
Imaging of axial spondyloarthritis. New aspects and differential diagnoses

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Received on August 31, 2018; accepted in
revised form on September 3, 2018.

Clin Exp Rheumatol 2018; 36 (Suppl. 114):
S35-S42.

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EXPERIMENTAL RHEUMATOLOGY 2018.

Key words: axial spondyloarthritis,
diffuse idiopathic skeletal
hyperostosis, osteitis condensans,
magnetic resonance imaging,
computed tomography

ABSTRACT

Axial spondyloarthritis (axSpA) is a chronic rheumatic disease characterised by inflammatory back pain and several other disease manifestations and comorbidities. The 2009 ASAS classification criteria differentiate between the classical ankylosing spondylitis or radiographic axSpA and non-radiographic axSpA based on the presence or absence of definite radiographic changes in the sacroiliac joints. Importantly, back pain in patients with axSpA may well have reasons other than axial inflammation or new bone formation. There are several important differential diagnoses such as diffuse idiopathic skeletal hyperostosis and osteitis condensans. This review summarises recent publications concerning the performance of imaging modalities in the field, such as conventional radiography, magnetic resonance imaging, computed tomography and dual energy x-ray absorptiometry including the trabecular bone score.

Introduction

Axial spondyloarthritis (axSpA) is a chronic rheumatic disease that is characterised by inflammatory back pain and several other disease manifestations and comorbidities (1). The 2009 ASAS classification criteria have led to a differentiation between the classical ankylosing spondylitis (AS) or radiographic axSpA and non-radiographic axSpA (nr-axSpA) based on the presence or absence of definite radiographic changes in the sacroiliac joints (2). Importantly, back pain in patients with axSpA may well have reasons other than axial inflammation or new bone formation (3).

This review summarises recent publications concerning imaging modalities in the field, such as conventional radiography (CR), magnetic resonance imaging (MRI), computed tomography (CT), as

well as tools to measure bone mineral density such as dual energy x-ray absorptiometry (DXA) including the trabecular bone score (TBS).

In detail, we address the following points:

1. Role of imaging for diagnosis and classification
2. Effect of biologic therapy on MRI findings
3. Radiographic progression
4. Osteoporosis and fractures
5. New imaging tools

Imaging for diagnosis and classification of axSpA

CR and MRI of the sacroiliac joints (SIJ) are important for diagnosis and classification of axSpA (1, 2). The Assessment of SpondyloArthritis international Society (ASAS) has published definitions for a positive MRI of the SIJ which have been recently updated (4).

Issues concerning specificity of bone marrow oedema on MRI

The significance of MRI for making a diagnosis of axSpA in the hand of rheumatologists has been recently highlighted (5, 6). However, in the last two years, there are increasing reports that the ASAS-defined MRI changes mainly based on 'bone marrow oedema suggestive of axSpA' are not as specific as previously thought (7-13). In particular, an overlap with early MRI-visible degenerative changes has been extensively studied (7, 8). In a study with 648 patients (8), (47% men, mean age 34 years), degenerative lesions were found in a similar percentage in patients with axSpA vs. no axSpA (about 70%). Of interest, Modic changes were found significantly more often in patients with no axSpA (12%) vs. axSpA (5%).

In addition, however, there is also increasing data on corresponding findings in patients with non-specific back pain (9), postpartum women (10), soldiers

Competing interests: B. Buehring has received research support and honoraria from GE Lunar; the other authors have declared no competing interests.

(11), runners (10), athletes (12), but also in the general population (13).

These data appear particularly important for use of the ASAS classification criteria (1), since these MRI data suggest that the imaging arm of the classification criteria is likely to recognise false positive classification and diagnoses. However, there may be a solution, since a more specific MRI result was only observed in the SIJ of axSpA patients: a 'deep' extensive bone marrow oedema (10). In the future it will be important to define clearly which MRI finding is stress-induced, degenerative, infectious, and/or non-specific *versus* specific for axSpA. This task will be difficult and require an extensive number of patients.

