Chapter 1

General Introduction

GENERAL INTRODUCTION

Background

Spondyloarthritis (SpA) is a heterogeneous disease that can either have a predominantly axial (cardinal manifestation: chronic back pain) or a predominantly peripheral (cardinal manifestation(s): arthritis, enthesitis or dactylitis) phenotype. The range of clinical features of SpA is broad and includes chronic (typically inflammatory) back pain, arthritis, enthesitis, dactylitis, as well as extra-articular manifestations such as psoriasis, uveitis and inflammatory bowel disease.[1]

Susceptibility to SpA is largely genetically determined, and its heritability has been estimated to be as high as 90%.[2] The disease is strongly linked to the Human Leukocyte Antigen B27 (HLA-B27), with HLA-B27 explaining 30-50% of the overall genetic risk. However, the influence of HLA-B27 on disease phenotype is controversial, with conflicting results published in the literature.[3,4] The contribution of environmental factors to the disease phenotype remains poorly characterised, with limited data published on dietary habits,[5] enteric and upper respiratory tract infections,[6,7] and cigarette smoking,[8] at the time the work presented in this thesis was developed. Therefore, the influence of genetic factors, such as HLA-B27, and environmental factors, such as smoking, on the phenotype and outcome of patients with axial SpA warranted further research.

In the last few years there has been a remarkable progress in our understanding of SpA among which the development and validation of classification criteria for axial and peripheral SpA by an international group of experts in the field, the Assessment of SpondyloArthritis international Society (ASAS), is probably the most eye-catching. Axial SpA can be further divided into radiographic (ie. ankylosing spondylitis [AS]) and non-radiographic axial SpA. This new classification approach has the advantage of better describing the disease, allowing an earlier identification and treatment of the disease and potentially leading to improved health outcomes.[9,10]

The development of validated tools (table 1) for measuring patient outcome has been a major contribution of ASAS to the field of axial SpA. These tools have stimulated clinical research in axial SpA and contributed to the success of a large number of drug development programmes and drug registration programmes.[11] Despite these remarkable developments, the way the various health outcomes in axial SpA relate to each other is still a matter of debate. The development of new methods of assessment, such as magnetic resonance imaging (MRI), which is capable of detecting acute and chronic lesions of the spine and the sacroiliac joints,[12-14] added more complexity to these relationships. Better understanding of the relationships between health outcomes in axial SpA, including imaging outcomes (those related to radiographic and MRI assessments, such as the development of syndesmophytes and MRI lesions), would result in better understanding of the disease and of the assessment

tools that are available for use in clinical practice and research studies.

Table 1. Assessment of SpondyloArthritis international Society (ASAS) core sets[10,11]

Domain	Instrument	For SMARD and PT	For CRK	For DCART
Function	BASFI	X	X	X
Pain	NRS/VAS (spine, at night, last week, due to AS) NRS/VAS (spine, last week, due to AS)	X	X	X
Spinal mobility	Chest expansion, modified Schober, occiput to wall distance, cervical rotation, lateral spinal flexion or BASMI	X	X	X
Patient global	NRS/VAS* (global disease activity, last week)	X	X	X
Stiffness	NRS/VAS* (spine, duration of morning stiffness, last week)	X	X	X
Fatigue	Fatigue question of BASDAI (NRS/VAS*)	X	X	X
Peripheral joints and entheses	Number of swollen joints (44-joint count) Validated entheses score		X	X
Acute phase reactants	CRP or ESR		X	X
Radiographs of the spine	Lateral lumbar and cervical spine			X

*ASAS prefers the use of a NRS. AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRK, clinical record keeping; CRP, C-reactive protein; DCART, disease-controlling anti-rheumatic treatments; ESR, erythrocyte sedimentation rate; NRS, numerical rating scale (0–10); PT, physical therapy; SMARD, symptom modifying anti-rheumatic drugs; VAS, visual analogue scale (0–10cm).

