerative conditions, such as osteitis condensans ilii or anatomical variations [10, 11]. Thus, confirmation of specific structural findings, especially surface erosion, can help to distinguish degenerative from inflammatory diseases, which was acknowledged in the recent update of the ASAS classification criteria [12, 13]. However, analogous to other spondyloarthropathies, e. g., psoriatic arthritis, axSpA is characterized by new bone formation, which occurs between acute episodes when the primary inflammation subsides. The end stage of this process, ankylosis, contributes significantly to the permanent restriction of movement and loss of function [14]. Therefore, new bone formation in



► **Fig. 1** X-ray of the lumbar spine illustrating findings in axial spondyloarthritis.

the form of the so-called backfill sign or syndesmophytes further helps in ascertaining the diagnosis of axSpA and differentiating it from other inflammatory conditions such as crystal or infectious disease [15]. Syndesmophytes are the hallmark imaging finding of axSpA, and their presence is used on a regular basis to follow up the course of the disease with imaging in order to identify non-responders to current treatment [12, 16]. Given the importance of new bone formation in axSpA as just outlined, this article provides a comprehensive overview of imaging appearances and how these findings can help in diagnosing axSpA and monitoring treatment response in patient follow-up.

Pathogenesis of axSpA

To understand the meaning of different imaging findings in axSpA, a good understanding of the underlying pathogenesis of the disease is helpful. Enteses are of particular importance in the pathogenesis of axSpA [17]. They are located in various parts of the skeleton and the primary channel for the transfer of mechanical forces. Of particular interest for axSpA is the attachment of the fibrous annulus of the disc. The exact pathophysiological background is still controversial. Both genetic (HLA-B27) and various environmental factors are discussed as potentially playing a role in the initiation and development of axSpA. A recent study suggests that biomechanical stress can trigger an excessive inflammatory response (termed “mechanoflammation”) [18].

Repetitive biomechanical stress makes the enteses susceptible to inflammation and new bone formation [19, 20]. Several other studies showed that axSpA patients working in physically

demanding occupations had more loss of function and radiological damage than patients with more sedentary jobs [21] and that greater mechanical stress was associated with more severe lumbar myofascial stiffness in axSpA patients [22, 23]. Microtrauma is therefore hypothesized to have a significant impact on enteses, triggering inflammation and osteoproliferation [24]. Furthermore, the relationship between post-inflammatory changes, like fat metaplasia as a precursor, and an increased risk of new bone formation in the spine [25] and SIJs [26] has also been investigated.

Clinical experience suggests that syndesmophytes tend to form at sites of inflammatory changes, such as spondylitis anterior [19, 27], which has been supported by histological evidence [28]. Overall, available data indicate that there is some association between inflammation and new bone formation and that new bone formation is to be understood as an excessive repair process following active inflammation [16, 29, 30].

New bone formation in the spine

Imaging is an important tool for correct diagnosis and therapy monitoring in axSpA. However, spinal lesions are still not considered as criteria for the classification of axSpA [31]. Only 25% of the patients with axSpA have inflammatory or structural changes in the spine at first presentation, and only 3–5% of patients show typical findings restricted to the spine without SIJ involvement [32], and some patients will never develop spine lesions in radiography or MRI. However, the appearance of new bone formation at the spine is an important imaging indicator for disease progression and requires an optimization of treatment [16].

Different types of new bone formation are found in the spine. Typical changes are non-bridging and bridging syndesmophytes, transdiscal ankylosis, and ankylosis of small joints and posterior elements.

Syndesmophytes

Syndesmophytes are new bone formations that remodel the outer margin of the intervertebral discs and typically have a vertical orientation [15]. They originate from the attachment of the annulus fibrosus at the vertebral corner. Precursor lesions are spondylitis anterior, fatty corner lesions, and corner erosion (so-called Romanus lesions) of the vertebral entesis [33–35], see ► **Fig. 1**. Therefore, these bony extensions form on the anterior, posterior, or lateral corners of the vertebral body and grow upward or downward [36] without reaching adjacent vertebral bodies. For this reason, they are known as “non-bridging” syndesmophytes [37]. Syndesmophytes are best visualized on sagittal and coronal cross-sectional imaging (► **Fig. 2**). The MRI signal intensity of syndesmophytes is typically similar to that of bone marrow in the T1-weighted sequence [38]. In fluid-sensitive pulse sequences, they can also have a higher signal when there is active inflammation. However, a small syndesmophyte with little bone marrow may be hard to detect with MRI, and radiography or low-dose CT is warranted for detection. However, the role of syndesmophytes in disease progression has not yet been clarified.



► **Fig. 2** Magnetic resonance imaging examples of new bone formation in the spine. **A** Patient with axial spondyloarthritis (axSpA) with both spinal ankylosis (white arrow) and syndesmophytes (white arrowheads) on T1-weighted image. These findings are also seen in the corresponding CT scan. Furthermore, bone marrow edema in the lumbar spine (black arrowhead) is seen in the STIR image. **B** Patient with diffuse idiopathic skeletal hyperostosis (DISH) of the spine. DISH leads to thick ossification of the anterior longitudinal ligament with a wavy pattern (white arrowheads) while the syndesmophytes in axSpA are more slender and vertically oriented.

Ankylosis

Ankylosis usually occurs at an advanced stage and is associated with extensive loss of motion [39]. In ankylosis, the joint or disc space stiffens due to bony fusion at the attachment sites of the annulus fibrosus (known as “bridging syndesmophytes”) and/or bony fusion of the facet joints [15]. Typically, bony fusion of the anterior and posterior vertebral body corners originates from the attachment of the annulus fibrosus at the vertebral corner [38]. Unlike non-bridging syndesmophytes, ankylosis is specific for axSpA. Its most advanced form has a characteristic imaging appearance known as “bamboo spine” [15] and has been observed in up to 15% of axSpA patients [40]. The MRI signal intensity is similar to that of syndesmophytes (► **Fig. 2, 3**). Although rare, ankylosis can also occur in young patients with a particularly severe disease course.

