Chapter 12

Summary and general discussion
Axial spondyloarthritis

Axial spondyloarthritis (SpA), including ankylosing spondylitis (AS) as the most well-known phenotype, is a chronic rheumatic inflammatory disease in which predominantly the axial skeleton is involved. The hallmark features of axial SpA are inflammation and structural changes of the sacroiliac (SI) joints and the spine. Pain, spinal stiffness, and loss of function limits the ability to perform daily activities [1-3]. Typical structural changes are the formation of syndesmophytes between vertebrae leading to ankylosis of the spine [1]. In contrast to this bone formation, axial SpA patients have an increased risk for bone loss, resulting in low bone mineral density (BMD) and vertebral fractures [4,5].

Axial SpA is an overall slowly progressive and heterogeneous disease with high inter-patient variability [6,7]. Treatment is given to reduce disease activity and to improve outcome. Conventional treatment includes non-steroidal anti-inflammatory drugs (NSAIDs) in combination with adequate patient education, physical exercise, or physical therapy. Treatment with biologicals, such as tumor necrosis factor-alpha (TNF-α) inhibitors and, very recently, IL-17 inhibitors, can be prescribed when patients have persistently high disease activity despite of conventional treatment [8,9].

The overall objective of this thesis was to evaluate disease outcome, especially bone-related outcome, during long-term follow-up of axial SpA patients treated according to (inter) national guidelines in daily clinical practice. The following topics are covered in this thesis:

**Part I** Long-term radiographic outcome of excessive bone formation in the spine of AS patients treated with TNF-α inhibitors,

**Part II** Radiographic outcome of excessive bone loss in the spine of AS patients,

**Part III** The influence of gender and BMI on disease outcome and the development of a physical activity questionnaire for axial SpA patients.

**GLAS cohort**

All studies described in this thesis were based on patient data from an ongoing, prospective, longitudinal, observational, cohort study in the North of the Netherlands; the ‘Groningen Leeuwarden Axial Spondyloarthritis’ (GLAS) cohort. The GLAS cohort started in November 2004 in the Medical Center Leeuwarden (MCL) and the University Medical Center Groningen (UMCG). The initial aim of the GLAS study was to evaluate clinical aspects of long-term treatment with TNF-α inhibitors in daily clinical practice, with a focus on bone-related outcome. Patients with active AS who started TNF-α inhibitor treatment were included in the cohort. Since the end of 2008, the inclusion criteria were extended to all consecutive axial
SpA patients, irrespective of disease activity and treatment regimen. The overall objective of the GLAS cohort is to combine up-to-date clinical care for axial SpA patients with clinical research to gain more knowledge about the long-term course of this disease.

The GLAS cohort is embedded in the daily clinical care of axial SpA patients. Consecutive axial SpA patients who visit the outpatient clinics of the MCL or UMCG are asked to participate in the cohort. After patients have given written informed consent, they are followed according to a fixed protocol and seen by specialized and trained rheumatologists, physician assistants, or rheumatology consultants every 6 to 12 months. The management and assessment of the disease is conducted according to the latest guidelines established by the Assessment in SpondyloArthritis International Society (ASAS), the European League against Rheumatism (EULAR), and the Dutch Society of Rheumatology (NVR) Spondyloarthritis working groups. [8] The domains and assessment core set for cohort studies as recommended by the ASAS/Outcome Measures in Rheumatology Clinical Trials (OMERACT) working group are used to evaluate disease status [10,11]. Disease activity, physical functioning, health-related quality of life, spinal mobility, presence of extra-articular manifestations (EAMs), radiographic changes, and bone mineral density are evaluated during follow-up. Patient symposia are organized every 2 years to inform patients about the disease, study results, and future plans, and to promote involvement in the cohort.

