Ankylosing spondylitis: Assessment and analysis of long-term outcome
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Summary and conclusions
SUMMARY AND CONCLUSIONS

The studies described in this thesis cover aspects of the assessment of Ankylosing Spondylitis (AS) and analysis of its long-term outcome. More specifically, in these studies the following topics were addressed. First, several facets of outcome assessment in AS were discussed and improved, in particular pertaining to disease activity, spinal mobility and radiographic damage. Second, the course of radiographic damage over time was analysed and better insight was obtained into the process of syndesmophyte formation. Finally, longitudinal relationships between disease activity, spinal mobility and radiographic damage and other potential determinants of these outcomes were investigated.

The studies were conducted in two cohorts: the Outcome in AS International Study (OASIS cohort) and the MOBILITY study. OASIS is a cohort of patients with prevalent AS, in which 217 patients from the Netherlands, Belgium and France have been included in 1996, and have been followed-up for 12 years. Clinical and radiographic data were collected at least every 2 years (during the first years of follow-up more often). Assessments included questionnaires, clinical investigations, physical examinations including spinal mobility measurements, laboratory assessments, and radiographic assessments of the pelvis, and the cervical and lumbar spine. The MOBILITY study was a cross-sectional study of normal individuals in whom a normal spinal mobility was expected and patients with conditions possibly affecting spinal mobility (e.g. back surgery and low back pain) were excluded. Recruitment was stratified by age, gender and height so that the population was balanced with respect to these factors, expected to influence spinal mobility. Participants were assessed once for their spinal mobility using a series of spinal mobility measurements.

In this final chapter we will summarize the main findings of the studies comprised in this thesis and also share our vision on research challenges in the field for the upcoming years.

Disease activity and function assessment
We started in chapter 2 with the proposal of a method for dealing with missing items in two patient-reported instruments; one to measure disease activity, the Bath AS Disease Activity Index (BASDAI), and the other to measure functional disability, the Bath AS Functional Index (BASFI). This study was conducted using the 12 year OASIS data. Up to one missing item for the BASDAI and three for the BASFI could be reliably imputed by averaging the remaining items. These imputation techniques yielded an agreement >90% and resulted in a difference between the original and the imputed scores of ≤0.7 (which is half of the smallest detectable change). We considered this acceptable and have therefore recommended this technique. It was compared with other imputation methods, such as imputation of the median, and lowest, middle or highest value, but the average of the remaining items consistently performed
best. So far, no clear instructions on how to deal with missing items were available and the proposed method is easy and can also easily be applied in clinical practice. Especially the BASDAI is frequently used for clinical decision-making: a BASDAI of 4 is a common cut-off to define eligibility for biologic therapy. With the proposed solution, one missing item will no longer preclude the calculation of the BASDAI and, hence, the score can still be taken into account to guide clinical decisions. Similarly, even when up to 3 items are missing can the BASFI still be calculated at an individual level, which can also contribute for clinical decisions, given the importance of functional disability as an outcome. Furthermore, we could hereby verify that missing data in BASDAI and BASFI items in our 12 year data from OASIS occurred very rarely (<2% of observations), facilitating longitudinal analysis (see below).