The ASAS core set of domains and instruments to assess and monitor patients with axial SpA includes several disease activity measures (table 1). In addition to the core set tools a composite index named the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has been extensively used to assess disease activity in axial SpA.[15] BASDAI combines six individual variables (fatigue, axial pain, joint pain and swelling, tender areas, intensity and duration of morning stiffness) into one single score and is a fully patient-oriented measure. However, it is well-described that patients and physicians have different perspectives about disease activity in axial SpA.[16] For example, patients may give more value to subjective symptoms like pain and fatigue, while physicians may give more value to objective signs like the number of swollen joints or to laboratory findings like the presence of elevated acute phase reactants. Therefore the correlation between patient and physician global assessments of disease activity is typically weak in axial SpA and the same applies to the correlation between BASDAI and physician global assessment.[16] Furthermore, BASDAI lacks specificity for inflammatory disease processes and does not take the redundancy and dependence of individual variables

Table 2. Measures of disease activity in axial spondyloarthritis

Instrument	Questions and calculation rules
BASDAI[15]	How would you describe the overall level of fatigue/tiredness you have experienced? How would you describe the overall level of AS neck, back or hip pain you have had? How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had? How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? How would you describe the overall level of morning stiffness you have had from the time you wake up? How long does your morning stiffness last from the time you wake up? Calculation: ((Q1 + Q2 + Q3 + Q4) + (Q5 + Q6) ÷ 2) ÷ 5
BAS-G[23]	Please place a mark on the scale below to indicate the effect your disease has had on your well-being over the last week. Please place a mark on the scale below to indicate the effect your disease has had on your well-being over the last six months. Calculation: Each question represents a different timeframe and should be interpreted individually.
Spinal pain[10]	On average, last week, how much pain of your spine due to AS did you have? On average, last week, how much pain of your spine due to AS did you have at night? Calculation: Each question is usually interpreted individually.
Mini-BASDAI[18]	How would you describe the overall level of fatigue/tiredness you have experienced? How would you describe the overall level of AS neck, back or hip pain you have had? How would you describe the overall level of morning stiffness you have had from the time you wake up? How long does your morning stiffness last from the time you wake up? Calculation: ((Q1 + Q2) + (Q3 + Q4) ÷ 2) ÷ 3
ASDAS[20]	How would you describe the overall level of AS neck, back or hip pain you have had? How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had? How would you describe the overall level of morning stiffness you have had from the time you wake up? How active was your spondylitis on average during the last week? C-reactive protein level (mg/L) or erythrocyte sedimentation rate level (mm/h) Calculation ASDAS-CRP: 0.12 x Q1 + 0.07 x Q2 + 0.06 x Q3 + 0.11 x Q4 + 0.58 x Ln(CRP+1) Calculation ASDAS-ESR: 0.08 x Q1 + 0.09 x Q2 + 0.07 x Q3 + 0.11 x Q4 + 0.29 x √(ESR)

BASDAI questions relate to the past week, response is either on a 0-10 NRS or on 0-10cm VAS, from 'none' to 'very severe', except for the duration of morning stiffness in which the anchors are 'zero hours' and '2 or more hours'. The same applies to mini-BASDAI and ASDAS questions extracted from the BASDAI. The anchors for the spinal pain questions are 'no pain' and 'most severe pain'. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BAS-G, Bath Ankylosing Spondylitis Patient Global Score; NRS, numerical rating scale; VAS, visual analogue scale; √(ESR), square root of the erythrocyte sedimentation rate (mm/h); Ln(CRP+1), natural logarithm of the C-reactive protein (mg/L) + 1.

into account. A modified version of the BASDAI (mini-BASDAI) without the questions about tender areas and joint pain/swelling has also been tested and did not perform better than the BASDAI.[17,18] BASDAI, mini-BASDAI, Bath Ankylosing Spondylitis Patient Global Score (BAS-G), spinal pain and ASDAS questions and calculation rules are presented in table 2.[10,19]

BASDAI has served the SpA community well for many years but its limitations led the ASAS group to develop a new composite measure for disease activity in axial SpA: the Ankylosing Spondylitis Disease Activity Score (ASDAS).[20,21] After this initial step, further validation and the development of clinically relevant cut-offs for the ASDAS became an important item on the axial SpA research agenda.

