Epidemiology and outcome of Ankylosing Spondylitis in Northern Norway

Gunnstein Bakland
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2. PUBLICATIONS INCLUDED

Paper I  Incidence and prevalence of Ankylosing Spondylitis in Northern Norway.  


Paper III Increased mortality in ankylosing spondylitis is related to disease activity.  
3. ABBREVIATIONS

AAU    Acute Anterior Uveitis
ANTXR2 Anthrax Toxin Receptor 2
AS     Ankylosing Spondylitis
ASAS   Assessment of Spondyloarthritis International Study group
BASDAI Bath Ankylosing Spondylitis Disease Activity Index
BASFI  Bath Ankylosing Spondylitis Functional Index
BASMI  Bath Ankylosing Spondylitis Metrology Index
BASRI  Bath Ankylosing Spondylitis Radiology Index
BiP    Binding immunoglobulin Protein
BMPR   Bone Morphogenic Protein Receptor
BMP-X  Bone Morphogenic Protein-X
DAN    Differential screening-selected gene Aberrative in Neuroblastoma
DKK-X  Dickkopf-X
ER     Endoplasmic Reticulum
ERAP1  Endoplasmic Reticulum AminoPeptidase1
ESSG   European Spondyloarthropathy Study Group
HLA    Human Leukocyte Antigen
IBD    Inflammatory Bowel Disease
IBP    Inflammatory Back Pain
IL-X   Interleukin-X
ILX-R  Interleukin-X Receptor
KIF21B Kinesin Family 21B
LRP-X  LipoProtein Receptor-X
MAD    Mothers Against Decapentaplegic (Drosophila protein)
MHC    Major Histocompatibility Complex
MMP-X  MatrixMetalloProteinases-X
mNY    Modified New York
MRI    Magnetic Resonance Imaging
mSASSS modified Stoke Ankylosing Spondylitis Spine Score
NK cell Natural Killer cell
NRS    Numeric Rating Scale
NSAIDs Non-Steroidal Anti-Inflammatory Drugs
OMERACT Outcome Measures in Rheumatology Clinical Trials
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PsA</td>
<td>Psoriatic Arthritis</td>
</tr>
<tr>
<td>RANK</td>
<td>Receptor Activator of NF-kB</td>
</tr>
<tr>
<td>RANKL</td>
<td>Receptor Activator of NF-kB Ligand</td>
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<tr>
<td>RUNX</td>
<td>Runt-related transcription factor</td>
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<tr>
<td>SAA</td>
<td>Serum Amyloid A</td>
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<tr>
<td>SIJ</td>
<td>Sacroiliac Joint</td>
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<tr>
<td>SMA</td>
<td>Smal pathway (Dwarfin sma protein of Caenorhabditis elegans)</td>
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<tr>
<td>SMAD</td>
<td>Combination of SMA and MAD</td>
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<tr>
<td>SMR</td>
<td>Standardized Mortality Ratio</td>
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<tr>
<td>SpA</td>
<td>Spondyloarthritis</td>
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<tr>
<td>SPARCC</td>
<td>Spondyloarthritis Research Consortium of Canada</td>
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<tr>
<td>STAT3</td>
<td>Single Transducer and Activator of Transcription 3</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WD</td>
<td>Work disability</td>
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<tr>
<td>Wnt</td>
<td>Wingless proteins</td>
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4. INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease universally affecting the sacroiliac joints (SIJ); in addition to sacroiliitis, AS also frequently affects the spine, where inflammation can be demonstrated both in entheses at the vertebral body, intervertebral disc and longitudinal ligaments, as well as in facet joints connecting adjacent vertebral bodies[1, 2]. The disease usually starts in young adults, and as no cure exists, it will follow the affected persons throughout life. The cause of the disease is not completely understood, but there is a clear genetic predisposition given the strong association with HLA B27 discovered in 1973 [3]. Over the last decade our understanding of the genetic background as well as diagnostic and therapeutic approach to the disease has undergone a remarkable transformation, which is likely to provide long-term benefits to AS patients [4-7]. Although there is data supporting evidence of long-term improved function in AS patients receiving modern treatment[8], many questions remain, such as if the new approach to patient management will also lead to improved survival and/or reduction of disability in AS.

I have held a personal interest in AS for more than 20 years, and took a more academic interest as a medical student. After entering rheumatology, it soon became clear to me that AS affected a relatively large proportion of our patients. AS had been the subject of research interest at the Department of Rheumatology since its foundation in 1978 and fortunately I have been able to nurture my interest in AS during residency through participation in this project. During the last decade, the care for patients with AS has changed dramatically, and it has been very exciting to be involved in this transition, both in patient care and in research.