Mobility

Thusfar spinal mobility, while being a central outcome in AS, had not yet been fully addressed in normal individuals. The Assessment of SpondyloArthritis international Society (ASAS), an international group of experts in the field of spondyloarthritis, recommends the assessment of spinal mobility measures, both in clinical practice and in clinical trials with therapeutic interventions. The recommended measures are: chest expansion, modified Schober’s test, occiput-to-wall distance, cervical rotation, and either lateral spinal flexion or Bath AS Metrology Index (BASMI). The BASMI, in turn, includes lateral spinal flexion, modified Schober, cervical rotation, tragus-to-wall distance and intermalleolar distance. In normal individuals (‘norms’), ‘normal values’ or ‘reference values’ for the different spinal mobility measures, commonly used in the assessment of patients with AS, were not known. We have conducted a study on normal individuals, the MOBILITY study, rigorously excluding any subject in whom ‘abnormal’ spinal mobility could be expected, so that ‘reference values’ for each spinal mobility measure could be derived (chapter 3). In anticipation of interference by age, gender and height, MOBILITY had a ‘latin-square design’. Recruitment was stratified for the three above-mentioned factors, which means that the study population is balanced with respect to those factors, and which further conveys the best power even with a relatively small sample, meaning that subtle relationships can be more efficiently identified. We first investigated the effect of age, height and gender on the different spinal mobility measures. A significant decrease in all spinal mobility measures was found with increasing age. Increasing height was associated with higher tragus-to-wall distance, lateral spinal flexion, chest expansion and intermalleolar distance. Female gender was associated with lower values of chest expansion or cervical rotation. In chapter 3, age- (and in some cases height-) specific reference intervals and percentiles for each of the spinal mobility measures are presented. Although gender was associated to some extent with some spinal mobility measures, its additional value in the reference intervals did not outweigh the increasing complexity of the model and of the consequent reference intervals. Age-specific, and in some cases height-
specific, reference intervals fitted the data best. Percentile curves were derived in analogy to the growth curves for the monitoring of children’s growth. The proposed reference intervals and percentile curves represent a clear way forward in the outcome assessment of AS, as we now know how spinal mobility measures perform in normal individuals and we can better interpret the same measures in patients with AS. An important age effect on all spinal mobility measures was found, which emphasizes that this needs to be taken into account when following patients with AS: likely some part of the impairment in mobility seen throughout the years is not attributable to the disease, but to normal aging. The proposed percentile curves also provide a tool for further research in patients with AS. They can be used as a reference of ‘normal values’ when comparisons between patients and normal individuals are necessary. Furthermore, percentile curves may have their value in the follow-up of patients with AS in order to find out if a patient increasingly deviates from his ‘personal curve’ over time. Whether this application has clinical relevance needs to be tested.

From the same MOBILITY study we have derived an imputation method for lateral spinal flexion (LSF) measurement, namely where LSF has been inappropriately recorded (which often happens). Lateral spinal flexion can be calculated as the difference in the lateral distances between middle fingertip-to-floor in the neutral position and middle fingertip-to-floor in maximum latero-flexion. If neutral fingertip-to-floor is missing, and only fingertip-to-floor distance at maximum flexion is recorded, true lateral spinal flexion cannot be calculated. This problem of inappropriate recording of an otherwise correctly performed measure was frequently found in OASIS and likely in other cohorts too, and hampers the apt calculation of LSF. We have shown that neutral fingertip-to-floor, which is a static measure, can be reliably approximated by height using a simple equation (chapter 4). This imputation method showed a very good fit of the data (R² = 0.84).

This imputation method enabled us to ‘recover’ several inappropriately recorded LSF values in OASIS.

Finally, we could perform a formal comparison of spinal mobility between patients with AS, using the 12 year OASIS data, and normal individuals, using the percentile curves. Our aim was to analyse if there is a hierarchical order for the occurrence of impairment of spinal mobility measures. This has never been properly investigated, since cut-off levels for normal vs. abnormal were lacking. As described in chapter 5, we have considered the spinal mobility measures recommended by ASAS. Spinal mobility measures were considered ‘impaired’ based on the cut-offs from the age-specific percentile curves derived from normal individuals. We have found that there is a clear fixed order in which the spine in AS gets involved: Lateral spinal flexion and modified Schober are most frequently impaired in patients with AS, followed by tragus-to-wall distance, then cervical rotation, then intermalleolar distance
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and at last chest expansion. This observation fuels the hypothesis of earliest involvement of the lumbar spine, followed by involvement of the thoracic spine and then the cervical spine. This fixed order of involvement of the spine was found across different patient groups, defined based on either gender, disease duration or the presence or extent of baseline syndesmophytes, all being factors potentially influencing spinal mobility. In addition, from this study we have also concluded that impairment in spinal mobility, defined as an impairment in at least one spinal mobility measure, can be detected by only measuring lateral spinal flexion and modified Schober. Such a simple screening strategy would miss only 9% of patients with an impairment of spinal mobility, while saving a lot of time involved to perform the full set of spinal mobility measurements. If one of the measures of lateral spinal flexion and modified Schober is impaired, a full set of mobility measures should be performed to be informed on the extent of spinal mobility impairment. This may have important implications for daily clinical practice where time is limited.