MRI has gained increasing importance over the last few years in the field of axial SpA due to its ability to show acute and chronic lesions that relate to axial SpA disease processes. Acute (inflammatory) lesions on MRI are best visualised by a short tau inversion recovery (STIR) sequence (bone oedema) or by a T1 post-gadolinium sequence (osteitis), while chronic lesions (fatty deposition/fat metaplasia, erosions, syndesmophytes and ankylosis) are best visualised by a T1-weighted turbo spin-echo sequence (Figure 1 and 2).[10,14] The recent MRI literature in axial SpA has focused on various disease aspects, namely the role of MRI for improved diagnosis, assessment of treatment effects, and predicting structural progression in patients with axial SpA.[22] New bone formation is a key feature of axial SpA that at the spinal level is represented by syndesmophyte formation/bridging, a type of lesion that is best seen on conventional radiographs. The possible association between MRI lesions of inflammation and fat metaplasia in the spine in relation to syndesmophyte formation/bridging (progression of structural damage) has emerged as one of the most intriguing and challenging research questions in the modern era of axial SpA.

Aims of this thesis

The work presented in this thesis has four objectives:

1. To improve and facilitate the assessment of disease activity in axial SpA using the ASDAS.
2. To increase our knowledge about the mutual relationships between health outcomes in axial SpA.
3. To increase our knowledge about the factors that influence phenotypic variability in axial SpA.
4. To clarify the relationship between MRI lesions and radiographic progression in axial SpA.

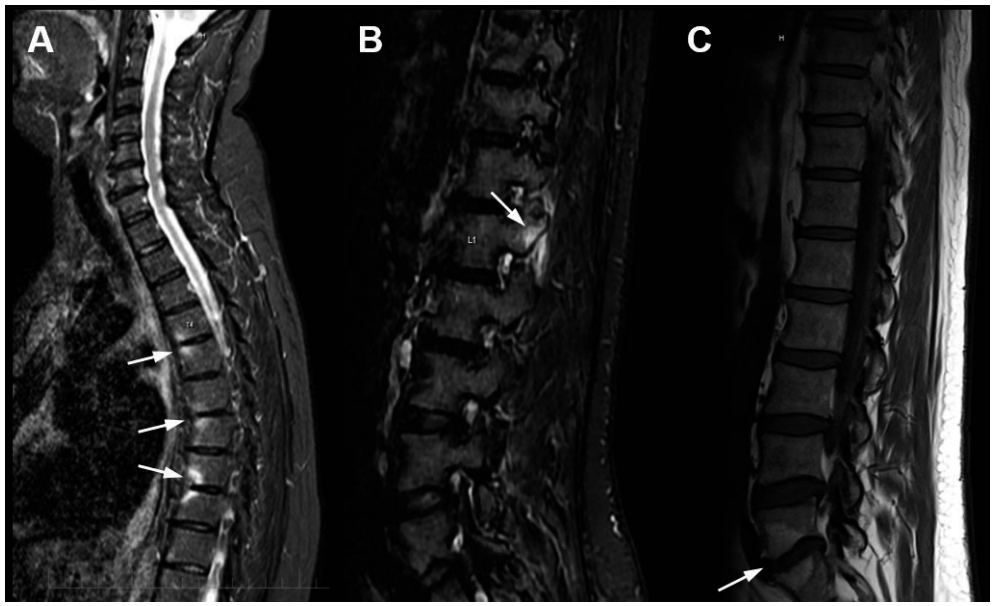

Figure 1. Anterior spondylitis (1A), STIR image showing corner bone marrow oedema at T4/5, T6/7 and T8/9. Arthritis of the zygoapophyseal joints (1B), STIR image showing inflamed facet joints at L1/2. Fatty deposition (1C), T1 image showing high signal intensity due to fatty deposition at L5/S1 anterior vertebral corners.[24]