Transdiscal ankylosis

Transdiscal ankylosis is a bony fusion ultimately resulting in ossification of the nucleus pulposus through remodeling and replacement of the intervertebral disc. Neither the anterior nor the posterior vertebral corners are involved, thus this type of ankylosis is also referred to as “non-corner ankylosis” [15]. In MRI, transdiscal ankylosis is hyperintense in T1 sequences and hypointense in fat-saturated T2-weighted sequences compared to the normal intervertebral disc. Transdiscal ankylosis usually occurs late and can occur independently of or in parallel to syndesmophyte formation [38]. Supposedly, inflammation of the disc in the form of non-septic spondylodiscitis (so-called Anderson type 1 lesions) precedes this process, which is highly specific for axSpA (► **Fig. 4**). Intervertebral ankylosis and transdiscal ankylosis serve as markers for advanced disease, as axSpA often begins in the SIJs, and are very specific for axSpA.

Small joints of the spine

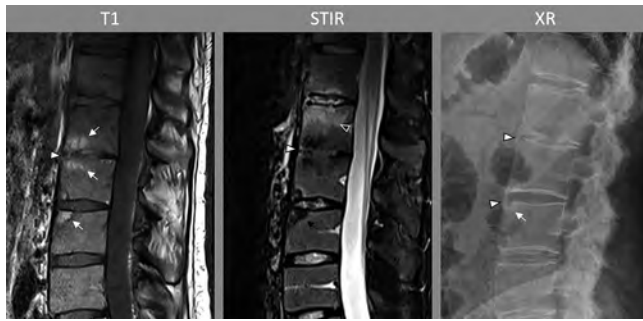
Besides the intervertebral discs and facet joints, multiple other spinal joints are commonly affected by axSpA. However, they are less commonly the target of imaging. Costovertebral and costovertebral joints are usually hard to depict by conventional sagittal MR imaging. Nonetheless, ankylosis of these joints can impair chest motion [41] and lead to respiratory problems. Currently, assessment of these joints is the domain of CT.

New bone formation in the SIJs

According to current recommendations, initial diagnostic imaging should focus on the SIJs when axSpA is suspected [13]. The SIJ is the most common site of changes detectable by imaging, since the inflammation begins here in the majority of cases [36]. The combination of active inflammation in the form of bone marrow edema and structural lesions, especially erosion and new bone formation, has the highest specificity for establishing the diagnosis [13]. As mentioned earlier, new bone formation is the hallmark of spondyloarthropathies and, thus, a significant finding for differential diagnosis. However, identifying these processes on imaging of the SIJs can be more challenging than in the spine.

Backfill

Backfill is defined as a high T1 signal in the SIJ space [26], suggesting fat tissue that has grown into a preexisting erosion [42]. There are three types of backfill [43], see ► **Fig. 5**. More specifically, it is defined as a high T1 signal on two consecutive slices and measuring 10 mm or more parallel to the subchondral bone plate on at least one slice [44, 45]. This is thought to be metaplastic tissue replenishing the erosively altered subchondral bone, but histopathological evidence is lacking [46]. A link of backfill to fat metaplasia of the subchondral bone was hypothesized because both often occur in parallel [26]. Supposedly, it follows a precursor lesion that shows a low T1 but high T2 signal and is referred to as inflammation at the site of erosion [46, 47]. Whether and how and under what circumstances backfill contributes to the development of joint ankylosis remains to be elucidated. Although it is deemed



► **Fig. 3** Imaging examples of structural spinal changes in a patient with axial spondyloarthritis (axSpA). Syndesmophytes and ankylosis are clearly seen on X-ray (XR) (white arrowheads) but are not visible on MRI (white arrowheads). Furthermore, the patient also had bone marrow edema (seen in the STIR sequence (black arrowhead)) and a romanus lesion (white and black arrows).

to be an intermediate step between erosion and ankylosis, its progression towards bridging of the joint space has not yet been successfully demonstrated. Its clinical impact, besides resembling a very specific sign for axSpA [26] and other spondyloarthropathies such as axial psoriatic arthritis, is also unknown. However, it has a high diagnostic value for axSpA and typically begins in the iliac part of the SIJ. Backfill is seen in approximately 38–63 % of patients with axSpA less than 45 years of age [44]. Although new bone formation is already a repair process and usually occurs only after abatement of active inflammation, even in so-called early cohorts, patients are found who show backfill [48] or radiographic progression in the SIJs after a short disease duration [49]. For a long time, erosion and new bone formation developing during therapy were considered to indicate radiographic progression [39]. However, recent studies suggest that the development of backfill and fat metaplasia during initial treatment with biological disease-modifying antirheumatic drugs (DMARDs) should be regarded as normal processes of repair and structural healing as they consistently occur once inflammation subsides [50]. Nonetheless, it is still a matter of debate whether biological or target-specific DMARDs have beneficial long-term effects regarding the development of new bone formation, i. e., whether backfill is successfully impeded as soon as the inflammation subsides.

