Chapter 1

General introduction

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General introduction

This thesis describes aspects of Spondylarthropathies (SpA), osteoporosis and vertebral fractures and the relationship between them. In addition, imaging of early Ankylosing spondylitis (AS), radiographic progression of longstanding AS and work participation will be studied. The introduction of this thesis gives a description of above mentioned topics and addresses different aspects of SpA studied in this thesis.

Classification criteria of Spondylarthropathies

Spondylarthropathies – or now commonly called Spondyloarthritis (SpA) – is a group of chronic systemic rheumatic disorders characterized by pain and inflammation of the spine and sacroiliac joints. SpA comprises a group of interrelated inflammatory diseases which constitute of several conditions with overlapping features, such as arthritis involving the axial skeleton with inflammatory back pain, uveitis, dermatological and gastroenterological involvement and a genetic association with HLA-B27. The group Spondylarthropathies includes different rheumatic disorders like Psoriatic arthritis (PsA), SpA associated with inflammatory bowel diseases (entero-associated arthritis), Reactive arthritis (ReA, which can occur after a bacterial infection), Juvenile onset SpA, Undifferentiated SpA (uSpA) and Ankylosing spondylitis (AS).

For many years the Amor criteria or criteria of the European Spondylarthropathy Study Group (ESSG) were used as classification criteria for SpA [1-3]. The ESSG criteria included a large number of clinical characteristics that were associated with these spinal inflammatory diseases, such as uveitis, psoriasis, inflammatory bowel disease, enthesitis and familial association (Table 1) [3]. In 2009 the ASAS classification was introduced, and the classification criteria of Spondylarthropathies were revised and renamed as Spondyloarthritis [4, 5]. Spondyloarthritis was divided in two subtypes: a subtype with predominantly axial manifestations (of the spine), axial SpA, and a subtype characterized by predominantly peripheral arthritis, peripheral SpA (Table 2) [6].

Axial SpA is subdivided in a non-radiographic axial SpA, without signs of sacroiliitis on the X-rays (but in some cases inflammation at MRI of the SI-joints) and Ankylosing spondylitis (AS) which requires sacroiliitis grade 2 bilateral or grade 3 unilateral on the X-ray according to the modified New York criteria [7].

Table 1. ESSG criteria for Spondylarthropathies

Inflammatory Back Pain	OR	**Synovitis** asymmetric or predominantly in the lower limbs

Plus at least one of the following:

- Enthesitis (heel)
- Psoriasis
- Crohn's disease, Colitis ulcerosa
- Urethritis/cervicitis or acute diarrhea within one month before arthritis
- Positive family history of SpA
- Buttock pain (alternating between right and left gluteal areas)
- Sacroiliitis

Dougados M et al. Arthritis Rheum 1991;34:1218.

Table 2. ASAS classification criteria for axial and peripheral SpA

≥ 3 months back pain and age at onset <45 years			Peripheral symptoms ONLY
Sacroiliitis on imaging* plus ≥1 SpA feature	OR	HLA-B27 plus ≥2 other SpA features	Arthritis or enthesitis or dactylitis PLUS

SpA features:	≥1 SpA feature	≥2 other SpA features
- Inflammatory back pain (IBP) - Arthritis - Enthesitis (heel) - Uveitis - Dactylitis - Psoriasis - Crohn's disease, Colitis ulcerosa - Good response to NSAIDs - Family history for SpA - HLA-B27 - Elevated C-reactive protein (CRP)	- Uveitis - Psoriasis - Crohn's/colitis - Preceding infection - HLA-B27 - Sacroiliitis on imaging	- Arthritis - Enthesitis - Dactylitis - IBP ever - Family history for SpA

* Sacroiliitis on imaging:
Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA OR definite radiographic sacroiliitis on X-ray according to the modified New York criteria.

Rudwaleit M et al. Ann Rheum Dis 2011;70:25.

In the period during which patient data were collected for the studies presented in this thesis, the old nomenclature of Spondylarthropathies (according to the ESSG criteria) and Ankylosing spondylitis (according to the Modified New York criteria) was still commonly used and for this reason the old nomenclature will be used in this thesis.