Radiographic damage and progression

At the start of the studies described in this thesis, the modified Stoke AS Spine Score (mSASSS) was considered the most reliable and sensitive to change scoring method to assess structural damage in AS. After this formal comparison between scoring methods had taken place, a slightly modified version of the mSASSS, the Radiographic AS Spinal Score (RASSS) was developed. The RASSS - in addition to the mSASSS - includes the lower thoracic vertebrae, under the hypothesis that most progression is found in these segments. Before starting our long-term analysis of radiographic damage in OASIS, we have conducted a comparison between the two radiographic scores. As described in chapter 6, both scoring methods were compared with respect to the validation criteria proposed by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT): 1) truth; (or: does the instrument measure what is intended? is the result unbiased and relevant?); 2) discrimination (or: does the measure discriminate between situations of interest?); and 3) feasibility (or: can the measure be applied easily, is it feasible to use in the context of clinical trials?)

Regarding the truth aspect, we have found that progression in the thoracic vertebrae was not significantly different from what was expected under the assumption that progression occurs in a balanced manner; in other words, progression was not more prominent in the thoracic spine. In terms of discrimination, both scoring methods showed similar effect sizes for progression despite a higher mean level of progression detected by the RASSS (which was expected because of the additional thoracic vertebrae included). Similar effect sizes for both measures, however, imply that the increased signal detected with the RASSS was offset by increased ‘noise’ (higher level of variance). Both methods showed similar reliability. Feasibility of the RASSS was strongly hampered by a lower availability (36% less compared to the mSASSS) of lower thoracic vertebrae on x-rays. Furthermore, in one third of the
radiographs in which the RASSS could be calculated, only one to two thoracic vertebral corners were accessible, which means that the calculation of the RASSS was based on imputed - and thus non-informative - vertebral corners in the lumbar spine (up to 3 missing corners per spine segment (cervical or lumbar) were allowed; if more vertebral corners were missing, the radiograph could not be included). In one third of the cases where RASSS was computed, the missing vertebral corners included the thoracic vertebrae. In particular feasibility aspects of the RASSS compared to the mSASSS fall short, and this is in our opinion not outweighed by better discrimination/reliability. In conclusion, therefore, the mSASSS remained to us the most appropriate scoring method to assess radiographic progression in patients with AS.

Consequently, for all the studies including radiographic damage (chapters 7-10), which were conducted with 12 year data from OASIS, we have used radiographic scores obtained by the mSASSS. In chapter 7, we have investigated the course of radiographic damage over time. Previous findings have been confirmed by us and radiographic progression was found to take place at a relatively ‘slow pace’. Progression is highly variable at the individual patient level. Approximately one quarter of the patients in OASIS did not show progression; one quarter had a high level of progression (arbitrarily defined as at least one 2 year interval with a progression of ≥5 mSASSS units); and half of the patients had an intermediate progression rate (≥2 mSASSS units per 2 years). Remarkably, radiographic progression seems to be entirely independent of disease- or symptom duration. Periods of steep progression can be found at any time in the course of the disease, even decades after disease onset, and after periods of relative or complete quiescence. Furthermore, 60% of the patients have developed at least one syndesmophyte over a period of 12 years, implying that syndesmophytes may occur in the vast majority of patients and not only in a bad-prognosis subgroup. So, even though radiographic progression may occur at a relatively slow pace, the chronic character of the disease and the rather unpredictable course in an individual patient assure an accrual of substantial damage over time in most patients. Since damage will – among others - lead to impairment in functional ability, this may have direct clinical consequences.

Using longitudinal data analysis, we have investigated for the first time the course of radiographic damage over time at the group level. We have used generalised estimating equations (GEE) and found an approximately linear course of progression of radiographic damage, with a remarkably stable progression rate of approximately 1 mSASSS unit per year. Radiographic progression was found to be more severe in HLA-B27 positive men (1.2 mSASSS units per year) and, as expected, in patients with a higher level of radiographic damage present at baseline (1.4 mSASSS units per year in patients with a baseline mSASSS ≥10 mSASSS units, the population median). In these groups of patients, physicians should be particularly alert for radiographic progression.
In chapter 8 we have analysed syndesmophyte formation in more detail. We were particularly interested in analyzing whether erosion, sclerosis and/or squaring as assessed on radiographs precede the development of syndesmophytes. These abnormalities are all scored at the vertebral corner level and are part of the mSASSS method. But there is also an important pathophysiological connotation.

