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Prediction and Prevention of Disease Progression in Early Axial Spondyloarthritis

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Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute phase reactants and cigarette smoking status predict radiographic progression in the spine in early axial spondyloarthritis. Arthritis Rheum 2012;64(5):1388-98.

Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2013;72(8):1430-2.

Poddubnyy D, Rudwaleit M, Listing J, Braun J, Sieper J. Comparison of a high sensitivity and standard C reactive protein measurement in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis. Ann Rheum Dis 2010;69(7):1338-41.

Heiland GR, Appel H, **Poddubnyy D**, Zwerina J, Hueber A, Haibel H, et al. High level of functional dickkopf-1 predicts protection from syndesmophyte formation in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71(4):572-4.

Poddubnyy D, Conrad K, Haibel H, Syrbe U, Haibel H, Appel H, Braun J, et al. Elevated serum level of the vascular endothelial growth factor predicts radiographic spinal progression in patients with axial spondyloarthritis. Ann Rheum Dis 2013. [Epub ahead of print]

Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German SPondyloarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2012;71(10):1616-22.

Für meine Frau Elena, unsere Tochter Veronika und meine Eltern.

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List of Abbreviations

AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS	ASAS endorsed disease activity score
BASDAI	the Bath Ankylosing Spondylitis Disease Activity Index
BASFI	the Bath Ankylosing Spondylitis Disease Functional Index
BASRI	the Bath Ankylosing Spondylitis Radiology Index
BMP	bone morphogenetic protein
CI	confidence interval
COX	cyclooxygenase
CRP	C-reactive protein
DMARD	disease-modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
EULAR	European League against Rheumatism
GESPIC	GErman SPondyloarthritis Inception Cohort
IL	interleukin
MMP-3	matrix metalloproteinase 3
MRI	magnetic resonance imaging
mSASSS	the modified Stoke Ankylosing Spondylitis Spine Score
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
SpA	spondyloarthritis
TNF α	tumor necrosis factor alpha
VEGF	vascular endothelial growth factor

1 Introduction

1.1 The spondyloarthritis concept

The term “spondyloarthritis” (SpA) is an umbrella term for a group of diseases sharing common clinical and genetic features, such as involvement of the axial skeleton (sacroiliac joints and spine), certain pattern of the peripheral joint involvement, development of enthesitis, dactylitis, acute anterior uveitis, presence of psoriasis or inflammatory bowel disease, and association with the HLA-B27 antigen. Depending on the predominant clinical manifestations, SpAs can be classified either as axial SpA (characterized by predominant involvement of the spine and/or sacroiliac joints as in ankylosing spondylitis (AS) and non-radiographic axial SpA), which is in the main focus of the current work, or as a peripheral SpA (peripheral arthritis which is usually asymmetric, affects predominantly the lower limb and is oligoarticular, enthesitis and/or dactylitis).

Non-radiographic (i.e., without definite sacroiliitis on X-ray) axial SpA and AS are considered now as two stages of one disease continuum referred to as axial SpA [1] – ***figure 1***. The rate of progression from non-radiographic (without radiographic sacroiliitis) to radiographic (with definite radiographic sacroiliitis, i.e., AS) was not well defined until recently, there are likely patients who remain at the non-radiographic stage during the entire course of the disease without progression to established AS. Similarly, with regards to structural damage in the spine (syndesmophytes, ankylosis) – not all patients with AS / axial SpA develop these changes. Although in AS sacroiliac joints are normally involved ahead of the spine in an estimated 10% of patients with AS / axial SpA syndesmophytes can be found in the absence of definite radiographic sacroiliitis [2].

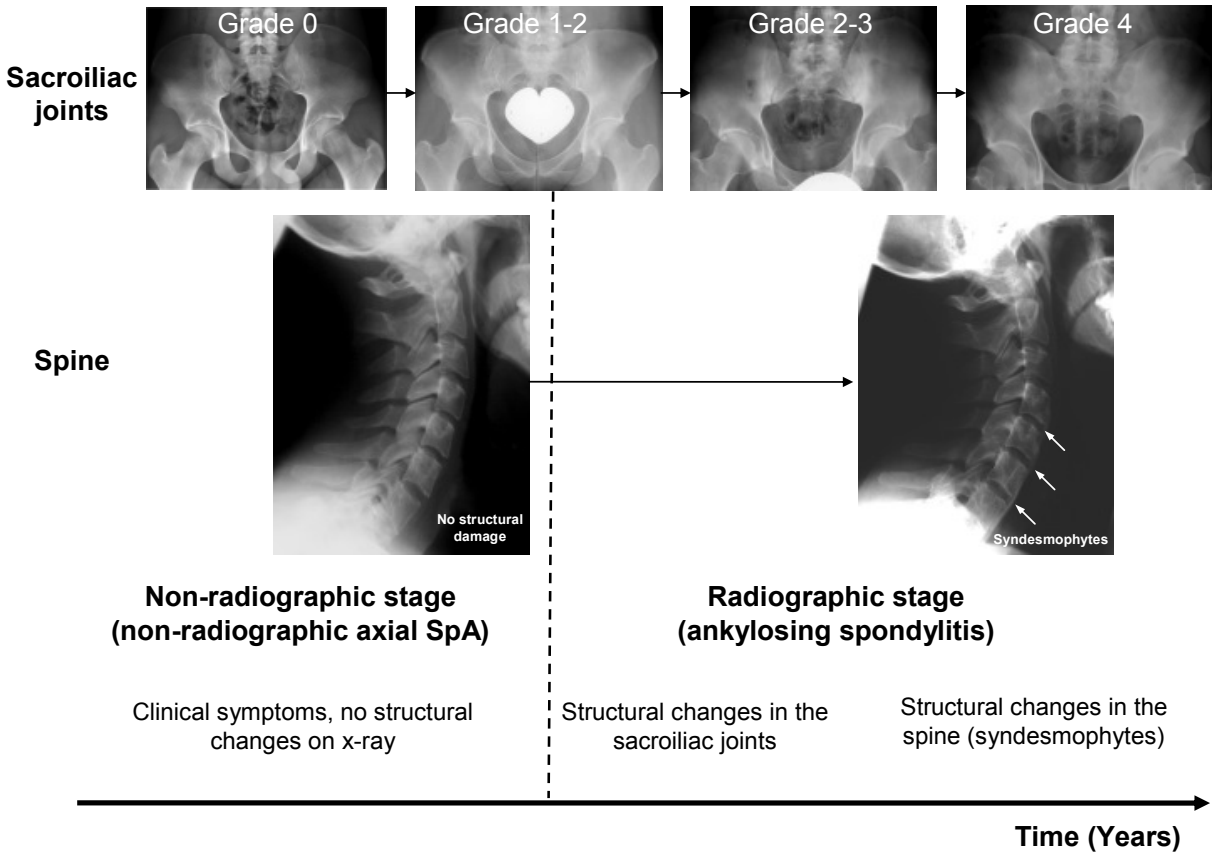

Figure 1. Continuum of axial spondyloarthritis.

At the early disease stage no or very little radiographic damage of the sacroiliac joints and in the spine can be visualized on X-rays (non-radiographic stage). The radiographic stage refers to the presence on X-rays of structural damage of the sacroiliac joints (radiographic sacroiliitis grade 2-4) and/or spine (syndesmophytes – bony bridges between vertebral bodies, spondylodiscitis, arthritis/ ankylosis of the facet joints).

Adapted from: Poddubnyy D, Rudwaleit M. Early spondyloarthritis. Rheum Dis Clin North Am 2012;38:387-403.

1.2 Epidemiology of spondyloarthritis

AS – the prototype disease of the SpA group – has an estimated prevalence of about 0.5% [3, 4] in the general Caucasian population (including Germany), while the estimated prevalence for the whole group of SpA is about 1.5-2% [3, 4]. The prevalence of AS and the whole group of SpA is related to the frequency of HLA-B27 in a given population. HLA-B27 is most prevalent in northern countries and is highest in the Haida Indians population (up to 50%) [5] giving a high prevalence of AS of about 6% [5]. In the central European population the HLA-B27 is as common as 6% to 9% [3, 6, 7], while in Japanese or Central and South African populations its prevalence - and, accordingly the SpA prevalence - is close to 0% [8, 9].

In the majority of patients the first symptoms of axial SpA (usually back pain) start in the 3rd or 4th decade of life. Males are about 2.5 times more often affected with AS than females and have in general more severe disease (more radiographic damage), while in the whole group of axial SpA, the male to female ratio is close to 1:1 [2].

About 40-60% of patients with AS have elevated serum C-reactive protein (CRP) [2, 10, 11]. AS patients with normal values of CRP may well have active disease according to clinical parameters which accounts for the poor correlation between CRP levels and clinical disease activity in AS in general [10].

In up to 40% of the patients with AS significant functional impairment may occur with a close relationship between the grade of impairment and the duration of the disease [12, 13]. However, the diagnosis of AS / axial SpA is commonly delayed by 8-10 years after the first symptom onset [14].

There are several factors contributing to the long diagnostic delay in AS / axial SpA. One of the most obvious is the usual application of a set of criteria (the modified New

York criteria for AS [15]) which require the presence of radiographic sacroiliitis for definite AS diagnosis - ***box 1***. Published in 1984, these criteria still remain a basis for the AS diagnosis in clinical practice in many countries. Since radiographic sacroiliitis usually develops rather late (after years) in AS, these criteria are obviously useless in patients with early disease.

Recent data from the early SpA cohort demonstrated that patients with non-radiographic axial SpA have the same level of pain and stiffness in comparison to patients with established AS [2] and, therefore, require effective treatment. Early diagnosis would lead to early initiation of appropriate and effective therapy [16, 17] that might improve outcome. Moreover, short disease duration and a good functional status were among predictors of a good clinical response to the tumor necrosis factor (TNF) α blocking agents [18-20], which represent the only one effective therapeutic option beyond non-steroidal anti-inflammatory drugs (NSAIDs) for axial disease [16].

Box 1. The modified New York criteria for ankylosing spondylitis.

Clinical criteria
Low back pain and stiffness for more than 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

Definite ankylosing spondylitis is present if the radiological criterion is associated with at least one clinical criterion.

1.3 Current classification criteria for spondyloarthritis

Two historical sets of criteria for SpA in general (Amor criteria [21] and the European Spondyloarthropathy Study Group (ESSG) criteria [22]) have been widely used in the past decades but have several limitation (e.g., absence of MRI as a diagnostic tool, no differentiation between axial and peripheral SpA, no possibility to classify patients with enthesitis without synovitis as SpA), which resulted in the development of new classification criteria for axial SpA by the ASAS group [23, 24] – ***figure 2***.

These criteria include two arms: 1) “imaging” arm – in order to fulfill the criteria patient should have sacroiliitis on X-ray or MRI and at least one additional SpA parameter; 2) “clinical” arm – for patients without sacroiliitis on imaging or lack of imaging information, HLA-B27 plus at least 2 further SpA parameters must be present. The sensitivity of the axial SpA criteria was 82.9%, specificity – 84.4% in the ASAS study population [24].

Thus, the development of the axial SpA criteria by ASAS was an important step towards a better definition of the early disease stage in SpA. Furthermore, in the most recent update of the international ASAS recommendations on the use of anti-TNF agents, fulfillment of ASAS classification criteria for axial SpA was included as an alternative to fulfillment of the modified New York criteria for AS [17].

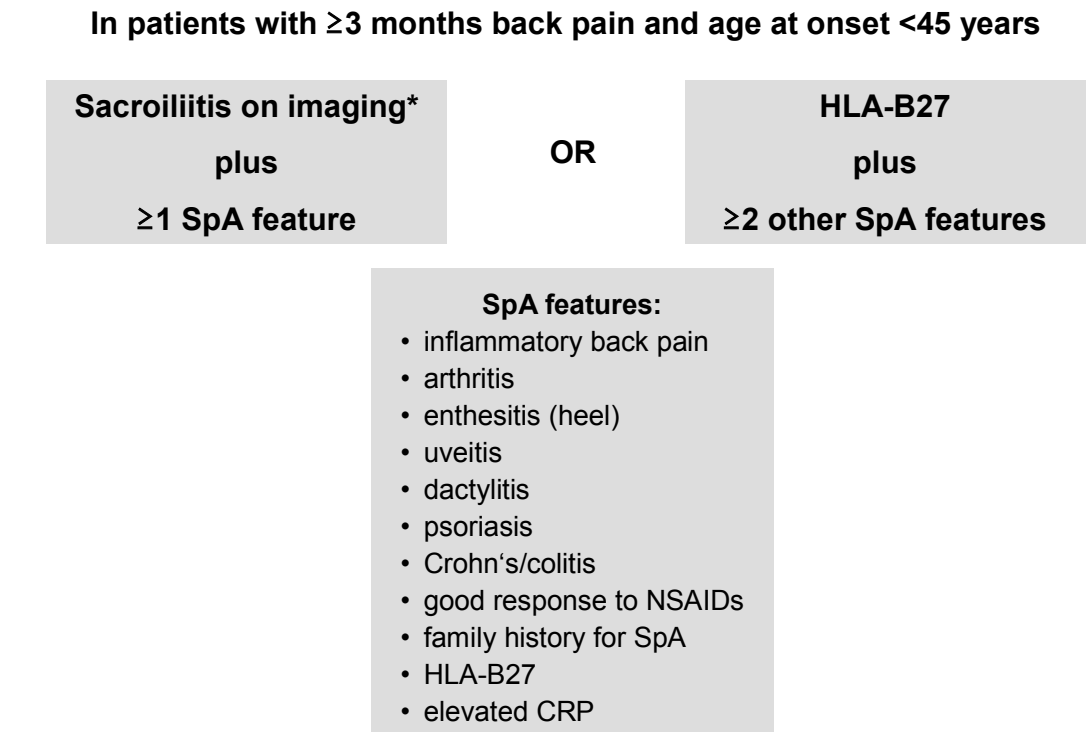

Figure 2. The ASAS classification criteria for axial spondyloarthritis.

