Imaging and scoring in ankylosing spondylitis

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ABSTRACT

Ankylosing spondylitis (AS), the prototype of the spondyloarthritides (SpA), is a disease subset but also a possible outcome of the SpA. Early diagnosis of sacroiliitis, the most frequent clinical symptom often accompanied by inflammatory back pain, and other inflammatory lesions of the spine such as spondylitis and spondylodiscitis, can be visualized early by magnetic resonance imaging (MRI). Chronic changes such as syndesmophytes are well detected by conventional x-rays of the spine, mostly lateral, in the lumbar spine also a.p. Active spinal inflammation can be demonstrated by MRI by using either the fat saturating STIR technique or by application of the contrast agent gadolinium-DTPA. This is especially useful in early and active disease, in young women and in children, and for the differential diagnosis of septic sacroiliitis. Because of the efficacy of the novel biologic agents directed against TNFα such as infliximab and etanercept in SpA there is a need for spinal imaging techniques that are more sensitive than conventional x-rays. The available scoring tools are limited in their sensitivity to change. Novel approaches using MRI have been recently proposed.

Introduction

Assessment of structural changes in ankylosing spondylitis (AS) is essential for diagnosis, management (disease activity) and outcome. The most important locations in AS are the sacroiliac joints and the spine.

The magnitude of the structural changes visible in the sacroiliac joints is relevant for the diagnosis of AS according to accepted criteria (conventional radiography), the measurement of disease activity (sequential x-rays, magnetic resonance imaging (MRI)) and the differentiation towards undifferentiated spondyloarthritis, septic sacroiliitis, osteoarthritis and other mechanic causes of back pain (computed tomography (CT), MRI).

The magnitude of the structural changes visible in the spinal structures are relevant for outcome (X-rays, MRI) and relevant for the assessment of disease activity (MRI).

Scoring of radiographs as an outcome measure in AS

Radiographic evidence of sacroiliitis is a prerequisite for the classification criteria for AS according to almost all proposals and criteria published over the last decades (1-5), with the exception of the ESSG criteria which concentrate on the characteristic clinical symptoms and history of SpA (6). In contrast, changes on radiographs have not been established as an important endpoint measure in AS to date. However, radiographic changes in the spine, hips and SI joints were selected as part of the core set for endpoints in clinical trials of DCART therapy (7).

Radiographs in AS are a result of a cumulative process of destruction over time and, thus, reflect the history of a pathology. The radiographs in AS change over time and, can be used to assess the serial evaluation of AS. Many different spinal structures are involved in this process (Table I).

If the disease modification of drugs need to be assessed - and this is now indeed needed for the obviously very effective anti-TNF agents (8) - demonstration of reduction or stopping of

Table I. Ankylosing spondylitis related (radiographic) pathology in the spine and joints.

Erosions
Sclerosis
Joint space narrowing
Blurring of joint margins
Spurs
(Pseudo)widening
Complete and incomplete bony fusion
Bony bridging
Squaring
Calcification
Syndesmophytes
Spondylophytes
Spondylo(discitis)

radiographic progression is as essential as in RA (9). However, the situation in AS is more complex than in RA. Changes in RA such as joint space narrowing and erosions are consequences of disease activity. In AS, it is possible that not all changes seen on radiographs are a result of disease activity but could rather reflect healing processes (e.g. new bone formation). For pragmatic reasons, as it stands now, all changes on AS radiographs should be regarded as result of an inflammatory process. Radiographs provide an assessment of cartilage and bone structure, but may not quantify inflammation. To be able to study the relation between changes on radiographs and the inflammatory process in more detail, reliable scoring methods are needed. These scoring methods can be useful to study natural history of disease, relation with disease activity and physical function, prognosis and efficacy of therapy. The choices to be made regarding the methodological issues depend on the purpose for which imaging is done (to classify, prognosticate, measure change over time) and might be different for each purpose.

Quite a large variety of changes can be seen on radiographs in AS patients, some in both the spine, and SI and peripheral joints, others at one site only.