Ankylosis

Ankylosis of the SIJ, i. e., the bony fusion of the SIJ, is the end-stage of inflammatory or traumatic processes of the SIJ [13]. It is considered a hallmark of advanced spondyloarthropathy [12, 13]. A characteristic feature is that the joint space has been completely or partially eliminated (► **Fig. 6**). On X-ray and CT, this is shown by a smooth bridging bony filling of the former joint space. In addition, MRI shows that fat tissue fills the articular space, which was previously occupied by cartilage, characteristically seen as a high T1 signal and low signal intensity in fat-saturated T2-weighted sequences [13]. Usually, inflammation of the joint will disappear as soon as complete ankylosis has occurred and inflammatory processes will be restricted to other joints or entheses. The extent to which backfill leads to ankylosis over time or whether it should be considered independently of this is still a matter of controver-

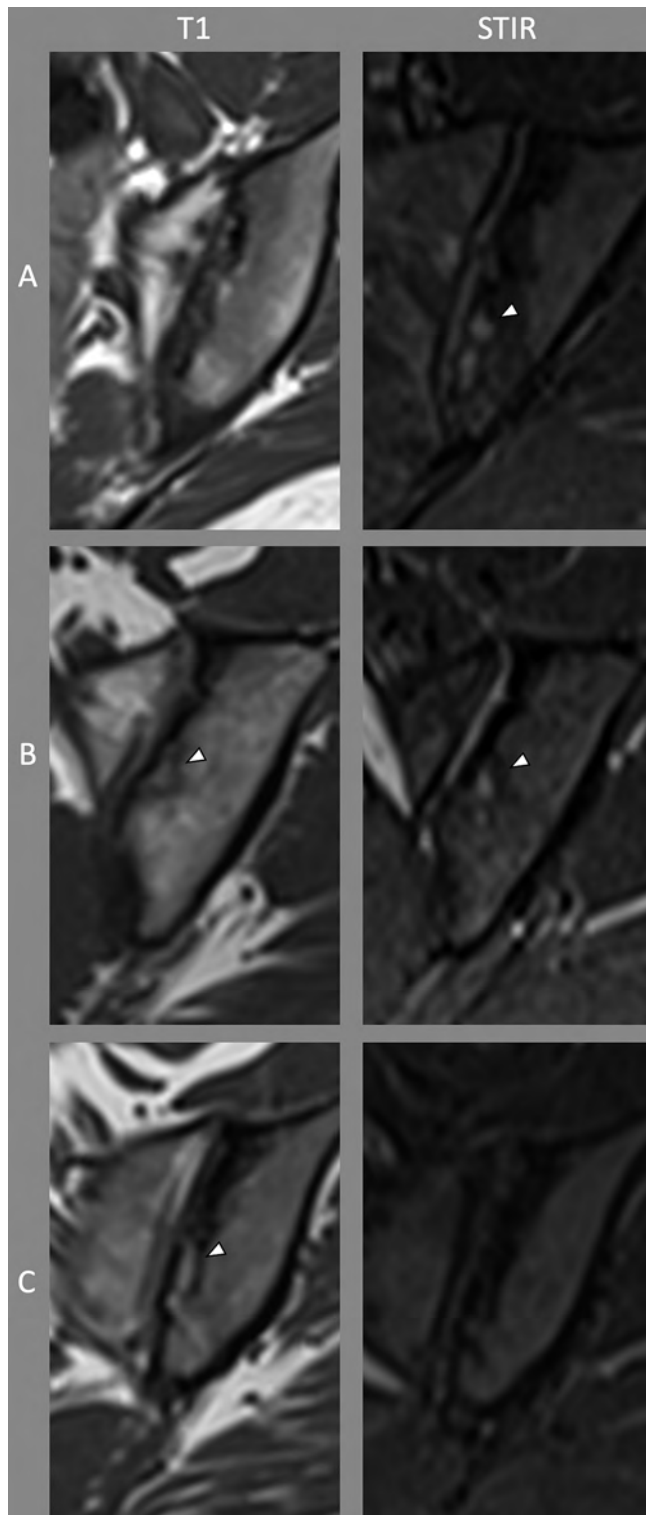


► **Fig. 4** Magnetic resonance imaging (MRI) of the spine. **A** Patient with typical Andersson I lesion (white arrowheads) in the lumbar spine with bone marrow edema (black arrowheads). Note that the erosion in T1 is filled with a high-intensity signal that represents inflammatory tissue and the beginning of new bone formation. **B** Andersson I lesion affecting only one part of the vertebral segment with accompanying fat lesion (white arrow) and bone marrow edema (black arrowhead). Note the signal difference at the end-plate representing backfill-like high T1 signal in the upper vertebra and high T2 signal at the lower vertebra (white open arrow). **C** High T1 signal with corresponding low STIR signal of the intervertebral disc indicating the presence of transdiscal ankylosis in a patient with radiographic SpA (black arrow).

sy. Ankylosis of the SIJs significantly degrades function and mobility [51], but due to the limited natural range of motion of the SIJ, this is generally less clinically apparent than ankylosis of the spine.

Important differential diagnoses

The accurate differentiation of axSpA-typical structural changes with new bone formation from other conditions is essential. For example, osteophytes are an important differential diagnosis for syndesmophytes. In contrast to syndesmophytes, osteophytic growths are characterized by their horizontal orientation. In cases of primary degenerative changes in the spine, alterations in the vertebral segments with narrowing of the intervertebral disc space are also characteristic, which is not characteristic in axSpA. Diffuse idiopathic skeletal hyperostosis (DISH), also known as “Forestier’s disease,” is characterized by thick, flowing ossification of the anterior longitudinal ligament (► **Fig. 2**). Changes associated with DISH are most commonly found in the thoracic spine and are usually unilateral on the right side, assuming that bone formation is inhibited by pulsations of the descending aorta on the left side. While DISH is predominantly observed in the vertebral column, partial ankylosis and capsule ossification of the SIJs are frequently observed. In contrast to intra-articular bridging seen in axSpA, bridging osteophytes anterior to the SIJs are more