CRP = C-reactive protein, MRI = magnetic resonance imaging, NSAIDs = non-steroidal anti-inflammatory drugs, SpA = spondyloarthritis

Adapted from: Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, 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;68:777-83.

1.4 Current treatment of axial spondyloarthritis

According to the ASAS / EULAR (European League against Rheumatism) [16, 17] treatment recommendations, NSAIDs and non-pharmacological methods of treatment (e.g., physiotherapy) are considered as a cornerstone of SpA treatment irrespectively of the predominant involvement (axial or peripheral). However, NSAIDs are especially effective in patients with axial involvement reducing substantially pain and stiffness in a majority of patients [25, 26]. Assessment of NSAIDs efficacy is usually possible if an NSAID is taken in a maximal recommended/tolerated dose continuously for at least two weeks, unless contraindicated. In case of inefficacy of the first NSAID it is recommended to try at least one another NSAID in a full therapeutic dose.

Classic disease-modifying anti-rheumatic drugs (DMARDs, such as methotrexate, sulfasalazine, or leflunomide) are normally not effective in axial disease, but might be beneficial in case of peripheral disease (first of all for peripheral arthritis) [27-29]. Therefore, DMARDs are currently reserved for patients with predominant peripheral manifestation. Local steroids are also recommended for treatment of peripheral manifestation (arthritis, enthesitis, dactylitis) but can be also effective in treatment of active sacroiliitis [30].

High disease activity (defined as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4) despite adequate NSAIDs treatment as described above in patients with predominant axial involvement and despite local steroids / DMARDs treatment in patients with predominant peripheral manifestations is usually considered as an indication for TNF α blockers [17]. A positive opinion of a rheumatologist based on the assessment of acute phase reactants, magnetic resonance imaging (MRI), radiographic data and radiographic progression of AS is also required.

Currently, there are nearly no further therapeutic options available for patients, who do not response to anti-TNF α therapy. However, several promising drugs including monoclonal antibody against interleukin (IL)-17 and interleukin-12/23 are under investigation now.

Use of analgesics can be recommended for patients, in whom pain can not be effectively reduced with other treatment methods described above [16].

Surgery might be of benefit in case of peripheral disease requiring synovectomy, in case of severe hip arthritis (hip arthroplasty), and, in patients with axial disease, in case of severe spinal deformities/ankylosis with a serious impact on patient's functional status and quality of life (spinal corrective osteotomy) [16].

1.5 Definition of disease progression in axial spondyloarthritis

When discussing disease progression in AS / axial SpA development of structural changes in the sacroiliac joints and in the spine is usually considered.

1.5.1 Structural damage in the sacroiliac joints

Plain radiography is a standard method of assessment of structural damage in the sacroiliac joints. The extent of the damage is usually scored according to the grading used in the modified New York criteria for AS [15, 31]: 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 partial ankylosis; grade 4 – severe abnormality – total ankylosis.

Three types of structural changes are considered here: sclerosis, erosions and joint space narrowing/ankylosis – ***figure 3***.

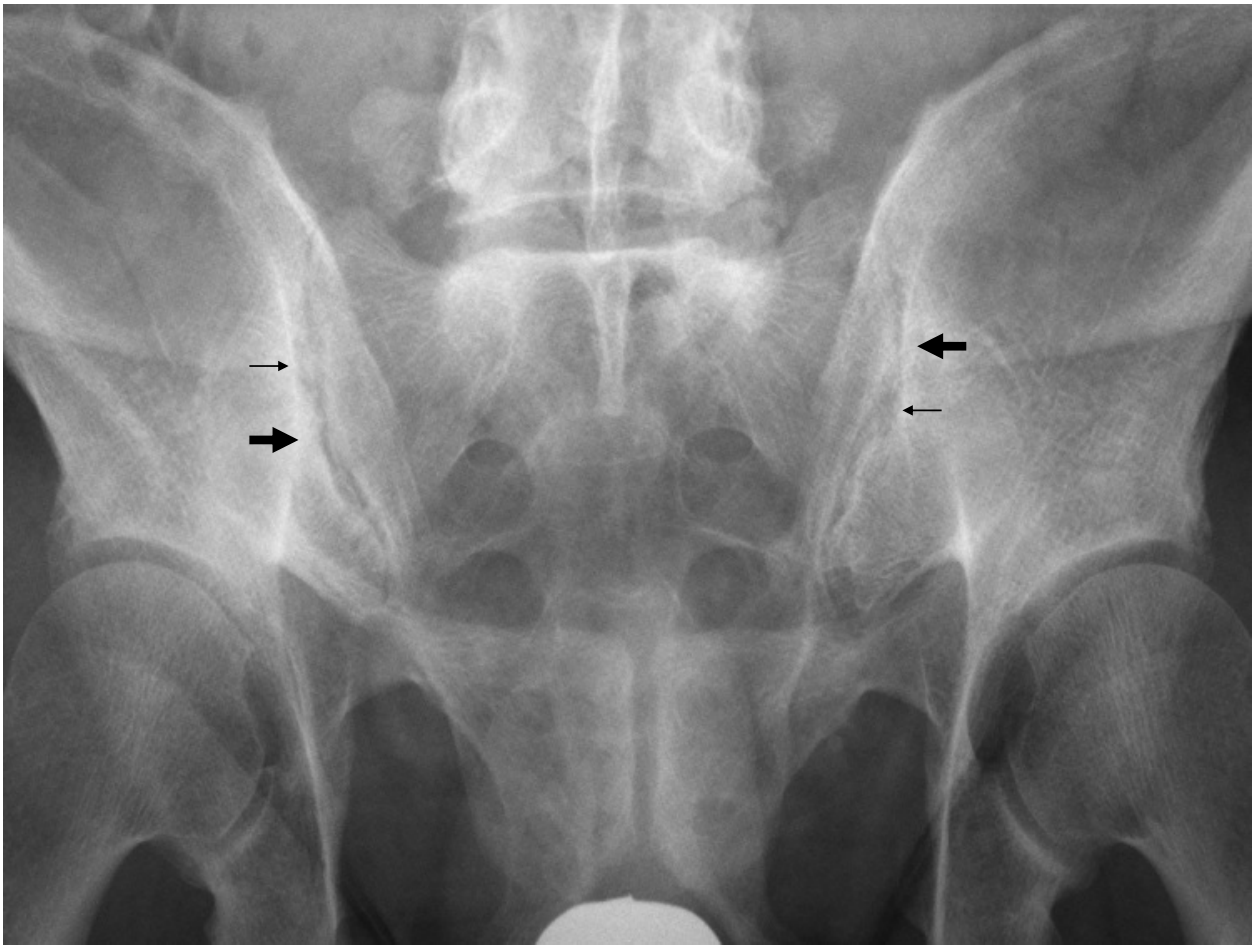

Figure 3. Plain radiography of the sacroiliac joints of a 51 years old male patient with ankylosing spondylitis.

Subchondral sclerosis, joint space narrowing (thick arrows) and erosions resulting in a joint space widening (thin arrows) giving an image of radiographic sacroiliitis grade III bilaterally.

Adapted from: Poddubnyy D, Sieper J. Radiographic progression in ankylosing spondylitis/axial spondyloarthritis: how fast and how clinically meaningful? Curr Opin Rheumatol. 2012;24:363-9.

There is a substantial overlap between destructive (erosions) and reparative (osteosclerosis and ankylosis reflecting new bone formation) changes at most of the stages making a split of radiographic structural damage into erosive and ankylosing

damage nearly impossible. The reading of pelvic radiographs and grading of sacroiliitis is generally difficult that is related, first of all, to the anatomical complexity of the sacroiliac joints and the suboptimal visualization using plain radiography. Van Tubergen *et al* showed that both radiologists and rheumatologists demonstrate only modest sensitivity and specificity for sacroiliitis detection and sizeable intraobserver variation [32].

Although x-rays are used for the assessment of the structural damage in the sacroiliac joints for a long time, there are no studies available in which progression of radiographic sacroiliitis was evaluated systematically at the early disease stage.

1.5.2 Structural damage in the spine

There is a number of possible structural changes in the spine representing structural damage in patients with ankylosing spondylitis visible on plain radiographs, including erosions, sclerosis, squaring of the vertebral bodies, syndesmophytes formation with subsequent ankylosis, joint space narrowing, erosions and ankylosing in the facet joints, spondylodiscitis and fractures. Usually, not all of these changes are included into evaluation of radiographic progression in axial SpA. The most typical and, probably, the most relevant radiographic sign of structural damage is a syndesmophyte – ***figure 4***, which is considered by all three commonly used scores for the assessment of radiographic damage and progression in the spine. The first is the Bath Ankylosing Spondylitis Radiology Index (BASRI) [33], which includes cervical and lumbar spine as a whole and, therefore, the sensitivity to change appears to be rather low. The second (the Stoke Ankylosing Spondylitis Spinal Score (SASSS) [34]) and the third (the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [35]) are more detailed scores accounting for structural changes on the vertebral level. Of these, the mSASSS has become today the standard method for assessment of radiographic progression of

AS / axial SpA. According to the mSASSS, anterior corners of the lumbar and cervical vertebrae in lateral views (24 in total) are scored using the following system: 0 – normal, 1 – erosion, sclerosis or squaring, 2 – syndesmophyte, 3 – bridging syndesmophyte (total score range 0-72).

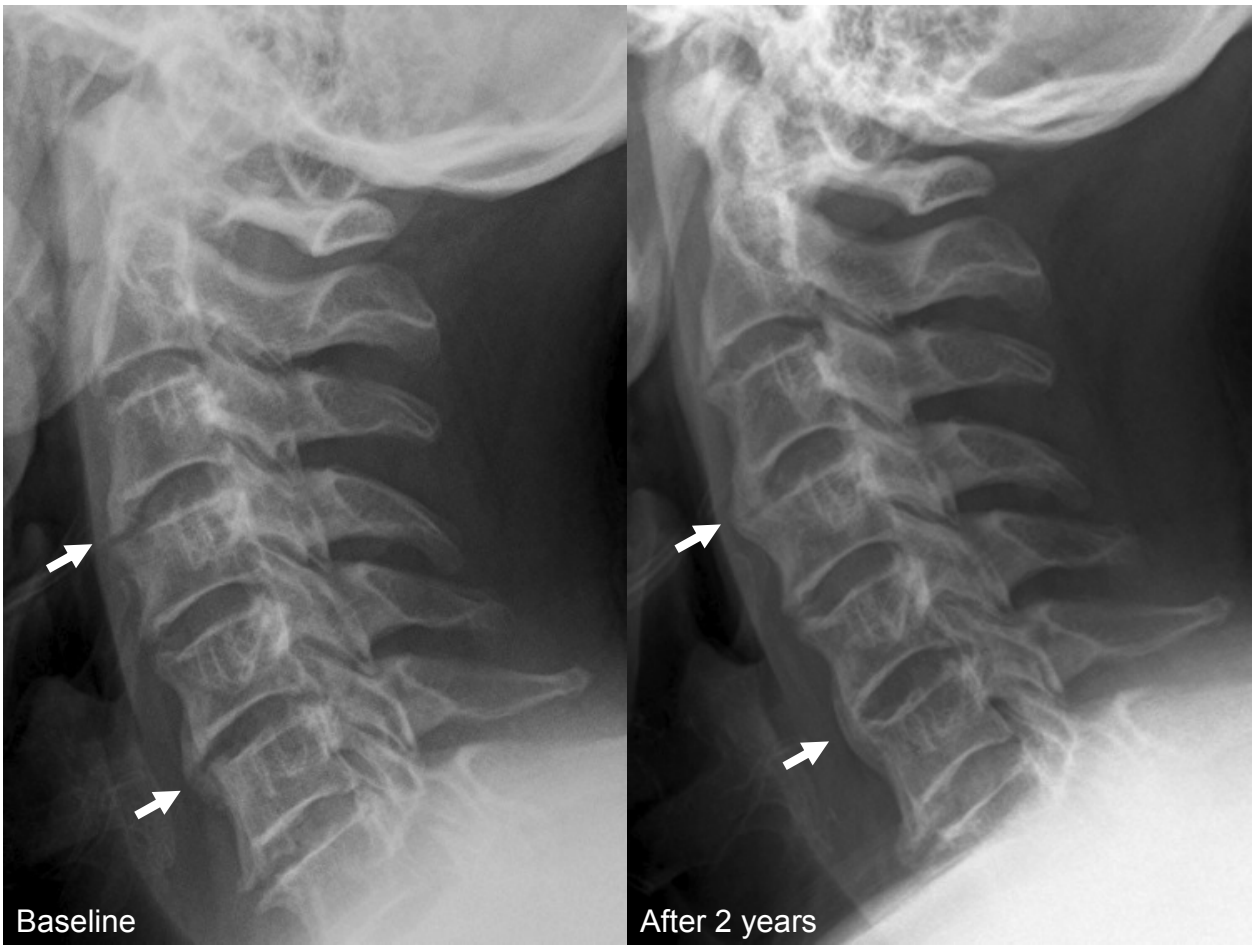

Figure 4. Natural course of radiographic progression of the structural changes in the cervical spine over 2 years in a 56 years old male patient with ankylosing spondylitis.