AS is predominantly an axial disease affecting the whole spine and sacroiliac joints, but also axial and root joints including hips and shoulders and peripheral joints. Based on the relative frequency of involvement, scoring changes in the spine, sacroiliac and axial (especially hip) joints are more important. In a recent data set on a group of 470 patients with a mean disease duration of 21 years (9) over 80% of the patients showed involvement of the cervical and/or lumbar spine, the majority (43%) in both parts. These data indicate the necessity to include both, the cervical and the lumbar spine, in the score. However, only 8% of the patients had changes only in the cervical and not in the lumbar spine. There are no data on involvement of the thoracic spine. This will most probably change by the use of MRI.

The two scoring methods published in full so far include the lumbar spine, none the thoracic spine and one the cervical spine (10-12).

However, many sites of the spine can be scored:

- the vertebra (fractures, squaring)
- the intervertebral spaces (discitis),
- the vertebral margins and ligaments (erosions, syndesmophytes, bony bridging)
- the zygapophyseal joints

Again, these can be scored on the anterior and dorsal site (on a lateral view), or on the right and left site (on an AP view, or three-quarter view).

For the assessment of the hips and sacroiliac joints an AP pelvis can be used. For the assessment of the spine both AP, lateral and threequarter views can be used. The latter are important for assessment of the zygapophyseal joints (13). The AP view of the cervical spine is hard to interpret and is not useful for scoring purposes. Both AP and lateral view of the lumbar spine can give additive information. These are both included in the Bath Ankylosing Spondylitis Radiology Index (BASRI, 10) (Table II), whereas the Stoke Ankylosing Spondylitis Spinal Score (SASSS) uses the lateral lumbar view only (11,12). It is not clear how much information is lost if one of the two views is omitted.

Table II. Bath Ankylosing Spondylitis Scores.

BASRI-s:

1. Scoring of
   - Sacroiliac joints (2-4)
   - Lumbar spine (0-4)
   - Cervical spine (0-4)
2. on a simple scale between 0-4
   - 0 = normal
   - 1 = suspicious
   - 2 = mild
   - 3 = moderate
   - 4= severe
3. Addition of these 3 scores to the BASRI-s (spine) score (2-12).

BASRI-h:

4. Scoring of
   - Hip joints (0-4) = BASRI-h (hip)
5. on a simple scale between 0-4
   - 0 = normal
   - 1 = suspicious
   - 2 = mild
   - 3 = moderate
   - 4= severe
6. Addition of these 4 scores to the BASRI-t (total) score (2-16).

Available radiographic scoring methods

Up to now, two scoring methods have been published in full papers: the SASSS (11) and the BASRI (10). One other method was published in a thesis (14) and one in abstract form only (15). The SASSS was published first, and includes the lateral view of the lumbar spine, and separately the sacroiliac joints. This is a detailed scoring system for the anterior and posterior site of the lumbar spine with a range from 0-72. The method described by Creemers is a modification of the SASSS. Only the anterior site of the spine is scored. However, now the anterior site of the cervical spine is also included. This results in the same range as the original SASSS.

The other method is the BASRI (10). To validate the BASRI, radiographs of 470 AS patients were scored using the New York criteria for the sacroiliac joints (Table III) and, similarly, grading the lumbar and cervical spine on a scale of 0-4 (for normal, suspicious, mild, moderate, and severe). These 3 scores were added together to produce the BASRI-s score (scored 2-12). Radiographs of 188 patients were used to test reproducibility. Blinded radiographs of 89 non-AS patients were included, randomly, to assess disease specificity. Sensitivity to change was assessed using 177 radiographs from 58 AS patients. Intra- and interobserver variation showed 75-86% and 73-79% complete agreement at all sites, respectively. Specificities of 0.83 – 0.89 suggested that the lumbar and cervical spine

Table III. Radiographic grading of sacroiliac changes in ankylosing spondylitis.

Grade 0	Normal
Grade 1	Suspicious
Grade 2	Sclerosis, some erosions
Grade 3	Severe erosions,widening of the joint space, some ankylosis
Grade 4	Complete ankylosis

BASRI scores were disease-specific. Sensitivity to change became apparent at 2 years ($P < 0.001$). Using a lateral view and an AP view of the lumbar spine was more sensitive than using a lateral view alone. Grading a set of radiographs (sacroiliac joints, lumbar spine, and cervical spine) took 30 seconds. The BASRI has been used first with and later without the inclusion of the hips. Depending upon the inclusion or exclusion of the hips the range is (2-12) or (2-16), respectively. Recently, a modification has been proposed changing the features of grades 3 and 4. This is called BASRI-s for the spine only, BASRI-h for the hips only, and BASRI-t for the summation of both (16).