5. HISTORIC BACKGROUND

AS is considered an ancient disease and it has been suggested that several of the Egyptian pharaohs suffered from AS, i.e. Ramses II (The Great), his son Merenptah and Amenhotep II[9]. However, it has been claimed that the skeletal findings in Ramses II could have been caused by diffuse skeletal hyperostosis (DISH)[10], although SIJs are not affected in this condition. The first reliable observation of the typical advanced/late stage skeletal findings of AS is attributed to an Irish physician, Bernard Connor (1666-1699)[11]. Nevertheless, it was not until the late 19th century that AS was identified as a separate entity, with Bekhterev, Marie and von Strümpel all publishing papers on the subject between 1893-1898[12]. Many decades later the pathological process of the disease was described in more detail, when
Romanus and Ydén in 1952 described superficial erosions on the anterior and antero-lateral surface of the vertebrae, also called spondylitis anterior or Romanus lesion. In 1937, Andersson described a more extensive lesion, involving both the anterior and posterior part as well as the discal surface of the vertebral body of the lumbar and thoracic spine on x-ray. These lesions were most frequent in an unstable segment with extensive ankylosis above and below[13]. It was John Ball who provided the first detailed histologic description of AS and recognised that the pathological process was characterised by enthesitis, which was distinctly different from what was known in RA. Firstly, the process was dominated by ossification, which did not occur in RA. Secondly, while the pathology in RA led to spinal instability (even though the cervical facet joints could be ankylosed in late RA), an increased stability was observed in AS. Thirdly, while the process was confined to the cervical spine in RA, it also included the thoracic and lumbar spine in AS. Fourthly, erosive lesions were found in the anterior, anterolateral and posterior attachment of the annulus fibrosus of the intervertebral discs in AS, but not in RA. Ball also described the different cells observed in an area of these lesions; predominately lymphocytes and plasma cells, but also neutrophils, and recognised that oedema is a dominating feature in the subchondral bone marrow[14]. Ball et al also described in detail the anatomical changes underlying the erosive spinal lesions and questioned the importance of inflammation in Andersson lesions or Romanus lesions; they suggested that the inflammation could be secondary to traumatic events as there was clearly evidence of spinal fractures in several patients[13].
6. PATHOGENESIS OF ANKYLOSING SPONDYLITIS

6.1 The target organ

The SIJs are located on either side of os sacrum at the junction with os ileum and is the prototypic joint affected in AS. The SIJ has a complex anatomy with an incongruent joint surface, which provides stability to the joint but makes it difficult to evaluate the SIJ surface on plain x-ray films. Surrounding ligaments and myofascial structures further enhance the stability, i.e. mm. lattisimus dorsi through the thoracolumbar fascia, mm. gluteus maximus, mm. biceps femoris and mm. piriformis. These muscles are functionally connected to SIJ ligaments, and can affect joint mobility. SIJ is a diarthrodial synovial joint, but only the anterior caudal third part of the interface between the ileum and sacrum is a true synovial joint, whereas the rest is comprised of fibrous ligaments[15]. The joint surface has a layer of, both hyaline and fibrous cartilage, which is uncommon in joints, and the fibrocartilage might be essential to the development of sacroiliitis as discussed later. The SIJ is subject to considerable physical stress through the vertebral column and pelvis, and there is only limited movement of the sacral base in anteroinferior or posterosuperior direction to the ileum, termed nutation and counter nutation, respectively. AS is not the sole cause of sacroiliitis, and trauma, infections and metabolic causes must be considered in the differential diagnosis. There is no pathognomonic test for sacroiliitis, but tests that have been used to evaluate the joint include knee-shoulder test and Patrick’s test, which evaluates movement of the hip joint and SIJ pain under stress, Gillet’s test, which evaluates movement in the joint, and Fortin finger test, where the patient localises the pain to the SIJ[16]. However, these tests have low specificity, and are not considered to be of diagnostic value.

An enthesis is the attachment site for tendons, ligaments, muscle fascias and joint capsules to bone. Although the clinical hallmark of AS is sacroiliitis, the primary target of the pathologic process seems to be the enthesis with subsequent development of enthesitis. Entheses are present in both the axial and appendicular skeleton, which explains the diverse clinical manifestations of enthesitis which can also involve synovial joints, fibrocartilaginous joints, syndesmoses and extra-articular entheses[17]. According to Benjamin & McGonagle[18] the enthesis has at least three functions. Firstly, it serves as an attachment for soft tissue to bone. Secondly, it preserves the structural integrity of soft tissue such as muscles, tendons and capsules by dissipation of mechanical stress and, thirdly, it enhances growth of bone in the adolescent individual. The enthesis can also be defined in a broader term as an “enthesis
organ”, where closely associated fibrocartilaginous structures contribute to reduction of mechanical stress. Based on the anatomy of the enthesis organ, three different types of fibrocartilaginous entheses have been identified: 1. The classical enthesis, 2. The ‘functional’ enthesis and 3. The ‘articular’ fibrocartilaginous enthesis, which are related differently to SpA based on their anatomical structure. The classical enthesis, as exemplified by the achilles tendon, contains enthesis fibrocartilage immediately adjacent to the bony surface, a sesamoid fibrocartilage in the deep part of the tendon, periosteal fibrocartilage on the tuberosity of the calcaneus, a retrocalcaneal bursa between the tendon and the bone and a synovial fold that is associated with the retromalleolar fat pad. The functional enthesis is a region where tendons or ligaments wrap around, but are not attached to, bony pulleys, while the articular fibrocartilaginous enthesis is a synovial joint with a fibrocartilaginous lining instead of hyaline cartilage lining. In the SIJ, there is a predominately fibrocartilaginous lining on the iliac side with hyaline cartilage lining on the sacral side. This changes with age, as hyaline cartilage gradually replaces fibrocartilage, and it has been speculated that this could be one reason why the onset of SpA after 40 years of age is rare[18], as sacroiliitis starts with a subchondral osteitis on the iliac side, that is more exposed to shear forces than the sacral side.

An association between enthesitis and arthritis was proposed by McGonagle et al in 1998[19] as they claimed that arthritis in SpA was a secondary to enthesitis, and that this trait separated SpA-like arthritis from RA-like arthritis.

