Spondyloarthritis : recognition, imaging, treatment

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General introduction

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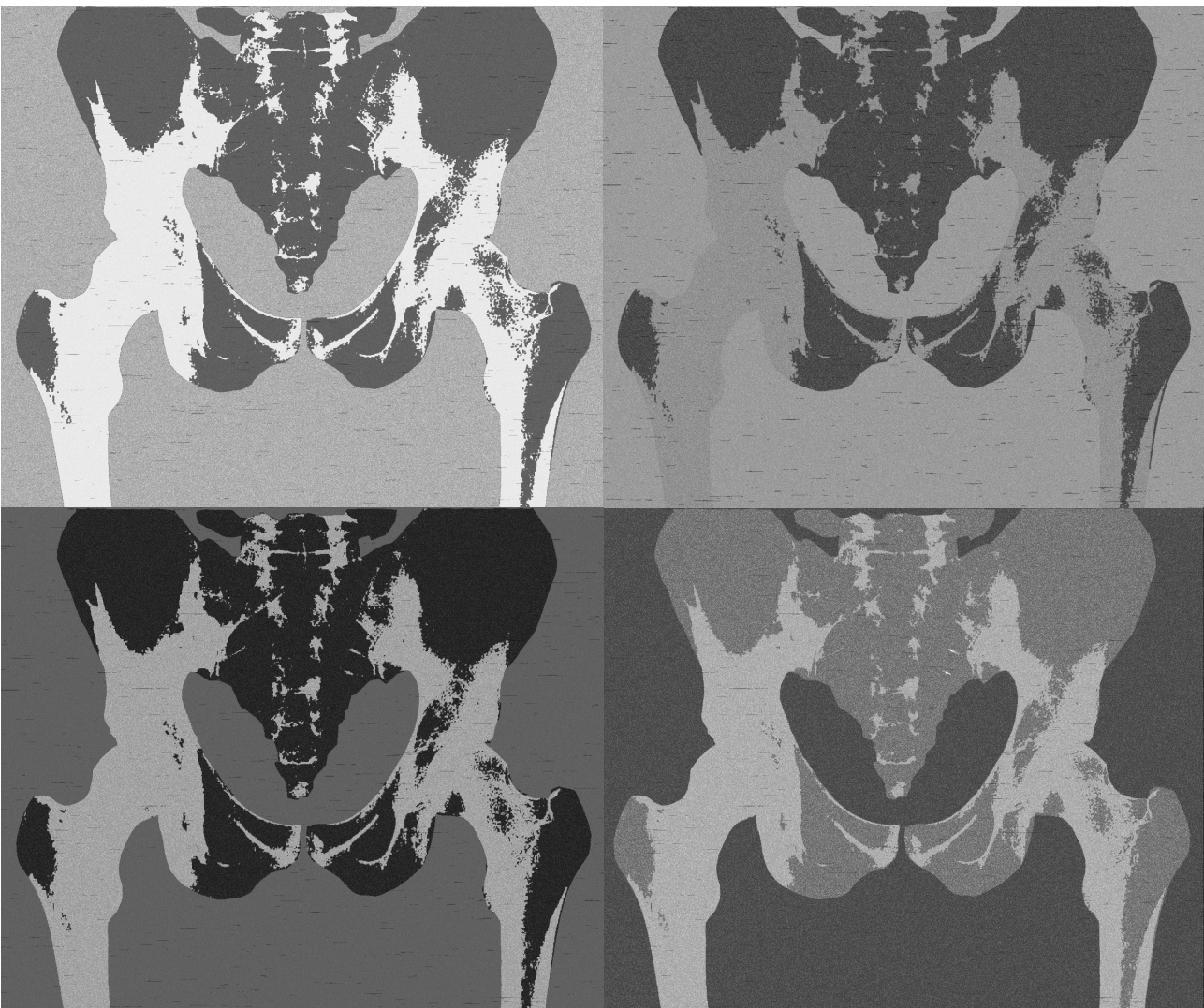


General introduction

The history of Ankylosing Spondylitis

Ankylosing spondylitis (AS; σκληρός= stiff σπονδύλων= vertebrae) is a chronic inflammatory rheumatic disease with a long history, primarily affecting the axial skeleton. For example, evidence of ossification of joints and entheses corresponding with lesions seen in AS was already seen in a 5000-year old Egyptian mummy [1]. Realdo Colombo, an Italian surgeon and professor in anatomy, probably described AS-like characteristics for the first time in 1559, and in 1691 Bernard Connor described pathologic changes of the skeleton possibly associated with AS [2, 3]. The symptoms and complaints of Leonard Trask (1805-1861) - he developed progressive severe thoracic kyphosis after he fell from a horse, resulting in invalidating disabilities - were extensively described as he was considered a medical curiosity. Until his death, his condition remained a medical mystery, however, post-mortem he was diagnosed with AS [4].