In a recent collaborative approach (17), two trained observers scored 217 sets of AS radiographs from baseline and one year follow-up, blinded for sequence, of an unselected cross sectional cohort of AS patients, followed longitudinally. The SI joints were scored in 5 grades by the New York method and the SASSS (Stoke Ankylosing Spondylitis Spine Score). Hips, cervical and lumbar spine were graded 0-4 according to the BASRI-spine (2-12). BASRI- spine and BASRI-hip (16) were combined to form BASRI-total (2-16). The anterior and dorsal site of the lumbar spine were also scored in detail with a total scoring range from 0-72 (SASSS). A similar scoring was applied to the anterior site of the cervical spine and this was combined with the anterior site of the lumbar spine to form the 'modified' SASSS (range 0-72). To assess change on an individual patient level, a smallest detectable difference (SDD) was estimated for data on a quasi interval scale (SASSS spine) and for the grading scales a change of at least 1 grade was defined as the minimum assessable difference.

In the first study with one year follow-up (17) BASRI was only moderately reliable, with Cohen's kappa ranging between 0.50 and 0.82 for intra, and 0.38-0.64 for interobserver reliability. Similarly, SI joint scores showed intraobserver kappa between 0.56 and 0.84, and interobserver reliability with kappa between 0.37 and 0.47. Larsen hip scores (18) proved unreliable: moderate intraobserver kappa of 0.47-0.58 and low interobserver kappa of 0.29. After retraining, interobserver kappa did not improve (0.45 and 0.17). In retrospect, a one-year period was too short to measure sensitivity to change. Observers agreed that no change occurred in up to 89% of cases. A measurable change of deterioration or improvement occurred rarely.

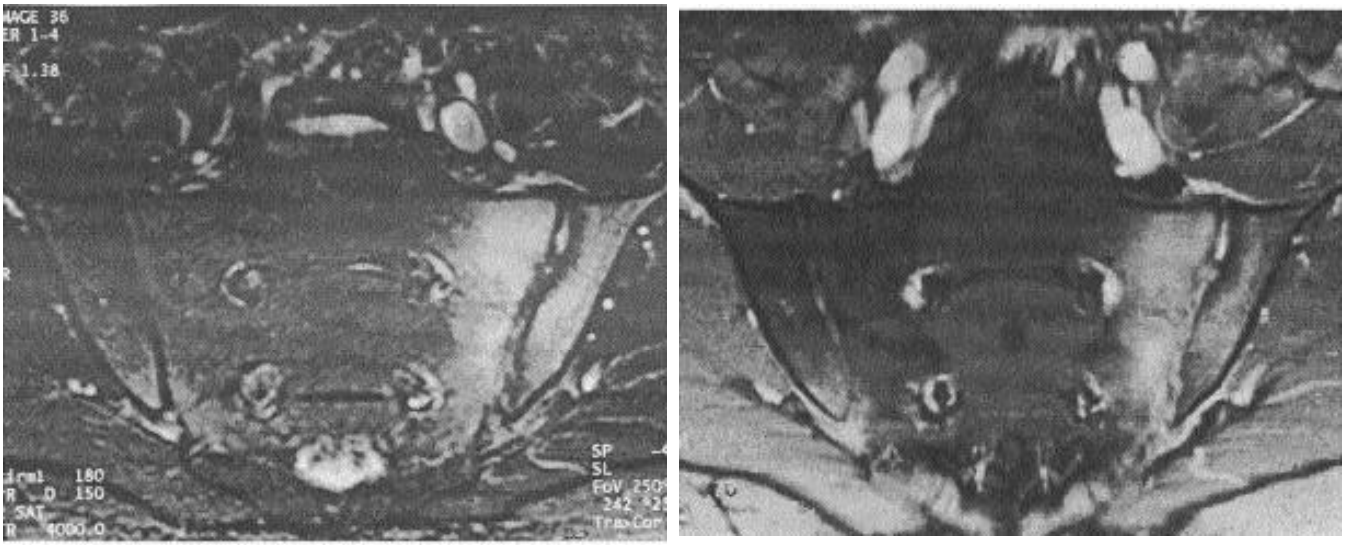
In a second study with two years of follow-up, the SI New York and SASSS showed intraobserver k's between 0.56 and 0.84 and interobserver k's between 0.37 and 0.47 (19). The reliability of BASRI-hip proved to be moderate to good: intraobserver k's of 0.66 and 0.67 and interobserver k of 0.40. SASSS scores of cervical and lumbar spine proved to be most reliable, with both high intra- and interobserver intraclass coefficients (ICC) between 0.90 and 0.96. For BASRI-spine and BASRI-total the ICC's were comparable with the SASSS scores, ranging between 0.85-0.95.