6.2 Formation of syndesmophytes
Development of syndesmophytes is often regarded as the hallmark of vertebral pathology in AS. They extend along the posterior and/or anterior longitudinal ligaments or the intervertebral discs of the spine, and by forming a bony bridge can unite adjacent vertebrae resulting in the typical ankylosis of AS[20]. Plain x-ray of the spine is considered the gold standard for evaluation of syndesmophyte formation, while MRI is the preferred method for detecting the underlying inflammation[21]. While several scoring methods have been developed to assess syndesmophyte formation, the mSASSS is now the preferred scoring method in studies of AS, and evaluates development of sclerosis, erosions, squaring, syndesmophytes and ankylosis[22]. ASAS recommend that radiographic evaluation to detect disease progression be not performed more frequently than every second year. Baraliakos et al[23] reported that 50.9 % of AS patients had no or minimal radiographic damage of the spine at baseline (mean disease duration 11.0 years) and that radiographic deterioration
occurred in 42.2 % of the cohort 2 years later, with patients with baseline radiographic
damage significantly more likely to progress.
Several studies have demonstrated an increased risk of syndesmophyte progression at sites
where MRI demonstrates inflammation[23, 24]. However, the rate of radiographic
progression in AS is not reduced, even after successful treatment with TNF-inhibition and
elimination of inflammation on MRI[21, 25]. As reduction of inflammation reduces
radiographic progression in RA, this contrary observation in AS came as a surprise, and has
led to a new focus of AS research; why is the rate of spinal radiographic progression not
affected by changes in inflammation?
To explain this, it is necessary to describe the normal regulation of bone formation. Two
types of bone formation is recognised; the endochondral and the membranous bone
formation[26], of which the former is dominant in AS. The only cell capable of bone
formation is the osteoblast, which differentiates from mesenchymal precursor cells. This
differentiation is induced by several peptides/molecules that will be described shortly.
Osteoblasts are stimulated by BMP; BMPs are members of the TGF-β superfamily, and are
involved in cell differentiation, survival and proliferation, not restricted to bone metabolism.
The intracellular signal mediated by the binding of BMP to BMPR, is dependant on the
phosphorylation of receptor regulated SMAD-proteins (R-SMAD), which eventually
activates or inhibits gene transcription in osteoblasts [27]. Prostaglandins, such as PGE2, are
also an important local factor in this regulation. BMP2 and PGE2 synergizes to induce
differentiation of mesenchymal precursor cells through activation of R-SMAD, and increased
levels of intracellular SMAD-proteins can be demonstrated in entesiophyte formation in
AS[28]. Wnt peptides are also an inducer of bone formation. Wnt peptides are a group of
signalling peptides involved in the Wnt-pathway, which also includes β-catenin[29]. It might
be that BMPs are more important early in the process of endochondral bone formation and
Wnts more significant in a later phase[26] Sclerostin is a member of the DAN family of
glycoprotein that is expressed in the osteocyte/osteoblast after transcriptor activation of the
c sclerostin gene (SOST) by transcription factor RUNX2[30], and inhibits bone formation
through Wnt inhibition[31]. Another inhibitor of Wnt is DKK1, a member of a family of
cysteine-rich proteins (DKK1, 2, 3 and 4) that serves as a natural inhibitor of Wnt[32].
Noggin is another inhibitor of BMP, and can be detected in chondrocytes during
endochondral bone formation. In animal models, haploinsufficiency of noggin, i.e. low
output or non-functional product of transcription of the only functioning gene copy, may lead to ankylosis [28].

Wnt promotes bone formation through induction of transcription of genes involved in osteoblast differentiation and bone formation. The phosphorylation of β-catenin is permitted through Wnt binding a membrane receptor complex in the membrane of mesenchymal cells consisting of LPR5/6 and frizzled receptors [32]. The activated β-catenin then translocates to the nucleus and induces transcription of genes involved in osteoblast differentiation[20]. Demonstration of phosphorylated β-catenin can thus be a surrogate marker of Wnt activation, and this is observed in syndesmophyte formation in AS[28]. Through DKK-1 and sclerostin, Wnt can be inhibited, and thus new bone formation reduced. DKK-1 then engages the same LPR5/6 receptor as Wnt, but in addition a co-receptor, kremen-1/2. This promotes internalization of the receptor, thereby reducing the signal from Wnt and reducing bone formation[32]. RANK/RANKL is also involved in bone homeostasis, and induces osteoclast differentiation and activation. Synovial fibroblasts and activated T-cells are the major sources of RANKL, thus contributing to osteoporosis in diseases characterised by inflammation[33].

In RA, a disease dominated by bone loss in affected joints, levels of DKK-1 and sclerostin are higher compared to controls, whereas AS patients demonstrate lower levels than the controls[31]. It is hypothesised that while inflammation might be the initial step during which TNF is probably important, the inflammation itself is not sufficient to induce bone

Figure 1. A very simplified illustration of regulation of bone formation.
formation. This seems to require an additional element of trauma or mechanical stress in the area of osteitis to induce the repair mechanism[26]. This was demonstrated in a study presented by Rik Lories at the Spondyloarthropathy congress in Gent 2008. Mice suspended by their tails in their cages, did not develop hind-foot arthritis and enthesiophytes/ankylosis, whereas the entire control group, that was not suspended, did. Subsequently, however, TNF actually inhibits bone formation through induction of sclerostin, DKK-1 and RANKL, and this explains the increased risk of osteoporosis normally observed in chronic TNF driven inflammation.

![Diagram](image)

**Figure 2.** Interaction between insult, inflammation and pathological repair processes in Ankylosing Spondylitis. At a certain point of time, repair processes are initiated (Inflammation/Repair switch) which start a perpetuating bone anabolic response driven by prostaglandins, Wnt and BMP proteins. In case of chronically persisting inflammation and the establishment of synovitis destructive bone-erosive processes dominate and prevent repair responses [20]. Courtesy of publisher.