In 1893, descriptions of what might have been AS were given by the neurologist and psychologist Vladimir Bekhterev, as well as by the neurologists Adolph Strümpell in 1897 and Pierre Marie in 1898 [4-6]. The disease was long known as morbus Bechterew and Pierre Marie Strümpell disease although it is not certain the cases these authors described were what is now known as AS. Initially, AS was not identified as a separate entity, but considered as a subtype of rheumatoid arthritis ("rheumatoid spondylitis") until the 1960s [5]. Only during the mid-1960s, AS was recognized as a separate entity with well-defined manifestations and radiographic criteria [6, 7].

Clinical manifestations and epidemiology

AS is characterized by inflammation in the sacroiliac joints (SI-joints) and the vertebrae, causing severe pain and stiffness in the back and/or buttock area. In some patients the inflammation ultimately leads to bone formation in the SI-joints and/or spine, thereby deteriorating spinal mobility resulting in impaired daily functioning. Complaints associated with AS usually start in the 2nd and 3rd decade of life, and by the age of 45 years, more than 95% of the patients are symptomatic [8, 9].

The cause of AS is multifactorial, consisting of genetic and environmental factors, but is not completely elucidated yet. Regarding genetic factors, a strong association with the major histocompatibility complex (MHC) class I human leukocyte antigen (HLA)-B27, present in 80-95% of the AS patients, is known [10]. In addition to the prototypical genetic risk factor HLA-B27, HLA-B60 is a modest risk factor for AS [11]. Moreover, several new genetic risk factors outside of the MHC locus, including genetic variants in the ERAP1 and IL-23 receptor gene, have been discovered recently [12].

Worldwide, the prevalence of AS varies depending on the prevalence of HLA-B27. In central Europe, the prevalence of HLA-B27 varies from 6 to 9% and the estimated prevalence of AS ranges between 0.1-0.7% [13-16]. In northern Europe the prevalence of HLA-B27 is higher, around 14%, and the estimated prevalence of AS is accordingly higher as well: 1.1-1.4% [17]. In the USA the prevalence of HLA-B27 is also around 6% and the estimated prevalence of AS is around 0.5% [18, 19], and among Haida Indians the prevalence of HLA-B27 is very high, around 50%, and the prevalence of AS is estimated around 6% [20].

In addition to complaints in the axial skeleton, AS patients may suffer from complaints in peripheral joints (peripheral arthritis, dactylitis and enthesitis) and extra-articular manifestations (uveitis, psoriasis and inflammatory bowel disease (IBD)), often with substantial overlap. The estimated prevalence of peripheral complaints and extra-articular manifestations differ in various studies, due to differences in inclusion criteria and methodological characteristics resulting in different study populations regarding clinical characteristics, as well as due to differences in geographical area. Pooled prevalence

revealed that approximately 25.8% (95% CI: 24.1%-27.6%) of the patients suffer from at least one episode of acute anterior uveitis during their disease course. Approximately 9.3% (95% CI: 8.1%-10.6%) of the patients have psoriasis, and the pooled prevalence of IBD is 6.8% (95% CI: 6.1%-7.7%) [21]. Reported prevalence of peripheral arthritis ranges from 14.4% to 46.6% [22-24], of dactylitis it ranges from 1.9 to 3.1% [23, 24] and the reported prevalence of enthesitis ranges from 9.8% to 49% [22-26].

Classification and diagnostic criteria

Appropriate diagnostic criteria for AS are lacking, but classification criteria are available. According to the modified New York criteria (table 1), the presence of radiographic sacroiliitis (grade at least 2 bilaterally or grade 3-4 unilaterally) in combination with one of the clinical criteria, is mandatory in order to classify a patient as AS [27].