An example of SIJ changes in a patient with axSpA and osteitis condensans is given in Figures 1 and 2, respectively.

Possible value of repeating MRI scans for diagnosis

The question whether a repetition of MRI makes clinical sense has been studied in the UK. The result is that short-term repeat MRI scans in patients under suspicion of early axSpA are relevant only in HLA-B27-positive male subjects (14). Another study also showed that initially negative MRIs of the SIJ may become positive on follow up (15).

Possible value of structural changes of SIJ in patients with axSpA in classification and diagnosis

While this discussion is mainly related to inflammatory MRI changes there is also increasing evidence that structural changes in the SIJ of patients with axSpA could have some value for classification and diagnosis of this disease (16-18). Radiographs, T1-weighted (MRI-T1) and low-dose CT of the SIJ of 110 patients with chronic back pain and a suspicion of axSpA, were scored for structural lesions; the mean age was 36 years and 52% were male (16). The clinical diagnosis was axSpA in 53%. MRI-T1 showed better sensitivity with significantly more correct imaging findings compared with CR for erosions (79% *vs.* 42%), joint space changes (75% *vs.* 41%) and overall positivity (85% *vs.* 48%), while there

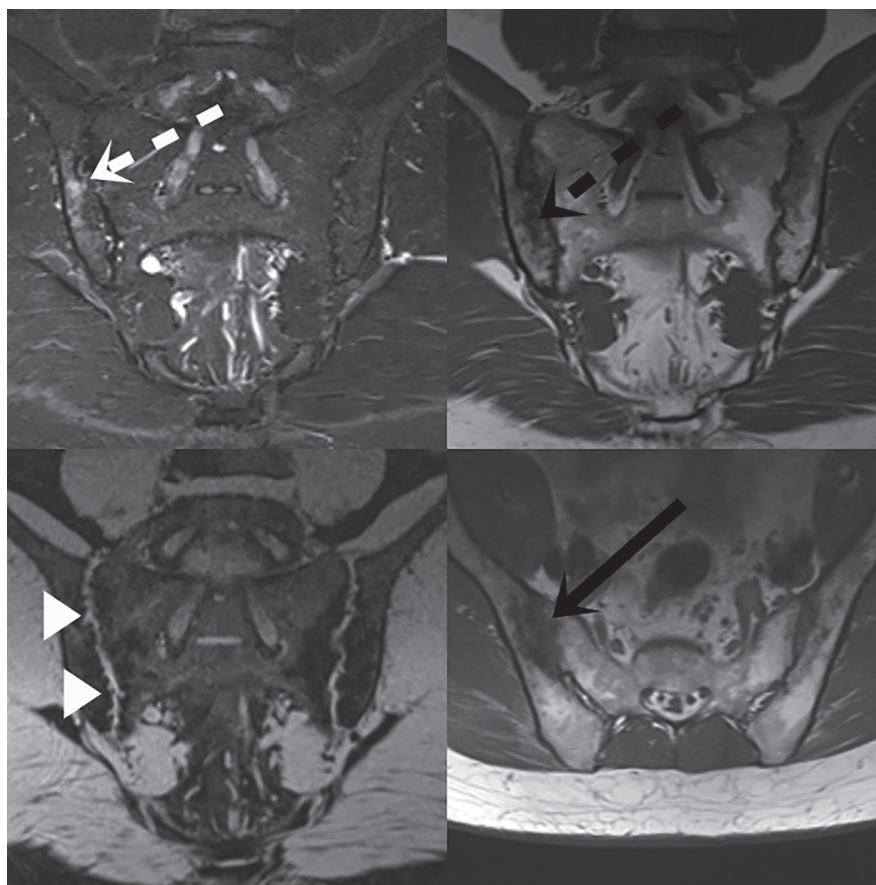


Fig. 1. MRI of SIJ in 45yo male with **established axSpA**. Oblique coronar T2w TIRM and T1w TSE 3mm (upper half from left to right), oblique coronar T1w VIBE 3D 0.9mm reformatted to 2mm and oblique transversal T1w TSE 3mm (lower half from left to right). Unilateral mild activity (dashed white arrow) on the right, ill defined paraarticular sclerosis (exemplarily dashed black arrow) and fatty metamorphosis. The joint space is obscured and unrateable in right lower quadrant (black arrow), T1w VIBE clearly depicts multiple tiny erosions of articular surface predominantly on the iliac side.