► **Fig. 5** Magnetic resonance imaging of the sacroiliac joints (SIJs) illustrating different types of backfill. **A** Type-A backfill showing inflammation at the site of the erosion in STIR sequence (white arrowhead). **B** Type-B backfill with high signal in T1-weighted and STIR sequence (white arrowhead). **C** Type-C backfill indicating fat metaplasia in an erosion cavity with high signal in T1-weighted sequence (white arrowhead).

common in DISH. However, it is important to note that imaging-based differentiation of these two entities is not always straightforward, as coexistence of both DISH and axSpA has been described in studies [52]. While active inflammatory findings, especially bone marrow edema, are also common in mechanical and degenerative conditions, the presence of structural lesions will drastically increase the specificity for inflammatory sacroiliitis. In addition, axSpA can be distinguished from other inflammatory conditions such as septic or gouty sacroiliitis by demonstrating new bone formation such as backfill – besides clinical and laboratory factors. Moreover, other important factors need to be considered to avoid false-positive conclusions. Distinguishing degenerative osteophytes and non-bridging syndesmophytes based on their imaging morphology is not reliable. Therefore, the sole presence of non-bridging syndesmophytes without other structural lesions or active inflammatory changes in the spine or sacroiliac joints is considered equivocal and is not recommended for the diagnosis of axSpA [12, 53]. Additionally, conditions like congenital vertebral fusion can mimic ankylosis in the course of the disease, which can be either partial or complete. Intervertebral fusion can also occur as a complication of infectious spondylodiscitis (e. g., Pott's disease).

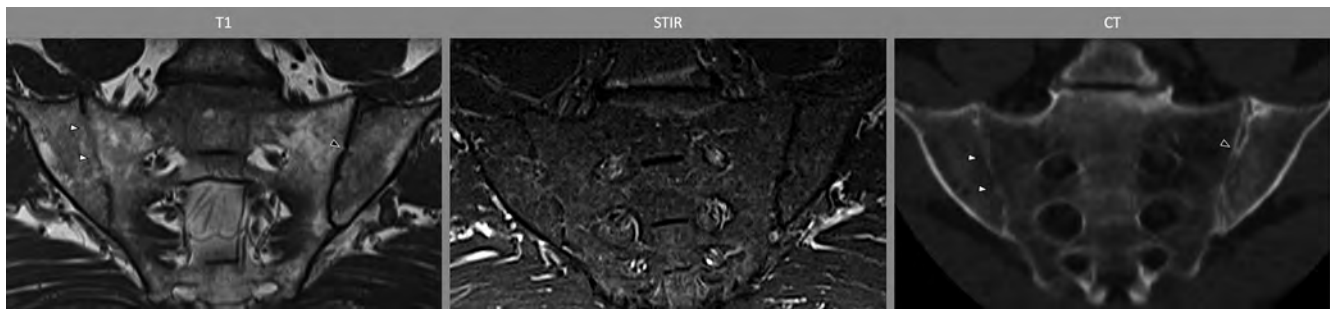
Imaging

Imaging has a crucial role in the diagnosis of axSpA and therapy monitoring [12, 13]. For this reason, imaging has a central role in the classification criteria used for study screening [7]. However, overemphasis on acute inflammatory changes in the MRI evaluation criteria with bone marrow edema/osteitis poses the risk of overdiagnosis, as such changes may also occur in other diseases [54]. Therefore, the current classification criteria pay more attention to the importance of structural lesions such as erosions and ankyloses for the specific diagnosis of axSpA [9].

The choice of the right imaging method depends on the location and whether the focus is on inflammatory or morphological structural changes [8, 37]. The three commonly used imaging modalities, X-ray, MRI and CT, differ significantly in their diagnostic accuracy for structural lesions and new bone formation [13]. Therefore, we discuss the respective strengths and weaknesses of each modality below.

X-ray

Early radiographic studies suggested that structural processes occurred relatively late in the disease course [55]. However, with advancing imaging techniques and better quality of MRI and low-dose CT, the majority of early axSpA patients will show minor structural lesions such as erosion and in time, new bone formation. Currently, an X-ray of the pelvis is recommended by ASAS as the primary imaging modality to detect structural changes of the SIGs [13]. Here, ankylosis of the SIJs is of particular importance, as the radiographic representation of backfill is currently not known – or backfill is simply not effectively detected by projection radiography. However, in recent years, many experts have started to advocate replacing the initial X-ray with MRI, especially for early diagnosis [56–58]. MRI will clearly detect most structural lesions



► **Fig. 6** Magnetic resonance imaging and computed tomography example of the sacroiliac joints (SIJs) in a patient with axial spondyloarthritis with partial ankylosis on the right side (white arrowheads) and initial new bone formation on the left side (black arrowhead). No bone marrow edema is seen in the STIR sequence.

and especially new bone formation [59]. For example, with radiography there is a risk of misinterpreting degenerative osteophytes as syndesmophytes. More subtle findings, such as backfill and transdiscal ankylosis, may escape detection. In fact, backfill can lead to erosion disappearing in the SIJ assessment and might contribute to the number of patients that show a reduction of sacroiliitis grading in therapy studies [60]. For this reason, X-ray is the modality with the lowest sensitivity and specificity. Unlike CT, radiography is not recommended for the assessment of the thoracic spine because its reliable interpretation is impeded by superposition of the ribs and other anatomy. However, studies show that the thoracic spine is most frequently affected by axSpA and that not only syndesmophytes but also erosion and ankylosis of costovertebral and facet joints are common findings [61]. Therefore, according to the related guidelines, an X-ray examination of the spine should not be performed routinely during the course of the disease, but rather on an as-needed basis [8]. There is one additional role for radiography in the diagnostic process. Grading according to the modified New York Criteria was only demonstrated for X-ray examinations. Therefore, the differentiation between two more or less distinct representations of axSpA, namely radiographic axSpA (i. e., axSpA with definite structural changes in radiography) and non-radiographic axSpA (i. e., axSpA without such changes) relies on radiography [62]. This is primarily a historical classification, involving mainly regulatory aspects for initiation of treatment. Furthermore, several scoring methods have been proposed to evaluate radiographic progression in ankylosing spondylitis. Among them, for example, is the “Stoke Ankylosing Spondylitis Spinal Score” (SASSS), which includes a detailed assessment of the posterior and anterior vertebral body edges of the lumbar spine using a scale ranging from 0 to 72 [63]. The SASSS modified by Creemers et al. (mSASSS) [64], which includes only the anterior region of the lumbar spine and additionally the cervical spine, has become more widely accepted [65].