Table 1: the modified New York criteria for Ankylosing Spondylitis.

Definite ankylosing spondylitis	If the radiological criterion is associated with at least 1 clinical criterion
Clinical criteria	Low back pain and stiffness for >3 months which improves with exercise, but is not relieved by rest.
	Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
	Limitation of chest expansion relative to normal values correlated for age and sex.
Radiological criterion	Sacroiliitis grade ≥2 bilaterally or grade 3-4 unilaterally
Grading of radiographic sacroiliitis	
Grade 0	Normal
Grade 1	Suspicious changes
Grade 2	Minimal abnormality – small localized areas with erosion or sclerosis, without alteration in the joint width
Grade 3	Unequivocal abnormality – moderate or advanced sacroiliitis with one or more of: erosions, evidence of sclerosis, widening, narrowing or partikal ankylosis
Grade 4	Severe abnormality – total ankylosis

Adapted from van der Linden et al. A&R 1984;27:361-8 [27].

However, it often takes 6-8 years from the onset of symptoms before radiographic sacroiliitis can be detected on plain radiographs [28-30]. It is thought that radiographic changes (erosions, sclerosis, joint space narrowing/widening, ankylosis) reflect the consequences of inflammation rather than inflammation itself [28-30] (figure 1).
However, the underlying mechanisms of the inflammatory process leading to new bone formation are not fully understood [31, 32]. Moreover, not every patient with symptoms will develop radiographic sacroilitis [28-30]. AS is therefore considered as the prototype disorder of the whole concept of spondyloarthritis (SpA), which is a group of interrelated rheumatic diseases with common features (figure 2).
Furthermore, in some SpA patients the disabling problems are not the back pain and/or stiffness of the back, but predominantly peripheral and/or extra-articular complaints, at least during some periods of the disease course. To be able to classify the whole group of SpA, the Amor and ESSG criteria have been developed in the 1990s. In these classification

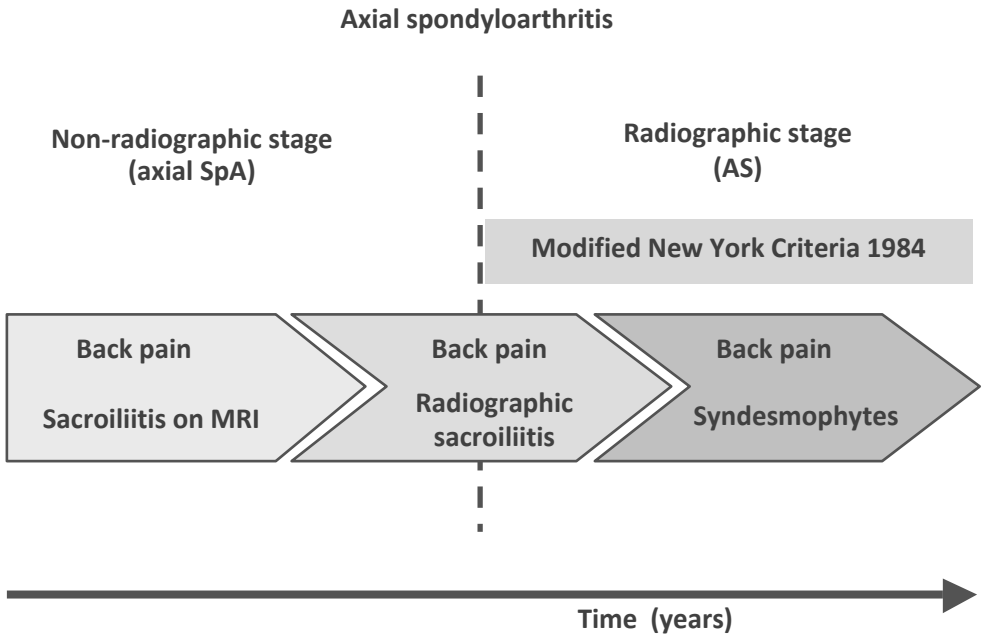


Figure 1: Axial spondyloarthritis. Reprinted from Rudwaleit et al. A&R 2005;52:1000-8 [29].