### 6.3 Biomarkers of Ankylosing Spondylitis

Later studies have demonstrated that there is an abundance of T-cells (CD3+, CD4+ and CD8+) in the subchondral bone marrow in biopsies from the SIJs and the spine in AS patients. B-cell (CD20+) numbers are increased in areas with persistently active
inflammation, as well as increased angiogenesis. Macrophages (CD68+) and osteoclasts are also found in increased numbers compared to controls[2, 34]. Appel et al reported that foci with increased number of T-cells, osteoclast and angiogenesis were seen in AS compared to osteoarthritis or RA patients, but only in bone marrow with intact cartilage lining. They suggested that the inflammatory process only takes place in the bone marrow and bone-cartilage interface, and that cartilage on the surface might be necessary for the induction of inflammation[35]. Immunochemistry studies have shown that Cathepsin K is strongly expressed by mononuclear cells, fibroblast-like cells and cells attached to the bone surface in areas of active disease. The same study reported that small mononuclear cells attached to bone expressed MMP1, a protease involved in osteochondral destruction, and invasion of these cells into bone was demonstrated at sites of enthesitis. In RA and OA control groups, only RA patients expressed MMP1 to the same extent, while neither group expressed Cathepsin K [36]. As both Cathepsin K and MMP1 are important proteases with collagenolytic capability, and this study included patients with longstanding AS, this is suggestive of continuous bone destruction in AS patients. It is also a demonstration, in situ, of simultaneous bone destruction and inflammation in AS patients with an increased expression of RANKL in spinal biopsies consistent with increased bone destruction. This is supported by another study showing a correlation between serum levels of sRANKL and osteoporosis in AS patients [37]. Im et al demonstrated increased osteoclast activity in AS patients compared to healthy controls, and found osteoclast activity to be correlated to ankylosis of SIJs, but not to disease activity by BASDAI or CRP[38]. As other studies have shown that MMP3 levels in serum is predictive of radiographic progression of AS[39], it is therefore reasonable to conclude that bone destruction is indeed involved in the new bone formation in AS, although the exact mechanism is yet to be revealed.

6.4 HLA B27 in the pathogenesis of AS

HLA B27 is strongly associated with SpA. HLA B27 is a member of the MHC class I molecules, which consists of HLA heavy chain and β2-microglobulin, see figure 3. The heavy chain is constructed by three polymorphic α-chains, encoded by the HLA gene, while the non-polymorphic β2M-chain is encoded by the β2M-gene[40].
Figure 3. Simplified sketch of a cell containing the endoplasmic reticulum (ER), a peptide to be presented to T-cells and a HLA molecule consisting of a heavy chain and β2-microglobulin.

HLA-molecules are present on every nucleated cell, and their main function is to process and present intracellular peptides to T-lymphocytes through expression on the cell’s surface. HLA B27 molecules are capable of initiating vigorous cytotoxic T-cell responses against certain viruses, and this capability is preserved in SpA patients, as illustrated in figure 4[41].

Figure 4. Hypothetical model for the role of HLA-B27. The formation of homodimers in the pathogenesis of spondyloarthritis. From McMichael and Bowness[41]. Courtesy of publisher.

The discovery of the association between AS and HLA B27 by Brewerton et al in 1973 [3] was a major breakthrough in the search of the pathogenesis of AS, but it has proven difficult to further elucidate the exact role of HLA B27 in AS. The prevalence of HLA B27 has been
described worldwide, and in general the frequency is higher in the circumpolar areas on the northern hemisphere [42], see figure 5 (appendix).

HLA B27 has been extensively studied, and more than 86 subtypes are now recognised according to the IMGT/HLA database as of January 5th 2012. The HLA B27 gene located in MHC-region of chromosome 6 transcribes to the HLA B27 molecule. The parent B27 allele, B*2705, is the most prevalent allele in the Western European Caucasian population, comprising some 90 % of HLA B27 in the region, while B*2702 is the second most prevalent (10 %). The distribution of subtypes worldwide, however, is influenced significantly by migrations across continents and by susceptibility to other diseases. Individuals with HLA B27 are for instance reported to be less resistant to infections with *P. falciparum*, thereby a negative selection of B2705 have occurred in regions endemic to malaria. This would be one possible explanation to the rare occurrence of this gene in sub-tropical areas, and to some extent the survival of mutations of B2705 in these areas, as the newer subtypes are not to the same degree negatively selected by malaria infections, see figure 5.

The association between HLA B27 and AS weakens as the population frequency of HLA B27 drops and when the original subtype, B2705, is mutated to other subtypes[42]. This could, however, be a consequence of the relative stability of HLA B27 negative patients in a population; when the frequency of HLA B27 in the population drops, the proportion of HLA B27 negative AS patients will increase.

Thus, in Eastern Asia subtypes B*2704 and B*2705 dominate, while in Southern Asia subtype B*2707 is frequently encountered. The subtype B*2706, which is also prevalent in some populations in Eastern and Southeast Asia (i.e. Thailand, Malaysia and Indonesia), appears to be only weakly associated with AS. The same applies to B*2709, which is found mainly in Sardinia[42]. The initial perception that these subtypes were absolutely protective against development of AS, has been challenged by reports of AS in individuals with B*2706/B*2709[43, 44]. The variable disease association is fascinating when one considers the subtlety of the structural alterations between, for instance, B*2705 and B*2709, which differ only at one amino acid position (116) where His has substituted Asp. Crucially, perhaps, this alteration occurs at the bottom of the peptide-binding groove, which greatly influences peptide binding by HLA B27[45]. A similar observation is made in several other conditions e.g. sickle-cell anaemia, thalassemia and variants of muscle dystrophy, where the risk of developing disease is associated to alterations in only one amino acid in a peptide sequence, [46-48].
The mechanism by which HLA B27 contributes to the development of AS, is not completely understood. Given the association between AS and IBD, gut bacteria could be directly involved in the pathogenesis. In 1992 it was hypothesised that *K. pneumonia* might cause AS [49], but it has proven difficult to confirm this and similar hypotheses. Currently, there are several theories to explain the involvement of HLA B27 in AS:

