Chapter 1

General introduction
Ankylosing Spondylitis

Ankylosing Spondylitis (AS), also known as Bechterew's disease, is a chronic, rheumatic disease of the axial skeleton with variable involvement of peripheral joints and extra-articular structures. The disease can cause irreversible deformities of the spine and joints and has a large impact on physical functioning. In the last 10 years, the use of tumor necrosis factor inhibitors (TNFi) has revolutionized the pharmacological treatment of AS, strongly impacting pain, stiffness, and functioning. Despite this impressive improvement in treatment options, one of the main research challenges is the absence of objective outcome measures to support current evidence of its effectiveness. Furthermore, there is only limited information on how to predict the long-term outcome of AS patients receiving TNFi in daily clinical practice. The development of a new performance-based outcome measure for physical functioning and the prediction of long-term physical functioning was the main aim of the research projects of this thesis.

Classification of AS

AS is the major subtype of a group of chronic, inflammatory, rheumatic diseases called spondyloarthritis (SpA). Recently the nomenclature of SpA was changed into axial and peripheral SpA [1]. Axial SpA consists of non-radiographic (i.e., without radiographic signs of sacroiliitis on x-rays) axial SpA (which might progress to AS) and AS according to the modified New York criteria [2], which includes radiographic changes of the sacroiliac joints (grade 2 bilateral or grade 3 unilateral). The classification of AS also requires inflammatory back pain, limited lumbar spinal motion in sagittal and frontal planes, or decreased chest expansion. Peripheral SpA is dominated by peripheral arthritis with less axial involvement and also includes reactive arthritis and psoriatic arthritis [3]. In this thesis only the definition of AS according to the modified New York criteria [2] will be used (Table 1).

Table 1: Modified New York criteria for ankylosing spondylitis [2]

1. Clinical criteria
   a. Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.
   b. Limitation of motion of the lumbar spine in the sagittal and frontal planes.
   c. Limitation of chest expansion relative to normal values correlated for age and sex.
2. Radiological criterion
   • Sacroiliitis grade ≥2 bilaterally or grade 3-4 unilaterally.

Definite AS if the radiological criterion is associated with at least one clinical criterion
Epidemiology of AS

Prevalence and incidence rates of AS vary between countries, depending on the prevalence in the population of the predisposing genes that encode the Human Leukocyte Antigen B27 (HLA-B27), which is more prevalent in the northern regions of the world. The prevalence of AS is estimated at between 0.1% and 1.4% globally. Across Europe, prevalence ranges between 2.9 and 26.3 per 10,000 (weighted mean 18.6 per 10,000) [4, 5]. Incidence rates vary between 0.5 and 14 per 100,000 people per year. The HLA-B27 antigen is present in 90% of AS patients [5].

AS affects young people, usually beginning in the second or third decade of life and men are more often affected than women. In Europe, the mean ratio is 3.8 males per female [4, 5].

Disease characteristics of AS

Aetiology
The cause of AS is unknown. Both hereditary and environmental factors are associated with the development of AS and immune mechanisms seem to play a key role. There is a strong genetic predisposition, associated with the HLA-B27 antigen, but recently some other contributing genes (e.g., ERAP1 and ERAP2) were identified [6]. In addition, environmental factors play a role: the onset of the disease might be triggered by bacterial infections such as Chlamydia, Salmonella, Shigella, Yersinia or Campylobacter, which also cause reactive arthritis [5].

Characteristics
AS is a chronic, progressive, inflammatory, rheumatic disease that mainly affects the axial skeleton and the sacroiliac joints. The hallmark of AS is inflammatory back pain caused by sacroiliitis. Patients mostly report a long duration of back pain (>3 months) with an insidious onset, alternating buttock pain, pain at night, and morning stiffness that improves with exercise, but not with rest [5]. Due to the high prevalence of back pain in the population, general practitioners’ unfamiliarity with AS symptoms, and the difficulty of diagnosis in the early phase of AS, there is an average delay of 8 years in diagnosis [7, 8].