Clinical characteristics of Spondylarthropathies

The overall prevalence of SpA in the population has been reported to be as high as almost 1.9% [8, 9]. However, there is a wide geographic variation in reported estimates of the prevalence of these diseases because of the close correlation with the prevalence of HLA-B27 in a given population. AS, as the prototype disease of the SpA group, has an estimated prevalence of about 0.5% [8, 10]. AS commonly starts in the second or third decade of life [11, 12], whereby men are affected two to three times more frequently than women [11] and the disease tends to be more severe in men [13].

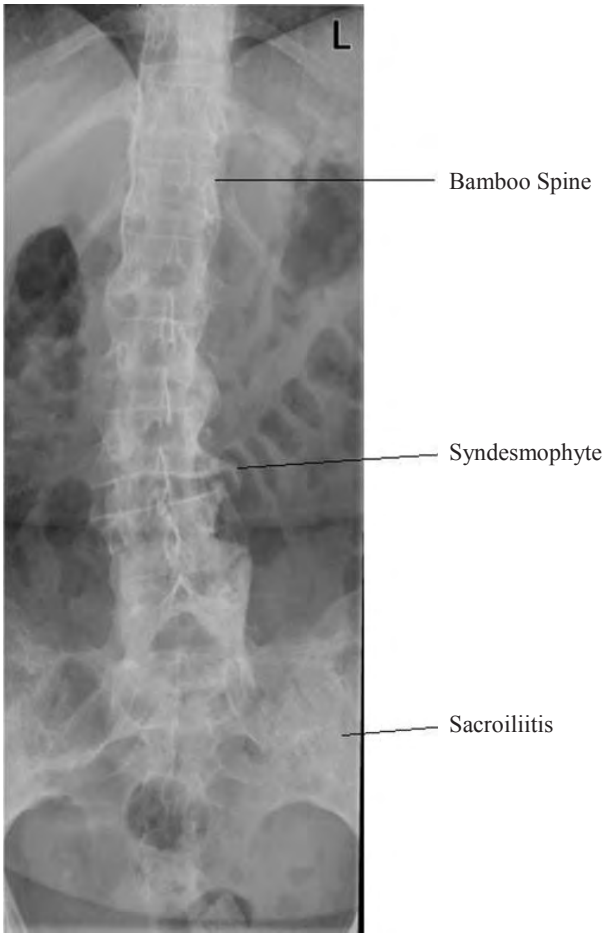
The pathogenesis of SpA as a whole, but also of AS is still poorly understood. The pathogenesis is considered to be a result of a complex interplay between genetic predisposition, the immune system and environmental factors (micro-organisms), leading to a disturbed immune system and chronic inflammation. In addition to a strong association with HLA-B27 (genetic predisposition), it has been shown that bacterial infections, such as Chlamydia or gastrointestinal infections (with Salmonella, Shigella, Yersinia or Campylobacter) may contribute to the development of SpA [14, 15].

The disease symptoms are pain in the buttock area (due to inflammation of the sacroiliac joints), back pain during the night and morning stiffness. This morning stiffness lasts at least one hour, but often many hours, and improves with exercise but is not relieved by rest. AS predominantly affects the axial skeleton with sacroiliac joint involvement (sacroiliitis) as its hallmark causing decreased spinal mobility. Besides the axial disease also more peripheral disease with articular manifestations (i.e. pain and stiffness) and extra-articular manifestations like uveitis, inflammatory bowel disease and psoriasis contribute to the burden of the disease.

The course of SpA disease and more specifically AS, varies between a mild form, without much functional disability, and a very severe, disabling form in a minority of cases. Several prognostic factors for severe disease were described, such as male sex, elevated CRP and early involvement of the hip joints [9, 16].

Inflammation can result in additional bone formation with the occurrence of syndesmophytes of the spine that may lead to ankylosis (and finally to a so called bamboo spine) and thoracic kyphosis (Figure 1).