1) The arthritogenic peptide hypothesis, or molecular mimicry hypothesis, suggests that specific self-peptides may bind to HLA B27 and initiate an inflammatory response. This loss of self-tolerance is considered the result of an infectious process, where an immune response is mounted against bacterial antigens that have sequence homology with self-peptides that subsequently can serve as immune stimuli. Such a self-peptide has not been described to satisfaction yet, but T-lymphocytes responsive to peptides derived from self have been demonstrated in AS patients[50]. This hypothesis would put AS in the group of autoimmune diseases and would require evidence of involvement of the role for HLA-molecules in antigen presentation to CD8+ T-cells. However, development of AS in the absence of functioning CD8+ T-cells in animal models questions this theory, and suggest that CD8+ T-cell restriction is not a prominent feature of AS pathogenesis[51].

2) Another theory suggests a non-classical role of HLA B27 in the pathogenesis and focuses on the misfolding of the HLA B27 heavy chain in the ER. Antigenic peptides form a complex with HLA heavy chain and β2M, that is folded into a three dimensional structure within the ER. Protein folding in HLA B27 complexes is slower than in other HLA molecules, and this *unfolded protein response (UPR)*, could give rise to signalling to macrophages to produce IL-23 and thereby activate T<sub>H</sub>17-cells to produce IL-17, which has a proinflammatory effects [50]. Recently, polymorphism in the ERAP1 gene, that encodes a protein involved in peptide trimming in the ER, was found only in HLA B27 positive AS patients. This suggests a possible interaction between HLA B27 and ERAP1, and supports peptide misfolding as a factor in AS-pathogenesis[52]. However, this tendency to misfold was not observed with subtype *B*2707 that is linked to AS development, [53].
Figure 6. Three different HLA-B27 structures and hypotheses as to how they might induce disease processes in ankylosing spondylitis [50]. Courtesy of publisher.

3) On the cell surface, $\beta_2$M might dissociate from the heavy chain of HLA B27, thereby creating free heavy chains. These heavy chains are then known to form homodimers, which are capable of engaging receptors on the surface of pro-inflammatory NK-cells and T-lymphocytes and thus activate these cells[50]. It has also been suggested that the formation of such homodimers can be the result of misfolding[4], see figure 6.

4) Finally, a third theory suggest that HLA B27 renders an individual more capable of clearing viral infections (e.g. HIV, Hepatitis C, influenza) and less so when dealing with intracellular bacteria such as Salmonella, Shigella or Chlamydia, creating a chronic or prolonged subclinical infection which contributes to susceptibility to AS[4].

### 6.5 Other genes in the pathogenesis of AS

It has been indicated that genetic factors could contribute more than 90 % to the overall susceptibility to AS, with various environmental factors contributing to the rest [54]. It is also reported that while less than 5 % of HLA B27 positive individuals will develop AS, around
20% of HLA B27 positive first-degree relatives of AS patients (HLA B27 positive) will develop the disease themselves[55]. Although HLA B27 is by far the best known and probably the single most important genetic factor in the development of AS, family studies have suggested that this gene accounts for not more than 40% of the genetic disease susceptibility[4]. This indicates that other genetic factors must be at play as well, and non-HLA B27 genes in the MHC-region have a substantial role in the pathogenesis of AS[56], including HLA B*40:01, with an attributable risk of 34% [56]. In 1989 Robinson et al found that the presence of HLA B*40:01 (HLA Bw60 when tested serologically) was increased in HLA B27 positive patients with AS, but not in HLA B27 negative cases. Patients expressing both the B40:01 allele and B27 allele had a three-fold increased risk of developing AS compared to those who only expressed B27 alone[57].

Due to the extreme complexity of the MHC region, it has proven difficult to successfully identify further which single gene(s) actually contributes to this increased risk, and studies with large sample sizes and extensive marker density would be required.

In terms of non-MHC genes, numerous candidate genes have been identified and confirmed in several GWAS studies. Among these are ERAP1, IL-23R, IL-1R2, KIF21B, ANTXR2 and STAT3, while other possible genes and genetic regions have inconsistently been associated with AS susceptibility [4]. In a recently published study several genes were either confirmed to be associated to AS or found to be strongly associated in replicated studies. RUNX3 is coding a transcription factor involved in differentiation of CD8 lymphocytes, whereas the expression of PTGER4 is increased in bone samples from AS patients compared to healthy controls[52]. This is summarized in table 1.