MRI

MRI has been increasingly used for the early diagnosis of axSpA, with the hypothesis that acute inflammation precedes structural bone lesions. However, its ability to depict structural lesions was controversial until very recently [59]. The main reason is that a

conventional T1-weighted pulse sequence cannot visualize bone directly but only indirectly via the signal from the bone marrow. This often results in mostly overestimation of erosions and syndesmophytes, which are often not surrounded by fat, and new bone formation without marrow signal is hard to differentiate from ligament structures, which all appear black in standard sequences [66]. There has been some effort to overcome these limitations by generating CT-like images from MRI [67], although no technique has yet gained acceptance for use in the clinical routine. This is also the reason why most clinical studies and standard follow-up protocols tend to use both MRI and X-ray for a complete assessment of structural and active inflammatory lesions of the SIJs and spine.

Unlike X-ray, MRI allows reliable visualization of backfill and (transdiscal) ankylosis. Both follow inflammatory lesions of the cartilage or affected disc. In the diagnostic process of axSpA, MRI is also recommended in patients with suspected axSpA and with, however, unremarkable X-ray of the SIJ. Moreover, the use of MRI in patients with confirmed axSpA and back pain will be performed in a complaint-oriented manner to detect inflammatory changes [8].

CT

CT is the reference standard for direct bone imaging. Its thin slices and high spatial resolution clearly depict the complex anatomy of the SIJs, allowing structural pathologies to be more clearly assigned. For example, syndesmophytes can be visualized more accurately than with either radiography or MRI [68, 69]. CT thus also allows a reliable differentiation from purely degenerative changes, such as spondylophytes. Furthermore, facet and costovertebral joints are also visualized with a significantly higher degree of accuracy. Structural changes can also occur here in the context of axSpA, which are not clearly visualized on MRI or X-ray, and therefore, are not yet the focus of imaging publications. Furthermore, CT also allows reliable assessment of subtle changes in the joints. Backfill, which eludes detection on X-ray, can be identified on CT scans as faintly calcified tissue.

Recent technical advances significantly reduce radiation exposure, thus allowing more frequent use of this technique in the rather young patient population with axSpA [57, 70]. However, standard CT techniques are not sensitive to active inflammation,

and dual-energy CT or comparable techniques are neither well investigated, nor can they be performed with similarly low doses [57]. In clinical practice, CT has been mostly reserved for patients with equivocal MRI findings.

PET in combination with CT or MRI

Several studies assessed the role of positron emission tomography (PET) for identifying both inflammatory and structural changes in axSpA imaging. PET can provide more insight into the underlying metabolic processes in the bone and joints. For example, several studies suggest that ¹⁸F-fluoride PET/MRI provides information on metabolic processes such as osteoblast activity, which in turn can be used as a predictor of syndesmophyte formation [71, 72]. Another study has investigated FAPI PET-CT (fibroblast activation protein inhibitors) to distinguish inflammatory and fibrotic activity [73]. While offering new possibilities for the early detection of tissue transformation, PET is still confined to research and has no role in routine clinical practice.

Conclusion

In this review we discussed the different types of new bone formation in patients with axSpA and their clinical relevance. Several imaging techniques are available to assess new bone formation, each with its specific strengths and weaknesses. New bone formation is considered the hallmark imaging finding, distinguishing spondyloarthropathies from other inflammatory conditions of the skeleton. However, examiners must be aware of other important conditions that mimic new bone formation in the context of axSpA. For this reason, the reliable identification of these findings is essential to gain crucial information on possible differential diagnoses and the response to treatment. Therefore, it is important to realize under what conditions the development of new bone formation should be regarded as healing of erosion or as persistent subclinical inflammation and disease progression. In this context, MRI and CT are particularly suitable to detect structural lesions and will gain more importance in the imaging of axSpA in the near future.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors thank Ms Bettina Herwig for language editing.