were no differences between x-rays and MRI-T1 sequence regarding specificity (>80% for all scores). MRI-T1 was inferior to CR only for sclerosis.

On the other hand, it has been stressed that fatty changes in the SIJ are also rather prevalent (50%) in subjects <45 years without evidence of axSpA (19). Another important finding of this study was that almost no individual without evidence of axSpA had erosions in the SIJ. However, this problem may be overcome by using quantitative cut-offs when using MRI STIR (inflammation, MRI-SI), MRI T1-weighted images (structural lesions, MRI-SI-s) and radiographs of the SI joints which was done in the SPondyloArthritis Caught Early-cohort (SPACE) in patients with chronic back pain ≥ 3 months, ≥ 2 years with an onset <45 years (18). In this study the previously proposed cut-offs for a positive MRI-SI-s which are based

on a low <5% prevalence in non-SpA patients were used: erosions ≥ 3 , fatty lesions ≥ 3 , fatty lesions and/or erosions (erosions/fatty lesions) ≥ 5 . Although the additional yield for a classification of axSpA was moderate, the cut-offs proposed appeared useful for diagnosis and classification of axSpA.

Complexities in diagnosis

In one report, even four features of axSpA were not considered good enough by rheumatologists if MRI and HLA B27 were negative (6). The authors of this review were asked to comment on this report, and argued that it is difficult to believe that so many features of axSpA are not sufficient for diagnosis – especially if no alternative explanation for the back pain is provided (21). The presence of four features as being sufficient for a diagnosis of axSpA are based on the diagnostic algorithm re-