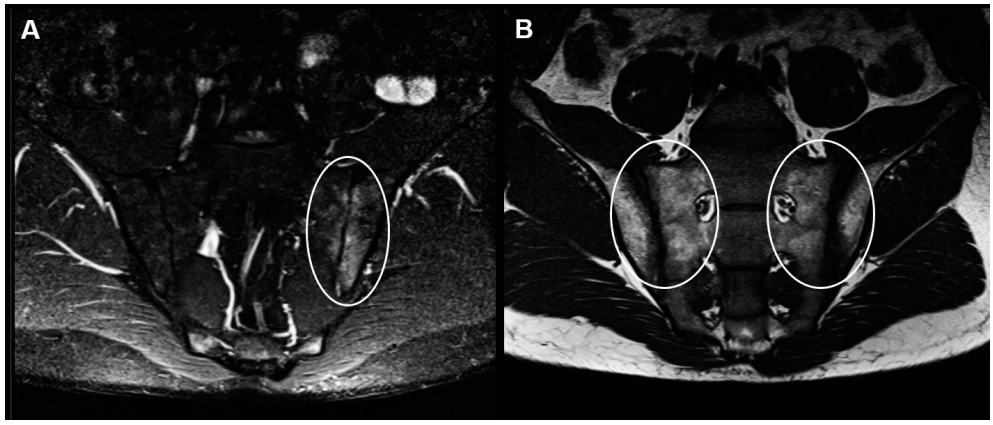

Figure 2. Left sacroiliitis (bone marrow oedema) in a patient with non-radiographic axial spondyloarthritis (2A), affected bone marrow areas (oval line) are located periarticularly (STIR). Fatty deposition in the same patient (2B), T1 image showing high signal intensity due to fatty deposition (oval lines) at both sacroiliac joints.[24]

This thesis focuses on the axial SpA subgroup, mainly on patients with AS. Three cohorts of patients have been studied:

1. The AS Study for the Evaluation of Recombinant infliximab Therapy (ASSERT) cohort[25]: ASSERT was a 24-week randomized controlled trial comparing infliximab monotherapy and placebo in patients with active AS, with an open extension until 102 weeks with all patients on infliximab. The ASSERT population includes patients with AS according to the modified New York criteria[26] with a BASDAI[15] and a spinal pain score ≥4 (range 0–10). Data from the ASSERT cohort is presented in **chapters 2, 4, 5, 6, 9, 10 and 11.**
2. The Norwegian Disease Modifying Anti-Rheumatic Drug (NOR-DMARD)[27] cohort: NOR-DMARD is a Norwegian register from 5 centers that includes consecutive patients with axial SpA (according to the treating rheumatologist) starting a new synthetic or biological DMARD regimen. Patients from the NOR-DMARD register are considered an appropriate representation of patients with axial SpA as seen by rheumatologists in Norway. Data from the NOR-DMARD cohort is presented in **chapter 2**.
3. The *Devenir des Spondyloarthropathies Indifférenciées Récentes* (DESIR) cohort[28]: DESIR is a longitudinal prospective cohort that includes adults aged over 18 and less than 50 years from 25 regional centers in France. Patients are required to have inflammatory back pain fulfilling either the Calin or Berlin criteria[29,30] with symptom duration more than 3 months and less than 3 years and symptoms suggestive of SpA according to the opinion of the local investigator. Data from the DESIR cohort is presented in **chapters 3, 7 and 8.**

Assessment of disease activity in axial SpA using the ASDAS

Due to the phenotypic heterogeneity of axial SpA and the possibility of the coexistence of several clinical manifestations, the use of single variables for disease activity assessment may lead to misrepresentation of disease activity. This is why composite indices can be useful tools for disease activity assessment in axial SpA. Composite scores integrate several different aspects of disease activity into one single numerical value, resulting in a more precise estimate of the construct 'disease activity' in comparison to the single variables of the composite score. Indices may also have the advantage of increased statistical power in clinical trials and observational studies. Furthermore, they improve the consistency of patient assessment and care across different clinical and research settings, and may help patients and doctors better understand the disease and its impact.[19,31-34]

The BASDAI has been the most widely used disease activity composite index in axial SpA.[15] However, it has limitations as mentioned above. The ASDAS is an algorithm that

combines elements of the BASDAI and patient global assessment with a laboratory measure of inflammation, either the C-reactive protein (CRP) level (preferred formula) or the erythrocyte sedimentation rate (ESR) (alternative formula).[20,21] The inclusion of an acute phase reactant in the ASDAS formula brings an objective component into the score. Moreover, ASDAS variables have different weights that take potential redundancy and dependency of variables into account, as a result of the statistical methods used to develop it (principal component analysis and discriminant function analysis).

The ASDAS has been developed by ASAS and several aspects of the truth, feasibility and discrimination of the score had already been tested when the work described in this thesis started.[20,21] However, clinically relevant cut-off values for disease activity states and response criteria using the ASDAS were still lacking. Such cut-offs are crucial to improve the interpretability and the clinical applicability of a continuous measure. The development of appropriate ASDAS cut-offs for disease activity states and response criteria and its validation in an independent dataset are described in **Chapter 2**.