Arrows indicate formation of the bridging syndesmophytes.

Adapted from: Poddubnyy D, Sieper J. Radiographic progression in ankylosing spondylitis/axial spondyloarthritis: how fast and how clinically meaningful? Curr Opin Rheumatol. 2012;24:363-9.

A fair estimation of the radiographic progression rates in patients with AS provided clinical trials with TNF α inhibitors: patients treated with infliximab, etanercept, adalimumab or golimumab demonstrated a mean mSASSS worsening of about 1.0 units over two years that was nearly the same as in the historic control (OASIS cohort) [36-39]. As a result, it was concluded that TNF α blockade has no benefit regarding radiographic spinal progression (at least in the short perspective). However, recent studies demonstrated that retardation of radiographic spinal progression might become evident in case of longer treatment and longer observation period (6-8 years) [40, 41], considering that inflammation and new bone formation are linked but not directly coupled in AS [42]. NSAIDs, in contrast, were found to be able to retard radiographic spinal progression in AS even after 2 years if given continuously in one clinical trial [43, 44] – data, which had not been confirmed so far. Furthermore, it is not clear until now how to identify patients who would benefit most from continuous NSAIDs therapy regarding progression of structural damage in the spine in axial SpA.

The strongest predictor of radiographic spinal progression in AS seems to be the presence of structural spinal damage (syndesmophytes) at baseline that has been shown in a number of studies [45-48]. However, at the early disease stage no radiographic spinal damage might bee seen initially, therefore there is an urgent need for reliable early predictors of radiographic spinal progression in axial SpA. This is of high clinical relevance, since currently available data indicate a clear association between radiographic damage in the spine and impaired spinal mobility [49, 50] as well as with the reduction of physical function [50, 51] in patients with axial SpA.

Thus, accurate prediction of disease progression at early disease stage and appropriate treatment adjusted to the risk of disease progression are important factors, which are likely to improve long-term outcome in axial SpA.

1.6 Aims of the current work

- To identify rates and predictors of structural damage progression in the sacroiliac joints in patients with early axial SpA.
- To identify rates and predictors of structural damage progression in the spine in patients with early axial SpA.
- To define the role of biomarkers in prediction of disease progression in early axial SpA.
- To identify possible ways of prevention of disease progression in early axial SpA.

2 Results

2.1 Rates and predictors of radiographic sacroiliitis progression in axial spondyloarthritis

As mentioned above, although non-radiographic axial SpA and AS are considered as two stages of one disease, the rates of progression from radiographic to radiographic stage remained unclear.

We investigated progression of radiographic sacroiliitis over 2 years in the German Spondyloarthritis Inception Cohort (GESPIC). GESPIC was established as a prospective cohort of patients with early SpA (non-radiographic axial SpA with symptom duration of ≤5 years and AS with symptom duration ≤10 years). Baseline characteristics of the cohort have been reported elsewhere [2].

For the current study we selected a total of 210 patients with definite axial SpA from GESPIC based on the availability of radiographs of sacroiliac joints at baseline and after two years of follow-up. Radiographs were centrally digitized and the sacroiliac joints were scored independently by two trained readers according to the grading system of the modified New York criteria for AS [15, 31]. The readers scored both time points simultaneously but were blinded for the time point and for all clinical data.

In total, 115 patients (54.8%) fulfilled the modified New York criteria for AS in their radiographic part in the opinion of both readers at baseline, while 95 patients (45.2%) were classified as non-radiographic axial SpA. After two years 11 patients (11.6%) from the group of non-radiographic axial SpA progressed in AS in the opinion of both readers. More patients with non-radiographic SpA (10.5%) as compared to AS (4.4%) showed an estimated “true” progression by at least 1 grade according to both readers, although the difference between the two groups was statistically non-significant.

An elevated level of CRP at baseline was the only significant predictor of radiographic sacroiliitis progression in non-radiographic axial SpA (odds ratio - OR = 3.65, 95% CI 1.19 to 11.15) and AS (OR = 5.08, 95% CI 1.02 to 25.38) that was also confirmed in the multivariate analysis. Importantly, the elevated level of CRP was also a significant predictor of progression of non-radiographic axial SpA to AS fulfilling the modified New York criteria (OR = 4.10, 95% CI 1.13 to 14.95 in the univariate and OR = 4.74, 95% CI 1.23 to 18.25 in the multivariate model).

Thus, progression of radiographic sacroiliitis after 2 years occurred only in a small percentage of patients with early axial SpA. About 12% of the patients demonstrated progression from non-radiographic to radiographic stage. An elevated level of CRP was found to be a strong positive predictor of sacroiliitis progression.

Own reference:

Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler H, et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70(8):1369-74.

http://dx.doi.org/10.1136/ard.2010.145995

2.2 Rates and predictors of radiographic spinal progression in axial spondyloarthritis

As already briefly mentioned above a number of works in established AS (with mean disease duration of >10 years throughout the studies) demonstrated a biannual progression rate of about 1 mSASSS point every two years with baseline structural damage (syndesmophytes) as a strongest predictor of radiographic spinal progression [45-47]. No data on the rates and predictors of radiographic spinal progression in early axial SpA were available.

In the present work we investigated rates and predictors of radiographic spinal progression over 2 years in patients with early axial SpA (both non-radiographic axial SpA with symptom duration of ≤5 years and AS with symptom duration ≤10 years) from the GESPIC cohort. A total number of 210 patients with axial SpA (115 with AS according to the modified New York criteria and 95 with non-radiographic SpA) were selected for this study based on availability of spinal radiographs (lumbar and cervical spine) at baseline and after 2 years of follow-up. Images were centrally collected, digitized, and subsequently scored independently by two trained readers in a concealed and randomly selected order according to the mSASSS scoring system. Significant radiographic spinal progression was defined as a worsening of the mean mSASSS score by ≥2 points over two years.

Among AS patients (n = 115) the mSASSS increased significantly from a mean ± standard deviation of 5.86 ± 10.30 at baseline to 6.81 ± 11.71 after 2 years ($p < 0.001$), resulting in a mean progression of 0.95 ± 2.78. In non-radiographic axial SpA (n = 95) the mean mSASSS also increased significantly from 2.30 ± 4.24 at baseline to 2.76 ± 5.26 after 2 years ($p = 0.01$), resulting in a mean progression of 0.46 ± 1.63 mSASSS units. Altogether, 14.3% of the patients with axial SpA showed radiographic spinal

progression defined as a worsening of the mSASSS score by ≥2 points over two years. This rate was higher in the group of patients with AS (20%) in comparison to non-radiographic axial SpA (7.4%). The following parameters were independently associated with radiographic spinal progression over two years: presence of syndesmophytes at baseline (OR = 6.29, 95% CI 2.77 to 14.26), elevated markers of systemic inflammation (erythrocyte sedimentation rate (ESR): OR = 4.04, 95% CI 1.82 to 8.97 and CRP: OR = 3.81, 95% CI 1.68 to 8.63), and cigarette smoking (OR = 2.75, 95% CI 1.25 to 6.05), that was confirmed in the multivariate logistic regression analysis. No clear association with radiographic spinal progression was found for HLA-B27 status, sex, age, disease duration, BASDAI, the Bath Ankylosing Spondylitis Disease Functional Index (BASFI), presence of peripheral arthritis, enthesitis, psoriasis, treatment with NSAIDs or with DMARDs at baseline. Based on the obtained data a prediction matrix models incorporating identified risk factors (syndesmophytes, elevated acute phase reactants and smoking) was constructed.

Thus, we not only confirmed a well-known role of syndesmophytes as a predictor of structural damage progression in the spine in axial SpA, but also identified for the first time two further important factors (elevated acute phase reactants and cigarette smoking), which independently predict radiographic spinal progression in early axial SpA.

Own reference:

Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute phase reactants and cigarette smoking status predict radiographic progression in the spine in early axial spondyloarthritis. Arthritis Rheum 2012;64(5):1388-98.

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Baseline Radiographic Damage, Elevated Acute-Phase Reactant Levels, and Cigarette Smoking Status Predict Spinal Radiographic Progression in Early Axial Spondylarthritis

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Objective. **To assess prospectively the rates and to explore predictors of spinal radiographic progression over 2 years in a cohort of patients with early axial spondylarthritis (SpA).**

Methods. **Two hundred ten patients with axial SpA from the German Spondyloarthritis Inception Cohort were selected for this analysis based on the availability of radiographs at baseline and after 2 years of followup. Spinal radiographs were scored by 2 trained readers in a blinded, randomly selected order according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Spinal radiographic progression was defined as worsening of the mean mSASSS by ≥2 units over 2 years.**

Results. **Among the patients with axial SpA, 14.3% showed spinal radiographic progression after 2 years (20% of those with AS and 7.4% of those with nonradiographic axial SpA). The following parameters were independently associated with spinal radiographic progression: presence of syndesmophytes at baseline (odds ratio [OR] 6.29, $P < 0.001$), elevated levels of markers of systemic inflammation (for the erythrocyte sedimentation rate, OR 4.04, $P = 0.001$; for C-reactive protein level time-averaged over 2 years, OR 3.81, $P = 0.001$), and cigarette smoking (OR 2.75, $P = 0.012$). These associations were confirmed by multivariate logistic regression analysis. No clear association with spinal radiographic progression was observed for HLA–B27 status, sex, age, disease duration, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, presence of peripheral arthritis, enthesitis, psoriasis, treatment with nonsteroidal antiinflammatory drugs, or treatment with disease-modifying antirheumatic drugs at baseline.**

Conclusion. **The presence of radiographic damage at baseline (syndesmophytes), elevated levels of acute-phase reactants, and cigarette smoking were all independently associated with spinal radiographic progression in patients with early axial SpA.**

The term axial spondylarthritis (SpA) refers to patients with radiographic sacroiliitis fulfilling the modified New York criteria for ankylosing spondylitis (AS) (1) and patients with nonradiographic axial SpA (i.e., patients without definite radiographic changes in the sacroiliac joints) (2). Both groups of patients can be

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Table 1. Baseline demographic and clinical characteristics of the patients*

Parameter	Nonradiographic axial SpA (n = 95)	Ankylosing spondylitis (n = 115)	All patients (n = 210)
Age, mean ± SD years	38.7 ± 9.9	36.8 ± 11.0	37.1 ± 10.6
Symptom duration, mean ± SD years	3.2 ± 2.2	5.2 ± 2.8	4.2 ± 2.7
Duration since diagnosis, mean ± SD years	1.0 ± 1.3	2.0 ± 2.0	1.5 ± 1.8
Male sex	32 (33.7)	75 (65.2)	107 (51.0)
HLA–B27 positive	69 (72.6)	97 (84.3)	166 (79.0)
Peripheral arthritis	16 (16.8)	15 (13.0)	31 (14.8)
Enthesitis†	23 (24.2)	23 (20.0)	46 (21.9)
Uveitis ever	15 (15.8)	27 (23.5)	42 (20.0)
Psoriasis ever	11 (11.6)	17 (14.8)	28 (13.3)
Inflammatory bowel disease ever	1 (1.1)	3 (2.6)	4 (1.9)
Family history of ankylosing spondylitis	16 (16.8)	19 (16.5)	35 (16.7)
BASDAI, mean ± SD, 0–10	4.2 ± 2.0	3.8 ± 2.2	3.9 ± 2.2
BASFI, mean ± SD, 0–10	2.8 ± 2.2	3.0 ± 2.4	2.9 ± 2.3
Treatment with NSAIDs	64 (67.4)	76 (66.1)	140 (66.7)
Treatment with DMARDs	26 (27.4)	35 (30.4)	61 (29.0)
Treatment with systemic steroids	6 (6.3)	6 (5.2)	12 (5.7)
Treatment with a TNFα blocker	1 (1.1)	4 (3.5)	5 (2.4)
Smoker, current	24 (25.3)	39 (33.9)	63 (30.0)
Modified SASSS, mean ± SD	2.30 ± 4.24	5.86 ± 10.30	4.25 ± 8.31
Syndesmophytes	13 (13.7)	35 (30.4)	48 (22.9)

* Except where indicated otherwise, values are the number (%) of patients. SpA = spondylarthritis; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; TNFα = tumor necrosis factor α; SASSS = Stoke Ankylosing Spondylitis Spine Score.
† Twelve enthesitis sites of the lower limbs plus optional sites elsewhere were assessed.

classified according to the recently developed Assessment of SpondyloArthritis international Society classification criteria for axial SpA (3,4). Ankylosis has long been regarded to be probably the most important long-term outcome parameter in AS (5), which is also reflected in the term "ankylosing" spondylitis. Indeed, a correlation between spinal structural damage, as measured by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), and both spinal mobility and physical function was observed in patients with AS in whom disease duration was longer than 3 years (6,7). Application of the mSASSS is currently the most frequently used method for scoring structural damage of the spine, because of better reliability and sensitivity to change (8) in comparison with the Bath Ankylosing Spondylitis Radiology Index (9) or the SASSS (10).

Studies addressing the extent of and risk factors for spinal radiographic damage in AS have usually been conducted in patients with longstanding disease (11–13). Here we report on the progression of structural damage in the spines of patients with early axial SpA from the German Spondyloarthritis Inception Cohort (GESPIC), including both patients with AS and patients with nonradiographic axial SpA. The baseline data for this cohort were recently reported elsewhere (14).