References

- Braun J, Bollow M, Remlinger G et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998; 41: 58–67. doi:10.1002/1529-0131(199801)41:1<58::AID-ART8>3.0.CO;2-G
- Sieper J, Rudwaleit M, Khan MA et al. Concepts and epidemiology of spondyloarthritis. *Best Pract Res Clin Rheumatol* 2006; 20: 401–417. doi:10.1016/j.berh.2006.02.001
- Rudwaleit M, Jurik AG, Hermann KG et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. *Ann Rheum Dis* 2009; 68: 1520–1527. doi:10.1136/ard.2009.110767
- Braun J, Sieper J. Ankylosing spondylitis. *Lancet* 2007; 369: 1379–1390. doi:10.1016/S0140-6736(07)60635-7
- Navarro-Compan V, Sepriano A, El-Zorkany B et al. Axial spondyloarthritis. *Ann Rheum Dis* 2021; 80: 1511–1521. doi:10.1136/annrheumdis-2021-221035
- Rudwaleit M, van der Heijde D, Khan MA et al. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004; 63: 535–543. doi:10.1136/ard.2003.011247
- Rudwaleit M, van der Heijde D, Landewe R et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777–783. doi:10.1136/ard.2009.108233
- Kiltz U, Braun J, Dgrh et al. [Long version on the S3 guidelines for axial spondyloarthritis including Bechterew's disease and early forms, Update 2019: Evidence-based guidelines of the German Society for Rheumatology (DGRh) and participating medical scientific specialist societies and other organizations]. *Z Rheumatol* 2019; 78: 3–64. doi:10.1007/s00393-019-0670-3
- Lambert RG, Bakker PA, van der Heijde D et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis* 2016; 75: 1958–1963. doi:10.1136/annrheumdis-2015-208642
- Hoballah A, Lukas C, Leplat C et al. MRI of sacroiliac joints for the diagnosis of axial SpA: prevalence of inflammatory and structural lesions in nulliparous, early postpartum and late postpartum women. *Ann Rheum Dis* 2020; 79: 1063–1069. doi:10.1136/annrheumdis-2020-217208
- Eshed I, Miloh-Raz H, Dulitzki M et al. Peripartum changes of the sacroiliac joints on MRI: increasing mechanical load correlating with signs of edema and inflammation kindling spondyloarthropathy in the genetically prone. *Clin Rheumatol* 2015; 34: 1419–1426. doi:10.1007/s10067-015-2976-0
- Baraliakos X, Ostergaard M, Lambert RG et al. MRI lesions of the spine in patients with axial spondyloarthritis: an update of lesion definitions and validation by the ASAS MRI working group. *Ann Rheum Dis* 2022. doi:10.1136/annrheumdis-2021-222081
- Maksymowych WP, Lambert RG, Ostergaard M et al. MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI working group. *Ann Rheum Dis* 2019; 78: 1550–1558. doi:10.1136/annrheumdis-2019-215589
- Vleeming A, Schuenke MD, Masi AT et al. The sacroiliac joint: an overview of its anatomy, function and potential clinical implications. *J Anat* 2012; 221: 537–567. doi:10.1111/j.1469-7580.2012.01564.x
- Hermann KG, Baraliakos X, van der Heijde DM et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. *Ann Rheum Dis* 2012; 71: 1278–1288. doi:10.1136/ard.2011.150680
- Baraliakos X, Listing J, Rudwaleit M et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. *Ann Rheum Dis* 2007; 66: 910–915. doi:10.1136/ard.2006.066415
- Jans L, van Langenhove C, Van Praet L et al. Diagnostic value of pelvic enthesitis on MRI of the sacroiliac joints in spondyloarthritis. *Eur Radiol* 2014; 24: 866–871. doi:10.1007/s00330-013-3074-9
- Cortes A, Hadler J. International Genetics of Ankylosing Spondylitis C et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 2013; 45: 730–738. doi:10.1038/ng.2667