ASDAS was developed and validated making use of conventional CRP (cCRP) tests. Lately, cCRP tests have increasingly been replaced by so-called high sensitivity (hs) CRP tests, both in clinical practice and in the research setting. However, it was unclear how differences between cCRP tests (with high detection limit) and hsCRP tests (with low detection limit) worked out with regards to the performance of the ASDAS. In **Chapter 3,** detailed analyses of how the ASDAS-CRP formula performs, of how low CRP values obtained by hsCRP influence the ASDAS-CRP, and of the agreement between different ASDAS formulae and imputation strategies, are presented. In addition, we have also determined the best way to calculate ASDAS-CRP when the cCRP level is below the limit of detection.

Knowledge about the mutual relationships between health outcomes in axial SpA

Measuring and monitoring health outcomes is of paramount importance in rheumatology and in medicine in general. Yet, quantifying health outcomes is a complex and challenging process. As mentioned above, the ASAS group has proposed several instruments to assess health outcomes in axial SpA.[11] These instruments cover distinct domains and are subdivided into core sets to be applied in different settings (table 1). These core sets include measures of physical function,[35] spinal mobility,[36] radiographic damage,[37,38] and several disease activity variables such as the assessment of spinal pain, patient global assessment of disease activity, the number of swollen joints, an enthesitis count, the duration of morning stiffness, the level of fatigue and acute phase reactants. Composite indices for measuring disease activity[19,33] and instruments to measure the level of MRI inflammation have also been developed for the assessment of axial SpA.[39,40] Understanding how health outcomes relate to each other in axial SpA and fit in a framework that allows their interpretation in a structured and integrated manner

would help to better understand the disease and the tools that we use to assess and monitor it.

Progressive limitation of spinal mobility is a hallmark of axial SpA and a predictor of poor long-term outcome. In **Chapter 4** we studied the determinants of limitation of spinal mobility in a large cohort of AS patients. An important novel aspect of this study was the inclusion of MRI spinal inflammation as one of the assessments/measures. Taking into account the possibility that spinal (MRI) inflammation may be an important and potentially reversible factor determining spinal mobility, we investigated the relationship between spinal mobility, radiographic damage of the spine and MRI spinal inflammation in patients with AS. This analysis was the starting point for further analyses looking at a broader spectrum of health outcomes. In **Chapter 5**, using a conceptual framework shared between several chronic diseases,[41,42] we investigated the relationship between health-related quality of life, physical function, clinical disease activity, spinal mobility and structural damage in detail and proposed a stratified model for health outcomes in AS.

MRI is currently considered a powerful tool to document treatment effects and the inflammatory burden of the disease; however, studies looking at the relationship between MRI inflammation scores and clinical and laboratorial disease activity assessments were scarce. In **Chapter 6**, using clinical and imaging cross-sectional and longitudinal data, we investigated the relationship between MRI inflammation and measures of clinical disease activity as well as treatment responses in patients with AS treated with a tumour necrosis factor alpha (TNF) blocker.

Knowledge about the factors that influence phenotypic variability in axial SpA

As mentioned above, the influence of HLA-B27 on the phenotype of axial SpA is controversial.[3,4] Furthermore, the contribution of HLA-B27 to the diagnosis, prognosis and management of axial SpA had previously been investigated mainly in AS but not in non-radiographic axial SpA. In **Chapter 7** we have analysed a cohort of patients with early axial SpA consisting of mainly patients with the non-radiographic form of the disease and investigated the contribution of HLA-B27 to phenotypic variability.

In addition to genetic factors, environmental factors may contribute to phenotypic variability. For example, in rheumatoid arthritis, smoking has reproducibly been linked to an increased risk of developing the disease and a gene-environment interaction between smoking and HLA-DRB1 shared epitope alleles´ has been described in several cohorts. This gene-environment interaction was only demonstrated in anti-citrullinated peptide antibody (ACPA)-positive and not in ACPA-negative disease, indicating that smoking may contribute to the pathway that is associated with ACPA-positive rheumatoid arthritis.[43,44]

Information on smoking influencing the outcome of axial SpA was scarce and the hypothesis that smoking could impact the outcome of patients with axial SpA had just been launched when the analyses reported in **Chapter 8** were published. This study aimed to determine the prevalence of smoking and its association with various clinical, functional and imaging outcomes in early axial SpA, including potential gene-environment interactions such as the interaction between smoking and HLA-B27 positivity.