The presence of erosion, sclerosis and/or squaring in a vertebral corner is scored as 1 and syndesmophytes are scored as 2 (or 3, if bridging), presuming that the former precede the latter, but this had never been formally investigated. Using the 12 year OASIS data, we have conducted a multilevel analysis, in order to adjust for the different levels (i.e. 24 vertebral corners) occurring in the same patient (within-patient correlation). In order to correctly assess whether erosions, sclerosis and/or squaring indeed precede syndesmophyte (bridging or not) formation, we have used 2 year time lags between the detection of erosion, sclerosis and/or squaring on the one hand, and the detection of a syndemophyte at the same level on the other hand. We have found that, while erosion, sclerosis and/or squaring were rather infrequently found (they form only 8-10% of the scores in the vertebral corners), their occurrence often precedes the detection of a new syndesmophyte (Odds Ratio (95% CI): 2.0 (1.7 - 2.3)). When split up, erosions (2.1 (1.6-2.8)) and sclerosis (5.1 (3.9 - 6.8)) but not squaring were statistically significantly associated with subsequent new syndesmophyte formation. According to a hypothesis formulated by Sieper et al., structural damage may start with osteodestruction (erosion), being a consequence of inflammation, followed by a repair response with ossification, the osteoproliferative phase. Our findings are in support of this theory that links inflammation to new bone formation via an intermediate step of osteodestruction in AS. Another theory postulates that a mechanical or inflammatory trigger may lead to a local inflammatory response triggering a subsequent repair reaction perpetuating a bone anabolic response.

As postulated in chapter 8 erosion and sclerosis may reflect parts of this ongoing process where erosion reflects destruction, and sclerosis may be the first step of the bone proliferation process. On the basis of these findings we hypothesize that erosions or sclerosis may precede the development of a new syndesmophyte. The 2 year interval of the radiographs that we had to commit to in this study may be too long so that we have missed the ‘real sequence’ of the process of syndesmophyte formation. For similar reasons a hypothetical order of the chain ‘erosion-sclerosis-syndesmophyte’ could not be investigated properly. Whether this sequence can be investigated in near future is doubtful since it may require frequent radiographs in large groups of patients.
Relationship between inflammation and radiographic progression

A main aim of this thesis was to explore the longitudinal relationship between inflammation, as measured by disease activity, and radiographic progression. Before the studies of this thesis were conducted, a relationship between C-reactive protein and 2 year radiographic progression had been described, but such a relationship could not be secured using the standard measures for AS disease activity. This fact coincided with the negative studies on inhibition of radiographic progression by tumor-necrosis factor-alpha-inhibiting (TNFi) biologicals. Both observations fuelled theories postulating an ‘uncoupling’ of inflammation and bone formation. The OASIS study provided an excellent setting to unravel this enigmatic relationship. It combined a long follow-up, with up to 7 sets of 2 yearly radiographs per patient, with an extensive assessment of disease activity not only with BASDAI, but also with the AS Disease Activity Score (ASDAS). Such a detailed longitudinal set-up allows longitudinal data-analysis that helps in detecting subtle relationships.

As described in chapter 9, we have first investigated whether baseline disease activity was associated with the development of radiographic damage over time (baseline analysis). We have found that baseline disease activity significantly modified the course of radiographic damage over time. This means that patients who have a higher disease activity at a given time point will have a higher level of progression of structural damage over the following years. Patients with inactive disease (ASDAS < 1.3) at baseline had an average progression of 0.7 mSASSS units every 2 years, whereas patients with very high disease activity (ASDAS > 3.5) at baseline had a progression of 3.1 mSASSS units/2 years. A similar relationship was found with increasing levels of baseline BASDAI, but the ‘dose-effect’ was less evident: patients with a BASDAI <4 at baseline had an average progression of 1.4 mSASSS units/2 years, while patients with a BASDAI ≥4 (2.7 mSASSS units/2 years) or those with a BASDAI >6 (2.0 mSASSS units/2 years) at baseline experienced more progression over time.