Currently, more than 600 axial SpA patients are included in the GLAS cohort. The drop-out rate is relatively low for a long-term cohort study (13% at 8 years of follow-up). The majority of patients with long-term follow-up have been treated with TNF-α inhibitors due to the initial inclusion criteria of the GLAS cohort. Therefore, this thesis mainly describes the results of patients treated with these biologicals.
PART I: RADIOGRAPHIC OUTCOME OF EXCESSIVE BONE FORMATION DURING TREATMENT WITH TNF-α INHIBITORS

Chapter 2 describes spinal radiographic progression in 176 AS patients treated with TNF-α inhibitors for up to 6 years (median follow-up duration was 3.8 years). Spinal radiographic damage was scored by two independent readers on lateral radiographs of the cervical and lumbar spine according to the modified Stoke AS spine score (mSASSS, range 0-72) [12]. To prevent reader bias regarding the knowledge of the applied therapy, radiographs were scored with unknown time sequence. Spinal radiographic progression was investigated using generalized estimating equations (GEE), a statistical method in which longitudinal associations could be explored taking into account the within-patient correlations. The mean progression rate was 1.3 mSASSS units per 2 years at the group level. At the individual patient level, a large variability in spinal radiographic progression was seen. Patients with baseline syndesmophytes showed a 4-fold higher progression rate than patients without syndesmophytes. Male patients showed a 2.5-fold higher progression rate than female patients.

In chapter 3, the course of spinal radiographic progression during treatment with TNF-α inhibitors was explored in a larger group of patients with up to 8 years of follow-up. In this study, radiographs were randomized together with radiographs of patients from a Dutch historical cohort not treated with TNF-α inhibitors and scored in chronological time order (mSASSS). This methodology was used to prevent reader bias regarding the knowledge of the applied therapy and to reduce the measurement error related to reading with unknown time sequence. The course over time was evaluated in patients with complete data over 4 years, 6 years, and 8 years of follow-up using different GEE time models (linear and non-linear models). GEE analysis in patients with 4 years of follow-up revealed that spinal radiographic progression followed a linear course with stable progression rates of 1.7 mSASSS units per 2 years. Patients with 6 and 8 years of follow-up showed a non-linear course of spinal radiographic progression with reducing progression rates from max. 2.8 mSASSS units during the 0-2 year time interval to min. 0.8 mSASSS units during the 6-8 year time interval. Although the number of patients with 8 years of follow-up was limited, diminishing radiographic progression was already seen during the 2-4 year and 4-6 year time interval. Similar results were found with sensitivity analysis after linear imputation of missing radiographic data at intermediate time points and with sensitivity analysis after adjustment for potential confounders.
Chapter 4 describes the influence of patient characteristics on the course of spinal radiographic progression in 80 AS patients treated with TNF-α inhibitors for 6 years. Spinal radiographic damage over time was significantly associated with male gender, older age, longer disease duration, current smoking status, higher BMI, and, most importantly, presence of baseline syndesmophytes. Patients with these risk factors for poor radiographic outcome showed the highest but also diminishing spinal radiographic progression over time. Radiographic progression rates reduced from max. 2.8 units during 0-2 year time interval to min. 0.9 units during 4-6 year time interval. Patients without risk factors showed stable and low progression rates of ≤1 mSASSS unit per 2 years.

The mSASSS as used for the assessment of spinal radiographic damage in AS includes only the anterior corners of the cervical and lumbar vertebral bodies. Previous studies have shown that other parts of the spine such as the facet (zygaphophyseal) joints are also affected in AS [13,14]. Chapter 5 describes radiographic damage and progression of the cervical facet joints scored according the method of de Vlam et al. [13], in 98 AS patients treated with TNF-α inhibitors for 4 years. Damage and progression of cervical facet joints were frequently observed; in 25% and 13% of the patients, respectively. Damage of cervical facet joints was associated with longer disease duration, higher disease activity, higher mSASSS, larger occiput-to-wall distance, and a history of extra-articular manifestations, including inflammatory bowel disease (IBD), uveitis, and psoriasis. In comparison, damage and progression of the cervical vertebral bodies assessed with mSASSS was observed in 52% and 26% of the patients, respectively. The majority of patients with radiographic progression of cervical facet joints did not show progression of vertebral bodies.