Over time, the disease can lead to bony ankyloses, causing decreased spinal mobility and abnormal posture because of flattening of the lumbar spine and accentuated dorsal spine kyphosis. Extra spinal manifestations frequently occur and include peripheral arthritis, enthesitis, uveitis, psoriasis, inflammatory bowel disease (IBD), cardiac involvement, and pulmonary involvement [5, 9]. Furthermore, AS is associated with a significantly increased risk of cardiovascular events (due to atherosclerotic disease and AS-specific cardiac manifestations [9-11]), and an increased risk of osteoporosis with vertebral fractures [12, 13].

Consequences
Due to inflammation, pain, and limitations in spinal mobility, AS patients can gradually experience substantial limitations in physical functioning and a decreased quality of life [5]. Furthermore, in comparison with the healthy population, AS patients have a lower cardio
respiratory fitness level [14], lower pulmonary function, and decreased exercise tolerance [15, 16]. AS patients are also more fatigued than the healthy population [17]. Fatigue is influenced by helplessness and depression [18] and strongly associated with pain [19] and decline in physical functioning and quality of life [20]. Low levels of physical fitness, fatigue, and co-morbid conditions like cardiovascular diseases increase the burden of disease and negatively influence physical functioning [5, 9].

AS is also associated with an increased economic burden. Work participation is decreased, even in early disease. Patients are more often unable to work, have more frequent episodes of sickness, more days’ sick leave per episode, a decrease in productivity, and a loss of household budget of ±1,400 Euro/patient/year due to out-of-pocket expenditures and income loss [21-23].

**Treatment of AS**

The aim of AS treatment is controlling symptoms and inflammation, preventing progressive structural damage, preserving or improving physical functioning, allowing participation, and maximising quality of life [24-26]. Optimal management of AS requires a combination of pharmacological and non-pharmacological treatment modalities (Figure 1).

Physical therapy, exercise, and patient education are the key elements of the non-pharmacological treatment of AS [24-26]. In physical therapy, exercise therapy is the most important treatment modality. It has been shown to positively influence pain, mobility, disease activity, depression, fatigue, respiratory measures, physical functioning, and quality of life [27].

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**Figure 1:** ASAS/EULAR Recommendations for the Management of ankylosing spondylitis [25]

(ASAS slide library)
Pharmacologically, two groups of drugs are the most effective in the treatment of AS: non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor inhibitors (TNFi). NSAIDs are considered the first-line therapy for patients with AS, and can reduce pain, stiffness, and inflammation effectively. Moreover, it has been postulated that NSAIDs might decrease the radiographic progression of the disease in the spine [26].

The introduction of TNFi has been the most revolutionary development in the treatment of AS in the past few years. Numerous, large, randomised, placebo-controlled trials with TNFi have shown impressive results in reducing pain and improving functioning. Although the five registered TNFi differ in the method of administration (i.e., infliximab intravenously, etanercept, adalimumab, golimumab, and certolizumab subcutaneously injected), they have all proven to be effective and safe, even in the long term. The efficacy is usually evaluated after 3-4 months of treatment and all TNFi show response rates between 50-75% [28-35]. Many AS patients experience continuous efficacy during several years of treatment.

Course and prognosis of physical functioning in AS

The course of physical functioning in AS patients varies between a mild disease with little functional disability, and a more severe disease leading to more extensive limitations in function and participation. On average, limitations in physical functioning increase over time, while the course of physical functioning is highly variable [36-39]. In patients with severe involvement, loss of function and structural damage develop mostly in the first 10 years of the disease [40].

Risk factors for a more severe disease and progressive limitations in physical functioning include male gender, early age of onset of the disease, high disease activity (i.e., Bath AS Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)), radiological damage, insufficient response to NSAIDs, peripheral joint disease (within 2 years or before the age of 16), and involvement of the hip joints. Life-style factors (e.g., smoking, lack of exercise) have also been associated with diminished physical functioning. Other risk factors for functional decline are concomitant diseases like cardiovascular diseases [39-47].