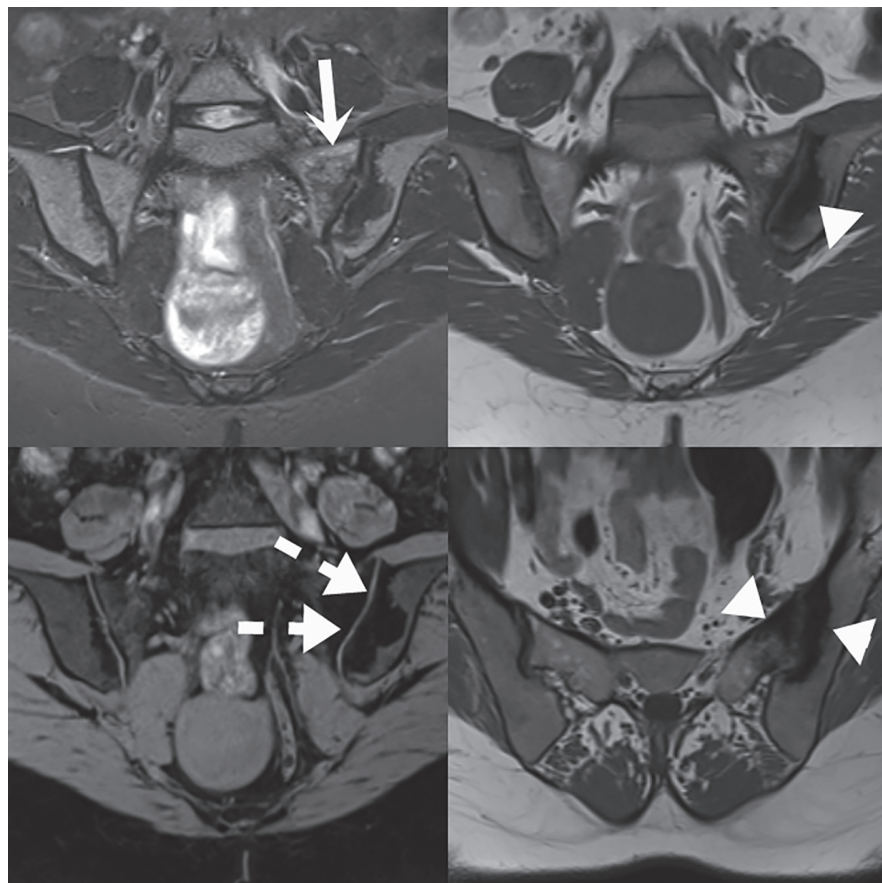


Fig. 2. MRI of SIJ in 38yo female multipara with chronic lower backpain caused by asymmetric predominantly left sided **osteitis condensans**. Oblique coronar T2w TIRM and T1w TSE 3mm (upper half from left to right), oblique coronar T1w VIBE 3D 0.9mm reformatted to 2mm slap and oblique transversal T1w TSE 3mm (lower half from left to right). Minute excentric paraarticular bone marrow oedema in most anterior ridge of sacrum in upper left quadrant (white arrow) and broad compact para-articular sclerosis (white arrowheads). T1w VIBE reveals smooth articular surfaces without erosive changes (dashed white arrows).

cently proposed by ASAS (20). In their response, the authors did provide those diagnoses by the rheumatologists (22). However, some questions remain because more than half of the diagnoses (28 out of 48) given in the patients with 3 or 4 axSpA features were either ‘missing’, non-specific back pain or even inflammatory back pain (22). These phenomena illustrate that early diagnoses of axSpA remain difficult in some patients. The main message of that study is that MRI and HLA B27 are regarded as very critical by rheumatologists who are reluctant to diagnose axSpA in the absence of positive results of these tests. This may suggest that the ASAS classification criteria have set the stage for that way to come to a diagnosis. Spinal inflammation as assessed by MRI is a frequent finding in patients with AS (30). However, in early dis-

ease, there is no gain if spinal MRI results are included in the imaging arm of the classification criteria because spinal inflammation in early disease occurs rarely without sacroiliitis (23). Current scoring systems have not included inflammatory and structural changes in posterior elements of the spine in axSpA. A recent publication suggests that including those structures in clinical trials could be valuable (24).

Distinguishing AxSpA from DISH

Diffuse skeletal hyperostosis (DISH), a systemic, relatively common condition, has been described first in 1950 (25) with radiographic changes partly mimicking AS. DISH is characterised by continuous ossification of ligaments and entheses, especially in the axial skeleton. Classification of DISH is being made when large bridging os-

teophytes occur in at least four adjacent thoracic vertebrae, as detected by conventional radiographs (26). Similarly, syndesmophytes, the hallmark of AS pathology, occur most frequently in the thoracic spine (27). Interestingly, the progression rate of new bone formation of patients with DISH and AS was found to be similar (28). An example of degenerative changes in the thoracic spine and DISH is given in Figures 3 and 4, respectively.

While this differential diagnosis is of no significance in early axSpA, it can become tricky in late disease stages. One of the major differentiating features is the presence or absence of SIJ abnormalities. In a recent retrospective study, 104 patients fulfilling the Resnick criteria for DISH (26) were compared to 106 age- and sex-matched control subjects (71% men, mean age 72 years) regarding the presence of intra- and extra-articular bridging osteophytes, spurs, subchondral cyst-like changes, erosions, and sclerosis in their SIJs (29). The frequency of anterior bridging (48% vs. 9%), posterior bridging (20% vs. 1%), enthesal bridging (34% vs. 4%), and joint ankylosis (23% vs. 0%) was significantly higher among patients with DISH. The most likely explanation for these findings is the age of the patients.