Based on the results in chapter 5, a composite scoring system, the combined AS spine score (CASSSS) was introduced and its additional value to the mSASSS was evaluated in chapter 6. In CASSS, the cervical facet joint scores of the method of de Vlam et al. (range 0-15) were incorporated in the mSASSS (range 0-72), leading to a score range of 0-87. CASSSS was compared to the original mSASSS according to the three aspects of the OMERACT filter, i.e. feasibility, discrimination, and truth [15]. Feasibility of CASSSS was very good; total scores could be calculated in >90% of the patients, no additional radiographs were necessary, and the assessment of cervical facet joints took only a few extra minutes. Inter-observer reliability was excellent for both scoring methods without an increase in the measurement error for CASSS. CASSSS resulted in a few more patients classified as having ‘definite damage’ (61% versus 57%) and ‘definite progression’ (55% versus 48%). With regard to truth, the construct
validity of CASSS was better since 46% of the patients had higher baseline scores, 25% had higher progression scores, and cervical rotation correlated better with CASSS than with mSASSS.

PART II: RADIOGRAPHIC OUTCOME OF EXCESSIVE BONE LOSS

Chapter 7 describes the prevalence and incidence of radiographic vertebral fractures in the thoracic and lumbar spine of 105 AS patients with active disease who were treated with TNF-α inhibitors for 4 years. Vertebral fractures were assessed by two readers according to the method of Genant et al. [16]. A reduction in vertebral height of ≥20% was defined as a radiographic vertebral fracture. At baseline, 27 (26%) patients had one or more radiographic vertebral fractures. New vertebral fractures were observed in 21 (20%) patients. Most prevalent and new developed fractures were mild (72% and 80%, respectively). The remaining fractures were moderate and one was severe. The 21 patients with new vertebral fractures were older, had longer smoking duration, worse physical function, lower lumbar spine BMD, and more frequently pre-existing vertebral fractures of moderate degree (≥25% height reduction). Lumbar spine BMD as well as hip BMD improved significantly during 4 years of TNF-α blocking therapy. However, patients with new vertebral fractures showed significantly less improvement in lumbar spine BMD than patients without new vertebral fractures.

Chapter 8 describes the prevalence and 2-year incidence of vertebral fractures in 292 AS patients treated with TNF-α inhibitors or conventional therapy. The same scoring method was used as described in chapter 7. At baseline, a total of 89 radiographic vertebral fractures were found in 59 (20%) patients. Only 2 fractures were symptomatic of which one received clinical attention. The majority of the fractures were mild, wedge shaped and located in the mid and low thoracic spine. During 2 years of follow-up, 15 (6%) patients developed 18 new fractures. Only one fracture was symptomatic and received clinical attention. In addition to patients with new fractures, 7 (2%) patients showed an increase in severity of existing fractures. In these 7 patients, mild fractures deteriorated to moderate fractures. The prevalence and incidence of new vertebral fractures was comparable between 184 AS patients with active disease who started TNF-α inhibitors and 108 AS patients with inactive disease who stayed on conventional treatment (21% versus 19% and 5% versus 6%, resp.). Clinical risk factors for vertebral fractures were: older age, higher BMI, longer smoking duration, larger occiput-to-
wall distance, more spinal radiographic damage, and low hip BMD. Occiput-to-wall distance was identified as an independent risk factor for having radiographic vertebral fractures. The use of NSAIDs at baseline was independently associated with a reduced risk of having and developing vertebral fractures.

PART III: INFLUENCE OF GENDER AND BMI ON DISEASE OUTCOME AND THE DEVELOPMENT OF A PHYSICAL ACTIVITY QUESTIONNAIRE FOR AXIAL SPA

In chapter 9, gender differences with regard to subjective and objective clinical outcome measures as used in daily clinical practice were explored in a cross-sectional study of 466 axial SpA patients who visited the outpatient clinic between 2011 and 2012. Female patients scored worse on all patient-reported outcome measures than male patients, i.e. women had higher Bath AS disease activity index (BASDAI), patient’s global score of disease activity, tender joint count, Bath AS functional index (BASFI), and AS quality of life questionnaire (ASQoL). Women also had higher AS disease activity score (ASDAS), a measure that combines subjective aspects (patient questions) and an objective aspect of disease activity, C-reactive protein (CRP). Objective, univariable measures of disease activity, i.e. CRP levels and swollen joint count, were comparable between female and male patients.