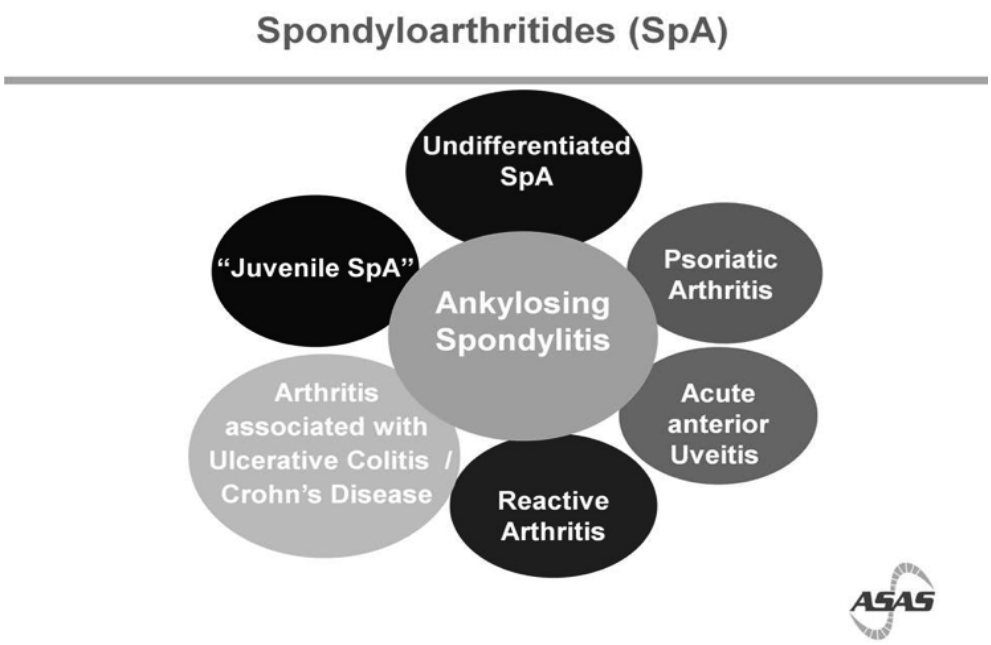


Figure 2: The concept of spondyloarthritis (SpA). Reprinted from the ASAS website [48].

criteria, radiographic sacroiliitis is included as one of the SpA-features, but in contrast to the modified New York criteria, it is not a mandatory criterion [33, 34]. The entry criteria of the ESSG criteria are inflammatory back pain (IBP) and/or peripheral arthritis. According to the ESSG criteria, patients with at least one of the entry criteria in combination with one minor criterion are classified as having SpA. The Amor criteria consist of a list of signs, none of which is required to classify a patient as having SpA [9, 35, 36].

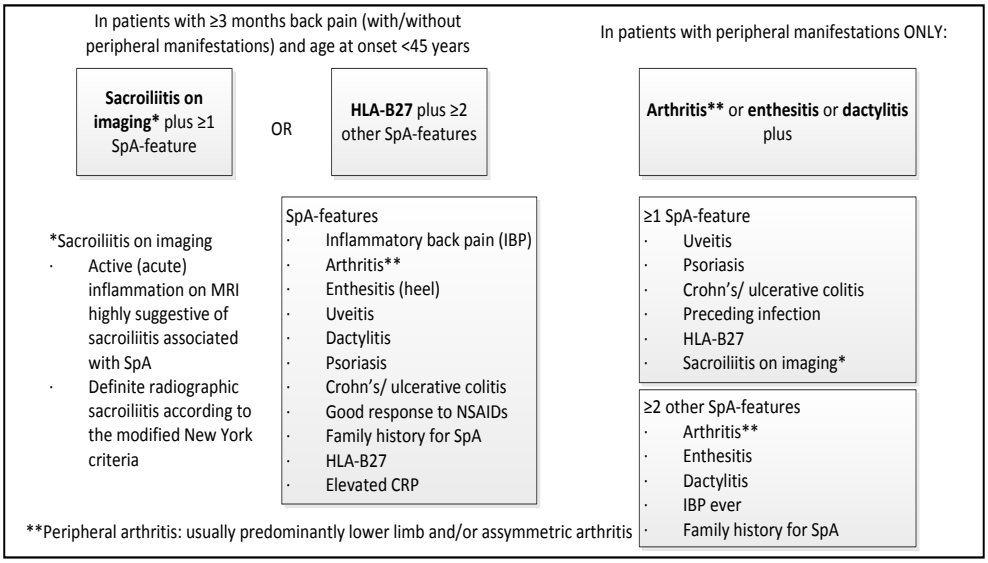


Figure 3: Combined use of the ASAS criteria for axial SpA and ASAS criteria for peripheral SpA in the entire SpA population. Reprinted from Rudwaleit et al. ARD 2011;70:25-31 [23].