In a second set of analyses (longitudinal analysis), time lagged autoregressive models were used, which technically enabled us to investigate the relationship between disease activity at a given time point and radiographic progression in the subsequent 2 years. It has for the first time been shown that disease activity unequivocally contributes to radiographic progression in the spine in AS: an increase in disease activity is followed by an increase in radiographic progression. The effect of disease activity on radiographic damage is actually rather impressive: an increase of one ASDAS unit in an individual patient is expected to lead to an increase of 0.7 mSASSS units progression over the next 2 years. Further, a patient with very high disease activity (ASDAS > 3.5) may in comparison to a patient with inactive disease (ASDAS < 1.3) expect an additional progression of 2.3 mSASSS units in the subsequent 2 years. Similar conclusions could be drawn for all disease activity measures used (i.e. ASDAS, BASDAI, CRP and/or patient’s global assessment of disease activity). Models with ASDAS...
as a disease activity measure showed a better fit than models with all other disease activity measures. Furthermore, there was a clearer ‘dose-effect relationship’ in the analyses with ASDAS: Unlike BASDAI states of disease activity, increasing ASDAS disease activity states were best associated with increased radiographic progression. This superb performance of ASDAS in comparison to other disease activity measures adds to the validity of ASDAS as the disease activity measure of choice. Moreover, the described relationship between disease activity and radiographic progression may provide an additional argument to pursue treat-to-target in AS/axial spondyloarthritis (SpA), in accordance with what has recently been proposed.

Having established the relationship between disease activity and radiographic progression, we were then particularly interested in identifying factors that may influence this relationship. First, we have demonstrated that this relationship was more pronounced in men and in patients with shorter symptom duration (less than the median of 18 years): While an increase of one ASDAS unit led to an increase of 0.98 mSASSS units/2 years in men, it did not measurably affect 2 year progression in women. Progression rates in women were particularly low, which may reflect a minimal progression in this group of patients but also a more unstable regression coefficient because the group of women was small. Similarly, in patients with shorter symptom duration (< 18 years) an increase of one ASDAS unit led to an increase of 0.84 mSASSS units/2 years, compared to only 0.16 mSASSS units/2 years in patients with longer symptom duration: It looks as if the detrimental effects of inflammation on radiographic progression extinguishes over time, a finding that may not be unexpected to experienced clinicians.

Although disease activity undoubtedly leads to radiographic progression, it should be emphasized that an important part of radiographic progression occurs in patients without any measurable disease activity (chapter 9). This underlines that syndesmophyte formation in AS is still not yet a fully explained process. One of the still unknown contributory factors to explaining radiographic progression is mechanical stress. Mechanical forces may also have a role in osteophyte formation in osteoarthritis. The OASIS cohort allowed us to further investigate the contribution of work-related mechanical forces in explaining radiographic damage since information on paid work has been collected routinely (chapter 10). In this study we have taken ‘job type’ (a physically demanding job versus a more sedentary job) as a proxy for ‘life-time mechanical stress’. Several confounding factors, such as smoking and socio-economic status, were taken into account. The longitudinal model described in chapter 9 was used as the template for the analysis. In chapter 10, we have shown that long-term physically demanding activities, operationalized as ‘physically demanding (‘blue collar’) job type amplified the detrimental effects of disease activity on radiographic progression, in comparison with a more sedentary (‘white collar’) job type: In ‘blue-collar’ workers versus
‘white collar’ workers every additional unit of ASDAS resulted in an increase of 1.2 vs. 0.2 mSASSS units/2 years (p=0.014 for the difference). These findings are in support of recent observations in animal models, showing that ‘mechanical strain’ leads to new bone formation. However, similar effects on the relationship between disease activity and radiographic progression were found for smokers and for patients with a lower socio-economic status (mainly measured as lower personal income). In a subsequent analysis we have tried to disentangle the effects of ‘job type’ and ‘smoking’ by analysis in relevant subgroups: In the subgroup of smokers, there was slightly (but not significantly) more effect of ASDAS on progression in ‘blue collar’ workers (1.5 mSASSS units 2 year progression per ASDAS unit) than in ‘white collar’ workers (1.2 mSASSS units). In the subgroup of non-smokers, ‘blue collar’ workers had a 2 year progression of 0.6 mSASSS units per ASDAS unit, but the model did not provide a final solution for ‘white collar’ workers (too few remaining patients and too little progression). So this study cannot provide final resolution and larger studies are needed. It may be that smoking and socio-economic status should be considered as confounders of a relationship that includes the relevance of mechanical forces rather than as (pathophysiological) determinants themselves. The main reason for this is ‘biological plausibility’. It is well known that ‘blue collar’ workers are more frequently smokers than ‘white collar’ workers and that ‘blue collar’ workers have on average a lower income than ‘white collar’ workers (and our findings were consistent with this).