- [19] Baraliakos X, Listing J, Rudwaleit M et al. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. *Arthritis Res Ther* 2008; 10: R104. doi:10.1186/ar2496
- [20] Jacques P, Lambrecht S, Verheugen E et al. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. *Ann Rheum Dis* 2014; 73: 437–445. doi:10.1136/annrheumdis-2013-203643
- [21] Ward MM, Reveille JD, Learch TJ et al. Occupational physical activities and long-term functional and radiographic outcomes in patients with ankylosing spondylitis. *Arthritis Rheum* 2008; 59: 822–832. doi:10.1002/art.23704
- [22] Masi AT. Might axial myofascial properties and biomechanical mechanisms be relevant to ankylosing spondylitis and axial spondyloarthritis? *Arthritis Res Ther* 2014; 16: 107. doi:10.1186/ar4532
- [23] Sardoo AM, Neto A, Pinheiro Torres R et al. The role of muscle in the susceptibility and progression of axial Spondyloarthritis: The MyoSpA Study Protocol. *Acta Reumatol Port* 2021; 46: 342–349
- [24] Van Mechelen M, Lories RJ. Microtrauma: no longer to be ignored in spondyloarthritis? *Curr Opin Rheumatol* 2016; 28: 176–180. doi:10.1097/BOR.0000000000000254
- [25] Baraliakos X, Heldmann F, Callhoff J et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. *Ann Rheum Dis* 2014; 73: 1819–1825. doi:10.1136/annrheumdis-2013-203425
- [26] Maksymowich WP, Wichuk S, Chiowchanwisawakit P et al. Fat metaplasia and backfill are key intermediaries in the development of sacroiliac joint ankylosis in patients with ankylosing spondylitis. *Arthritis Rheumatol* 2014; 66: 2958–2967. doi:10.1002/art.38792
- [27] Romanus R, Yden S. Destructive and ossifying spondylitic changes in rheumatoid ankylosing spondylitis (pelvo-spondylitis ossificans). *Acta Orthop Scand* 1952; 22: 88–99. doi:10.3109/17453675208988998
- [28] Engfeldt B, Romanus R, Yden S. Histological studies of pelvo-spondylitis ossificans (ankylosing spondylitis) correlated with clinical and radiological findings. *Ann Rheum Dis* 1954; 13: 219–228. doi:10.1136/ard.13.3.219
- [29] Chiowchanwisawakit P, Lambert RG, Conner-Spady B et al. Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. *Arthritis Rheum* 2011; 63: 2215–2225. doi:10.1002/art.30393
- [30] Maksymowich WP, Chiowchanwisawakit P, Clare T et al. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. *Arthritis Rheum* 2009; 60: 93–102. doi:10.1002/art.24132
- [31] Braun J, Bollow M, Sieper J. Radiologic diagnosis and pathology of the spondyloarthropathies. *Rheum Dis Clin North Am* 1998; 24: 697–735. doi:10.1016/s0889-857x(05)70038-7
- [32] Khan MA, van der Linden SM, Kushner I et al. Spondylitic disease without radiologic evidence of sacroiliitis in relatives of HLA-B27 positive ankylosing spondylitis patients. *Arthritis Rheum* 1985; 28: 40–43. doi:10.1002/art.1780280107
- [33] Lee SJ, Kim JY, Choi YY et al. Predictive value of semi-quantitative index from F-18-fluoride PET/CT for treatment response in patients with ankylosing spondylitis. *Eur J Radiol* 2020; 129: 109048. doi:10.1016/j.ejrad.2020.109048
- [34] Idolazzi L, Salgarello M, Gatti D et al. 18F-fluoride PET/CT for detection of axial involvement in ankylosing spondylitis: correlation with disease activity. *Ann Nucl Med* 2016; 30: 430–434. doi:10.1007/s12149-016-1080-0
- [35] Raynal M, Bouderraoui F, Ouichka R et al. Performance of (18)F-sodium fluoride positron emission tomography with computed tomography to assess inflammatory and structural sacroiliitis on magnetic resonance imaging and computed tomography, respectively, in axial spondyloarthritis. *Arthritis Res Ther* 2019; 21: 119. doi:10.1186/s13075-019-1903-1
- [36] Maksymowich WP. MRI and X-ray in axial spondyloarthritis: the relationship between inflammatory and structural changes. *Arthritis Res Ther* 2012; 14: 207. doi:10.1186/ar3786
- [37] Sieper J, Rudwaleit M, Baraliakos X et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; 68 (Suppl. 2): ii1–ii44. doi:10.1136/ard.2008.104018
- [38] Laloo F, Herregods N, Jaremko JL et al. New bone formation in the intervertebral joint space in spondyloarthritis: An MRI study. *Eur J Radiol* 2018; 109: 210–217. doi:10.1016/j.ejrad.2018.11.007
- [39] Braun J, Kiltz U, Baraliakos X. Significance of structural changes in the sacroiliac joints of patients with axial spondyloarthritis detected by MRI related to patients symptoms and functioning. *Ann Rheum Dis* 2022; 81: 11–14. doi:10.1136/annrheumdis-2021-221406
- [40] Baraliakos X. Imaging in Axial Spondyloarthritis. *Isr Med Assoc J* 2017; 19: 712–718
- [41] Ramiro S, van der Heijde D, van Tubergen A et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Ann Rheum Dis* 2014; 73: 1455–1461. doi:10.1136/annrheumdis-2014-205178
- [42] Weber U, Pedersen SJ, Ostergaard M et al. Can erosions on MRI of the sacroiliac joints be reliably detected in patients with ankylosing spondylitis? – A cross-sectional study. *Arthritis Res Ther* 2012; 14: R124. doi:10.1186/ar3854
- [43] Diekhoff T, Poddubnyy D, Proft F et al. New bone formation at the sacroiliac joint in axial spondyloarthritis: characterization of backfill in MRI and CT. *Rheumatology (Oxford)* 2023. doi:10.1093/rheumatology/kead142
- [44] Laloo F, Herregods N, Varkas G et al. MR signal in the sacroiliac joint space in spondyloarthritis: a new sign. *Eur Radiol* 2017; 27: 2024–2030. doi:10.1007/s00330-016-4587-9
- [45] Laloo F, Herregods N, Jaremko JL et al. MRI of the sacroiliac joints in spondyloarthritis: the added value of intra-articular signal changes for a “positive MRI”. *Skeletal Radiol* 2018; 47: 683–693. doi:10.1007/s00256-017-2830-3
- [46] Zhang Y, Guo Z, Wang L et al. Baseline Severity of Sacroiliitis and Extensive Fat Metaplasia Predicts the Progression of Backfill at the Sacroiliac Joint in Patients With Axial Spondyloarthritis. *Front Immunol* 2022; 13: 887470. doi:10.3389/fimmu.2022.887470
- [47] Wetterslev M, Ostergaard M, Sorensen IJ et al. Development and Validation of 3 Preliminary MRI Sacroiliac Joint Composite Structural Damage Scores in a 5-year Longitudinal Axial Spondyloarthritis Study. *J Rheumatol* 2021; 48: 1537–1546. doi:10.3899/jrheum.201075
- [48] Hu Z, Wang X, Qi J et al. Backfill is a specific sign of axial spondyloarthritis seen on MRI. *Joint Bone Spine* 2016; 83: 179–183. doi:10.1016/j.jbspin.2015.05.011
- [49] Heuft-Dorenbosch L, Landewe R, Weijers R et al. Performance of various criteria sets in patients with inflammatory back pain of short duration; the Maastricht early spondyloarthritis clinic. *Ann Rheum Dis* 2007; 66: 92–98. doi:10.1136/ard.2006.053918
- [50] Maksymowich WP, Wichuk S, Dougados M et al. Modification of structural lesions on MRI of the sacroiliac joints by etanercept in the EMBARK trial: a 12-week randomised placebo-controlled trial in patients with non-radiographic axial spondyloarthritis. *Ann Rheum Dis* 2018; 77: 78–84. doi:10.1136/annrheumdis-2017-211605
- [51] Mogard E, Lindqvist E, Bremander A et al. Risk factors for development and persistence of chronic widespread pain in spondyloarthritis: a population-based two-year follow-up study. *Scand J Rheumatol* 2019; 48: 460–468. doi:10.1080/03009742.2019.1602163
- [52] Kuperus JS, Waalwijk JF, Regan EA et al. Simultaneous occurrence of ankylosing spondylitis and diffuse idiopathic skeletal hyperostosis: a