Both the ESSG and Amor classification criteria were developed before Magnetic Resonance Imaging (MRI) became widely available. Yet, the introduction of MRI in the field of SpA made it possible to detect inflammation in the SI-joints and spine, which is considered the first step in the development of structural damage as seen in AS [31, 32]. In 2009, the Assessment of SpondyloArthritis international Society (ASAS) proposed two classification criteria sets for SpA (figure 3). One set can be applied in patients with predominantly peripheral manifestations (peripheral SpA) [23] and the other set in patients with predominantly axial manifestations (axial SpA) [30]. For the first time in history, MRI was included in classification criteria for SpA and plays an important role in especially the axial SpA criteria. The axial SpA criteria can only be applied in patients with back pain for more than 3 months and the onset of back pain before the age of 45 years and consists of two arms. In the imaging arm, patients can be classified as axial SpA if one SpA-feature is present in addition to sacroiliitis on MRI or radiographs sacroiliitis [30]. Patients can be classified as axial SpA in the clinical arm if in addition to HLA-B27 positivity two other SpA-features are present [30]. The classification criteria for peripheral SpA can be applied in patients with currently peripheral manifestations only. In order to classify a patient as having peripheral SpA, other SpA-features should be present in addition to peripheral arthritis compatible with SpA (usually asymmetric and/or predominantly involvement of the lower limb), enthesitis or dactylitis. A patient with current peripheral arthritis/enthesitis/dactylitis can fulfill the ASAS peripheral SpA criteria if at least one of the following SpA-feature is present: uveitis, psoriasis, IBD, preceding infection (urethritis/cervicitis or diarrhea within one month before the onset of arthritis/enthesitis/dactylitis), HLA-B27 positivity or sacroiliitis on imaging. A patient with current

peripheral arthritis/enthesitis/dactylitis can also fulfill the ASAS peripheral SpA criteria if at least two of the following SpA-features are present: peripheral arthritis compatible with SpA (present or past), enthesitis (present or past), dactylitis (present or past), IBP ever, or a positive family history for SpA (figure 3) [23]. Definitions of all SpA-features are given in table 2.

Table 2: Definitions of SpA-features applied in the ASAS classification criteria for axial and peripheral spondyloarthritis.

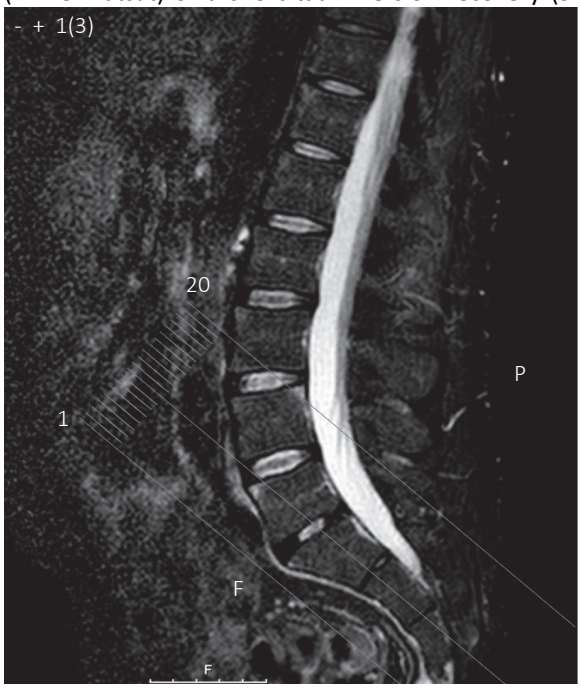
SpA-feature	Definition
Inflammatory back pain (IBP)	IBP according to experts: 4 out of 5 of the following paramters present: 1. Age at onset <40 years 2. Insidious onset 3. No improvement with exercise 4. No improvement with rest 5. Pain at night (with improvement upon getting up)
Arthritis	Past or present active synovitis diagnosed by a physician
Enthesitis (heel)	Heel enthesitis: past or present spontaneous pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus
Uveitis	Past or present uveitis anterior, confirmed by an ophthalmologist
Dactylitis	Past or present dactylitis, diagnosed by a physician
Psoriasis	Past or present psoriasis, diagnosed by a physician
Inflammatory bowel disease (IBD)	Past or present Crohn's disease or ulcerative colitis, diagnosed by a physician
Good response to NSAIDs	24-48 hours after a full dose of a non-steroidal anti-inflammatory drug (NSAID) the back pain is not present anymore or is much better
Family history	Presence in first-degree (mother, father, sisters, brothers, children) or second-degree (maternal and paternal grandparents, aunts, uncles, nieces and nephews) relatives of any of the following: 1. Ankylosing Spondylits 2. Psoriasis 3. Uveitis 4. Reactive Arthritis 5. Inflammatory Bowel Disease
Elevated CRP	C-reactive protein (CRP) concentration above upper normal limit in the presence of back pain, after exclusion of other causes for elevated CRP concentration
HLA-B27	Positive testing according to standard laboratory techniques
Sacroiliitis by radiographs	Bilateral grade 2-4 or unilateral grade 3-4 sacroiliitis on plain radiographs, according to the modified New York criteria
Sacroiliitis by MRI	Active inflammatory lesions of sacroiliac joints with definite bone marrow edema/osteitis, suggestive of sacroiliitis associated with spondyloarthritis