Implications of findings and a perspective on future research

In the studies described in this thesis a lot of focus has been laid on two important themes in the broader field of axial SpA:

1. The assessment and interpretation of spinal mobility in AS

2. The link of inflammation and inappropriate bone formation in AS

Both themes will be discussed below with regard to their impact on future research in the broader field of axial SpA. Of importance here is that our main observations pertain to patients with AS, but that recent research has focused more on patients with axial SpA, that includes AS but is not synonymous. The assumption –that will be on the research agenda for many aspects of the disease anyway– here is that findings in AS can be generalised to the entire field of axial SpA.

1. The value of spinal mobility assessment

Historically, spinal mobility has always been a very appealing topic in the field of AS, likely because it could be measured in so many different manners, including so many different parts of the spine. But ‘multitude’ is not necessarily an advantage. Many of the proposed
spinal mobility measures lack sufficient inter-reader reliability; we do not know if spinal mobility measures can be used to monitor within-patient change; until recently, we did not know about spinal mobility in the ‘normal population’; a multitude of available assessments invites to pick out the most convenient one, and so on.

Apart from these metric characteristics of spinal mobility assessments, there is a fundamental flaw in the available knowledge regarding ‘truth aspects’ of measurements. Do they really measure what they intend to measure, and are impairments truly relevant with regard to long-term outcome? Do changes in the level of impairment, eg. induced by medicines, truly reflect an improvement in health?

It is this type of questions that deserve attention in the research of patients with axial SpA. Now we slowly deviate from the narrow disease AS towards the broader disease axial SpA, and tend to pick up patients far earlier than before, due to improved classification and diagnosis, we will find more and more patients with still normal spinal mobility measures. Using the MOBILITY-based normal values, we are better suited to follow-up these patients with regard to spinal mobility, determine if the occurrence or worsening of spinal mobility impairment has clinical relevance in axial-SpA patients, find out if treatment-induced change is also clinically relevant, and so on.

May be more important, even, is to expand on the observations made in OASIS suggesting to us that there is a strict order in the measures that get consecutively impaired. Careful prospective analysis of existing cohorts with patients with axial SpA with short symptom duration will inform us if this order in AS extends to axial SpA. That is important information not only from a clinical perspective but also in order to guide pathophysiological research and research on imaging: One may hypothesize that the order in which measurements ‘fall out’ has implications for the determination of the most promising site of interest in pathophysiological research, and in this way ‘simple assessment’ of spinal mobility may guide basic scientific research in axial SpA.

On a second note, it would be wise to seek consensus about which measures should be used in busy clinical practice, but also in research studies, in order to optimally make use of the limited time. It may even be possible to design a better index for measuring spinal mobility impairment.

2. Inflammation and syndesmophyte formation
The link we have proven in this thesis between inflammation and structural progression has clearly filled an unexplained lacuna in our knowledge about the consequences of inflammatory process in AS. This link is close to ‘dogmatic’ in chronic inflammatory
rheumatology: No-one ever disputes the statement that inflammation leads to radiographic progression in diseases such as rheumatoid arthritis (RA) and psoriatic arthritis. While there is ample pathophysiological argument to explain an absence of such a relationship in AS (eg. radiographic progression is bone formation rather than bone destruction) many clinical investigators will feel ‘reassured’ that a disease like AS also behaves like a classic inflammatory rheumatic disease. But not only that: The proof of such a connection opens up the gate again to further investigate the effects of profound suppressors of inflammation on syndesmophyte formation. Fortunately, we have those ‘suppressors’ available for research, but classic trials in AS have shown that TNFi-drugs do not measurably inhibit 2 year radiographic progression. The question that awaits resolution is whether ‘no effect on progression’ is simply true, or whether a methodological ‘deficit’ is at the basis of this finding.

In our attempts to clarify a link between inflammation and radiographic progression we have developed a longitudinal model for analysis that can perfectly serve as a template to further investigate this link in patients with axial SpA and potentially to investigate the effects of drugs on this link. Like we have found ‘job type’ (blue collar work vs white collar work) to be of influence on the longitudinal relation between disease activity and radiographic progression, we could also investigate the longitudinal effects of medicines (such as non-steroidal anti-inflammatory drugs (NSAIDs) or TNFi or non-TNFi biologicals) on this relationship. What we need for that is a sufficiently long follow-up (eg. 10 years or more) and repeated measurements of structural abnormalities.