Figure 1. Lumbar spine and SI-joint in Ankylosing spondylitis



Radiological progression in AS mainly consists of new bone formation compatible with syndesmophytes formation or growth, instead of bone resorption known as in most rheumatologic diseases [17, 18]. The modified Stokes Ankylosing Spondylitis Spine Score (mSASSS) is a validated measurement used as index of radiological progression of the disease of the cervical and lumbar spine [19]. The mSASSS describes changes of the vertebra (erosions, squaring, sclerosis) and stages of growth of syndesmophytes (score 0-3)

at cervical (C2-Th1) and lumbar level (Th12-S1). The mSASSS scores a total of 24 sites, has a maximum of 72 and the minimal recommended interval to determine radiographic changes is two years [19].

The process of inflammation with bone repair results in ankylosis of the sacroiliac joints (grade 4) in a large number of AS patients (Figure 1). For the diagnosis of definite AS fulfillment of the modified New York criteria is required: bilateral sacroiliitis grade 2-4 or unilateral sacroiliitis grade 3 or 4 plus at least one criterion out of 3 (inflammatory back pain, limited lumbar spinal motion in sagital and frontal planes, and decreased chest expansion relative to normal) [7].

Treatment starts with physical therapy and regular exercises or sports in combination with Non Steroidal Anti-Inflammatory Drugs (NSAIDs) [20, 21]. NSAIDs in an adequate anti-inflammatory dosage decrease pain and morning stiffness, and might even delay the radiographic progression [22]. Several studies have shown that selective COX-2 inhibitors (such as etoricoxib and celecoxib), which have less gastrointestinal side effects than the classical NSAIDs, are very effective in AS as well [23, 24]. In contrast with other rheumatic diseases such as Rheumatoid arthritis, most Disease Modifying Anti-Rheumatic Drugs (DMARDs) do not seem to be effective in AS, except for sulphasalazine which has shown to be effective in AS patients with peripheral arthritis [20, 21]. Major therapeutic improvement was made possible in SpA by the introduction of biologicals, especially Tumor Necrosis Factor α (TNF-α) inhibitors. At the time most of the studies of this thesis were performed, three TNF blocking agents were available for AS: infliximab (administered intravenously) and the subcutaneous drugs adalimumab and etanercept [25-27]. These TNF blockers provided large improvement of pain and stiffness in the majority (60%) of the AS patients with high disease activity (defined as insufficient response to NSAIDs and a high BASDAI >4 [28].

Definition of osteoporosis and vertebral fractures

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increased fracture risk [29, 30]. The diagnosis of osteoporosis is made by measuring bone mineral density (BMD) of the hip and/or spine using a dual X-ray absorptiometry machine (DXA). BMD reflects the amount of bone mass present, which is the ratio between the amount of mineral measured and the projected area. The World Health Organization defines osteoporosis as a BMD

<2.5 standard deviations in spine and/or hips below the mean BMD of a young adult reference population (T-score). A T-score >-1.0 is defined as 'normal', a T-score between -1.0 and -2.5 as 'low bone mass or osteopenia' and a T-score <-2.5 as 'osteoporosis' [30]. The Z-score is the T-score with a correction for age [30].

Osteoporosis without a clear cause, apart from aging and postmenopausal, is called primary osteoporosis, while osteoporosis due to other causes (such as in SpA) is called secondary osteoporosis. There are numerous risk factors identified for bone loss in the general population, amongst others genetic, nutritional, hormonal, lifestyle factors, and concomitant diseases or treatments influencing bone metabolism such as age, sex, insufficient calcium and vitamin D intake, low body weight, menopausal status, premenopausal oophorectomy, lack of physical activity, smoking, previous fractures and chronic glucocorticoid use [31].

The clinical significance of osteoporosis lies in the fact that fractures can occur. It has been shown that the risk of fractures increases as bone mineral density declines [32-34]; fracture risk increases 1.5 to 3-fold or more for each standard deviation (SD) decrease in bone mineral density [30]. The beforementioned include vertebral fractures, fractures of the distal forearm and hip fractures, but the risk of fractures at many other sites are also increased when bone density is reduced. Fractures, the endpoint of a decreased bone mineral density, cause considerable morbidity, loss of quality of life, mortality and health care costs [35].