Reprinted from Rudwaleit et al. ARD 2009;68:777-83 [30].

Since the clinical presentation of SpA is heterogeneous and because of the lack of diagnostic criteria, diagnosing SpA can be challenging for physicians, especially in the absence of (radiographic) sacroiliitis. Because no single shared distinguishing feature exists, the diagnosis is usually based on the combination of symptoms, the findings of physical examination, imaging and laboratory results [37, 38]. To assist in the diagnostic process, a tool based on Bayes' theorem has been developed by a group of rheumatologists, incorporating all relevant SpA-features [35]. The formula of this tool, which is known as the Berlin algorithm, allows calculation of the disease probability for any individual patient with IBP according to the clinical presentation, and the final post-test probability may help in making the diagnosis of axial SpA. In general, three other SpA-features in addition to the presence of IBP result in a probability of about 90% for axSpA. However, the drawback of this algorithm is that it is developed for patients with IBP, while it is becoming more and more evident that many patients with axial SpA do not have IBP, and vice versa, that many patients with IBP do not have axial SpA [8, 39].

Magnetic Resonance Imaging

To provide a solid basis for the application of MRI of the sacroiliac joints (MRI-SI) in the ASAS axial SpA criteria, ASAS developed recommendations how to perform an optimal MRI-SI and how to define a positive MRI-SI [40, 41]. Inflammatory changes are best visualized by a water-sensitive sequence; a T2-weighted turbo spin-echo sequence with fat-saturation (T2 TSE fatsat) or a short tau inversion recovery (STIR) sequence with a high resolution. The latter has a robust performance and a high sensitivity and is therefore preferred. Structural changes such as erosions and fatty depositions are best visualized using a T1-weighted turbo spin-echo sequence (T1 TSE). Therefore, ASAS recommends to perform T1 TSE sequence and STIR sequence of the SI-joints in a semi-coronal section orientation along the long axis of the sacral bone with slices of 4mm thickness using an MR machine with a field strength of 1.5 Tesla (figure 4) [40].



Alternatively, the administration of a paramagnetic contrast medium (gadolinium-chelate; Gd) in a T1 TSE sequence with fat saturation (T1 TSE fatsat) could be considered as it occasionally gives additional value, especially in depicting enthesitis and capsulitis.

Figure 4: Scout view of the SI-joints in a semi-coronal section orientation along the long axis of the sacral bone.