Chapter 10 describes the prevalence of overweight and obesity in relation to clinical outcome in 461 axial SpA patients from the GLAS cohort. BMI data were compared with gender-matched data from a population-based cohort study in the same geographical region with comparable age distribution, the LifeLines cohort (n=136,577). In our axial SpA population, overweight (BMI ≥25-<30kg/m²) was present in 37% of the patients and obesity (BMI ≥30kg/m²) in 22% of the patients. In the general LifeLines population, overweight and obesity were present in 43% and 15% of the participants, respectively. In axial SpA, overweight and obese patients were significantly older, had longer symptom duration, and more often comorbidity, especially hypertension, than patients with normal BMI. Interestingly, presence of obesity was significantly associated with worse clinical outcome measures, including worse score on BASDAI, ASDAS, CRP, ESR, BASFI, and ASQoL.

In chapter 11, a disease-specific, patient-reported questionnaire was introduced for the assessment of physical activity in axial SpA. A qualitative study with a stepwise approach
was used to modify an existing, validated physical activity questionnaire for the general population, the Short QUestionnaire to Assess Health-enhancing physical activity (SQUASH). This questionnaire measures the duration, frequency, and intensity of physical activities during transport, work, household, and leisure time, including sports. Semi-structured in-depth interviews were performed with 9 experts in the field of axial SpA and a focus group was organized with 8 axial SpA patients. Multiple requirements for adaptations were proposed and discussed. In total, 15 adaptations were implemented and the SQUASH was modified into a more standardized, disease-specific questionnaire, the axSpA-SQUASH. The most important adaptations concerned: explanation, rewording, and standardization of response options throughout the questionnaire and addition of more response possibilities and clarification of examples related to the domains of the SQUASH (e.g. inclusion of exercise therapy, other transportation activities, and childcare).
GENERAL DISCUSSION

Bone formation in axial SpA

Radiographic progression in relation to pathophysiology

Excessive bone formation in axial SpA is a complex and multifactorial process that varies greatly between patients, also during treatment with TNF-α inhibitors as shown in chapters 2 and 3. In the past century, knowledge about axial SpA is extremely increased, but the underlying pathophysiological mechanisms are not yet completely understood. Genetics, the immune system, biomechanical stress, and environmental factors are considered as factors that contribute to new bone formation [17-19].

In the historical Outcomes in AS International Study (OASIS) with a follow-up duration up to 12 years, spinal radiographic progression followed a linear course at the group level with a mean progression rate of 2 mSASSS units per 2 years [7]. Spinal radiographic progression was found to be longitudinally associated with assessments of disease activity. A higher BASDAI, ASDAS, or CRP at the start of a 2-year time interval was associated with more radiographic progression during the next 2 years of follow-up [20]. These findings suggest that inhibition of inflammation and, thereby, reducing disease activity seems beneficial to reduce spinal radiographic progression in axial SpA.

Shortly after the discovery that TNF-α inhibitors are very effective in reducing disease activity and improving clinical outcome in AS, open-label extension studies were performed to investigate the effect of TNF-α inhibitors on spinal radiographic outcome. These studies did not show a significant difference in spinal radiographic progression after 2 years of TNF-α blocking therapy compared to TNF-α blocker naive AS patients from historical cohorts [21-24]. Prospective and retrospective studies with up to 8 years of follow-up reported about a possible relationship between TNF-α inhibitors and less spinal radiographic progression in AS over time [25,26]. In our prospective cohort of AS patients treated with TNF-α inhibitors, a deflection of spinal radiographic progression was found after more than 4 years of follow-up (chapter 3). This deflection was especially seen in patients with an increased risk of poor radiographic outcome, e.g. baseline syndesmophytes and male gender. Patients without risk factors showed very slow, linear spinal radiographic progression (chapter 4). These results show that TNF-α inhibitors cannot stop radiographic progression immediately. However, long-term inhibition of inflammation with these agents diminishes and may even prevent spinal radiographic progression over time [27].
An explanation of this possible delayed effect is given by the TNF-brake hypothesis [28,29]. TNF-α is a key pro-inflammatory cytokine in axial SpA that upregulates Dickkopf-related protein-1 (Dkk-1), an antagonist of the Wingless (Wnt) signaling pathway for new bone formation. Processes of new bone formation are downregulated at sites of active inflammation whereas processes of bone resorption are upregulated. When inflammatory lesions resolve, the levels of TNF-α reduce. As a result, repair processes can be activated and less Dkk-1 expression allows Wnt signaling to stimulate new bone formation at sites of resolved inflammation. This may explain the (ongoing) formation of new bone in axial SpA, also after start of TNF-α inhibitor treatment [28]. The TNF-brake hypothesis also assumes that persistent reduction of inflammation will prevent the development of new inflammatory lesions resulting in less activated repair processes and a reduction of spinal radiographic progression over time [29].