Over a 2 year period no difference was found in mean, median and SD for SI New York, SI SASSS and BASRI-hip score (20). For these three methods 0.3-1.2% of the patients deteriorated ≥1 grade according to both observers and they agreed in up to 89 % of patients that no change occurred. BASRI-spine and BASRI-total also showed limited change in mean, median and SD at baseline and 2 years. Of all patients 7.5% and 7.4% deteriorated ≥ 1 grade in BASRI-spine and BASRI-total and both observers agreed in only up to 48% that no change occurred. In case of SASSS (spine) the SDD was lowest (7.5) for the 'modified' SASSS. There was little difference in mean and median on baseline and after two years: 13.8, 6.7 and 15.0, 7.6 resp., but only very few patients (0.8%) deteriorated more than the SDD in 'modified' SASSS score. Observers agreed up to 92% that no change occured.

Taken together, in AS, radiological scoring methods are moderately to excellently reliable. The combined BASRI scoring methods (BASRI-s and BASRI-t) and especially the SASSS showed good or excellent reliability. Even with a scoring interval of two years the interobserver reliability remained very good. The reliability of the relatively new scoring method for the hips (BASRI-h) proved to be more disease specific (16) than the Larsen grading for RA (18) that is also often applied to score the hips in AS. For all scoring methods the complete concordance rates for the observers were rather low. The developers of the BASRI method found good to excellent complete concordance rates (21) for the hips between 78 and 95%. They found good concordance rates (73-81%) for BASRI applied on lumbar and cervical spine and they reached comparable concordance rates for the SI New York method (78-86%). Concordance rates for the SASSS method have not been reported by the developers.

Only BASRI-s and BASRI-t were able to detect change in a considerable number of patients over a two-year period. This change could not be identified by the other graded and detailed scoring methods. In case of BASRI-s and BASRI-t observers agreed in about 50% that no change occurred. Unfortunately, it still needs to be concluded that relevant change occurred rarely because observers agreed in only 7.5% of cases that real change of at least 1 grade occurred. This indicates that it is difficult to score AS radiographs and that we might need another scoring system which is more sensitive to change. At the other hand, these data are from an unselected group of patients. It is not clear what the progression will be in a group of patients with active disease selected for e.g. TNF-blocking agents. It also needs to be stressed that there is a subgroup of patients with rapid progression of disease which we might just have to detect earlier.

The developers of the BASRI-h found significant change after 1 year using Wilcoxon signed rank test for nonparametric data in 60 patients. For BASRI-s they found significant change after 2 years ($n = 31$) and after 1 year 30% of 20 cases showed change of at least 1 grade but this was not significant. In 1999 they reported the magnitude of change for the BASRI-s was from 7.0 to 7.9 in 2 years and 42% of 31 patients



(a) **(b)**

Fig. 1. Severe acute sacroiliitis in the left sacroiliac joint of a young male patient with undifferentiated spondyloarthritis (normal sacroiliac x-rays) as detected by the STIR technique (**a**) and after application of gadolinium-DTPA (**b**). Note that some edema/enhancement is also seen in the dorsal part of the right sacroiliac joint.

showed change in BASRI-s score (21). In these studies sensitivity to change was not specified for BASRI-t. These data were obtained in selected patients that were not followed according to a fixed protocol but radiographs were taken dependent on the clinical situation.