However, the STIR sequences and the T1 post-Gd sequences give largely overlapping information [42, 43]. Therefore, the administration of Gd is not recommended by ASAS [40].
The clear presence of one BME lesion highly suggestive of SpA visible on a T2 or STIR sequence (or alternatively osteitis (on T1 post-Gd)) located in the typical anatomical areas

(subchondral or periarticular bone marrow) on at least two consecutive slices or the clear presence of several lesions on a single slice allows to define the MRI-SI as positive. The presence of isolated synovitis, enthesitis or capsulitis without the presence of BME (or osteitis) is only occasionally seen [42] and is not sufficient for a positive MRI-SI [41]. Furthermore, the presence of isolated structural lesions without concomitant BME (or osteitis) does not suffice for the definition of a positive MRI-SI either [41].
In addition to the dichotomous evaluation of an MRI-SI according to the ASAS definition, MRI-SIs can be evaluated in a semi-quantitative manner, for example according to the Spondyloarthritis Research Consortium of Canada (SPARCC) method [44]. The SPARCC-score ranges from 0 to 72 points and has a high sensitivity to change. Therefore, the SPARCC-score is of particular value in clinical trials, testing the efficacy of (biological) treatment in terms of changes in inflammation over time.

Treatment

In 2006, ASAS in collaboration with EULAR developed evidence -based recommendations for the management of AS in order to contribute to the improvement of outcomes in patients [45]. Treatment should not only aim on improving signs and symptoms, but also on improving function and socioeconomic factors as well as preventing structural damage, thereby improving the quality of life of patients [46]. The standard treatment of AS patients consists of a combination of non-pharmacological and pharmacological treatment. The non-pharmacological treatment comprises education, exercise, physical therapy, rehabilitation, patient associations and self-help groups. Pharmacological treatment comprises treatment with non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclo-oxygenase 2 (COX-2) inhibitors, as first line drug. NSAIDs may rapidly improve spinal pain, peripheral joint pain and function. In patients with peripheral complaints, disease modifying antirheumatic drugs (DMARDs), including sulfasalazine and methotrexate, might be considered, but effect on axial complaints is lacking. Moreover, in patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations, treatment with tumor necrosis factor-alpha (TNF-α) inhibitors should be considered [45].

Outline of this thesis

The recognition and treatment of SpA has been improved a lot over the last 10-15 years. These improvements resulted, inter alia, in the development of the ASAS classification criteria. At the same time, the ASAS classification criteria are contributing to further enhancements. Moreover, the treatment armamentarium has been broadened with TNF-α inhibitors.
However, there are still major challenges in recognizing, diagnosing, classifying and treating (early) SpA patients. Those aspects will be addressed in this thesis in three dedicated parts. Part I focuses on the early recognition of SpA and on the evaluation of classification criteria of SpA. The focus of part II is on the role of imaging in the early diagnosis of SpA. The current recommendations for management of AS and axSpA and the evidence as the base for these recommendations is the focus of part III.
The studies described in part I and II are largely performed in the SPondyloArthritis Caught Early (SPACE)-cohort and the DEvenir des Spondylarthropathies Indifférenciées Récentes (the evaluation of outcome of recent onset undifferentiated spondyloarthritis; DESIR)-cohort [25]. Both cohorts include patients with back pain to study - among other research questions - how patients with SpA can best be differentiated from patients without SpA, which factors are predictive for SpA and which factors are predictive for the progression of the disease. Therefore, information about the presence/absence of all SpA-features in all patients is collected in both the SPACE-cohort and the DESIR-cohort. Besides the similarities

between the two cohorts, small differences exist. The DESIR-cohort is a purely French cohort, with 25 participating centers across France, while the SPACE-cohort started as a Dutch single-center cohort in the LUMC. In the meantime, the SPACE-cohort has become an international multi-center cohort with participating centers in Norway, Italy and Sweden in addition to other participating hospitals in the Netherlands as well. Another difference between the DESIR-cohort and the SPACE-cohort is that the DESIR-cohort includes patients with inflammatory back pain (≥3 months, but <3 years) aged 18-50 with a suspicion of SpA while the SPACE-cohort includes patients with chronic back (pain ≥3 months, but ≤2 years) with the onset <45 years. As a consequence, the populations in both cohorts are slightly different.