It is important to increase knowledge of risk factors and mechanisms of changes in physical functioning, because this can provide direction to additional treatment strategies that prevent further functional decline. This is particularly important for AS patients treated with TNFi in daily clinical practice, because most data derive from randomised controlled trials (RCTs). These trials showed a marked and sustained improvement in physical functioning after TNFi treatment. However, in clinical practice the outcome and course may differ considerably between patients. In contrast to patient populations in RCTs, patients in observational studies are selected based on less strict inclusion and exclusion criteria and are therefore more heterogeneous [48]. There is, however, a paucity of long-term observational studies that investigate the limitations in physical functioning in TNFi-treated patients in terms of outcome, course, and risk factors. Most studies were either performed in patients only
receiving NSAIDs, or were based on RCTs with TNFi instead of inception cohorts, which aim to identify predictors of treatment response instead of functional decline, or were based on cross-sectional or short-term (< 1 year) results. Therefore, more observational studies exploring the limitations in physical functioning in AS patients receiving TNFi in daily clinical care in terms of long-term outcome, course, and risk factors, are necessary.

**Outcome assessment**

Outcome measurement in AS is complicated. Elevation of common laboratory measures such as ESR and CRP is frequently absent in AS patients and does not always reflect disease activity. Despite having active disease, up to 40% of AS patients never exhibit elevated CRP or ESR levels. Levels are more likely to be raised in patients with peripheral joint involvement or significant extra-articular disease such as IBD than with purely axial disease. Therefore, the use of inflammatory markers for the assessment of disease activity or response to treatment is limited [49-51].

Another outcome parameter is the assessment of structural damage. Radiographic progression is, however, a slow process and not very sensitive to change in the short term. The minimal interval to detect significant radiographic progression is two years [5].

As a consequence, predominantly subjective, self-reported measures (i.e., questionnaires) are used for the outcome assessment of AS. Four important tools for AS assessment were developed 20 years ago by a group of physiotherapists, researchers, rheumatologists, and patients from Bath (where an AS-specific health resort was located):

1. a global assessment of well-being, (Bath AS Global, BASG) [52]
2. a quantification of the mobility of the axial skeleton, (Bath AS Metrology Index, BASMI) [53, 54]
3. a measure of patient-reported disease activity and (Bath AS Disease Activity Index, BASDAI) [55]
4. a measure to define and monitor physical functioning (Bath AS Functional Index, BASFI) [56].

Since then, these indices have been commonly used to describe the disease state and progression of individual patients and as outcome parameters for clinical trials.

Currently, the response and continuation of TNFi treatment are still based on a 50% improvement in the BASDAI-score, whereas the cut-off value of 4 (range 0-10) discriminates effectively between a well (< 4) or poorly (> 4) controlled disease [57]. In addition, the BASDAI is embedded in the ASAS (Assessment of Spondyloarthritis international Society) 20 response (ASAS20). The ASAS20 response includes self-reported questions in four domains: patient global, spinal pain, inflammation (questions 5 and 6 of the BASDAI), and function (BASFI). Response on the ASAS20 implies an improvement of ≥20% (and ≥1 unit) in at least 3 domains, and no worsening of ≥20% (and ≥1 unit) in the remaining domain. Recently, a new
disease activity parameter, the ASDAS, was developed, which incorporates three questions of the BASDAI and the patient global score, (in addition to an acute phase reactant (CRP or ESR) [58]. In this thesis only the BASDAI and ASAS20 were used as outcome for disease activity, because at the time of this study ASDAS had not yet been introduced.

The assessment of limitations in physical functioning in AS is also primarily based on questionnaires. The ASAS prefers the BASFI questionnaire, but also recommends the Dougados Functional Index (DFI) [59]. The BASFI questionnaire is a disease-specific, reliable, and responsive outcome measure that consists of eight questions regarding physical functioning and two questions reflecting the patient’s ability to cope with everyday life [56, 60].