PATIENTS AND METHODS

GESPIC patients. Patients included in GESPIC were required to have a definite clinical diagnosis of axial SpA according to the treating rheumatologist. Patients with axial SpA were further classified by the local rheumatologist based on radiographic findings, and irrespective of the presence of concomitant psoriasis or inflammatory bowel disease (IBD), as having either AS or nonradiographic axial SpA. The classification of AS was based on fulfillment of the modified New York criteria (1), and the duration of symptoms was restricted to ≤10 years at the time of inclusion. The classification of nonradiographic axial SpA was based on fulfillment of the European Spondyloarthropathy Study Group criteria (15), with minor modifications (14), and the maximum duration of symptoms was ≤5 years.

Radiographs of the spine and sacroiliac joints were obtained at baseline and after 2 years. Based on availability, radiographs for 210 GESPIC patients (115 patients with AS and 95 patients with nonradiographic axial SpA) were selected for this analysis. The baseline characteristics of these patients are shown in Table 1. Previously, we reported cross-sectional data on 462 GESPIC patients (14). GESPIC patients who could not be included in this analysis due to the lack of full sets of radiographs were largely comparable with the included patients (those for whom radiographs were available) in terms of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (16), the C-reactive protein (CRP) level, the erythrocyte sedimentation rate (ESR), the Bath Ankylosing Spondylitis Disease Functional Index (BASFI) (17), HLA–B27

positivity, smoking status, and treatment. The only significant difference was a lower proportion of male patients in the nonradiographic axial SpA subgroup with radiographs compared with those without radiographs (34% versus 48%; $P = 0.039$), while there was no such difference among patients with AS (64% versus 64%).

Radiographs and scoring. Radiographs of the sacroiliac joints and the lumbar and cervical spine were obtained by the local investigator at baseline and after 2 years of followup. Available radiographs were centrally digitized, blinded, and scored in random order independently by 2 trained readers (DP and HH). Both readers were blinded to all clinical data.

Radiographic sacroiliitis was scored from grade 0 (normal) to grade 4 (ankylosis) according to the modified New York criteria (1). Spinal radiographs were scored according to the mSASSS (6). Briefly, using lateral views only, the anterior vertebral edges of the lumbar and cervical spine were scored as follows: 0 = normal; 1 = erosion, sclerosis, or squaring; 2 = syndesmophytes; and 3 = bridging syndesmophytes (total range 0–72).

Ethics committee approval. The study protocol was approved by the central ethics committee of the coordinating center (Charité Universitätsmedizin, Campus Benjamin Franklin, Berlin, Germany) and by all local ethics committees of the participating centers. Written informed consent was obtained from all patients.

Statistical analysis. Status scores for baseline and followup were calculated using the mean scores determined by both readers. Radiographic progression was determined by calculating the difference between the mean baseline and followup values. Of the total number of vertebral corners, scores were missing for 3.4% at baseline and 4% at followup, due to lack of visualization (18). Missing scores were substituted with scores for the respective vertebral corners at the other time point, if available, or with a score of zero if scores for both time points were missing.

Spinal radiographic progression was defined as worsening of the mSASSS by ≥2 units over 2 years (6,19). Such worsening is characterized by the development of minor changes (erosion, squaring, or sclerosis) at ≥2 vertebral corners, the formation of a new syndesmophyte at a previously normal site (progression from a score of 0 to a score of 2) or at 2 sites that showed minor changes at baseline (progression from a score of 1 to a score of 2 at each site), or progression of 2 opposing nonbridging syndesmophytes to bridging syndesmophytes. In addition, a separate analysis of new syndesmophyte formation was performed. New syndesmophytes were considered to be present at a given vertebral corner only if the scores determined by both readers were <2 at baseline and ≥2 at year 2.

Agreement between readers was estimated by the intraclass correlation coefficient (ICC). The smallest detectable change was calculated as suggested by Bruynesteyn et al (20). Fisher's exact test, the chi-square test, the Mann-Whitney U test, and Wilcoxon's test for paired samples were applied as appropriate. Nonparametric analysis of covariance (21) was used to compare changes in the mSASSS between groups after adjustment for the mSASSS status at baseline. Ninety-five percent confidence intervals (95% CIs; determined using Wilson's method [22]) were calculated for the rates of spinal radiographic progression.

In order to identify parameters associated with spinal radiographic progression (i.e., worsening of the mSASSS by ≥2 units), univariate and multivariate logistic regression analyses were performed. Parameters significantly associated with radiographic progression in the univariate analysis were included in the multivariate logistic regression analysis, with the variable progression/no progression as the dependent variable. In additional analyses, the formation of new syndesmophytes (yes/no) was applied as the dependent variable. Odds ratios (ORs) and 95% CIs were calculated for each parameter. *P* values less than 0.05 were considered significant.

RESULTS

Agreement between readers. Agreement between the 2 readers regarding mSASSS status was very good at baseline (ICC 0.93 [95% CI 0.90–0.94]) and at year 2 (ICC 0.92 [95% CI 0.90–0.94]). Agreement regarding change in the mSASSS was moderate (ICC 0.43 [95% CI 0.31–0.53]) and corresponded to the smallest detectable change scores of 3.7 for individual readings and 2.6 for the mean of both readings (on which the analysis was based).

Spinal radiographic progression in axial SpA. First, we assessed the mean change in the mSASSS in both subgroups and the entire cohort after 2 years. Among patients with AS (n = 115), the mean ± SD mSASSS increased significantly, from 5.86 ± 10.30 at baseline to 6.81 ± 11.71 after 2 years ($P < 0.001$), resulting in a difference of 0.95 ± 2.78 units. In patients with nonradiographic axial SpA (n = 95), the mean ± SD mSASSS also increased significantly, from 2.30 ± 4.24 at baseline to 2.76 ± 5.26 after 2 years ($P = 0.01$), resulting in a difference of 0.46 ± 1.63 units (Figure 1). The difference in the mean change in the mSASSS between patients with AS and patients with nonradiographic axial SpA was not statistically significant ($P = 0.23$; $P = 0.29$ after adjustment for radiographic status at baseline), nor was the difference between AS patients with a symptom duration of ≤5 years (0.63 ± 1.92 mSASSS units; n = 61) and those with a symptom duration of >5 years (1.31 ± 3.49 mSASSS units; n = 54) ($P = 0.46$; $P = 0.56$ after adjustment). Figure 2 shows the change in the mSASSS after 2 years. In the entire cohort of patients with axial SpA (n = 210), the mean ± SD mSASSS was 4.25 ± 8.32 at baseline and 4.98 ± 9.56 after 2 years ($P < 0.001$), resulting in a difference of 0.73 ± 2.34 units.

Next, we assessed the proportion of patients fulfilling the prespecified definition of definite radiographic progression, i.e., worsening of the mean mSASSS score by ≥2 units after 2 years. In total, 14.3% (95% CI 10.2–19.7%) of the patients in the entire axial SpA cohort (n = 210) had spinal radiographic progres-

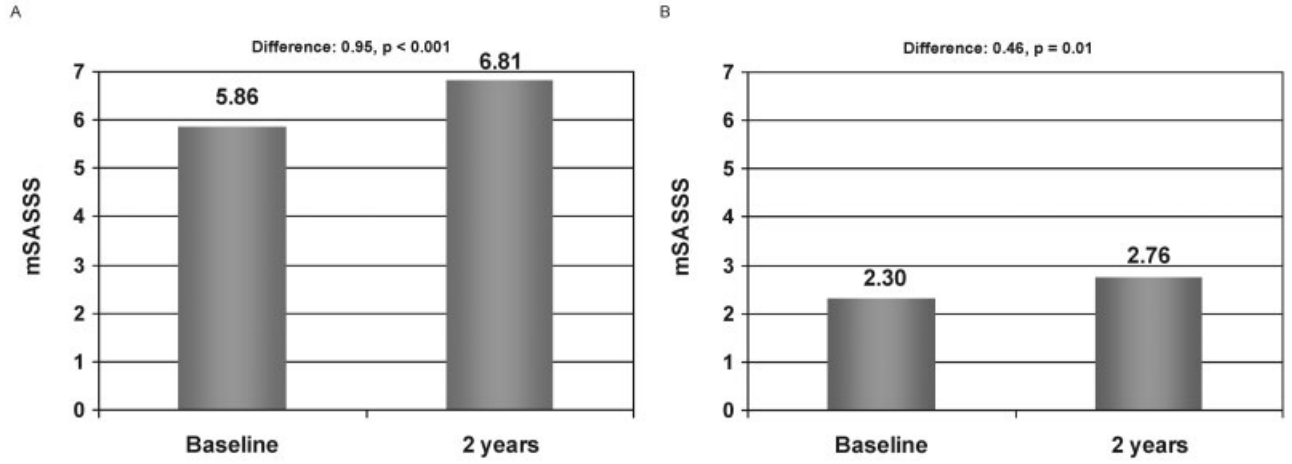

Figure 1. Spinal radiographic progression as assessed by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) over 2 years in patients with ankylosing spondylitis (n = 115) (**A**) and patients with nonradiographic axial spondylarthritis (n = 95) (**B**). Values are the mean.

sion according to this definition. This rate was higher in patients with AS (20% [95% CI 13.7–28.2%]) compared with that in patients with nonradiographic axial SpA (7.4% [95% CI 3.6–14.4%]) (P = 0.01). The rates of spinal radiographic progression were similar between AS patients with a symptom duration of ≤5 years and those with a symptom duration of >5 years (19.7% and 20.4%, respectively). Among the entire cohort, 4.3% (95% CI 2.3–7.9%) of the patients had improvement in the mSASSS of ≥2 units, with no statistically significant difference between AS patients (5.2% [95% CI 2.4–10.9%]) and patients with nonradiographic axial SpA (3.2% [95% CI 1.1–8.9%]) (P = 0.56).

Syndesmophytes at a given vertebral corner of the cervical or lumbar spine, as identified by both readers, were present at baseline in 30.4% (95% CI 22.8–39.4%) of patients classified as having AS and in 13.7% (95% CI 8.2–22.0%) of patients classified as having nonradiographic axial SpA (P = 0.005). There were no differences in the frequency of syndesmophytes at baseline between patients with AS in whom the duration of symptoms was ≤5 years and those with a symptom duration of >5 years (29.5% and 31.5%, respectively). New syndesmophytes after 2 years, as scored by both readers, occurred in 11.3% (95% CI 6.7–18.4%) of patients with AS (8.2% of those with a symptom duration of ≤5 years and 14.8% of those with a symptom duration of >5 years) and in 3.2% (95% CI 1.1–8.9%) of patients with nonradiographic axial SpA. Progression of syndesmophytes (i.e., transformation from nonbridging to bridging) occurred in 3.8% (95% CI 1.9–7.3%) of the patients, all but one of whom also showed formation of new syndesmophytes.

At followup, 11.6% of the patients with nonradiographic axial SpA had experienced progression to definite radiographic sacroiliitis, thus fulfilling the mod-

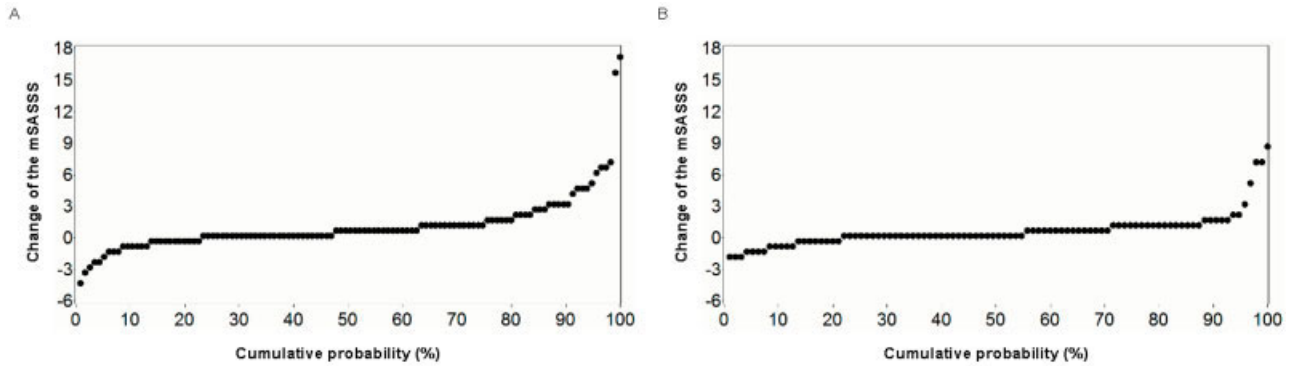

Figure 2. Changes in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) over 2 years in patients with ankylosing spondylitis (n = 115) (**A**) and patients with nonradiographic axial spondylarthritis (n = 95) (**B**).