One of the research questions we have is to assess the performance of existing classification criteria, including the recently developed ASAS axial SpA and peripheral SpA criteria. It is of particular interest to know the performance of the ASAS axial SpA and peripheral SpA criteria as this has not yet been evaluated in another cohort than the validation cohort. Some experts in the field impeach the ASAS axial SpA criteria as they question whether patients fulfilling the clinical arm reflect the same disease as patients fulfilling the imaging arm. Since the inclusion criteria of the SPACE-cohort yield also the inclusion of a control group with similar age, gender and symptom duration as the patients with axial SpA, the SPACE-cohort offers the opportunity to investigate this research question. The results of this investigation, as well as an extensive description of the SPACE-cohort, are presented in **chapter 2**. Some experts in the field who fear that the ASAS peripheral SpA criteria are not specific enough impeach the ASAS peripheral SpA criteria too. Therefore, a very similar analysis on the performance of the various classification criteria as described in **chapter 2**, is performed in the Early Arthritis Clinic (EAC)-cohort in **chapter 3**.

The Leiden EAC-cohort is a population-based prospective cohort, started in 1993 in order to detect and treat inflammatory disorders early in the disease state, especially early rheumatoid arthritis (RA). Patients with suspected arthritis are referred by general practitioners to the LUMC as soon as possible, and are seen within 2 weeks from referral. Patients are included in the EAC-cohort if arthritis of recent onset (<2 years) is confirmed by the rheumatologist [47]. Since it is known that up to 67% of the SpA patients with a symptom duration <2 years report arthritis as the first symptom, SpA and PsA are important parts of the differential diagnosis. Therefore, the EAC-cohort is a suitable cohort to try to answer this research question.

In **chapter 4**, the performance of the Berlin algorithm is evaluated. The inclusion criterion of the Berlin algorithm is IBP, however, the increasing evidence that not all patients with axial SpA have IBP stimulated us to propose two modifications of the algorithm. We test these proposed modifications in the SPACE-cohort since the inclusion criteria of the SPACE-cohort are chronic back pain (and not IBP) thereby offering the possibility of yielding axial SpA patients without IBP. In addition, we tested the proposed modifications in the original validation cohort of the ASAS classification criteria (**chapter 4**).

The focus of part II is on the role of imaging in classifying and diagnosing patients. It is known that it is challenging to reliably judge imaging of the SI-joints, especially plain radiographs. However, the consequences of a different judgment of the same set of imaging by different readers on the classification of patients, and in turn the consequences of a possibly other classification on the access to treatment is not known. As the DESIR-cohort contains judgments of MRIs and X-rays of the SI-joints by local radiologists and/or rheumatologists as well as judgments of the same images by central trained readers, this cohort offered the unique opportunity to study this. In **chapter 5** the evaluation of X-rays of the SI-joints by local readers is compared to the evaluation by central readers in terms of agreement on abnormal versus normal SI-joints permitting to diagnose radiographic sacroiliitis. **Chapter 6** is about the role of differences in judgments by local readers and central readers of all

imaging (combined radiographs and MRI of the SI-joints) and the effect on the ASAS axial SpA criteria.

Nowadays, more and more trials are being performed in patients with non-radiographic axial SpA. Eligibility of patients for these trials is often based on the judgment of local readers on a positive/negative MRI (ASAS definition). Within clinical trials, semi-quantitative scoring methods like the SPARCC-score method are used to measure changes in inflammation over time, evaluated by central trained readers. However, interreader reliability of the SPARCC-score in terms of smallest detectable change (SDC) is not known. Moreover, it is known that inflammation may spontaneously change over time, but it is not sufficiently investigated how many SPARCC-score points these spontaneous changes comprise. Furthermore, in case one needs to link the read for eligibility to the efficacy reading, it is not known what SPARCC-score cut-off value the equivalent is of a positive MRI (ASAS definition). These three questions are addressed in **chapter 7**.

As the field of SpA is rapidly moving, the ASAS in collaboration with EULAR intends to update the current recommendations for both the treatment of AS with TNF-α inhibitors and the recommendations for the management of AS which is the focus of part III. Preambles to these updates, up-to-date overviews regarding the implementation of these recommendations worldwide and regarding clinical trials and publications on AS therapy were needed. First, a comparison of national recommendations on TNF-α inhibitor use is made, with a focus on the similarities and differences compared to the ASAS/EULAR recommendations of 2006 (**chapter 8**). Second, a systematic literature review about the management of AS with non-pharmacological treatment and non-biologic drugs is performed (**chapter 9**). Third, a systematic literature review on biologic treatment of AS is performed (**chapter 10**). The results of these studies are presented to the working group of international experts who met during ASAS workshops to develop the new management recommendations, presented in **chapter 11**.

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