- systematic review. *Rheumatology (Oxford)* 2018; 57: 2120–2128. doi:10.1093/rheumatology/key211
- [53] de Hooge M, van den Berg R, Navarro-Compan V et al. Patients with chronic back pain of short duration from the SPACE cohort: which MRI structural lesions in the sacroiliac joints and inflammatory and structural lesions in the spine are most specific for axial spondyloarthritis? *Ann Rheum Dis* 2016; 75: 1308–1314. doi:10.1136/annrheumdis-2015-207823
- [54] Diekhoff T, Lambert R, Hermann KG. MRI in axial spondyloarthritis: understanding an “ASAS-positive MRI” and the ASAS classification criteria. *Skeletal Radiol* 2022; 51: 1721–1730. doi:10.1007/s00256-022-04018-4
- [55] Mau W, Zeidler H, Mau R et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *J Rheumatol* 1988; 15: 1109–1114
- [56] Lambert RGW, Hermann KGA, Diekhoff T. Low-dose computed tomography for axial spondyloarthritis: update on use and limitations. *Curr Opin Rheumatol* 2021; 33: 326–332. doi:10.1097/BOR.0000000000000803
- [57] Diekhoff T, Hermann KGA, Lambert RG. Future of Low-Dose Computed Tomography and Dual-Energy Computed Tomography in Axial Spondyloarthritis. *Curr Rheumatol Rep* 2022; 24: 198–205. doi:10.1007/s11926-022-01075-5
- [58] Poddubnyy D, Diekhoff T, Baraliakos X et al. Diagnostic evaluation of the sacroiliac joints for axial spondyloarthritis: should MRI replace radiography? *Ann Rheum Dis* 2022; 81: 1486–1490. doi:10.1136/ard-2022-222986
- [59] Diekhoff T, Hermann KG, Greese J et al. Comparison of MRI with radiography for detecting structural lesions of the sacroiliac joint using CT as standard of reference: results from the SIMACT study. *Ann Rheum Dis* 2017; 76: 1502–1508. doi:10.1136/annrheumdis-2016-210640
- [60] Maksymowych WP, Claudépierre P, de Hooge M et al. Structural changes in the sacroiliac joint on MRI and relationship to ASDAS inactive disease in axial spondyloarthritis: a 2-year study comparing treatment with etanercept in EMBARK to a contemporary control cohort in DESIR. *Arthritis Res Ther* 2021; 23: 43. doi:10.1186/s13075-021-02428-8
- [61] Lee S, Lee JY, Hwang JH et al. Clinical importance of inflammatory facet joints of the spine in ankylosing spondylitis: a magnetic resonance imaging study. *Scand J Rheumatol* 2016; 45: 491–498. doi:10.3109/03009742.2016.1150506
- [62] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361–368. doi:10.1002/art.1780270401
- [63] Aaverns HL, Oxtoby J, Taylor HG et al. Radiological outcome in ankylosing spondylitis: use of the Stoke Ankylosing Spondylitis Spine Score (SASSS). *Br J Rheumatol* 1996; 35: 373–376. doi:10.1093/rheumatology/35.4.373
- [64] Creemers MC, Franssen MJ, van't Hof MA et al. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Ann Rheum Dis* 2005; 64: 127–129. doi:10.1136/ard.2004.020503
- [65] van der Heijde D, Braun J, Deodhar A et al. Modified stoke ankylosing spondylitis spinal score as an outcome measure to assess the impact of treatment on structural progression in ankylosing spondylitis. *Rheumatology (Oxford)* 2019; 58: 388–400. doi:10.1093/rheumatology/key128
- [66] Braun J, Baraliakos X, Golder W et al. Analysing chronic spinal changes in ankylosing spondylitis: a systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. *Ann Rheum Dis* 2004; 63: 1046–1055. doi:10.1136/ard.2003.019968
- [67] Deppe D, Hermann KG, Proft F et al. CT-like images of the sacroiliac joint generated from MRI using susceptibility-weighted imaging (SWI) in patients with axial spondyloarthritis. *RMD Open* 2021; 7. doi:10.1136/rmdopen-2021-001656
- [68] de Koning A, de Bruin F, van den Berg R et al. Low-dose CT detects more progression of bone formation in comparison to conventional radiography in patients with ankylosing spondylitis: results from the SIAS cohort. *Ann Rheum Dis* 2018; 77: 293–299. doi:10.1136/annrheumdis-2017-211989
- [69] de Bruin F, de Koning A, van den Berg R et al. Development of the CT Syndesmophyte Score (CTSS) in patients with ankylosing spondylitis: data from the SIAS cohort. *Ann Rheum Dis* 2018; 77: 371–377. doi:10.1136/annrheumdis-2017-212553
- [70] Gervaise A, Osemont B, Lecocq S et al. CT image quality improvement using Adaptive Iterative Dose Reduction with wide-volume acquisition on 320-detector CT. *Eur Radiol* 2012; 22: 295–301. doi:10.1007/s00330-011-2271-7
- [71] Buchbender C, Ostendorf B, Ruhlmann V et al. Hybrid 18F-labeled Fluoride Positron Emission Tomography/Magnetic Resonance (MR) Imaging of the Sacroiliac Joints and the Spine in Patients with Axial Spondyloarthritis: A Pilot Study Exploring the Link of MR Bone Pathologies and Increased Osteoblastic Activity. *J Rheumatol* 2015; 42: 1631–1637. doi:10.3899/jrheum.150250
- [72] Sawicki LM, Lutje S, Baraliakos X et al. Dual-phase hybrid (18) F-Fluoride Positron emission tomography/MRI in ankylosing spondylitis: Investigating the link between MRI bone changes, regional hyperaemia and increased osteoblastic activity. *J Med Imaging Radiat Oncol* 2018; 62: 313–319. doi:10.1111/1754-9485.12687
- [73] Kuwert T, Schmidkonz C, Prante O et al. FAPI PET Opens a New Window to Understanding Immune-Mediated Inflammatory Diseases. *J Nucl Med* 2022; 63: 1136–1137. doi:10.2967/jnumed.122.263922