Table 2. Association of clinical, radiographic, and laboratory parameters with spinal radiographic progression*

Parameter	Univariate analysis		Multivariate analysis†							
			Model 1, baseline CRP		Model 2, time-averaged CRP		Model 3, baseline ESR		Model 4, time-averaged ESR	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Worsening of the mSASSS by ≥2 units over 2 years										
AS vs. nonradiographic axial SpA	3.14 (1.28–7.69)	0.012	1.80 (0.64–5.03)	0.264	1.63 (0.58–4.60)	0.358	1.73 (0.62–4.79)	0.294	1.79 (0.64–4.99)	0.269
Syndesmophytes, present vs. absent‡	6.29 (2.77–14.26)	<0.001	5.12 (2.11–12.44)	<0.001	4.78 (1.96–11.69)	0.001	4.56 (1.85–11.22)	0.001	4.81 (1.97–11.76)	0.001
Sex, male vs. female	2.14 (0.95–4.82)	0.067	0.99 (0.38–2.55)	0.980	1.00 (0.38–2.60)	0.996	1.03 (0.40–2.68)	0.954	1.02 (0.39–2.63)	0.973
CRP, >6 mg/liter vs. ≤6 mg/liter	2.47 (1.12–5.44)	0.025	1.71 (0.70–4.17)	0.237						
CRP over 2 years, >6 mg/liter vs. ≤6 mg/liter§	3.81 (1.68–8.63)	0.001			2.50 (1.01–6.20)	0.047				
ESR, >20 mm/hour vs. ≤20 mm/hour	4.04 (1.82–8.97)	0.001					2.74 (1.14–6.60)	0.025		
ESR over 2 years, >20 mm/hour vs. ≤20 mm/hour§	3.37 (1.52–7.46)	0.003							1.94 (0.79–4.81)	0.150
Current smoking, present vs. absent	2.75 (1.25–6.05)	0.012	2.52 (1.06–5.99)	0.037	2.41 (1.01–5.76)	0.048	2.54 (1.06–6.09)	0.037	2.31 (0.96–5.51)	0.060
Formation of new syndesmophytes over 2 years¶										
AS vs. nonradiographic axial SpA	3.91 (1.08–14.15)	0.038	2.40 (0.50–11.43)	0.271	1.48 (0.28–7.97)	0.647	2.15 (0.47–9.88)	0.327	1.89 (0.37–9.70)	0.446
Syndesmophytes, present vs. absent‡	32.94 (7.15–151.69)	<0.001	33.70 (7.28–195.30)	<0.001	31.69 (6.10–164.64)	<0.001	33.03 (6.38–171.0)	<0.001	32.27 (6.19–168.19)	<0.001
Sex, male vs. female	1.67 (0.58–4.77)	0.341	0.40 (0.10–1.55)	0.184	0.40 (0.10–1.72)	0.563	0.40 (0.10–1.58)	0.191	0.37 (0.09–1.58)	0.180
CRP, >6 mg/liter vs. ≤6 mg/liter	1.95 (0.70–5.47)	0.202	0.95 (0.27–3.38)	0.940						
CRP over 2 years, >6 mg/liter vs. ≤6 mg/liter§	7.85 (2.16–28.50)	0.002			4.77 (1.12–20.42)	0.035				
ESR, >20 mm/hour vs. ≤20 mm/hour	3.36 (1.19–9.50)	0.022					1.64 (0.49–5.46)	0.423		
ESR over 2 years, >20 mm/hour vs. ≤20 mm/hour§	7.24 (2.39–21.92)	<0.001							4.14 (1.14–15.0)	0.031
Current smoking, present vs. absent	2.53 (0.90–7.07)	0.077	2.43 (0.72–8.24)	0.154	2.19 (0.62–7.77)	0.225	2.41 (0.71–8.21)	0.159	1.84 (0.51–6.68)	0.352

* Spinal radiographic progression was defined as worsening of the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) by ≥2 units or formation of new syndesmophytes over 2 years in patients with axial spondylarthritis (SpA; n = 210). OR = odds ratio; 95% CI = 95% confidence interval.

† Nagelkerke's R^2 values for models with progression of ≥2 mSASSS units and new syndesmophyte formation as dependent variables were as follows: for model 1, 0.228 and 0.402, respectively; for model 2, 0.247 and 0.450, respectively; for model 3, 0.254 and 0.404, respectively; for model 4, 0.232 and 0.447, respectively.

‡ Presence of at least 1 syndesmophyte in the cervical or lumbar spine (lateral views), as determined by both readers.

§ Time-averaged value; C-reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) were determined at baseline and every 6 months thereafter during 2 years of followup.

¶ Occurrence of at least 1 new syndesmophyte over 2 years, as determined by both readers.

ified New York criteria for AS (23). However, no difference was observed in either the mean ± SD change in the mSASSS (0.49 ± 1.70 units in patients who showed no progression to AS versus 0.27 ± 0.96 in patients who progressed to AS; $P = 0.53$) or the formation of new syndesmophytes (7.1% versus 0%; $P = 0.36$).

Predictors of spinal radiographic progression in axial SpA. Univariate logistic regression analysis of the entire cohort of patients with axial SpA demonstrated that the following baseline variables were significantly associated with an increase of ≥2 mSASSS units after 2 years: presence of syndesmophytes at baseline (OR 6.29), classification as AS, i.e., presence of definite radiographic sacroiliitis (OR 3.14), elevated CRP level (OR 2.47), elevated ESR (OR 4.04), and current smoking (OR 2.75) (Table 2).

Interestingly, although an elevated CRP level at baseline was associated with radiographic progression (OR 2.47) in the univariate regression analysis, the association was even stronger using time-averaged elevated CRP levels over 2 years, defined as a mean CRP level >6 mg/liter over 5 time points including baseline and 4 followup visits every 6 months thereafter (OR 3.81). There was also a significant association between an elevated time-averaged ESR and spinal radiographic progression (OR 3.37), which was, however, not stronger than the association with an elevated baseline ESR (Table 2).

Only a trend was observed for male sex (OR 2.14 [95% CI 0.95–4.82], $P = 0.067$) and HLA–B27 positivity (OR 1.81 [95% CI 0.60–5.50], $P = 0.30$) as potential predictors of radiographic progression. Variables such as age, BASDAI, BASFI, presence of peripheral arthritis, enthesitis, psoriasis, family history of SpA, and therapy with nonsteroidal antiinflammatory drugs (NSAIDs; yes/no) or disease-modifying antirheumatic drugs (DMARDs; yes/no) at baseline were not significantly associated with spinal radiographic progression (data not shown). Due to the small numbers of patients with a history of IBD as well as patients treated with systemic steroids or tumor necrosis factor α (TNFα) blockers (Table 1), these variables were not included in the regression analysis.

When the 2 subgroups of patients (AS and nonradiographic axial SpA) were analyzed separately, the same trends were observed. However, in the subgroup of patients with nonradiographic axial SpA, only the presence of syndesmophytes at baseline was significantly associated with spinal radiographic progression (OR 11.7 [95% CI 2.3–60.8], $P = 0.003$); other factors did not reach statistical significance, probably due to the small number of patients with radiographic progression (n = 7). In the AS subgroup, the parameters that showed a significant association were the same as those demonstrated in the entire cohort.

Variables that were significantly associated with radiographic progression in the univariate analysis were entered into a multivariate logistic regression analysis. Sex was also included as a variable, because it showed borderline significance in the univariate analysis. Because all 4 variables reflecting systemic inflammatory activity (i.e., CRP level at baseline, time-averaged CRP level over 2 years, ESR at baseline, and time-averaged ESR) showed a significant association with spinal radiographic progression in the univariate analysis, we constructed 4 multivariate models, each of which included one of these markers of systemic inflammation (Table 2). In all 4 multivariate models, the presence of syndesmophytes at baseline remained significantly and independently associated with radiographic progression, and the association with current smoking remained in all but 1 of the models (Table 2). An elevated CRP level at baseline (model 1) and an elevated time-averaged ESR (model 4) lost statistical significance in the multivariate analysis. Nevertheless, the time-averaged CRP level (model 2) was significantly and independently associated with radiographic progression in the multivariate analysis, as was an elevated ESR at baseline (model 3).

Based on these data, 2 prediction matrix models were constructed incorporating the variables baseline syndesmophytes, smoking status, and elevated acute-phase reactants (either ESR or CRP) in order to illustrate the additive effects of these independent predictors (Figure 3). Inclusion of the baseline CRP level in the prediction model seemed to be justified, given the significant association of the time-averaged CRP with radiographic progression. Obviously, the time-averaged CRP level over 2 years cannot be used as a predictor but demonstrates clearly the importance of active systemic inflammation for the development of structural damage in the spine. As shown in Figure 3B, if both smoking and an elevated CRP level were present at baseline, for example, the risk of radiographic progression increased from 4% to 20% in patients without baseline damage, and from 19% to 55% in patients in whom syndesmophytes were present at baseline.

Regarding the development of new syndesmophytes after 2 years as a dependent variable, the strongest association was observed for the presence of syndesmophytes at baseline: new syndesmophytes developed in 29.2% of the patients who had syndesmophytes at baseline and in only 1.2% of patients without syndesmophytes at baseline (OR 32.9) (Table 2). Fur-

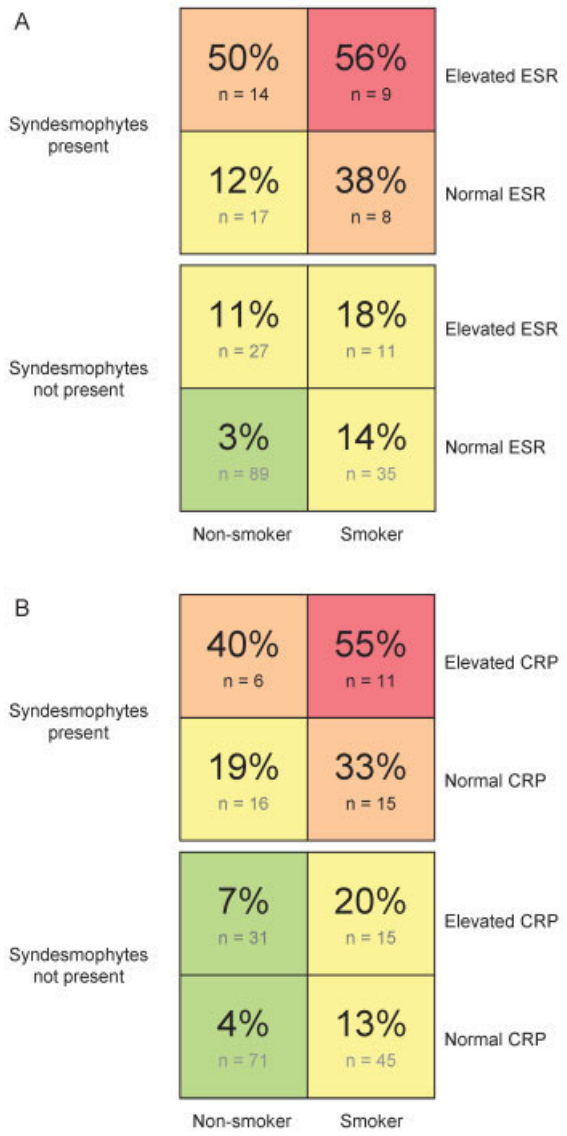

Figure 3. Prediction matrix models of the association of baseline syndesmophytes, acute-phase reactants, and smoking status with spinal radiographic progression over 2 years in patients with axial spondylarthritis (n = 210). **A,** Association of the erythrocyte sedimentation rate (ESR), syndesmophytes, and smoking; an elevated ESR was defined as >20 mm/hour. **B,** Association of the C-reactive protein (CRP) level, syndesmophytes, and smoking; an elevated CRP level was defined as >6 mg/liter. The percentages represent patients with spinal radiographic progression (≥2 modified Stoke Ankylosing Spondylitis Spine Score units over 2 years).

thermore, elevated baseline ESR (OR 3.4), elevated time-averaged ESR (OR 7.2), elevated time-averaged CRP level (OR 7.9), and fulfillment of the modified New York criteria at baseline (OR 3.9) were significantly associated with formation of new syndesmophytes in the univariate analysis, while the statistical significance for smoking status was only borderline (OR 2.5) (Table 2). Statistically nonsignificant trends were observed for HLA–B27 status and male sex. In the multivariate analysis, baseline syndesmophytes and acute-phase reactants (time-averaged CRP level and ESR) remained significantly associated with new syndesmophyte formation (Table 2).

Analyses performed for each reader separately (Table 3) revealed similar rates of radiographic progression and the same variables associated with radiographic progression.

DISCUSSION

We investigated radiographic progression of damage in the spine over a period of 2 years in patients with early axial SpA from GESPIC, a longitudinal observational study, and identified predictors of progression. One of the frequently encountered problems of longitudinal observational cohorts such as GESPIC is a relatively high withdrawal rate. For the current analysis, we selected 210 GESPIC patients based on the availability of full sets of radiographs. Apart from a lower proportion of male patients in the nonradiographic axial SpA subgroup with radiographs compared with the proportion among those without radiographs (34% versus 48%), the groups were similar regarding disease activity, function, and treatment, suggesting that the subgroup of patients with available radiographs was representative of the entire cohort. Both the mean symptom duration of 5.2 years in patients with AS and the low mean mSASSS of 5.86 units at baseline reflect the early-disease character of this inception cohort. In comparison, in cohorts with longstanding AS (18,19,24–27) with symptom durations of at least 10–20 years, the mean mSASSS was typically 12–20 units, i.e., at least twice as high as that in our inception cohort. In our cohort, however, syndesmophytes were already present at baseline in ~30% of the patients with AS. Among patients with nonradiographic axial SpA (mean symptom duration 3.2 years), the mean mSASSS at baseline was only 2.3, and 13.7% of patients had syndesmophytes.