This analytical template is unprecedented in many ways. First, it has allowed us to investigate the contributory role of ‘mechanical forces’ on the relationship between disease activity and syndesmophyte formation, but also of other, at first glance unrelated, factors such as smoking and socio-economic factors. Apparently, the analytical model that we have developed works! The contributory role of ‘mechanical forces’, in our studies approximated by ‘job type’, sets the stage for in-depth research into the pathophysiological mechanisms behind syndesmophyte formation. Does syndesmophyte formation indeed resemble osteophyte formation in osteoarthritis? To what extent is the pathophysiology of osteoarthritis the same as that of axial SpA? Is syndesmophyte formation indeed an inappropriate reaction of the vertebral bodies to mechanical stress?

But such a complicated association may also have implications for clinical practice: Since decennia we have recommended patients with AS to intensively perform regular exercises, in order to improve or maintain mobility. If true, the proven associations between disease activity, mechanical forces and radiographic progression may result exactly into what doctors try to avoid: Development of structural damage. Careful analysis in well-designed cohorts with meticulous follow-up will have to give resolution.
Second, the template we have proposed may serve to disentangle complex pathophysiological relationships that have an epidemiological basis. The best example is the effect we have established for ‘smoking’ being an effect modifier of the relationship between disease activity and radiographic progression. This effect was similar to the effect of ‘job type’. But insufficient statistical power prevented us from investigating into detail which factor is truly important: Mechanical forces, smoking or both? Obviously, these factors are not independent: Patients with a ‘blue collar’ job type more often have a smoking history, and the same is true for ‘socioeconomic status’. We should not forget that ‘socioeconomic status’ is a determinant of many important predictive relationships in rheumatology. May be the truth is that ‘socioeconomic status’ is a reflection of some other biologically more plausible factor that awaits careful analysis to be disentangled from its confounders.

Third, the longitudinal model we have developed out of necessity to prove a subtle relationship in a disease with very slow progression may have value in other inflammatory disease in- and outside rheumatology. Usually, prediction models have been relatively simple coupling a ‘baseline factor’ (such as disease activity) to subsequent radiographic progression. Such models suffice if this relationship is rather strong, as for disease activity vs. radiographic progression in RA. Sometimes, though, it may prevent investigators from factoring-in sufficient ‘detail’: The observation that ‘mechanical forces’ modify the relationship between disease activity and radiographic progression in AS has important implications for the pathophysiology. Here, ‘confounding’ and effect modification lose their negative connotations, and open up interesting new angles. In analogy, the application of our analytical template in cohorts of patients with RA, undifferentiated arthritis or ‘pre-RA’ may help unraveling important pathophysiological mechanisms. We will work out one potentially relevant example.

Suppose, the question to be addressed is if the presence of a certain genetic polymorphism predisposes to a ‘bad outcome’ defined as radiographic progression above a certain level in patients presenting with undifferentiated arthritis (UA). Usually, one investigates the presence vs the absence of such a factor with regard to a relevant outcome in a large cohort of patients with UA using logistic regression that allows adjusting for multiple factors that may also influence that outcome. Such an analysis is only successful if the contribution of the genetic factor is very ‘strong’, which is hardly if ever the case in this type of research.

In the analytical template we have proposed here, we would make use of prior knowledge establishing the relationship between disease activity and radiographic progression. We would establish that relationship in a longitudinal cohort preferably including multiple coupled observations of disease activity and radiographic damage per patient. In such a set-up we would investigate the interaction between disease activity and the genetic factor on
radiographic progression rather than the influence of the genetic factor itself on radiographic progression (with or without adjustment for disease activity).

Such a set-up implies a paradigm-shift in predictive research of chronic diseases. But in our experience this approach is far more suitable to find subtle but relevant predictors in an arena in which appropriate treatment will prevent you to study the natural outcome of disease and its predictors.

In summary, the studies reported in this thesis have emphasized two important themes: 1) the value of spinal mobility assessment; and 2) the relevance and implications of the established link between inflammation and syndesmophyte formation in AS.

We have described here how these findings may affect our current thinking about the pathophysiology and clinical care of patients with axial SpA, and how they may provide guidance to future clinical epidemiological and pathophysiological studies in the field of axial SpA.
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