Extra-articular manifestations belong to the typical picture of axial SpA, help the physician to recognize the disease and make a diagnosis, and may determine the prognosis and influence health outcomes in axial SpA. In **Chapter 9** we have focused on one extra-articular manifestation in particular - psoriasis. The main reason for doing that was that there had been few studies assessing the differences between axial SpA patients with and without concomitant psoriasis, and in this chapter we compared demographic, clinical and imaging characteristics between AS patients with and without this extra-articular manifestation.

Relationship between MRI lesions and radiographic progression in axial SpA

Structural damage in axial SpA is characterised by excessive bone formation, with syndesmophytes being the typical lesions.[45,46] The processes driving syndesmophyte formation are not completely understood.[47,48] One theory postulates that inflammation and osteoproliferation are related, and that initially, inflammation triggered by unknown stimuli (eg. mechanical stress or infectious agents) drives a bone catabolic process where the Wnt pathway and dickkopf-1 (Dkk-1) upregulation play a prominent role; later on, as inflammation fluctuates and is intermittently dampened, the bone catabolic process may give rise to a bone anabolic response characterized by reactive osteoproliferation.[49,50] Another theory suggests that inflammation and repair are unrelated phenomena and that the same triggers can independently activate inflammatory and stromal cells, with the activation of stromal cells leading to endochondral bone formation.[51] If inflammation is indeed the principal trigger of repair responses, a strong case can be made for early and/or prolonged anti-inflammatory treatment, namely with TNF-blockers. On the other hand, if inflammation and repair are independent pathways triggered by common factors, specific therapies targeting stromal pathways may be needed to prevent new bone formation in AS.

MRI provides an indirect and non-invasive method of investigating elements of the pathophysiology of new bone formation in AS. Fat deposition can be seen on T1-weighted sequences and bone marrow edema (reflecting inflammation) can be seen on T2-weighted sequences with fat suppression, such as the STIR sequence.[13,52,53] However, conventional radiography is still the gold-standard method to assess syndesmophyte formation/bridging[54] because tissues with low proton density such as cortical bone and paravertebral ligaments exhibit low or no signal intensity in all pulse sequences and are

difficult to differentiate on MRI scans.[55]

Understanding the axial SpA pathophysiological processes and elucidating the relationship between MRI lesions (particularly bone marrow oedema/osteitis - which is an inflammatory lesion - and fat deposition – which is a chronic lesion) and new bone formation have attracted much attention from the SpA scientific community. There is a large debate about whether stopping structural progression in axial SpA is therapeutically possible.[47,48]

In **Chapter 10**, we have initially investigated the relationship between inflammation on MRI and the formation/growth of syndesmophytes. We did so by looking at inflammation at the vertebral unit level and at the patient level and investigating its potential contribution to new bone formation in patients with AS treated with a TNF-blocker. This analysis was prompted by the results of two previous smaller studies showing an association between MRI inflammation and new bone formation in AS.[56,57] Subsequently, one additional study addressing this topic showed consistent results with previous publications.[58] After the publication of these 4 studies, advancing insight pointed to the potential importance of fat deposition in the sequel of inflammation and syndesmophyte formation.[59-61] We therefore decided to re-read all MRIs of the patients in the ASSERT study and to do a far more detailed assessment in order to be able to investigate the role of fatty lesions in this process. We scored all the ASSERT images at the vertebral corner level according to the presence or absence of MRI inflammation as well as fat deposition. In **Chapter 11,** we have analysed multiple combinations of MRI lesions at three different time points, including a sequence analysis, specifically addressing the hypothesis that vertebral corner inflammation could contribute to fat deposition which in turn could contribute to new bone formation.

A summary and general discussion about the findings of this thesis is presented in **Chapter 12**. A summary of this thesis in Dutch is provided in **Chapter 13**.