When using the mSASSS to assess spinal damage in AS, both overestimation and underestimation may occur. Overestimation may result from degenerative changes in the spine that can be mistaken as AS-associated lesions. To minimize overestimation, both readers were trained, and agreement between both readers was required for determination of the presence of a syndesmophyte at a particular site. Underestimation may also occur because the thoracic spine, a site where inflammation and damage often take place, is not scored

Table 3. Spinal radiographic progression according to the individual readers*

	Reader 1	Reader 2
mSASSS at baseline, mean ± SD	4.40 ± 8.34	4.10 ± 8.61
mSASSS at year 2, mean ± SD	5.19 ± 9.49	4.78 ± 10.00
mSASSS progression over 2 years, mean ± SD	0.79 ± 2.46	0.68 ± 3.05
Worsening of the mSASSS by ≥2 units over 2 years, % of patients	18.6	24.3
Parameters associated with worsening of the mSASSS by ≥2 units over 2 years in univariate analysis		
AS vs. nonradiographic axial SpA	1.23 (0.61–2.50)	2.16 (1.11–4.21)†
Syndesmophytes, present vs. absent‡	4.65 (2.21–9.79)†	3.88 (1.94–7.78)†
Sex, male vs. female	1.49 (0.74–3.01)	1.52 (0.80–2.88)
CRP, >6 mg/liter vs. ≤6 mg/liter	1.68 (0.83–3.37)	1.25 (0.66–2.37)
CRP over 2 years, >6 mg/liter vs. ≤6 mg/liter§	2.10 (1.04–4.25)†	1.72 (0.91–3.26)
ESR, >20 mm/hour vs. ≤20 mm/hour	2.55 (1.24–5.23)†	2.08 (1.07–4.04)†
ESR over 2 years, >20 mm/hour vs. ≤20 mm/hour§	2.60 (1.26–5.37)†	1.79 (0.91–3.55)
Current smoking, present vs. absent	2.10 (1.03–4.30)†	2.18 (1.13–4.22)†

* Except where indicated otherwise, values are the odds ratio (95% confidence interval). See Table 2 for other definitions.
† $P < 0.05$.
‡ Presence of at least 1 syndesmophyte in the cervical or lumbar spine (lateral views), as determined by both readers.
§ Time-averaged value; C-reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) were determined at baseline and every 6 months thereafter during 2 years of followup.

by the mSASSS due to limited visibility of the thoracic vertebrae caused by the overlying lungs (28).

After 2 years, the mSASSS had increased by an average of 0.95 units in AS patients in our cohort, which is very similar to reported increases of ~1.0 unit (range 0.8–1.4) in various AS cohorts in which the disease duration is usually longer (18,25–27,29,30). This implies that the average progression rate in early AS (symptom duration <10 years) is not different from that in longstanding AS. The agreement between both readers for mSASSS status (ICC 0.93 and ICC 0.92 for baseline and followup scores, respectively) was very good but was only moderate for score changes (ICC 0.43), a well-known phenomenon that has also been observed in clinical trials in AS (25,27). Importantly, when each reader was analyzed separately, similar results were obtained (Table 3), suggesting overall consistency.

Interestingly, in AS patients with a symptom duration of ≤5 years, mean radiographic progression appeared to be lower than that in patients with a longer symptom duration: the mean progression after 2 years was 0.63 mSASSS units in AS patients with symptoms for ≤5 years, whereas it was 1.31 units in AS patients with symptoms for >5 years (and 0.46 in patients with nonradiographic axial SpA). However, the proportion of patients with radiographic progression (worsening of the mSASSS by ≥2 units) over 2 years was nearly the same among AS patients with a symptom duration of ≤5 years (19.4%) and those with a symptom duration of >5 years (20.4%) and was substantially higher than that in the nonradiographic axial SpA group (7.4%). Furthermore, there was no difference between AS patients with a symptom duration of ≤5 years and those with a symptom duration of >5 years regarding the frequency of syndesmophytes at baseline (29.5% and 31.5%, respectively) and only a trend toward a higher frequency of new syndesmophyte formation in the latter group (8.2% and 14.8%, respectively). New syndesmophytes occurred in 3.2% of the patients with nonradiographic axial SpA, which corresponds to the overall lower mean rate of radiographic progression. Thus, spinal radiographic progression might occur in susceptible patients quite early in the disease course.

Whether the trend for less radiographic progression, on average, in patients with symptoms for ≤5 years (both patients with AS and those with nonradiographic axial SpA) bears any clinical implication is currently unclear. These data may indicate that preventing structural damage using any intervention might be especially rewarding in the first 5 years of disease. Such a window of opportunity, if it exists, is supported by the finding in our cohort that systemic inflammation and smoking were predictors of radiographic progression in patients with early axial SpA (see below) but possibly not in those with longstanding disease, as reported by other investigators (31).

In this cohort, 3 variables (baseline radiographic damage, elevated acute-phase reactants, and smoking status) were independently associated with radiographic progression and, therefore, can be considered as predictors of radiographic progression in axial SpA. Among these, baseline radiographic damage (syndesmophytes) was the strongest predictor. The association between baseline radiographic damage and further progression has been previously reported in longstanding AS but not in early disease (11,12,31,32). Regarding acute-phase

reactants, the baseline CRP level, the baseline ESR, and the time-averaged CRP level and ESR were all significantly associated with radiographic progression after 2 years in univariate analyses. Of these, both the time-averaged elevated CRP level over 2 years (OR 3.81) and the baseline ESR (OR 4.04) remained independently associated with radiographic progression in multivariate regression analyses (OR 2.50 and OR 2.74, respectively). The time-averaged elevated CRP level better reflects a status of persistent systemic inflammation as compared with an elevated baseline CRP level or baseline ESR only, thereby adding validity to the predictive role of systemic inflammation.

Of note, in our earlier cross-sectional analysis of baseline data from GESPIC, we observed an elevated CRP level at baseline to be significantly associated with both the presence of syndesmophytes in patients with AS and the presence of radiographic sacroiliitis in all patients with axial SpA. This finding led us to speculate that the CRP level might also predict radiographic progression during followup, which indeed turned out to be the case (14).

Several years ago, Amor et al conducted a retrospective analysis and identified an elevated ESR as a predictor of severe disease in AS and other spondylarthritides (33). However, in prospective observational cohorts of longstanding AS such as the Outcome Assessments in Ankylosing Spondylitis International Study (OASIS), markers of inflammatory activity did not emerge as independent predictors (31). The only obvious variable that might explain these discordant results is the different disease duration in these cohorts. GESPIC is a unique cohort of patients with early axial SpA and a short symptom duration (inception cohort), whereas in OASIS and many other AS cohorts, the mean symptom duration is ~20 years or more. Active inflammation undoubtedly plays an important role in the pathogenesis of AS by inducing a response that eventually leads to new bone formation (34). However, syndesmophyte growth, once initiated, might be less dependent on inflammation (35); therefore, no clear correlation between radiographic progression and the CRP level or the ESR has been observed in longstanding and advanced disease (31), and anti-TNF agents failed to inhibit radiographic progression in patients with longstanding AS over a period of 2 years (25–27). Moreover, recent investigations revealed the important role of the wingless pathway, which is uncoupled from common inflammatory pathways, in the development of syndesmophytes in AS (36–38).

This study is the first to demonstrate that smoking predicts radiographic progression in axial SpA. Previously, smoking was shown to be associated with functional impairment (39–42) and the radiographic severity of AS (39,43). It is well known that components of tobacco smoke have multiple effects on immune cell responses, cytokine production, and oxidative stress activation (44,45). Moreover, cigarette smoking has been recognized as a factor that increases susceptibility to rheumatoid arthritis (46–49), systemic lupus erythematosus (50), and IBD (51). In rheumatoid arthritis, no clear influence of smoking on radiographic progression was observed (52), although smokers have been shown to respond less well to therapy compared with nonsmokers (53). The exact mechanisms of the influence of smoking on radiographic progression in SpA have to be further investigated. In any case, smoking is a lifestyle factor that is potentially modifiable. The prediction matrix models we created illustrate the effects of smoking versus nonsmoking, which should encourage patients to stop smoking.

In the univariate analysis, the presence of definite radiographic sacroiliitis was significantly associated with spinal radiographic progression over 2 years, but significance was lost in the multivariate analysis. This indicates that, by itself, radiographic damage in the sacroiliac joints cannot be considered an independent factor for spinal radiographic progression. The current study showed weak and statistically nonsignificant associations between spinal radiographic progression and both male sex and HLA–B27 positivity; both of these variables have been associated with radiographic progression in previous studies of AS (13,31). No clear association was observed for age, disease duration, the BASDAI, the BASFI, the presence of peripheral arthritis, enthesitis, psoriasis, a family history of SpA, and therapy with NSAIDs or DMARDs at baseline. Treatment with NSAIDs versus no NSAID treatment (and any DMARD versus no DMARD) at baseline, as applied in our analyses, was not associated with radiographic progression. However, more detailed analyses taking into account the dosage and intensity of NSAID treatment (continuous versus intermittent) over time (30) may provide deeper insights into any potential disease-modifying effect of NSAID therapy.

In summary, average radiographic progression during the first 10 years of SpA is similar to that in longstanding disease, according to published data. During the first 5 years of disease, however, the rate of radiographic progression may be lower. Baseline damage, elevated acute-phase reactant levels, and smoking at baseline were independently associated with spinal

radiographic progression in this cohort of patients with early disease. Thus, therapeutic interventions that target systemic inflammation during the first 5–10 years of disease ("window of opportunity") and cessation of smoking may effectively modify the disease course. It will be interesting to see whether investigations in other cohorts of patients with early SpA will confirm our findings.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sieper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Poddubnyy, Haibel, Listing, Märker-Hermann, Zeidler, Braun, Sieper, Rudwaleit.

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2.3 A dose-dependent impact of tobacco smoking on radiographic spinal progression in axial spondyloarthritis

In the data presented above, tobacco smoking status itself was found to be an independent predictor of radiographic spinal progression in axial SpA. In a number of observational studies in AS, smoking was consistently found to be associated with worse function and quality of life impairment [52-56], as well as more severe radiographic damage in the spine [52, 57]. In a recent observational study in early axial SpA, smoking was associated with earlier disease onset, higher disease activity, more structural damage, and poorer function and health-related quality of life [58].

Therefore we decided to investigate in more details the relationship between tobacco smoking and development of structural damage in the spine in patients with axial SpA in GESPIC with a special focus on a dose-dependent association and a relationship between smoking and activity of systemic inflammation.

Again, 210 patients with axial SpA (115 with AS and 95 with non-radiographic axial SpA) from GESPIC were included. Besides mSASSS, we used in the current analysis an extended syndesmophytes count, which included not only lateral views of the cervical and lumbar spine but also antero-posterior views of the lumbar spine. Significant radiographic spinal progression was defined as 1) worsening of the mSASSS by ≥2 units after 2 years, and 2) development of a new syndesmophyte or progression of existing syndesmophytes (formation of a bridging syndesmophyte from two single syndesmophytes) after 2 years. Smoking status and smoking intensity (non-smoker, 10 cigarettes a day and less, 11 to 20 cigarettes, and more than 20 cigarettes a day) were assessed every 6 months during 2 years of follow-up.

The mean mSASSS change over 2 years was 2.2 ± 4.6 in heavy smokers (n = 28), as compared to 0.47 ± 1.48 in moderate smokers (n = 43, p = 0.006) and 0.52 ± 1.72 in non-smokers (n = 139, p = 0.001). Worsening of the mSASSS by ≥2 units over 2 years was observed in 28.6% of heavy smokers, as compared to 18.6% in moderate smokers, and 10.1% among non-smokers (p = 0.008 vs. heavy smokers). The rate of new syndesmophytes formation and/or growth of existing syndesmophytes was highest in heavy smokers (25%) as compared to moderate smokers (9.3%, p = 0.074) and to non-smokers (8.6%, p = 0.013). Importantly, the same trend was observed for the time-averaged serum level of C-reactive protein: 12.4 ± 12.9 mg/l in heavy smokers as compared to 8.6 ± 10.3 mg/l in moderate smokers and 6.3 ± 6.6 mg/l in non-smokers (p = 0.002 vs. heavy smokers).

Thus, we could demonstrate that tobacco smoking has a dose-dependent effect on radiographic spinal progression in axial SpA, which may be mediated through a higher inflammatory state induced by components of tobacco smoke. Smoking cessation might have a positive impact on the progression of structural damage in the spine and, therefore, might be beneficial in terms of the long-term outcome of axial spondyloarthritis.

Own reference:

Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2013;72(8):1430-2.

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2.4 The role of C-reactive protein as a marker of disease activity in patients with axial spondyloarthritis

In the light of the important role of CRP as a predictor of radiographic progression in the sacroiliac joints and in the spine, it is also a relevant question, whether CRP correlates also with clinical disease activity in axial SpA. Several earlier works in established AS, which used a standard method of CRP detection, were not able to find a correlation between CRP and clinical parameters of disease activity [10, 11]. However, standard (routine) CRP assays do not quantify the CRP concentrations below the upper normal limit which may be relevant as shown in rheumatoid arthritis, for example [59]. In GESPIC, we performed a comparison of standard and high sensitive (hs) CRP assays in their correlation with clinical disease activity parameters in patients with axial SpA.

A total of 269 patients with axial SpA (153 with AS and 116 with non-radiographic SpA) were included. HsCRP was measured using particle-enhanced immunoturbidimetric method with the lowest detected level of 0.1 mg/l. HsCRP values were compared to results of routine turbidimetric CRP test with the lowest detected level of 6 mg/l.

In patients with AS hsCRP showed a better than routine CRP correlation with clinical parameters: for instance, with general pain ($\rho = 0.340$, $p<0.001$, vs. 0.253, $p = 0.002$ for hsCRP and routine CRP, respectively), spinal pain ($\rho = 0.247$, $p = 0.002$ vs. 0.177, $p = 0.029$), night pain ($\rho = 0.325$, $p<0.001$ vs. 0.253, $p = 0.002$), intensity of morning stiffness ($\rho = 0.213$, $p = 0.008$ vs. 0.168, $p = 0.039$). Only hsCRP demonstrated significant correlation with the level of enthesitis-related discomfort in tender areas (BASDAI question 4, $\rho = 0.173$, $p = 0.032$) and the overall BASDAI value ($\rho = 0.173$, $p = 0.034$). In the patients with non-radiographic axial SpA, hsCRP correlated with the level of enthesitis-related tenderness only ($\rho = 0.224$, $p = 0.018$).