The developers of the SASSS methods found significant change over a group of 28 patients in 1 year using Mann-Whitney U test with a mean change of 4.1 points (range 0-72) in SASSS-total and a mean change of 1 grade in SASSS for the sacroiliac joints (22). In this study the order in which the radiographs were scored was known in contrast with our study. This is known to markedly influence the results. Calculation of 95% limits of agreement using the Bland and Altman method can only be applied reliably in scores with interval scales with large ranges such as the SASSS scores.

Most methods were unable to detect change over this two year period because only few individuals show real radiological change over a two year period in an average AS population. Comparing all radiological AS studies available at the moment we recommend to use the New York method for the SI joints because it is most widely used. The BASRI-hip should be used because it is the only AS disease specific method for the hips available and to score the spine we recommend the BASRI. The BASRI-s and BASRI-t can be distinguished from the SASSS methods for the spine by its feasibility, it also takes into account the AP view of the lumbar spine and it was the only method which showed change in a considerable number of patients over a two year period. Further study is needed with sets of radiographs in which progression of damage is likely, e.g. sets with a 5 year interval or in a AS population with a short disease duration because these patients tend to show more radiological change. Additional studies where AS radiographs are scored in both random and chronological order are warranted to assess the difference in methodology. Importantly, the smallest detectable differences of the methods (23) need to be especially assessed in the patient subgroups with very active and early disease.

There are two different concepts on the mode of radiographic and functional progression of AS during the first 10 years after disease onset. While two groups reported that the most rapid progression occurred in this period (24, 25), another group recently reported (26) that in their patient population radiographic progression was linear with no significant changes between the decades.

Detection of inflammatory spinal lesions in AS by MRI

There is increasing evidence that not only sacroiliac (Fig. 1), but also spinal inflammatory lesions (Fig. 2) can be nicely detected by MRI using the STIR

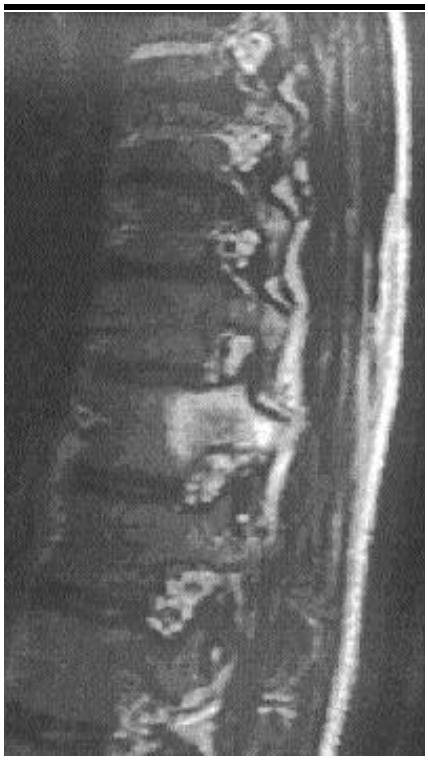


Fig. 2. Acute spondylitis posterior with costovertebral arthritis of the 6th vertebra of the thoracic spine in a 35-year old female AS patients (normal x-ray of the thoracic spine).

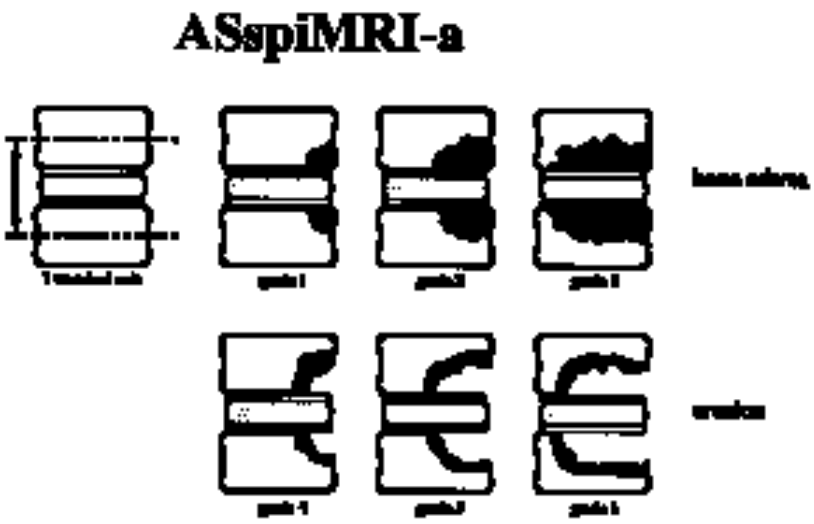


Fig. 3. Ankylosing spondylitis MRI activity score.