In another retrospective study, 281 consecutive MRI examinations of the SIJ in patients with low back pain (59% female, mean age 44 years) were evaluated for the presence of inflammatory and structural lesions according to the ASAS definition (30). Sacroiliac inflammation was found in 25% and other diagnoses in 31%, while the majority had normal findings (44%). In detail, osteitis condensans ilii (9%), anatomic variants (5%), septic sacroiliitis (5%), degenerative findings (4%), DISH (1.5%), mechanical stress (0.7%), malignancy (0.3%) were diagnosed. Patients with alternative diagnoses were older than those with axSpA (62 vs. 47 years). Alternative SIJ pathologies were significantly more common in females (30).

In a small study it was reported that spinal inflammation suggestive of axSpA was also found in DISH patients (31). This was confirmed in a larger study with 53 symptomatic DISH pa-

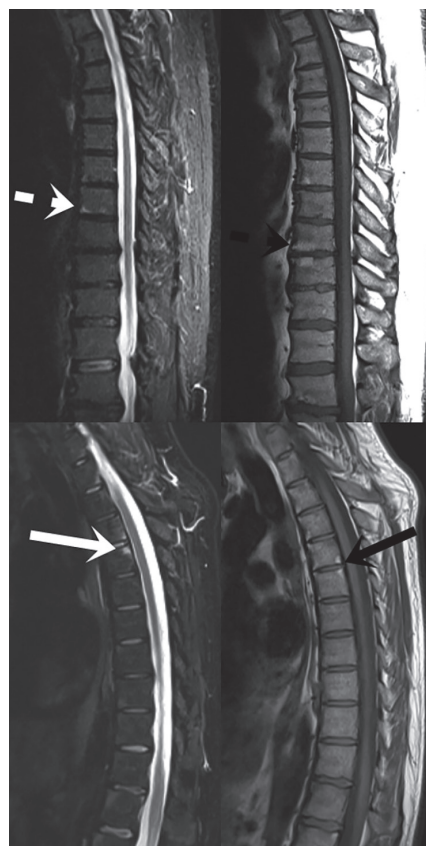


Fig. 3. MRI of thoracic spine in 60yo male with degenerative back pain (upper half) and 35yo male with newly established axSpA (lower half). Sagittal T2w TIRM 3mm (left) and T1w TSE 3mm (right). Endplate oriented linear bone marrow oedema (white dashed arrow) and fatty metamorphosis (black dashed arrow) plus multisegmental intervertebral disc dehydration and marginal spondylotic spurs in degenerative spine. Triangular shaped active (white arrow) and chronic (black arrow) corner lesions in axSpA.

tients with spinal MRIs (27). The mean Spondyloarthritis Research Consortium of Canada (SPARCC) score of the spine, which, however, has not been evaluated for DISH, was about 18. Two thirds of the patients (67.3%) had at least 1 fatty corner. Thirty patients (57.7%) met the ASAS definition of a spine MRI suggestive of axial SpA, but only 6 patients (15.8%) with an available SIJ MRI had sacroiliitis according to the ASAS criteria, and only 1 patient (3.3%) had ≥ 3 erosions in the SIJ (32).