More recently, novel insights into the pathophysiology of bone formation of axial SpA have been described. Influences of biomechanical stress and other pro-inflammatory cytokines in addition to TNF-α, such as interleukin (IL)-23, IL-17 and IL-22, have been found to play a role in the excessive bone formation in axial SpA [30-32]. Treatment with IL-17 is now available for axial SpA and studies with IL-12/23 inhibitors are under way. The future will learn us whether these new treatments can reduce new bone formation in axial SpA.

Assessing spinal radiographic progression; pitfalls in the methodology

Due to the overall slow and very heterogeneous process of bone formation in axial SpA, the evaluation of spinal radiographic progression brings along multiple methodological challenges. The EULAR working group recommends radiography of the spine, not repeated more frequently than every 2 years, and use of the mSASSS for the assessment of spinal radiographic progression in axial SpA patients [12,33]. The reliability of the mSASSS is very good but the ability to discriminate between small changes is limited, especially over a short period of time [34]. The smallest detectable change (SDC), the change that can be detected without a measurement error, over a 2 years period is often larger than the mean progression rate (chapter 3) [7]. Therefore, longer follow-up or very large study populations are needed to detect ‘true’ changes beyond the measurement error.

A scoring method in which more elements of the spine are included may help to improve the sensitivity to change. In chapter 5, we have shown that cervical facet joints are frequently affected in AS. Incorporating the cervical facet joint scores of de Vlam et al. in the mSASSS
resulted in a broader range of scores without an increase in the measurement error (chapter 6). With this composite scoring method named CASSS, more patients with spinal radiographic progression were captured. In combination with the high feasibility and the possibility to extract mSASSS scores from CASSS, this scoring method would be relevant in this slowly progressive disease.

The sensitivity to change of the scoring method will also improve when radiographs are scored in chronological time order (chapter 3) [35,36]. Scoring with known time sequence reduces the measurement error as negative progression will not be scored. However, reader bias concerning the applied therapy should be taken into account, for example by randomizing the radiographs with radiographs of patients on conventional therapy or from a historical cohort study.

Finally, it is important to take into account patient selection and completion bias. As known from literature and also demonstrated in chapter 2-4, different patient characteristics can affect the course of spinal radiographic progression [6,7,25,37-39]. An accurate description of patient selection, patient characteristics, and number of patients over time is important. When patient numbers differ over time due to drop-outs or incomplete data, complete case analysis, analysis in different sub groups, sensitivity analysis after imputation of missing data, and/or adjustments for patient characteristics with known influence on radiographic outcome should be performed using advanced, repeated measures statistics.

**Bone loss in axial SpA**

**Vertebral fractures and pathophysiology**

Although the focus in axial SpA outcome research is mainly on excessive bone formation, we have shown that radiographic vertebral fractures are common in axial SpA (chapter 7 and 8). In line with bone formation, the etiology of vertebral fractures is probably multifactorial. Genetic and hormonal factors, immobility due to pain or spinal stiffness, inflammation, and presumably also biomechanical stress, may play a role in the development of vertebral fractures in axial SpA [40-42].