and the dynamic technique with gadolinium (27, 28). Since more effective therapies have now become available for the SpA in form of anti-TNF agents, objective evidence of improvement by modern imaging technology becomes increasingly important. Of interest, three recent pilot studies have used MRI to document improvement of inflammatory spinal disease (29-31). Importantly, the detection of spinal lesions by MRI allows to localize the main inflammatory spot with some precision, also in areas which used to be difficult for imaging techniques. This might facilitate side directed therapy in the future.

Scoring spinal lesions detected by MRI

Based on our experience with spinal MRI in recent years we propose a grading system (Table IV and Fig. 3) that has recently been evaluated in 20 AS patients who took part in the RCT on infliximab in AS (32). The preliminary analysis suggests that especially the activity score is reliable with good intra- and interobserver correlations and sensitivity to change over a short period of 3 months. One example of a

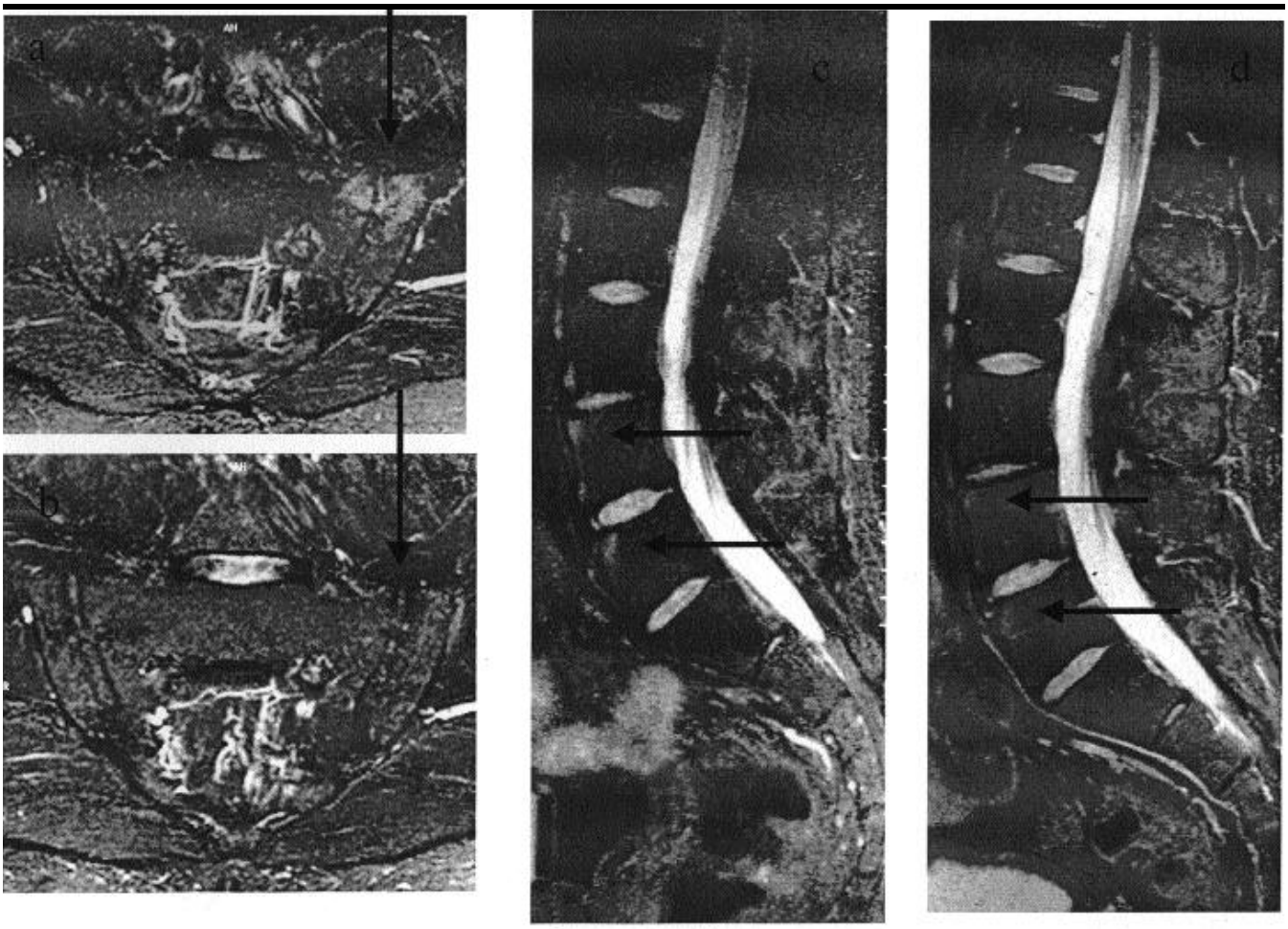


Fig. 4. Sacroiliac (**a, b**) and spinal (**c, d**) MRIs (STIR technique) of a patient with ankylosing spondylitis treated with infliximab before (**a, c**) and after therapy (**b, d**). Sacroiliitis is located in the ventral part of the left sacroiliac joint and spondylitis at the anterior rim of vertebrae 3-5 in the lumbar spine. (Photos provided courtesy of Dr. M. Bollow, Bochum, Germany).

Table IV. A preliminary score of MR grading of spondylitis: MRI spine score.

Differential assessment of inflammation and ankylosis
Semiquantitative analysis of at least two images/lesion
Scoring of all accessible vertebrae from CS 2 – S 1 (n = 23)
Including the intervertebral space and the discs
One vertebral unit = Lower half of vertebra above plus Upper half of vertebra below
Proposed scoring system: a. activity score: 0-6 for every vertebral unit assessed (n=138): bone marrow edema by STIR and/or enhancement after contrast bone marrow edema by STIR and/or enhancement after contrast plus erosions b. chronicity score: 0-6 for every vertebral unit assessed (n=138): sclerosis, erosions, syndesmophytes, partial fusion, ankylosis