126 patients (46.8% of the whole group) – 65 patients with AS (42.5%) and 61 patients with non-radiographic axial SpA (52.6%) – had a level of routine CRP <6 mg/l. In the AS subgroup with a negative routine CRP there was a clear trend for an increased level of pain, stiffness, and functional impairment in patients with higher hsCRP concentration. Such trend was less pronounced in patients with non-radiographic axial SpA.

Thus, hsCRP correlates better than routine CRP with clinical disease activity parameters in patients with axial SpA that is most likely related to a wider range of concentrations especially in subnormal area captured by the hsCRP assay. Therefore, hsCRP could be superior to standard CRP in assessing disease activity in axial SpA.

Own reference:

Poddubnyy D, Rudwaleit M, Listing J, Braun J, Sieper J. Comparison of a high sensitivity and standard C reactive protein measurement in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis. Ann Rheum Dis 2010;69(7):1338-41.

http://dx.doi.org/10.1136/ard.2009.120139

2.5 The role of biomarkers in prediction of radiographic spinal progression in patients with axial spondyloarthritis

Besides CRP (and ESR), several further biomarkers relevant for the prediction of radiographic spinal progression in AS / axial SpA were identified in the last years. Maksymowych W *et al* identified matrix metalloproteinase 3 (MMP-3) to be an independent predictor of radiographic progression in AS: elevated (>68 ng/ml) serum levels of this biomarker had a sensitivity of 75%, a specificity of 64%, and an unadjusted OR = 5.4 (adjusted OR = 9.4) for mSASSS worsening by ≥3 units over 2 years [47]. Further, the serum level of sclerostin (a member of the DAN family of glycoproteins, which have been reported to antagonize bone morphogenetic protein (BMP) activity and to consequently inhibit bone formation) over time was significantly higher in AS patients without syndesmophyte growth than in AS patients with syndesmophyte growth in the GESPIC cohort. In the multivariate logistic regression analysis the adjusted odds ratios for developing new syndesmophytes was 0.23, 95% CI 0.05 to 1.10 per unit increase in the transformed mean sclerostin level of the patient [60]. Sclerostin shares many characteristics with the Wnt antagonist dickkopf-1, which blocks Wnt-stimulated bone formation and in consequence also indirectly affects BMP-mediated bone formation [61]. Therefore we investigated the relationship between serum levels of dickkopf-1 and radiographic spinal progression in AS patients in GESPIC.

2.5.1 Protective value of dickkopf-1 for radiographic spinal progression in patients with ankylosing spondylitis

A total of 65 patients with AS were selected based on the availability of serum samples at baseline, year 1 and year 2 and spinal radiographs at baseline and year 2. None of the patients was treated with TNF blockers. Radiographs of the lumbar and cervical spine were scored by three readers blinded for time points using the mSASSS. Patients

were divided into different groups depending on whether there were syndesmophytes present at baseline or not and whether there was a growth of syndesmophytes. Functional and total serum dickkopf-1 levels were measured.

The functional dickkopf-1 level was significantly higher in patients with no syndesmophyte growth (6.78 ± 5.48 pg/ml) compared with those patients with syndesmophyte growth (4.13 ± 2.10 pg/ml, p = 0.025). This difference remained significant (p = 0.002) when controlled for risk factors of syndesmophyte growth (presence/absence of syndesmophytes at baseline, CRP status, continuous/non-continuous treatment with non-steroidal anti-inflammatory drugs, gender, disease duration and HLA-B27 status) by multifactorial non-parametric variance analysis (Brunner test). Furthermore, considering the mean of the three dickkopf-1 levels per patient higher levels of functional dickkopf-1 (over 10 pg/ml) are exclusively found in patients with no new syndesmophyte formation. No significant difference between AS patients with syndemosphyte formation (2481.2±1409 pg/ml) and those without syndesmophyte formation (2052.0±1278 pg/ml) was found when total dickkopf-1 levels were measured. Thus, in AS patients with no syndesmophyte formation, significantly higher functional dickkopf-1 levels were found suggesting that blunted Wnt signalling suppresses new bone formation and consequently syndesmophyte growth and spinal ankylosis.

Own reference:

Heiland GR, Appel H, **Poddubnyy D**, Zwerina J, Hueber A, Haibel H, et al. High level of functional dickkopf-1 predicts protection from syndesmophyte formation in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71(4):572-4.

http://dx.doi.org/10.1136/annrheumdis-2011-200216

2.5.2 Predictive value of the vascular endothelial growth factor for radiographic spinal progression in axial spondyloarthritis

First, we investigated a panel of biomarkers related to the processes of bone / cartialage formation or destruction in a pilot study in patients with axial SpA from GESPIC. We identified / confirmed several biomarkers (MMP-3, bone morphogenetic protein 2, procollagen type II N-propeptide and vascular endothelial growth factor (VEGF)), which discriminated between patients with and without radiographic progression among those subjects who were at high risk for such a progression due to the presence of syndesmophytes and elevated CRP at baseline [8]. Of these, VEGF seemed to have a highest predictive value regarding radiographic spinal progression as demonstrated in a small group (n = 54) of patients with AS [9] – data that required confirmation in a larger study. VEGF is a signal protein that plays a crucial role in angiogenesis and therefore is relevant for the process of new bone formation and, especially, endochondral ossification [62]. Previously, serum levels of VEGF were found to be elevated in patients with AS, a correlation with clinical and laboratory markers of disease activity and a decrease during anti-inflammatory therapy were demonstrated [63-69].

Altogether 172 patients with definite axial SpA (95 with ankylosing spondylitis and 77 with non-radiographic axial SpA) were included in the current study. Spinal radiographs obtained at baseline and after 2 years of the follow up were scored independently by two trained readers in a concealed and randomly selected order according to the mSASSS scoring system and for the presence of syndesmophytes. Radiographic spinal progression after 2 years was defined as 1) mSASSS worsening by ≥2 units, and 2) new syndesmophyte formation or formation of a bridging syndesmophyte from two single syndesmophytes. Serum VEGF levels were detected at baseline.

Mean baseline VEGF values were significantly higher in patients with mSASSS worsening by ≥2 units after 2 years (n = 22) as compared to those without progression (562 ± 357 vs. 402 ± 309 pg/ml, respectively, p = 0.027) and in patients with syndesmophyte formation (n = 18) as compared again to those without new bone formation (579 ± 386 vs. 404 ± 307 pg/ml, respectively, p = 0.041).

In the whole group of axial SpA, elevated VEGF (>600 pg/ml – a cut-off defined on the basis of the receiver operating characteristic analysis) had a sensitivity of 36%, a specificity of 83%, and an OR = 2.9, 95% CI 1.1 to 7.5 as a predictor of mSASSS worsening by ≥2 units over 2 years; after adjustment for the presence of radiographic damage at baseline (syndesmophytes), elevated CRP, smoking status, presence of definite radiographic sacroiliitis, sex, HLA-B27 status, and treatment with NSAIDs and TNF α blockers at baseline the OR was 4.2, 95% CI 1.2 to 14.1. Similarly, for the prediction of syndesmophyte formation / progression, a VEGF-value >600 pg/ml demonstrated a sensitivity of 39%, a specificity of 83%, and an OR = 3.1, 95% CI 1.1 to 8.8, after adjustment for the same confounders the OR was 8.5, 95% CI 1.8 to 40.5.

Importantly, VEGF as a predictor of radiographic spinal progression performed especially well in patients who were already at high risk for such a progression due to the presence of syndesmophytes at baseline (n = 48). In these patients, VEGF serum level of >600 pg/ml had a sensitivity of 53%, a specificity of 97% and an OR = 36.6, 95% CI 3.9 to 341.5 as a predictor of mSASSS worsening by ≥2 units over 2 years; after adjustment for other confounders the OR was 58.9, 95% CI 3.4 to 1030.1. Similarly, as a predictor of syndesmophyte formation / progression elevated VEGF had a sensitivity of 47%, a specificity of 94%, and an OR = 13.6, 95% CI 2.4 to 78.3, after adjustment for other confounders the OR was 19.0, 95% CI 2.4-149.2.

Thus, elevated serum level of VEGF (>600 pg/ml) was found to be highly specific as a predictor of radiographic spinal progression in patients with axial SpA, especially in patients who are at high risk for further progression due to the presence of syndesmophytes. Therefore, VEGF might improve the prediction model based on the assessment of syndesmophytes, CRP / ESR and smoking status and might be useful in identification of patients who would especially benefit from a therapy targeting new bone formation in the spine in patients with axial SpA.

Own reference:

Poddubnyy D, Conrad K, Haibel H, Syrbe U, Haibel H, Appel H, Braun J, et al. Elevated serum level of the vascular endothelial growth factor predicts radiographic spinal progression in patients with axial spondyloarthritis. Ann Rheum Dis 2013. [Epub ahead of print]

http://dx.doi.org/10.1136/annrheumdis-2013-203824

2.6 Retardation of radiographic spinal progression in axial spondyloarthritis with non-steroidal anti-inflammatory drugs

NSAIDs are considered as a first line therapy in patients with axial SpA including AS [16]. However, it has been suggested that NSAIDs might not have only a good symptomatic but also a disease-modifying effect. It had been shown in a small retrospective study by Boersma at al some time ago that a continuous use of phenylbutazone was associated with retardation of spinal ossification in AS [70]. In a more recent study by Wanders *et al*, continuous (daily) use of NSAIDs was also associated with an inhibition of radiographic progression in the spine over two years as compared to on-demand use [43]. However, these reports have not been confirmed so far. Furthermore, NSAIDs influence on radiographic progression in early axial SpA (especially in a non-radiographic form) has not been investigated.

In order to address these question, 164 patients with axial SpA (88 with AS and 76 with non-radiographic axial SpA) from GESPIC were selected based on availability of spinal radiographs at baseline and after 2 years of follow-up and of on the availability of the data on NSAIDs intake. Spinal radiographs were scored by two trained readers in a concealed randomly selected order according to the mSASSS system [35]. In addition to lateral views, anteroposterior views of the lumbar spine (left and right corners of the vertebral bodies from Th12 to S1) were scored for the presence of syndesmophytes.

Data on NSAIDs intake (dose and frequency of intake) were collected at baseline and every 6 months thereafter during 2 years of follow-up. An score of the NSAID intake [71], as recommended by ASAS, accounting for both dose and duration/regiment of drug intake (0 – no NSAIDs intake at all, 100 – daily NSAIDs intake in a dose equivalent to diclofenac 150 mg over the whole period of interest) was calculated. High NSAIDs

intake was defined as a mean NSAIDs intake score over 2 years of ≥50, low NSAIDs intake – as a mean NSAIDs intake score <50.

The mean mSASSS change over two years in AS was 0.02 ± 1.39 in patients with high NSAIDs intake versus 0.96 ± 2.78 in the subgroup with low NSAIDs intake, respectively, p = 0.142. Similarly, less AS patients in the group with high NSAIDs intake showed radiographic spinal progression defined as a worsening of the mSASSS score by 2 units and more over two years in comparison to the patients with low NSAIDS intake: 8.3% versus 21.9%, respectively, p = 0.142; unadjusted odds ratio OR = 0.33, 95% CI 0.07 to 1.55, p = 0.159. After adjustment for baseline structural damage, elevated C-reactive protein and smoking status, AS patients with high NSAIDs intake had a significantly lower likelihood of radiographic progression (mSASSS worsening by ≥2 units): OR = 0.15, 95% CI 0.02 to 0.96 in comparison to patients with low NSAIDs intake.

The positive effect of the NSAIDs intake on radiographic spinal progression was nearly exclusively evident in patients who were at high risk for radiographic progression due to the presence of syndesmophytes and elevated acute phase reactants: in this group mean mSASSS progression was 4.36 ± 4.53 in patients with low NSAIDs intake vs 0.14 ± 1.80 with high intake, p = 0.02, while there was nearly no progression in patients without both risk factors (0.35 ± 1.07 vs 0.07 ± 1.06, respectively; p = 0.48). In non-radiographic axial SpA, no significant differences regarding radiographic progression between patients with high and low NSAIDs intake was found, probably due to a low rate of radiographic spinal progression in this group in general.

Thus, we could confirm that high NSAIDs intake (nearly equivalent to continuous intake) over 2 years is associated with retarded radiographic spinal progression in AS, and especially in patients with risk factors for radiographic spinal progression (syndesmophytes and elevated CRP). Interestingly, a post-hoc analysis of the Wanders

et al study, which included more advanced patients with AS, revealed that effect of slowing radiological progression with continuous NSAID therapy was more pronounced in patients with elevated CRP or ESR levels [44]. In non-radiographic axial SpA this effect is less evident, probably due to a low grade of new bone formation in the spine at this stage.

Own reference:

Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Marker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German SPondyloarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2012;71(10):1616-22.

http://dx.doi.org/10.1136/annrheumdis-2011-201252

3 Discussion

In the presented works we were able to identify rates and predictors of disease progression in axial spondyloarthritis. We found that about 12% of patients with non-radiographic axial SpA developed definite radiographic sacroiliitis fulfilling the radiographic criterion of the modified New York criteria for AS after two years. These data are in line with the previous works reporting outcomes of non-radiographic / undifferentiated SpA. For instance, Sampario-Barros *et al* reported that 10% of the patients progressed from undifferentiated SpA to AS over 2 years [72] and 24.3% of the patents progressed over 5 to 10 years [73]. In the earlier report by Schattenkirchner *et al* a 25% progression rate of undifferentiated SpA to AS was observed after a period from 2 to 6 years [74]. Similarly, 59% of the patients with no definite diagnosis of AS at baseline developed definite AS after 10 years of follow-up in the study by Mau *et al* [75].