Vertebral fractures are measured using the standardized semi-quantitative method of Genant et al [36]. The vertebral fractures are assessed at lateral radiographs of the thoracic and lumbar spine (T5-L4). In Genant's semi-quantitative assessment, vertebrae receive a severity grade based on the visually apparent degree of vertebral height loss. Reduction in height is divided in grades on a scale of 0-3; grade 0 (normal) represents a reduction in anterior, middle and/or posterior vertebral heights of less than 20%, grade 1 (mild) represents a reduction of 20-25%, grade 2 (moderate) represents a reduction of 25-40% and grade 3 (severe) more than 40% reduction. Vertebral fractures were defined as reduction of ≥20% of the vertebral body height [36].

Bone changes in Spondylarthropathies

Ankylosing spondylitis is a chronic and severe inflammatory disease of the axial skeleton and joints, which leads to new bone formation leading to ankylosis of the axial skeleton and

sacroiliac joints, and impairment of spinal mobility. Inflammation associated with trabecular bone loss leads to increased bone loss and finally osteoporosis which may result in vertebral fractures. The apparent paradox here is the extensive bone formation on the one hand and bone loss on the other hand [37]. Although it seems paradoxical to have both excessive bone formation and also bone loss, the latter is a consistent feature of inflammatory diseases (like also in Rheumatoid arthritis, Systemic lupus erythematosus), which are also associated with secondary osteoporosis [38].

Osteoporosis is a known complication in longstanding and severe AS, but is also already present in AS patients with a more mild form and in earlier stage of disease [39, 40]. The reported prevalence of osteoporosis in terms of low BMD in AS patients varies from 19% to 62% [41, 42]. This large variation may reflect the variation between measurement method, anatomical site, study-population, disease-duration and the difficulties in assessing BMD in AS [39, 43]. Since AS leads to formation of syndesmophytes and ankylosing, this will influence the BMD measurements by DXA. Therefore measurement of an alternative site, such as the femoral neck, is necessary for a reliable measurement of bone mass in more advanced disease. Measurement of the femoral neck BMD showed to correlate well with vertebral fracture risk and the degree of inflammation [44].

Vertebral fractures are commonly reported in several surveys in AS patients, although the prevalence is also here highly variable mainly due to differences in recruitment methods of the patients. The prevalence reported is ranging from 4 to 58% [45]. Risk factors for vertebral fractures known in longstanding AS patients include sex (men more than women), age, low body weight, low BMD, disease duration, more syndesmophytes formation, disease activity, peripheral joint involvement, and spinal restriction of movement [45-51]. Fractures of the vertebral body in AS can result in serious complications as neurological deficits, acute or chronic back pain and can lead to progression of hyperkyphosis [48, 52].

Imaging of early Spondylarthropathies

The onset of complaints in SpA is often gradual and it takes many years before the disease AS comes to full expression and definite radiographic sacroiliitis appears according to the modified New York criteria [7]. Consequently, the diagnosis is often delayed by 5 to 10 years, especially in patients with an early or incomplete clinical picture [9, 53, 54].

Much effort has been put in new techniques to diagnose the disease in an earlier stage. Nowadays, magnetic resonance imaging (MRI) is commonly used for detection of sacroiliitis and inflammation of the spine in early AS. MRI enables to detect (early) inflammation by visualization of tissue edema or enhanced gadolinium contrast uptake or both [55, 56]. However, chronic AS changes, such as new bone formation in the spine (syndesmophyte formation), tend to be less well visualized on MRI than on radiographs [57]. Positron emission tomography (PET) combined with computed tomography (CT) is another interesting imaging modality for diagnosing AS. PET allows imaging of functional tissue changes in the whole-body by targeting binding sites (58). The combination of PET and computed tomography (CT) combines the unique properties of imaging of pathophysiology and anatomical CT imaging as reference [59].

Work participation in early Spondylarthropathies

Since AS usually emerges already in the third decade of life and involves axial joints leading to pain and stiffness in the back or involves the peripheral joints leading to arthritis or tendinitis and eventually extra-articular manifestations, patients often suffer from functional limitations. In consequence of these functional limitations imposed by the inflammatory disease, patients encounter restrictions in social participation, including work participation [60]. Work participation is not only important because it contributes to the quality of life of the individual patient but also because of its economic consequences for the patient itself and society [61]. Work participation can be reduced because of the functional limitation by not having a paid or unpaid job, but also more 'invisible' by reporting more sick leave (absenteeism), having reduced productivity while being at work (presenteeism), more need for help or reporting changes to working hours and type of work. From studies in longstanding AS it is known that older age at disease onset and holding a manual job were associated with withdrawal from work, while sick leave was associated with disease activity and physical functioning [60, 62].