Self-reported questionnaires like the BASFI can evaluate physical functioning fast, safely, and simply, require no space or special equipment, carry no risk of accident, and are not influenced by observer bias. They are, however, susceptible to subjective interpretation by the patient (under- or overestimation), because they only indicate the perceived level of physical functioning during daily activities, described in standardized questions. The perceived level of physical functioning can be influenced by needs, priorities, attitudes, poor cognitive function, culture, language, education, personality traits, depression, and pain [61-71]. Furthermore, strong correlations of psychological variables (helplessness, depression, and passive coping) and the BASFI questionnaire have been shown [72], and BASDAI and BASFI scores often show large and rapid variations over time in a given patient [73]. This is the main reason why an alternative outcome measure of physical functioning, not influenced by patient perception, is needed. Such a tool can be of great value in evaluating the effects of treatments like physical or TNFi therapy.

The development of performance-based measures could be a solution to overcome the subjectivity of self-reported measures. In performance-based measures an individual is asked to perform a specific task that is evaluated in a uniform manner using predetermined criteria, which may include counting of repetitions or timing of the activity as appropriate. Whereas a questionnaire refers to what individuals think they can do, a performance-based test shows what individuals can actually do. Although performance-based tests are a simplification of the demands associated with activities of daily life [70], they offer the potential of better reproducibility, greater sensitivity to change, and are less influenced by poor cognitive function, culture, language, and education [71].

Thus far, performance-based tests for AS were not available. The development and use of performance-based tests of physical functioning could offer a more valid way to assess changes in physical functioning over time and evaluate the effects of therapy in clinical trials.
Aim

The first part of this thesis focuses on the development and evaluation of a performance-based assessment tool of physical functioning in AS. In the second part of this thesis the limitations in physical functioning in patients treated with TNFi in daily clinical practice are examined in terms of long-term outcome, course, and predictors.

Outline of this thesis

Chapter 1 describes the epidemiology, classification, characteristics, treatment, and outcome assessment of Ankylosing Spondylitis.

For the evaluation of the disease course and effectiveness of TNFi therapy, physical functioning is an important outcome measure. Since objective outcome measures thereof are lacking for AS, eight performance-based tests of physical functioning based on items of the BASFI questionnaire were developed. Instead of asking patients whether they had, for instance, more or less difficulty with bending over to pick up a pen from the ground, the time patients took to perform this task was monitored. Research questions pertaining to the development of these tests were formulated.

Chapter 2

- What is the test-retest reproducibility (intra-rater reliability and agreement) of the performance-based measures of physical functioning in patients with AS?

Chapter 3

- What is the association between the performance-based measures of physical functioning and the BASFI questionnaire in AS patients?
- What is the association between exertion and pain experienced during performance-based testing and the BASFI questionnaire?
- What are the associations between performance-based tests of physical function and (i) disease activity (assessed with BASDAI) and (ii) impairments in axial mobility (assessed with BASMI)?

Chapter 4

- Do AS patients show improvement on performance-based tests of physical function after 3 months of TNFi therapy?
- Do patients who are classified as ‘non-responders’ according to ASAS20 criteria, show improvement in performance-based physical functioning?
- What are the differences between performance-based and self-reported (BASFI questionnaire) physical functioning after 3 months of TNFi therapy?
Chapter 5

• Which selection of performance-based tests are reliable, show improvement in physical functioning after TNFi therapy, generate the equivalent information as the full set, and is feasible for use in daily clinical practice?

The long term evaluation of physical function (BASFI) and spinal mobility (BASMI) after the start of TNFi was studied in Chapter 6. The research questions in this chapter were:

• What is the 3-year outcome and course of physical functioning and spinal mobility impairments in patients routinely treated with TNFi?
• What are predictors of the 3-year outcome and course of physical functioning and spinal mobility impairments in these patients?

Chapter 7 consists of an overall discussion of the research presented in this thesis.
References


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