patient who significantly improved on infliximab is shown in Figure 4. This score needs to be further evaluated in the upcoming clinical trials on infliximab and etanercept for the treatment of active AS. There is also a possibility that in addition to assessments of CRP (8) activity of spondylitis on the basis of a spinal MRI may preselect patients as candidates for anti-TNF therapy

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Bone density in ankylosing spondylitis

The increased prevalence of osteoporosis and vertebral fractures in AS is well established. In a recent study from France (33), the 2-year rate of bone mineral density (BMD) changes at the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry, at baseline and after 2 years. Fifty-four patients (35 men, 19 women; mean age 37.3 ± 11.3 years, mean disease duration 12.4 ± 8.6 years) were included. After 2 years, BMD did not change at the lumbar spine (+0.75% ± 3.5, p = 0.23), and decreased at the femoral neck (-1.6% ± 4, p = 0.006). The 24 month percentage change in femoral neck BMD was related to persistent systemic inflammation, defined using ESR (mean percentage change -4.1% ± 5.7 and -1.2% ± 3.9 in patients with and without persistent inflammation; respectively; p = 0.007). The results of this study suggest that persistent inflammation might be an etiologic factor of bone loss in AS. Measurement of bone density may be used as an outcome criterium in AS studies.

Summary

– In addition to clinics, sacroiliac x-rays remain the basis for a diagnosis of AS.

– MRI, using contrast material and fat saturation techniques such as STIR, is useful for the diagnosis of sacroiliitis in early stages of disease.

– Spinal x-rays are the basis for the detection of AS-specific bony changes in the spine such as syndesmophytes and ankylosis. Spinal x-rays are of very limited value in clinical studies because proposed scoring systems lack sensitivity to change. However, rapid change does occur in a subgroup of patients which are often diagnosed and recognized late.

– MRI, using contrast material and fat saturation techniques such as STIR, is useful for the detection of acute spinal inflammation in AS. These acute changes can be detected as early as after 3 months of anti-TNF therapy.

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