Treatment with TNF-α inhibitors can improve BMD of the lumbar spine and, to a lesser extent, at the hip in axial SpA, (chapter 7) [4]. However, new vertebral fractures are still observed during treatment with these drugs (chapter 7) and no differences were found between patients on TNF-α inhibitor treatment or conventional treatment during 2 years
of follow-up (chapter 8). An increase in the number of patients with radiographic vertebral fractures during 2 years of TNF-α inhibitor treatment was also found in a small prospective observational cohort study in 49 axial SpA patients [43]. Previous analysis of bone turnover markers in 72 AS patients from the GLAS cohort showed that especially bone-specific alkaline phosphatase (BALP), a marker that plays a central role in the mineralization process of bone, increases during 3 years of TNF-α inhibitor treatment [44]. A mineralization does not necessarily represent good bone quality. Since our data were derived from an observational cohort study, no conclusions could be drawn about the effect of TNF-α inhibitors on the development of radiographic vertebral fractures.

In line with previous axial SpA studies and studies in postmenopausal women from the general population, vertebral fractures do not occur along the whole spine [45-49]. Vertebral fractures occurred most often in the mid- and low thoracic spine (chapter 7 and 8). Mechanical stress of vertebral bodies in these parts of the spine in combination with the already weakened bone structure in axial SpA can result in radiographic vertebral fractures without major trauma, even at a relatively young age (chapter 8) [50]. Patients with vertebral fractures had a larger occiput-to-wall distance and more spinal radiographic damage (chapter 7 and 8). Fusion of the spine in a fixed, forward-stooped posture with larger occiput-to-wall distance increases the mechanical stress on the vertebrae which may result in an increased risk of more radiographic vertebral fractures. Since occiput-to-wall distance was an independent risk factor for the presence of vertebral fractures, this measurement can act as an indicator for the presence of vertebral fractures in axial SpA.

**Assessing vertebral fractures: pitfalls in the methodology**

Bone loss is often evaluated using BMD assessment in the daily clinical practice of axial SpA. However, BMD of the lumbar spine (AP view) might not be a reliable representation of real bone loss of the vertebral bodies, especially in patients with advanced disease [41]. BMD measured by dual-energy X-ray absorptiometry (DXA) can be overestimated by the presence of syndesmophytes, ligament calcifications, and fusion of facet joints [41]. Furthermore, two-dimensional DXA images do not reflect the microarchitecture and composition of the vertebral bodies, two important properties of bone quality [51]. Data about radiographic vertebral fractures, the final outcome of poor bone quality and bone loss of the vertebral body, is therefore very relevant.
The diagnosis of vertebral fractures in axial SpA is complicated by the lack of symptoms and difficulties in the discrimination between back pain complaints caused by inflammation and spinal stiffness or by vertebral fractures [52]. As a consequence, the vast majority of fractures do not receive clinical attention (chapter 8). Routinely screening for radiographic vertebral fractures is desirable in axial SpA, especially in patients with large and progressing occiput-to-wall distance. Lateral radiographs of the thoracic and lumbar spine are appropriate options to screen for vertebral fractures. Most fractures are found in the thoracic spine. Therefore, this region should definitely be included.

For the assessment of vertebral fractures on spinal radiographs, the semi-quantitative method of Genant is the best available scoring method [16]. This method allows readers to judge whether a deformity demonstrates a vertebral fracture, natural variation, or is caused by degenerative changes. Subsequently, the vertebral heights are measured and the relative height reduction can be calculated. In axial SpA, the discrimination between radiographic vertebral fractures and non-fracture deformities can be difficult, especially regarding mild fractures. Structural changes such as erosions, blurring of joint margins, syndesmophytes, spondylolysis, and calcification of the ligaments can limit the interpretability. Furthermore, a small difference in the angle of the radiograph in combination with the arbitrary cut-off values of the method of Genant (≥20% height reduction) can limit the reproducibility of assessing mild fractures. Some studies have used a different cut-off value (≥25% height reduction) to define vertebral fractures [49,53]. However, several studies in postmenopausal osteoporotic women and the results of our two studies showed that mild fractures can deteriorate to moderate vertebral fractures within 2 years of follow-up. Furthermore, mild fractures can act as a risk factor for the development of new vertebral fractures [54-56]. Therefore, the identification of mild fractures, in addition to moderate and severe fractures, seems relevant in axial SpA. Current research is now focusing on the development of new algorithms to improve the diagnosis of vertebral fractures in axial SpA [57,58].
Patient characteristics in relation to bone-related outcome

Multiple patient characteristics are associated with excessive bone formation and bone loss in axial SpA. Some are associated with both aspects of bone-related outcome (Figure 1).