IL-23R is also associated to AAU, IDB and psoriasis, whereas it is still not clear whether ERAP1 is associated solely to AS. In addition to peptide trimming, ERAP1 has another known function as it cleaves cell surface receptors (IL-1R2, IL-6Rα and TNFR1) of proinflammatory cytokines[58] thereby down regulating the biological activity of these cytokines. A malfunctioning ERAP1 could therefore contribute to sustaining the state of inflammation in AS.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Localisation</th>
<th>Associated biological function.</th>
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<tbody>
<tr>
<td>ERAP-1</td>
<td>5q15</td>
<td>Peptide trimming in ER.</td>
</tr>
<tr>
<td>IL-23R</td>
<td>1p31.3</td>
<td>Promotes differentiation of naïve CD4 T-cells into helper Th17 T-cells.</td>
</tr>
<tr>
<td>IL-1R2</td>
<td>2q11-12</td>
<td>Decoy receptor. Interfering with binding of IL-1 to IL-1R1.</td>
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<tr>
<td>KIF21B</td>
<td>1q31</td>
<td>Involved in transport of cellular components along axonal and dendritic microtubules.</td>
</tr>
<tr>
<td>ANTXR2</td>
<td>4q21</td>
<td>Binds to collagen IV and laminin. Possibly involved in extracellular matrix adhesion.</td>
</tr>
<tr>
<td>STAT3</td>
<td>17q21</td>
<td>Cytoplasmic transcription factor. Activated by several cytokines.</td>
</tr>
<tr>
<td>RUNX3</td>
<td>1p36</td>
<td>Differentiation of CD8+ lymphocytes</td>
</tr>
<tr>
<td>PTGER4</td>
<td>5p13</td>
<td>↑ expression in bone biopsies in AS</td>
</tr>
</tbody>
</table>

Table 1. Non-MHC genes associated to AS and their assumed biological function or association.
7. CLASSIFICATION AND DIAGNOSIS OF AS

AS is classified as one of several entities within the disease group of Spondyloarthritis (SpA), which also includes psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), reactive arthritis (ReA), a subgroup of juvenile arthritis (JCA) and undifferentiated spondyloarthritis (uSpA)[59], see figure 7.

![Spondyloarthritis Classification Diagram](image)

Figure 7. The group of Spondyloarthritis including ankylosing spondylitis (AS), enterocolitis-associated arthritis (EA), psoriatic arthritis (PsA), reactive arthritis (ReA), juvenile chronic arthritis (JCA) and undifferentiated spondyloarthropathy (USpA).

The classification of AS evolved from the earliest Roma criteria[60], published in 1961, to the New York criteria and finally the modified New York criteria (mNY) which were published in 1984[61]. With each set of criteria alterations were made to increase sensitivity and specificity, e.g. the introduction of inflammatory back pain by Calin et al to the modified New York criteria[62]. These criteria consist of both clinical and radiological variables, with radiographic sacroileitis as the *sine qua non* condition.

Ideally, classification criteria should enable the clinician to separate similar, but different conditions in order to make reliable assumptions regarding response to therapy and long-term prognosis. Although classification criteria are meant to facilitate scientific work by ensuring homogeneity of study cohorts, they are not necessarily suited to be diagnostic criteria. Whereas classification criteria therefore must give emphasis to specificity to ensure homogeneity, diagnostic criteria usually emphasise sensitivity in order to include a greater
number of patients. Nonetheless, there has been a widespread application of the mNY criteria in the diagnostic approach of patients with suspected AS.

Because the development of radiographic lesions in the SIJ is both a slow process that is also difficult to verify on plain X-ray, the universal requirement for radiographic evidence of sacroiliitis has typically led to a considerable diagnostic delay of 5-8 years on average in AS patients[5, 63]. Not only are the SIJs notoriously difficult to evaluate on plain x-ray, but studies have shown that the potential for improvement of the reading process through further education and training, is limited[64]. Likewise, the rate of the radiographic changes implies that an interval of two or more years is necessary to detect any changes to the spine[65].

There have been several propositions of an alternative, broader classification scheme, which would lead to a diagnosis of SpA as opposed to AS. The Amor criteria and the European Spondyloarthritis Study Group (ESSG) criteria are examples of such alternative criteria [66, 67] and have led to a debate whether to ‘lump’, using the broader SpA criteria, or ‘split’, using the more stringent mNY criteria in the diagnostic evaluation of patients [68]. The SpA criteria did not resolve the issue of diagnostic delay in a satisfactory manner, but it was a string of technical and medical innovations that forced a new development in this matter. The therapeutic possibilities for these patients changed dramatically with the introduction of anti-TNFα therapy around the start of this millennium[69]. Standard therapy until then had been limited to NSAIDs, paracetamol and occasionally sulfasalazine. Previously there were no major immediate therapeutic consequences from diagnosing AS, but now the patients and the rheumatologists found the potential benefits of establishing an early diagnosis to be substantial and tangible. During the same period of time, the more widespread availability and application of MRI led to a shift in the diagnostic approach to patients with inflammatory back pain [70]. As MRI allowed imaging of the inflammatory processes in the SIJ, clinicians soon adopted this in their diagnostic and therapeutic approach [71]. There is an inclination towards equalling inflammation of the SIJ with the future development of sacroiliitis as described in the mNY criteria, but recent publications indicate that this assumption may be incorrect. Bennett et al suggested that merely one third of patients presenting with typical inflammatory lesions in the SIJs on MRI will develop the chronic damage described in the mNY criteria within eight years; the extent of inflammation and presence of HLA B27 were the main predictors for radiographic sacroiliitis[72]. Similar observations have been made regarding inflammation in the spine, where MRI evidence of inflammation of the corners of
the vertebrae carries a fourfold (20 vs. 5%) risk of syndesmophyte formation[24]. But as with the SIJ, inflammation on MRI does not necessarily lead to chronic skeletal damage demonstrable on x-ray. Thus, presently the finding of inflammation on MRI is not synonymous with radiographic mNY criteria, and raises the question whether AS should or should not be diagnosed on the bases of inflammatory lesions on MRI alone.