Importance of early recognition and diagnosis

Spondylarthropathies can have a varying presentation and course of disease. The interrelated group of disorders shares a common genetic background and often familial clustering, but has a variable expression in individual patients ranging from relatively mild disease, not coming to medical attention, to severe disease with severe loss of function and

quality of life. Especially in the early phase, the disease can be difficult to diagnose and the delay can take many years. In the last decades a lot of effort has been put in methods to diagnose the disease in an earlier stage such as by using MRI for the detection of sacroiliitis. However, despite the availability of better diagnostic methods and improved treatment strategies, there is still much to optimize since the pathogenesis is still not elucidated, it is not clear in whom and when complications of the disease will express and, besides that, also the new treatment strategies do not decrease the progression of the disease. The ongoing functional loss can lead to a decreased quality of life. Therefore, it is important to investigate the complications and impact of Spondylartropathies in an early stage of the disease to be able to intervene as early as possible.

The Early SpA cohort Amsterdam

Most studies in this thesis were performed in the large outpatients referral center Reade (the former Jan van Breemen Institute) and VU University Medical Center in Amsterdam. An Early SpA cohort was started and patients with a recent diagnosis (less than 2 years) of Spondylarthropathies were included. All patients fulfilled the classification criteria for SpA according to the ESSG criteria [3]. The diagnosis Spondylarthropathy consisted of AS, Undifferentiated SpA, patients with inflammatory back pain and Psoriatic arthritis (PsA), inflammatory bowel diseases, or Reactive arthritis and Juvenile SpA. The formation of the Early SpA cohort Amsterdam gave the opportunity to study the disease course, complications of the disease and also the impact on social and work participation.

Outline of the thesis

This thesis describes early Spondylarthropathies and the paradox of bone and beyond. It contains three sections: bone mineral density and vertebral fractures in Spondylarthropathies, imaging in early SpA and work participation in early SpA.

Section 1

The first section contains studies considering low bone mineral density and vertebral fractures in Spondylarthropathies. Since bone loss is a well known complication of AS with a long disease duration and since little is known about the degree of osteoporosis in the total group of SpA or in more early disease stage, a literature review was performed first. In

Chapter 2 the literature about the prevalence of decreased bone mineral density in AS with a short disease duration (<10 years) was reviewed. In **Chapter 3** the prevalence and risk factors of low bone mineral density in early SpA patients with a disease duration of less than two years was studied. In **Chapter 4** we examined in this early SpA population the prevalence of vertebral fractures and the associated demographic and disease related variables. In addition, bone mineral density and vertebral fractures in active AS were investigated. **Chapter 5** investigates the effects of TNF-α blocking therapy of etanercept in active AS patients on bone mineral density, vertebral fractures, bone-markers and radiographic progression after two years of treatment. Since treatment with TNF-α blockers decreases inflammation and has been shown to be effective in increasing bone mineral density, it might have also positive effects on other clinically relevant outcome measures.

Section 2

The second section of this thesis deals with imaging of early AS. Diagnosing AS in an early stage is still a challenge. **Chapter 6** describes the results of a pilot study in which the potential of PET-CT for imaging AS activity is investigated by studying three different tracers, with as reference MRI imaging and conventional radiographs. Inflammation tracers [18F]FDG and [11C](R)PK11195 were studied in patients with AS with low and high disease activity, and these inflammation tracers were compared with the bone tracer [18F]Fluoride in additional patients with high disease activity.

Section 3

Finally, the third section deals with the burden of Spondylarthropathies and Ankylosing spondylitis in daily life. Among patients with Spondylarthropathies, studies on work participation are mainly performed in patients with longstanding AS and especially data in patients with recently diagnosed disease are lacking. **Chapter 7** explores the impact of early Spondylarthropathies (patients with apparent low disease activity) on work participation and investigates the variables associated with work outcomes.

At last, this thesis presents a summary of the results, a general discussion and recommendations.

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