REFERENCES

1. Machado P, Landewé R, van der Heijde D. New developments in the diagnosis and treatment of axial spondyloarthritis. Clinical Investigation 2013;3:153-71.
2. Breban M, Miceli-Richard C, Zinovieva E, Monnet D, Said-Nahal R. The genetics of spondyloarthropathies. Joint Bone Spine 2006;73:355-62.
3. Khan MA, Kushner I, Braun WE. Comparison of clinical features in HLA-B27 positive and negative patients with ankylosing spondylitis. Arthritis Rheum 1977;20:909-12.
4. Linssen A. B27+ disease versus B27- disease. Scand J Rheumatol Suppl 1990;87:111-8; discussion 8-9.
5. Claudepierre P, Sibilia J, Roudot-Thoraval F, et al. Factors linked to disease activity in a French cohort of patients with spondyloarthropathy. J Rheumatol 1998;25:1927-31.
6. Rihl M, Klos A, Kohler L, Kuipers JG. Infection and musculoskeletal conditions: Reactive arthritis. Best Pract Res Clin Rheumatol 2006;20:1119-37.
7. Martinez A, Pacheco-Tena C, Vazquez-Mellado J, Burgos-Vargas R. Relationship between disease activity and infection in patients with spondyloarthropathies. Ann Rheum Dis 2004;63:1338-40.
8. Averns HL, Oxtoby J, Taylor HG, Jones PW, Dziedzic K, Dawes PT. Smoking and outcome in ankylosing spondylitis. Scand J Rheumatol 1996;25:138-42.
9. Rudwaleit M, van der Heijde D, Landewe R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70:25-31.
10. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl 2:ii1-44.
11. van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessments in Ankylosing Spondylitis. J Rheumatol 1999;26:951-4.
12. Lambert RG, Bakker PA, van der Heijde D, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. Ann Rheum Dis 2016.
13. Hermann KG, Baraliakos X, van der Heijde DM, et al. Descriptions of spinal MRI lesions and definition of a positive MRI of the spine in axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI study group. Ann Rheum Dis 2012;71:1278-88.
14. Rudwaleit M, Jurik AG, Hermann KG, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis 2009;68:1520-7.
15. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
16. Spoorenberg A, van Tubergen A, Landewe R, et al. Measuring disease activity in ankylosing spondylitis: patient and physician have different perspectives. Rheumatology (Oxford) 2005;44:789-95.
17. Heuft-Dorenbosch L, van Tubergen A, Spoorenberg A, et al. The influence of peripheral arthritis on disease activity in ankylosing spondylitis patients as measured with the Bath Ankylosing Spondylitis Disease Activity Index. Arthritis Rheum 2004;51:154-9.
18. Song IH, Rudwaleit M, Listing J, Sieper J. Comparison of the Bath Ankylosing Spondylitis Disease Activity Index and a modified version of the index in assessing disease activity in patients with ankylosing spondylitis without peripheral manifestations. Ann Rheum Dis 2009;68:1701-7.
19. Machado PM, Raychaudhuri SP. Disease activity measurements and monitoring in psoriatic arthritis and axial spondyloarthritis. Best Pract Res Clin Rheumatol 2014;28:711-28.
20. Lukas C, Landewe R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18-24.
21. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811-8.
22. Pedersen SJ, Maksymowych WP. Recent Advances in Imaging of the Axial Skeleton in Spondyloarthritis for Diagnosis, Assessment of Treatment Effect, and Prognostication. Curr Rheumatol Rep 2015;17:60.
23. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol 1996;35:66-71.
24. Boyesen P, Machado P. Measuring Disease Activity and Damage in Arthritis (Chapter 44). In:

Bijlsma JWJ, Hachulla E, eds. EULAR Textbook on Rheumatic Diseases. London, UK: BMJ Publishing Group Ltd; 2015.

25. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582-91.
26. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
27. Kvien TK, Heiberg, Lie E, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol 2005;23:S188-94.
28. Dougados M, d'Agostino MA, Benessiano J, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. Joint Bone Spine 2011;78:598-603.
29. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. JAMA 1977;237:2613-4.
30. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum 2006;54:569-78.
31. Tugwell P, Bombardier C. A methodologic framework for developing and selecting endpoints in clinical trials. J Rheumatol 1982;9:758-62.
32. van der Heijde DM, van't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177-81.
33. Machado P, van der Heijde D. How to measure disease activity in axial spondyloarthritis? Curr Opin Rheumatol 2011;23:339-45.
34. Machado PM, Landewe RB, van der Heijde DM. Endorsement of definitions of disease activity states and improvement scores for the Ankylosing Spondylitis Disease Activity Score: results from OMERACT 10. J Rheumatol 2011;38:1502-6.
35. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
36. van der Heijde D, Landewe R, Feldtkeller E. Proposal of a linear definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and comparison with the 2-step and 10-step definitions. Ann Rheum Dis 2008;67:489-93.
37. Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64:127-9.
38. van der Heijde D, Landewe R. Selection of a method for scoring radiographs for ankylosing spondylitis clinical trials, by the Assessment in Ankylosing Spondylitis Working Group and OMERACT. J Rheumatol 2005;32:2048-9.
39. Lukas C, Braun J, van der Heijde D, et al. Scoring inflammatory activity of the spine by magnetic resonance imaging in ankylosing spondylitis: a multireader experiment. The Journal of rheumatology 2007;34:862-70.
40. van der Heijde D, Landewe R, Hermann KG, et al. Is there a preferred method for scoring activity of the spine by magnetic resonance imaging in ankylosing spondylitis? J Rheumatol 2007;34:871-3.
41. Fries JF. Toward an understanding of patient outcome measurement. Arthritis Rheum 1983;26:697-704.
42. Tennant A, McKenna SP. Conceptualizing and defining outcome. Br J Rheumatol 1995;34:899-900.
43. Sparks JA, Costenbader KH. Genetics, environment, and gene-environment interactions in the development of systemic rheumatic diseases. Rheum Dis Clin North Am 2014;40:637-57.
44. Bax M, van Heemst J, Huizinga TW, Toes RE. Genetics of rheumatoid arthritis: what have we learned? Immunogenetics 2011;63:459-66.
45. van Tubergen A, Ramiro S, van der Heijde D, Dougados M, Mielants H, Landewe R. Development of new syndesmophytes and bridges in ankylosing spondylitis and their predictors: a longitudinal study. Ann Rheum Dis 2012;71:518-23.
46. Baraliakos X, Listing J, Rudwaleit M, et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis 2007;66:910-5.
47. Machado P. Anti-tumor necrosis factor and new bone formation in ankylosing spondylitis: the controversy continues. Arthritis Rheum 2013;65:2537-40.
48. Ostergaard M, Sorensen IJ. Magnetic resonance imaging--key to understanding and monitoring disease progression in spondyloarthritis? J Rheumatol 2015;42:1-4.
49. Schett G, Rudwaleit M. Can we stop progression of ankylosing spondylitis? Best Pract Res Clin Rheumatol 2010;24:363-71.
50. Sieper J, Appel H, Braun J, Rudwaleit M. Critical appraisal of assessment of structural damage in

ankylosing spondylitis: implications for treatment outcomes. Arthritis Rheum 2008;58:649-56.

51. Lories RJ, Luyten FP, de Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. Arthritis Res Ther 2009;11:221.

52. Lambert RGW, Pedersen SJ, Maksymowych WP, Chiowchanwisawakit P, Østergaard M. Active Inflammatory Lesions Detected by Magnetic Resonance Imaging in the Spine of Patients with Spondyloarthritis – Definitions, Assessment System, and Reference Image Set. The Journal of rheumatology 2009;84:3-17.

53. Østergaard M, Maksymowych WP, Pedersen SJ, Chiowchanwisawakit P, Lambert RGW. Structural Lesions Detected by Magnetic Resonance Imaging in the Spine of Patients with Spondyloarthritis – Definitions, Assessment System, and Reference Image Set. The Journal of rheumatology 2009;84:18-34.

54. Mandl P, Navarro-Compan V, Terslev L, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015.

55. Han JS, Kaufman B, El Yousef SJ, et al. NMR imaging of the spine. AJR American journal of roentgenology 1983;141:1137-45.

56. Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Ther 2008;10:R104.

57. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Ostergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. Arthritis Rheum 2009;60:93-102.

58. Pedersen SJ, Chiowchanwisawakit P, Lambert RG, Ostergaard M, Maksymowych WP. Resolution of inflammation following treatment of ankylosing spondylitis is associated with new bone formation. J Rheumatol 2011;38:1349-54.

59. Chiowchanwisawakit P, Lambert RG, Conner-Spady B, Maksymowych WP. Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. Arthritis Rheum 2011;63:2215-25.

60. Baraliakos X, Heldmann F, Callhoff J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 2014;73:1819-25.

61. Maksymowych WP, Morency N, Conner-Spady B, Lambert RG. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. Ann Rheum Dis 2013;72:23-8.