This prompted the ASAS group to establish a new set of classification criteria, which enabled a diagnosis of axial SpA, and incorporated MRI findings, but also allowed for a SpA diagnosis in the absence of radiographic evidence of present or previous inflammation in the SIJ[73]. It is today generally believed that the initial inflammation of AS starts in the subchondral bone marrow, and MRI can detect this process. Patients in this pre-radiographic phase of the disease are reporting the same level of symptoms and burden of disease as characteristic of AS[63], even though they may not develop the ankylosis characteristic of longstanding AS. Nevertheless, it is likely that the inflammation driving this process carries the risk of many of the complications typical of AS. This new broad criteria set for SpA is shown in figure 8, and illustrates how classification is altered when our understanding and knowledge of the clinical and pathological bases of a condition increases. However, it would probably be essential to evaluate the effect and performance of the new criteria at some point.
ASAS classification criteria for axial SpA
(in patients with back pain ≥ 3 months and age at onset < 45 years)

Sacroiliitis on imaging*
plus
≥ 1 SpA feature**

or

HLA-B27
plus
≥ 2 other SpA features**

**SpA features:
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease/ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

* Sacroiliitis on imaging:
  - Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
  - Definite radiographic sacroiliitis according to mod. New York criteria

Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset < 45 years.
Imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%.
** Note: Elevated CRP is considered a SpA feature in the context of chronic back pain

Figure 8. The ASAS classification criteria for axial SpA, from Rudwaleit[73]. Courtesy of publisher.
8. EPIDEMIOLOGY OF AS

The occurrence of AS has been described in several populations on several continents, and in general, AS prevalence correlates with HLA B27 prevalence[42]. Among the highest ever reported, is the prevalence of AS in the Haida people of British Columbia, Canada, and Alaska, US. In two studies by Gofton et al, it was reported that the prevalence of HLA B27 was 50%, and 6-10 % of male adults had evidence of sacroiliitis[74, 75], but if the Rome criteria of AS were deployed, 6.2 % were found to satisfy these criteria[76]. In a Russian study of the Chukotka region, the prevalence of HLA B 27 was 32 % with AS observed in 0.4 %[77]. Studies of the population in North Norway have revealed estimates of HLA B27 frequencies in the two dominant subgroups of the population, Norsemen of 15.9 % and Samis 24 %[78, 79]. Likewise, the prevalence of AS in the same populations has been estimated to be 1.1-1.4 % in the former population and 1.8 % in the latter[79, 80].

While early publications were from areas with a suspected high occurrence of the disease, several publications the last years are from areas with mid-to-low prevalence of HLA B27 and AS/SpA. In Germany, Braun et al calculated the prevalence of SpA and AS to be 1.9 % and 0.86 %, respectively among blood donors [81], which is substantial in a population with a frequency of HLA B27 of 9.3 %. In populations with lower frequency of HLA B27, the observed prevalence of AS or SpA is lower as well. In China, several studies estimate HLA B27 prevalence in the Han population to range from 3.6-5.7 %. An impressive 17 studies on AS prevalence in China had been published by 2008, of which 14 had been performed in the Han population. The range of reported prevalence of AS was 0.19 - 0.54 %, although most studies reported 0.2-0.3 %. The prevalence of AS was 0.24 % and 0.06 %, respectively, in two large studies, each with more than 20.000 participants of multi-ethnic populations. Interestingly, in three studies the prevalence of undifferentiated SpA (uSpA), was 3 to 4 times the prevalence of AS[82]. That was also the case in a recent Swedish study, reporting that SpA and AS had a prevalence of 0.45 % and 0.12 %, respectively, in the southern part of the country[83]. In our own unpublished data, we find a similar relationship between AS and axial SpA according to the ASAS criteria, indicating that the association is relatively stable.
AS has not been a common disease on the African continent, and this might partly be explained by the natural selection discussed previously. However, there are some publications on the occurrence of HLA B27 and AS in Africa. In 1997, Brown et al published a study of a particular ethnic group, the Fula, in Gambia. They reported a HLA B27 prevalence of 6 %, distributed between the wild type B2705 (68 %) and B2703 (32 %), both known to be associated with AS[84]. The truly remarkable finding was, that in an evaluation of more than 1100 persons not a single case of AS was found [84]. It seemed Gambian individuals with HLA B27 were not at increased risk of developing AS, or, alternatively, some other genetic or environmental factor imposed a protective influence. The low prevalence of AS in this region was confirmed in review of AS in sub-Saharan Africa, where only 26 cases of AS was reported in South-Africa, Togo and Zimbabwe among black Africans [85].

Regarding the incidence of AS, few publications have been dedicated to this subject; in a study from Rochester county, Minnesota, US, the incidence rate was stable over the period 1935 to 1989 at 7.3 per 100,000 person years[86]. This was in line with the estimated annual incidence rate of 6.9 per 100,000 person years in Finland based on a national registry of patients receiving reimbursed therapy for AS. [87]. In Greece, where the prevalence of HLA B27 is about 6 %, a study reported AS incidence rate of 1.5 per 100,000 person years[88]. The estimates of HLA B27 in Japan are less than 1 %, with the estimated incidence rate of AS at 0.48 per 100,000 person years[89].
9. CLINICAL FEATURES OF AS

The group of SpA has some characteristic clinical features that separates these diseases from other rheumatic conditions; an association with HLA B27 and no association with rheumatoid factor; arthritis of SIJ and occasionally peripheral joints; involvement of the enthesis; extra-articular involvement of the skin, gastrointestinal tract, anterior structures of the eye, heart, kidney and lung[1]. SpA patients also experience general symptoms associated with chronic disease, such as fatigue, weight-loss, low-grade fever and normocytic anaemia. The strong association to HLA B27 has been discussed above.