Figure 1. Schematic overview of associations of patient characteristics with bone loss and bone formation in the GLAS-cohort.

Abbreviations: mSASSS: Modified Stoke AS spine score; EAMs: Extra-articular manifestations; IBD: Inflammatory bowel disease; ASDAS: AS disease activity scale; CRP: C-reactive protein; BASFI: Bath AS functional index; OWD: Occiput-to-wall distance; BMD: Bone mineral density; NSAID: Non-steroidal anti-inflammatory drugs; BMI: Body mass index.
Gender
As known from literature and confirmed in our cohort, males are more prone to develop spinal radiographic damage than females [59,60]. Female patients, on the other hand, scored higher on patient-reported outcome measures of disease status (chapter 9). Objective measures of disease activity such as CRP levels and swollen joints were not significantly different between female and male patients. Pooled analysis of data from clinical control studies in 1,283 AS patients treated with etanercept, sulfasalazine or placebo, also showed that female patients scorer higher on BASDAI and patient’s global disease activity assessment than male patients [61]. These results suggest that female patients may experience their symptoms worse than males. From previous studies, it is known that women tend to differ in their health approach and how they communicate their health problems [61]. This should be taken into account when interpreting patient-reported outcome measures in both daily clinical practice and clinical studies, especially when subjective measures such as the BASDAI are used for clinical decision making. Other cut-off values for different stages of disease activity (e.g. high versus low) might be needed for male and female axial SpA patients.

Age, disease duration, and disease severity
The results of this thesis confirmed that older AS patients with longer and more severe disease, e.g. higher disease activity, worse physical functioning, and worse spinal mobility had more spinal radiographic damage and/or radiographic vertebral fractures (Figure 1) [38,41]. A history of EAMs, including inflammatory bowel disease (IBD), uveitis, and psoriasis, was only significantly associated with radiographic damage of the cervical facet joints, not with damage of vertebral bodies. The association with uveitis has also been found in a small cross-sectional study of 50 AS patients in which 37% of patients with facet ankylosis had a history of uveitis [13]. Facet joint damage is further frequently present in psoriatic arthritis [63,64]. So far, the exact underlying pathophysiology of facet joint involvement and extra articular manifestations is not known.

In line with previous studies, the presence of baseline syndesmophytes is the most important, independent predictor for radiographic progression of the vertebral bodies [38,65]. Our results showed that the presence of (partial) ankylosis of cervical facet joints was the independent predictor for radiographic progression of facet joints (chapter 5). For the development of new vertebral fractures, the presence of (moderate) radiographic vertebral fractures may act as a predictor, as confirmed by other studies [54,55].
**NSAID use**

Previous studies have described a possible positive effect of NSAID use on spinal radiographic progression [66,67]. However, the Effects of NSAIDs on RAdiographic Damage in Ankylosing Spondylitis (ENRADAS) trial investigated primarily the effect of continuous versus on demand use of NSAIDS on 2-year radiographic progression and did not demonstrate any differences [68]. In our cohort, we could also not found any association between NSAID use and spinal radiographic progression, possibly because NSAID use decreased rapidly over time due to the good clinical effect of TNF-α inhibitors. However, patients using NSAIDs at baseline had a reduced risk of the presence and development of radiographic vertebral fractures. A comparable association has been found in previous AS studies [69,70]. Literature describes contradictory theories about the underlying mechanism regarding the influence of NSAIDs on bone. Some studies suggested that NSAIDs interfere with bone healing while other studies declared that NSAID use can have a protective effect on bone loss since pain relief may result in more physical activity which helps in maintaining bone mass [40].