MRI findings in response to therapy

Considerable evidence indicates that anti-TNF (33) and anti-IL17 (34) therapies are not only clinically efficacious, but also lead to substantial reductions in MRI signals suggestive of spinal inflam-

mation. However, no study has shown that full MRI remission and absence of MRI signals of spinal inflammation occurs in all treated patients (35, 36). One recent study concentrated also on structural changes in the SIJ as assessed by MRI and the SPARCC score (37). The change between baseline and 12 weeks was significantly greater in patients treated with etanercept *versus* placebo for mean erosion score (-0.57 vs. -0.08) and backfill score (0.36 vs. 0.06). This was also the case for the subgroup of patients with SIJ inflammation on MRI. Although statistically significant, these changes appear of minor clinical significance. This is especially true for backfill which represents an outcome that can be challenged on a pathogenetical basis: 1. what is the evidence that the postulated healing of erosions is a relevant clinical event? 2. is it not more likely that a cartilage or bone repair mechanism in axSpA is rather the starting point for ankylosis to occur? This point does not question at all that the EMBARK study has indicated the value of etanercept *versus* placebo, leading to approval of the drug for patients with nr-axSpA. This includes MRI findings showing a reduction of inflammation in the SIJ – one example of a successful treat-to-target strategy (38).

Functional relevance of structural changes in the axial skeleton

The question of the functional relevance of structural changes in the SIJ has been systematically assessed in a study with 210 early axSpA patients with less than 10 years of symptom duration, who had radiographs of the SIJ at baseline and after 2 years of follow-up, scored according to the modified New York criteria grading system (39). In an analysis adjusting for structural damage in the spine (modified Stoke AS Spine Score - mSASSS), disease activity (Bath AS Disease Activity Index - BASDAI and C-reactive protein level) and gender, revealed that a change by one radiographic sacroiliitis grade in one joint is associated with BASFI/BASMI worsening by 0.10/0.12 points, respectively, independently of disease activity and structural damage in the spine. Although it does not seem to

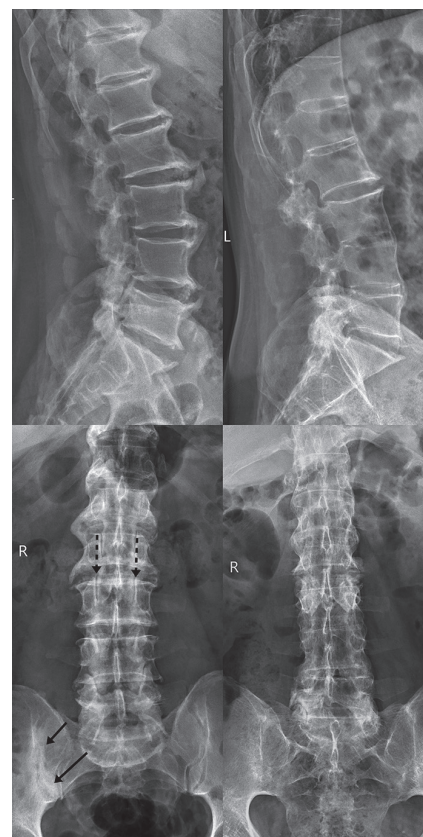


Fig. 4. Radiographs of 45 yo male with DISH (left half). Broad unilateral pontifying capsular ossifications (black arrows) obscure the right SIJ simulating ankylosis, multisegmental hyperostotic pontifying spondylophytes, the joint space of facet-joints (dashed black arrows exemplarily at level L2/3) are clearly depictable and not fused. 58 yo male with long standing ankylosing spondylitis (right half), incomplete bamboo spine with sparing of level L2/3 und L5/S1 due to residual mobility of these segments. Multisegmental syndesmophytes and fused facet-joints, bilateral total ankylosis of SIJ.

be entirely clear how this influence on function and mobility could take place based on the physiologic function of the SIJ, since these joints are essential for effectively transferring loads between the spine and legs (40), it may well be that there is a minor effect also on spinal function and mobility.

Using the same patient cohort, an association between mSASSS and BASFI was found that was independent of disease activity parameters (BASDAI and CRP), presence of definite radiographic sacroiliitis and gender. However, the association between mSASSS and BASMI was stronger, also adjusted (41). These data indicate that, over time, an increase of 20 and 12 mSASSS points is responsible for a mean increase of

one BASFI or one BASMI unit, respectively. Disease activity (BASDAI) also showed a significant association with BASFI and BASMI indicating an influence of both, inflammation and new bone formation on function and mobility. The relative weight of these influences is likely to change over time and the course of the disease, and it of course varies in of individual patients.