Radiographic sacroiliitis has been used in the past mostly for diagnostic purposes while the assessment of the ankylosis of the spine has been established as an important long-term outcome parameter in AS because of its correlation with spinal mobility and function [50, 51]. Whether progression of radiographic sacroiliitis with development of total ankylosis, for example, does have any impact on the mobility and function of the axial skeleton is still to be determined.

We demonstrated that CRP as a marker of systemic inflammatory activity is not only an important disease activity parameter in axial SpA (which is also acknowledged in a recently developed ASAS endorsed disease activity score – ASDAS [76, 77]) but also an important predictor of structural damage development in the sacroiliac joints and in the spine. Elevated CRP was also found to be associated with the presence of radiographic sacroiliitis and syndemophytes in the publication concerning the baseline characteristics of patients in GESPIC [2]. These data demonstrated the important role of

high inflammatory activity for progression of structural damage in the axial skeleton and for transition from non-radiographic to radiographic stage of axial SpA. An association between CRP level and sacroiliitis progression was not reported in the previous studies, because information about CRP level was not available [72-75, 78], with the exception of the study by Huerta-Sil G *et al*, in which elevated CRP and erythrocyte sedimentation rate, whatever was available, were analyzed together, but showed only a trend for the association with the progression from undifferentiated SpA to AS [79]. Beyond CRP there is only one known factor which was shown to be predictive for the progression of radiographic sacroiliitis: active inflammation on MRI of sacroiliac joints [80]. In GESPIC no MRIs of the sacroiliac joints were available but these data are clearly in line with our data indicating a leading role of inflammation in the development of structural damage in the sacroiliac joints in patients with axial SpA.

Elevated CRP (and to a further extent another marker of inflammation – ESR) was found to be independently associated with structural damage development in the spine in patients with axial SpA. Importantly, elevated time-averaged CRP demonstrated a stronger association with radiographic spinal progression than baseline CRP. Time-averaged CRP reflected better a status of persistent systemic inflammation as compared to elevated baseline CRP or baseline ESR only, thereby adding validity to the predictive role of systemic inflammation. In the cross-sectional analysis of baseline data from GESPIC, elevated CRP at baseline was also significantly associated with the presence of syndesmophytes in AS patients [2].

Several years ago Amor *et al* identified elevated ESR as a predictor of severe disease in AS and other SpAs in a retrospective analysis [81]. However, in prospective observational cohorts of longstanding AS such as OASIS, for example, markers of inflammatory activity did not emerge as independent predictors [48]. The only obvious

variable that might explain these discordant results is the different disease duration in these cohorts. GESPIC is a unique cohort of early axial SpA with short symptom duration (inception cohort), whereas in OASIS and many other AS cohorts the mean symptom duration is about 20 years or more. Active inflammation plays undoubtedly an important role in AS pathogenesis by inducing a response which eventually leads to new bone formation [42]. However, syndesmophyte growth, once initiated, might be less dependent on inflammation [82] and, therefore, no clear correlation between radiographic progression and CRP or ESR has been found in longstanding and advanced disease [48]. Moreover, recent investigations revealed the important role of the Wnt pathway, which is uncoupled from common inflammatory pathways, in the development of syndesmophytes in AS [83-85].

The strongest predictor of radiographic spinal progression in axial SpA in GESPIC was the presence of radiographic damage (syndesmophytes). The association of baseline damage with further progression has been reported before in longstanding AS but not in early disease [45-48].

In our works we demonstrate for the first time that smoking predicts radiographic progression in axial SpA. Furthermore, we demonstrated that tobacco smoking has a dose-dependent influence on radiographic spinal progression in patients with axial SpA: heavy smokers (patients who smoked more than 10 cigarettes a day) showed not only the highest absolute worsening of the mSASSS over two years, but also higher rates of mSASSS worsening by two units and more over two years and syndesmophyte formation/progression over the same period of time as compared to those who smoked up to 10 cigarettes a day and as compared to non-smokers. Previously, smoking was found to be associated with functional impairment [52-55] and radiographic severity of AS [52, 57].

We found a clear dose dependent association between smoking and activity of systemic inflammation measured by CRP. Importantly, this association was found not only for baseline values, but also for time-averaged CRP values indicating persistent activity of systemic inflammation in smokers. Along this line, data from the French spondyloarthritis cohort (DESIR) also showed that active inflammatory lesions in the sacroiliac joints and in the spine as detected by MRI were significantly more frequent in smokers as compared to non-smokers [58]. Taken together, these findings provide a pathophysiological link between smoking and radiographic spinal progression in axial SpA, suggesting that increased activity of systemic inflammation might indeed play a key role for radiographic progression.

Based on the combination of the risk factors for radiographic spinal progression (syndesmophytes, elevated acute phase reactants and smoking) we created a predictive matrix model, which might be helpful for estimation of a probability of radiographic spinal progression in individual patients. However, even in the presence of all 3 risk factors, the probability of radiographic spinal progression in the next 2 years is about 50% only. In order to improve the predictive model we investigated a number of biomarkers which are related to the process of new bone formation. It has been shown that Wnt-antagonists sclerostin and dickkopf-1 are protective regarding radiographic spinal progression in axial SpA. Later, we identified a biomarker with probably the strongest predictive value for the structural damage development in the spine – VEGF. We were able to show that VEGF serum level of >600 pg/ml is able to predict radiographic spinal progression with high specificity especially in patients who are already at risk for such a progression due to the presence of syndesmophytes.

The process of osteogenesis representing the morphological substrate of syndesmophyte formation in patients with axial SpA is closely associated with the

process of angiogenesis [86]. VEGF is required for an effective linking of angiogenesis and osteogenesis [86, 87]. VEGF plays also a key role in the process of endochondral ossification [62, 87], which might be relevant for the ankylosing process in axial SpA. Various cells are responsible for the production of VEGF: fibroblasts, hypertrophic chondrocytes, and osteoblasts [87, 88]. A wide range of physical (i.e. mechanical stress [89]) and chemical stimuli (e.g., prostaglandin E1 and E2 [90, 91], bone morphogenetic proteins 2, 4, and 6 [92]) increase VEGF expression and secretion.

It has been shown previously that VEGF is elevated in axial SpA / AS in comparison to healthy controls [63, 64, 68], that it correlates with markers of disease activity (BASDAI [64], acute phase reactants including CRP [63, 64]), and it decreases substantially under anti TNF α therapy [65-69]. Thus, VEGF might be a unique biomarker coupling processes of inflammation and new bone formation in axial SpA. Whether VEGF might be a treatment target and whether VEGF is able to predict radiographic spinal progression in patients under anti-TNF therapy should be investigated in further studies.

The question of prevention of disease progression (primarily in the spine since progression of radiographic sacroiliitis seems to be much less relevant for the long-term outcome) is another important question we addressed in our works. Continuous inhibition of inflammation and smoking cessations in smokers seems to be the most reasonable ways of retardation of radiographic spinal progression in axial SpA. However, the most potent anti-inflammatory drugs in axial SpA – TNF α inhibitors – have failed to show an inhibitory effect on progression of spinal damage over a period up to 4 years [36-39]. One of the possible explanation for this phenomenon is an uncoupling of inflammation and new bone formation in axial SpA at a certain time-point resulting in independence of the ongoing process of new bone formation from the activity of inflammation [42]. Therefore, there are two theoretical possibilities to retard

radiographic spinal progression: either to start this therapy early enough (“window of opportunity”) in order to inhibit inflammation prior to start of new bone formation, or to use continuous inhibition of inflammation long enough (>4 years) in order to prevent new areas of syndesmophyte growth. Currently we only have data supporting the second possibility: retardation of radiographic spinal progression might become evident in case of longer treatment (6-8 years) [40, 41].

However, inhibition of radiographic spinal progression can also be achieved if drugs with direct antiosteoproliferative effects are used. NSAIDs represent a drug class with such properties. There are several observational studies indicating a retardation of fracture healing [93] or loosening of the hip endoprosthesis [94] related to NSAIDs use. Furthermore, NSAIDs have been used for the prevention of heterotopic ossification after orthopaedic surgery, e.g., total hip arthroplasty [95], hip resurfacing [96], or fractures (e.g., acetabular fractures) [97].

The observed inhibition of new bone formation by NSAIDs can probably best be explained by the inhibition of prostaglandins (especially prostaglandin E_2) synthesis mediated by cyclooxygenase- 2 (COX-2) [98]. Prostaglandin E_2 is able to stimulate new bone formation by increasing the replication and differentiation of osteoblasts [99]. Prostaglandins also support blood supply to the site of new bone formation by causing vasodilatation and by promoting angiogenesis [100, 101]. In experiments with COX-2 knockout mice, healing of the stabilized tibia fracture was delayed in comparison to wild-type animals and to COX-1 knockouts [102]. Similarly, NSAIDs were able to retard a BMP-7 induced ectopic bone formation in an experimental mouse model indicating an important role of COX-mediated prostaglandin synthesis in new bone formation [103]. Since retardation of the new bone formation is related to COX-2 inhibition, no substantial differences are expected between different NSAIDs, because in therapeutic

concentrations all NSAIDs, independently from their COX-selectivity, inhibit COX-2 to nearly the same extent [104].

In GESPIC we were able to confirm that continuous treatment with NSAIDs is able to retard radiographic spinal progression in axial SpA. Furthermore, we identified predictors of good radiographic response to NSAIDs: presence of syndesmophytes and elevated CRP, since the inhibitory effect of high/continuous NSAIDs intake of progression of structural damage in the spine was nearly exclusively seen in patients with these risk factors.

If the structure-modifying effect of NSAIDs in axial SpA will be confirmed in further studies, it would be an additional argument to administer NSAIDs more consequently, especially in patients with clinical indications for NSAIDs and in patients who are at risk for radiographic spinal progression due to the presence of syndesmophytes and elevated acute phase reactants. The potential cardiovascular, gastrointestinal and other side effects of continuous NSAIDs intake has been investigated in greatest details and we have argued recently that the benefit of such a treatment normally outweighs the risk in axial SpA [105]. Further, a trial combining TNF-blocker and NSAIDs treatment would especially be of interest addressing the question whether new bone formation can be inhibited, in addition to suppressing inflammation and improving signs and symptoms.

4 Summary

Disease progression in axial SpA refers to the development of structural damage in the sacroiliac joints and in the spine. In the German Spondyloarthritis Inception Cohort (GESPIC), which includes patients with early axial SpA (AS with symptom duration up to 10 years and non-radiographic axial SpA with symptom duration up to 5 years), we investigated rates and predictors of structural damage progression in the sacroiliac joints and in the spine.

In the sacroiliac joints, the rate of definite sacroiliitis development (i.e. progression from non-radiographic axial SpA to AS) was 11.6% after two years. Elevated level of CRP was found to be the only significant predictor of progression from non-radiographic axial SpA to AS fulfilling the modified New York criteria.

In the spine, the rate of radiographic progression was 0.95 ± 2.78 mSASSS units in AS and 0.46 ± 1.63 mSASSS units in non-radiographic axial SpA. The following factors were independently predictive for significant radiographic spinal progression (mSASSS worsening in 2 units and more or development of new syndesmophytes) over two years: the presence of structural damage (syndesmophytes) at baseline, elevated acute phase reactants (CRP or ESR) and smoking. Furthermore, smoking demonstrated a dose-dependent impact on the development of structural damage in the spine in axial SpA with the highest progression rate (mSASSS worsening 2.2 ± 4.6 over 2 years) in patients who smoked more than 10 cigarettes a day. The negative effect of smoking on radiographic spinal progression seemed to be mediated by increased activity of systemic inflammation (as reflected by CRP) in smokers.

Further, several biomarkers with predictive/protective value for radiographic spinal progression were identified, among others dickkopf-1 (with protective value) and VEGF (with predictive value). Elevated serum level of VEGF (>600 pg/ml) was found to be

highly specific as a predictor of radiographic spinal progression in patients with axial SpA, especially in patients who were at high risk for such a progression due to the presence of syndesmophytes. Therefore, VEGF is a biomarker, which is able to improve the predictive model for radiographic spinal progression based on syndesmophytes, acute phase reactants and smoking status assessment.

We were able to demonstrate that high NSAIDs intake (more than 50% of the maximal recommended dose) is able to retard radiographic spinal progression in axial SpA. AS patients with high NSAIDs intake had a significantly lower likelihood of radiographic progression even after adjustment for baseline structural damage, elevated C-reactive protein and smoking status. Importantly, the positive effect of the NSAIDs intake on radiographic spinal progression was nearly exclusively evident in patients who were at high risk for radiographic progression due to the presence of syndesmophytes and elevated CRP.

Thus, investigation of predictors of structural damage development opened ways for prevention of radiographic progression and, therefore, for improvement of the long-term outcome. These ways are: early initiation of effective anti-inflammatory therapy, smoking cessation, and continuous administration of NSAIDs (unless contraindicated) in symptomatic patients, especially in the presence of syndesmophytes and elevated CRP.

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7 Erklärung

§4 Abs. 3 (k) der HabOMed

Habilitationsordnung der Medizinischen Fakultät

Charité - Universitätsmedizin Berlin

Hiermit erkläre ich, dass

1. weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wird bzw. wurde,
2. die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
3. mir die geltende Habilitationsordnung bekannt ist.

....
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