**Life style factors: Smoking and high BMI**

An important finding of the studies in this thesis was that lifestyle factors such as smoking and high BMI were associated with the presence and development of both spinal radiographic damage and radiographic vertebral fractures (Figure 1). In addition, our cross-sectional analysis showed that a higher BMI was associated with more comorbidities and worse clinical outcome, including higher disease activity and worse physical functioning and quality of life, despite of treatment with NSAIDs or TNF-α inhibitors (chapter 10). Previous studies showed less treatment response to TNF-α inhibitors in obese AS patients [71,72]. An unhealthy lifestyle, components of tobacco smoke, and adipose tissue in overweight and obese patients may activate immune responses leading to higher secretion of pro-inflammatory cytokines [39,73]. In addition, other factors such as physical inactivity can lead to worse bone-related and clinical outcome. Therefore, clinicians and patients should be aware of the negative consequences of an unhealthy lifestyle on disease outcome in axial SpA.

**Physical activity**

Although physical activity is considered to be a cornerstone in the management of axSpA that can affect disease outcome, the assessment of physical activity is not included in the core set of disease outcomes and measuring instruments as recommended by the ASAS/Outcome Measures in Rheumatology Clinical Trials (OMERACT) working group [10]. Therefore, we
have developed a disease-specific physical activity questionnaire in collaboration with axial SpA patients and experts (chapter 11). Data obtained from the axSpA-SQUASH will provide insight into the performed activities and perceived intensity of axial SpA patients during transport, work, household, and leisure time, including sports. Data can be used to develop physical activity guidelines and to investigate the relationships with disease outcome and other lifestyle factors. According to axial SpA patients and experts, this disease-specific physical activity questionnaire would be a relevant addition to other measuring instruments proposed by the ASAS/OMERACT working group for axial SpA. The next step will be further validation of the axSpA-SQUASH, which was beyond the scope of this thesis.

CONCLUSIONS

The studies in this thesis provided an overview of bone-related outcome and its associations with patient characteristics in a large, prospective, observational cohort study of axial SpA patients in the daily clinical practice.

The deflection in spinal radiographic progression with reducing progression rates during treatment with TNF-α inhibitors may suggest that long-term treatment with these drugs can reduce radiographic progression. However, the assessment of spinal radiographic progression is challenging in axial SpA because of the overall slow process of bone formation and large variation between individual patients. The composite scoring method CASSS, in which the cervical facet joints are incorporated in the mSASSS, seems a promising scoring method that can detect more patients with spinal radiographic damage and progression.

Radiographic vertebral fractures were frequently observed in axial SpA. In daily clinical practice, a stepwise approach with routinely assessing the occiput-to-wall distance in combination with radiography of the thoracic and lumbar spine will help clinicians to detect these fractures in axial SpA.

The expression of the disease can differ between axial SpA patients. Male patients were more prone to develop spinal radiographic damage whereas female patients experienced their symptoms as more severe than male patients. These gender differences should be taken into account in clinical decision making. Also the influence of lifestyle factors on disease outcome should be taken into account. Smoking and higher BMI were associated with poor
bone-related and clinical outcome. Promoting a healthy lifestyle, including cessation of
smoking, weight reduction in case of obesity, and supporting physical activity are important
goals in the management of axial SpA.

The axSpA-SQUASH is a disease-specific, self-reported questionnaire that can easily be used
in clinical studies, daily clinical practice, and for self-management. The axSpA-SQUASH will
give better insight into the level of daily physical activity of individual patients. This will help
us to develop more tailored advice in future concerning physical activity in axial SpA.

In addition to radiographic and clinical data as presented in this thesis, more data are
collected in the GLAS cohort. For example, serum, plasma, urine, and DNA samples are
collected every visit and bone turnover markers are measured. With all these data collected,
the GLAS cohort provides very valuable data of axial SpA patients in the daily clinical practice.
Combining these data with other axial SpA cohorts will increase the current knowledge
about the disease course during treatment in daily clinical practice. Furthermore, the GLAS
cohort provides data to further investigate the underlying pathophysiological mechanisms
of excessive bone formation and bone loss in axial SpA.
REFERENCES