Radiographic progression in axSpA

There is now increasing evidence from retrospective cohort studies that anti-TNF therapy does reduce spinal bone formation over time (42, 43). However, even though the progression rates are low (44) also with IL-17 antagonists (45, 46) it has to be stressed that there is no cessation of radiographic progression but rather a deceleration. Comparisons with historical cohorts do often show no significant differences, which may be explained on the basis of a low sample size and limited sensitivity to change in status of the mSASSS (47). Established risk factors for radiographic progression include male sex, the presence of syndesmophytes at baseline, extended MRI changes in the SIJ, elevated CRP levels, smoking (48), and heavy manual work may also be a relevant risk factor (49).

In the EMBARK trial, there was also an analysis on radiographic progression in the SIJ at 104 weeks. The total SIJ score improved in the etanercept (n=154) group (-0.14) which can be possibly explained by measurement error, but it worsened in the control (n=182) group (+0.08). The adjusted difference between groups was minor but statistically significant (50).

The rate of radiographic structural progression in the SIJ in patients with radiographic (AS) or nr-axSpA over 2 years has been studied in the DESIR cohort, in which 449 had baseline and 2-year pelvic radiographs (51). Of these patients, 47% were men, mean age 34 years, 61% HLA B27+, and 37% had MRI evidence of sacroiliitis. The percentages of patients who switched from nr-axSpA to AS was low (4.9%). However, a similar proportion switched from AS to nr-axSpA (5.7%) which is unlikely to occur but rather suggests a measurement error.

The mean change in the total SIJ score (range 0-8) was small but highly statistically significant. The potential baseline predisposing factors were current smoking, HLA-B27 positivity, and inflammation of the SI joints on MRI.

The 5-year data from the same cohort (n=416 patients) showed that the net progression rate from nr-axSpA to AS was 5.1% (52). A change of at least one grade was seen in 13.0% of the patients, 10.3% ignoring a change from grade 0 to 1. MRI evidence of inflammation at baseline predicted structural damage after 5 years in HLA B27+ and in HLA-B27- patients, the latter to a lesser degree (52).

Osteoporosis and fractures

Osteoporosis defined as a 'progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture' is one of the common co-morbidities of axSpA (53). According to recent meta-analyses, the vertebral fracture risk is significantly increased (2 to 4-fold) compared to individuals who do not have AS. By contrast, the risk for non-vertebral fractures appears to be equal or only slightly increased (54-57).

Osteoporotic fractures are known to lead to significant morbidity and, in case of vertebral and hip fractures, also to increased mortality. Additionally, it is well established that the presence of one fracture clearly increases the risk for future fractures (58-61). However, it should be emphasised that that two thirds of all vertebral fractures do not immediately cause clinical symptoms and many are missed, even if a radiograph is taken. This risk seems to be even further increased in patients with axSpA (56, 62, 63).

Dual-energy x-ray absorptiometry (DXA) assessing bone mineral density (BMD) remains the "gold-standard" to assess osteoporosis and the risk of fracture due to its precision, minimal radiation exposure and wide availability. Nevertheless, DXA clearly has limitations, as do all measures. One particular problem in patients with axSpA is that DXA calculates areal BMD of the ver-

tebral bodies rather than true volumetric BMD as seen in a quantitative CT. This means that anything radiodense such as aortic calcifications, but also degenerative changes and calcification of the ligaments will 'artificially' increase BMD measurement in the lumbar spine, producing falsely elevated scores. Therefore, it is of no surprise that lumbar spine BMD is not a risk factor for vertebral fractures in patients with AS but BMD at the femur neck or the total proximal femur is (55).

DXA densitometers can also be used to screen for vertebral fractures. Considering how many vertebral fractures are missed clinically, the lateral vertebral fracture assessment (VFA) technique should be added to standard BMD assessments if recent imaging of the thoracic and lumbar spine is not available. There is guidance from the International Society for Clinical Densitometry how to perform these assessments and report results (64, 65). More advanced imaging such as MRI is necessary to determine the age of a fracture or to ensure that the fracture is not a pathologic one, due to malignancy (66).

More recently, DXA images of the lumbar spine BMD have been used to estimate the trabecular microarchitecture by calculating a "trabecular bone score" (TBS; 67, 68). Several studies have shown that TBS predicts fracture risk independent of BMD and can improve fracture risk prediction when added to the fracture risk assessment tool FRAX (67-70). Only few studies have studied the use of TBS in patients with axSpA. The main findings were that individuals with axSpA and fractures had lower TBS scores and that disease activity was associated with low values (71-73). However, no prospective data on the prediction of fractures are available to date.

Other imaging tools such as ultrasound, quantitative CT and MRI hypothesised to potentially better predict osteoporosis and fracture risk are currently being evaluated (74, 75). However, they should not to be used currently in routine clinical care because evidence is still lacking. Some methods have been evaluated in axSpA indicating possible clinical usefulness (76-78).

New imaging tools

Future directions in imaging of axSpA comprise by the further development of the already existing imaging techniques as well as by the application of new techniques for identification of disease specific processes.

In diffusion weighted imaging (DWI), the intensity of each image element (voxel) reflects the best estimate of the rate of water diffusion at that location. Because the mobility of water is driven by thermal agitation and highly dependent on its cellular environment, the hypothesis behind DWI is that findings may indicate early pathologic changes. Available data regarding the usefulness of DWI sequences to provide sensitive and specific MRI results for diagnosing AS are somewhat contradictory (79, 80). The application of low radiation dose CT (ld-CT) has capacity to identify structural changes in the spine of patients with AS (81, 82). Both visualisation of syndesmophytes at a single time point and development of new syndesmophytes after 2 years of follow-up have been tested in an international cohort of patients with established AS by ld-CT, showing that this imaging method can detect more syndesmophytes than conventional radiographs. Whether this imaging method can sufficiently detect structural changes in a shorter follow-up than 2 years remains to be shown.

In addition, new studies on MRI are now exploring the use of this imaging technique as a substitute of conventional radiographs for identification of structural changes in the sacroiliac joints. In a first study comparing MRI and ld-CT (16), MRI-T1 was found to be superior to conventional radiography for detection of structural lesions in patients with axSpA. In a more recent analysis, the modern volume-interpolated breathhold examination (VIBE) MRI sequence was found to be more sensitive than T1-weighted MRI in identifying erosions in the SIJ, especially in younger patients, possibly due to the capacity of VIBE-MRI to identify structural changes in the cartilage that have not yet extended to the underlying bone (83). Currently, further research is undertaken to evaluate and

directly compare the available imaging methods of the SIJs and spine in early and later stages of axSpA.

Finally, more advanced imaging techniques such as positron-emission tomography (PET) in combination with CT or MRI are also under investigation in axSpA. The usage of specific tracers such as the glucose analogue [18F] FDG or tracers with high affinity to peripheral benzodiazepine receptors that are mainly expressed on macrophages, which again are known to be involved to the development of inflammatory activity in patients with AS, such as [11C] (R) PK11195, is already under investigation in this disease (61). Similarly, other tracers that are more specific for the detection of the osteoblastic activity such as 18F-labeled fluoride are also investigated for the detection of concomitant osteoproliferative processes at the site of active (inflammation) or chronic (fat metaplasia or sclerosis) lesions in both the spine and the SIJ (84). In addition, very recently the treatment effect of biologic DMARDs in patients with established ankylosing spondylitis was also demonstrated in a pilot study using hybrid imaging of PET and CT (85).

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