By many considered the prototypical SpA condition, AS is the most frequently and thoroughly described disease entity in this group. The onset of the disease is typically in the middle of the 3rd decade of life, and as no cure exists, AS will affect patients for the remainder of their lifespan, although in varying degrees. There is a preponderance of male AS patients that varies from 1.2:1 to 9:1, but it is possible this gender difference have been exaggerated in the past[90]. The arthritis observed in AS universally affects the SIJs, which yields low back pain or buttock pain radiating along the posterior part of the lower limbs, but rarely beyond the knees. According to Calin (in Textbook of Rheumatology, pp754-765[60]), the onset of pain is typically insidious, alternating from either side and often diffusely localised. The arthritis may affect peripheral joints in up to 20-40 % of patients, but tends to be asymmetrical and affect larger joints predominantly in the lower limbs[60]. The arthritis may be erosive and cause major loss of function.

The symptoms of enthesitis are dominated by pain and the widespread distribution of the enthesis. Typically, it will affect large enthesis or areas with a considerable element of physical stress, e.g. the attachment of the achilles tendon or plantar fascia on the calcaneus, the spina ilica anterior superior and posterior superior, crista iliaca or the junction of the costae and sternum and the attachment of ligaments and capsules in the spine. This contributes significantly to both the peripheral and axial pain and stiffness reported by patients. The patients then typically experience inflammatory pain characterised by; morning stiffness of varying intensity and duration; pain at night with improvement upon getting up; improvement of pain with moderate exercise, but no
improvement at rest; pain relief from NSAIDs. In the course of the disease, ankylosing lesions might lead to reduced mobility of the spine and, to a lesser degree, large joints such as hips and shoulders. The resulting reduction in level of functioning can be severe[91].

Extra-articular complications of AS may be sub-clinical, indicating that AS patients need to be screened for these features, or it may become a dominating, easily recognised clinical feature. The dermatological and gastroenterological involvement is mainly psoriasis and various degrees of IBD[1], and AS is associated to IBD in 5 to 10 % of the patients[92] and to psoriasis in about 15 %[93], in which case one could argue that the patients have SpA, not AS. However, subclinical gut mucosal inflammation is demonstrated in AS in up to two thirds of the patients[94].

Involvement of the eye is not rare, and one or more episodes of acute anterior uveitis are reported in 16-40 % of patients[60, 91, 95]. In the adult patient this usually presents as a painful, red eye, with blurred vision, and without treatment the condition can severely damage vision.

According to Calin[60], up to 10 % of AS patients will develop cardiovascular complications after 30 years of disease duration; the most common cardiac involvement is aortic incompetence, conduction disturbances and cardiomegaly, whereas pericarditis rarely occurs. In a systematic review of 44 consecutive AS patients at an outpatient clinic by transoesophageal echocardiography (TEE), alterations at the aortic root or valves were seen in 82 % of AS patients versus 27 % in the control group. In a follow-up of 25 patients, 20 % developed severe complications such as heart failure, valve replacement, stroke or death compared to only 3 % in the control group. These findings were correlated to disease duration, but not disease activity, severity or treatment[96]. Whereas valvular disease and conduction disorders are typical complications of AS, rheumatic diseases in general are associated with an increased prevalence of cardiovascular events[97-100], as cardiovascular events are correlated to inflammation[101]. In a study by Hollan et al, SpA patients requiring coronary arterial bypass grafting were found to be significantly younger than the control group of non-rheumatic patients[102]. Several studies also indicate an effect of inflammation on vascular function. Increased aortic stiffness and reduced myocardial performance in AS
patients has been found to correlate to disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[103]. In a study by van Eijk et al, endothelium-dependant vasodilation and recruitment of skin capillaries were impaired in AS patients compared to a control group, and improved after treatment with TNF-inhibitors[104]. Disease activity may thus be related to microvascular function. AS patients also have subclinical atherosclerosis and arterial stiffness assessed by ultrasound of the common carotid artery, unrelated to disease activity[105].

Based on radiographic findings fibrosis of the pulmonary apices has been described as a rare but potential lethal complication[60] in 1.3 % of patients with AS[106]. Death due to pulmonary complications was 2.5-2.9 times more frequently among AS patients than expected[107]. However, using more sensitive modalities such as CT-scans, 9 to 16% have been found to have fibrosis present[108, 109]. Otherwise, a wide range of pathological findings observed on HRCT scans include emphysema, bronchiectasis, ground glass opacities, pleural thickening and apical fibrosis, occurring in around half of the patients in non systematic studies on small cohorts[110]. A large Taiwanese study reported apical fibrosis in 2.9 % of 2136 patients based on review of medical records, including radiographs. The cause of apical fibrosis in unknown, but interestingly, in 65 % (40 patients) of patients with apical fibrosis infection with M. Tuberculosis was either microbiologically verified (19 patients) or suspected[111]. This may, however, be a secondary phenomenon, as it is possible that abnormal lung parenchyma enhances the virulence of microbes, while fibrosis itself could be caused by defective apical ventilation or mechanical stress due to impaired mobility of the thoracic spine and thorax in AS[110].

Renal disease has been recognised in AS primarily as IgA nephropathy and renal amyloidosis. IgA deposits in the mesangium may cause nephropathy, which can occur many years after the onset of AS, with patients usually in the 4th decade. IgA nephropathy is often asymptomatic and only identified by screening for proteinuria and haematuria. It is likely associated with a higher level of serum IgA observed in SpA, but it does not appear to be a very common complication, and is rarely reported[112]. In fact, a French study of patients with IgA nephropathy could not find an increased prevalence of spondylitis compared to the normal population[113].
Renal amyloidosis in SpA, on the other hand, is the result of elevated levels of serum amyloid A (SAA) over a prolonged period of time. SAA is an acute phase reactant, which can be deposited in various tissues, and adversely affect the tissue’s normal function. Amyloid deposits can be detected in several organs, but if deposited in the renal system, proteinuria is an early finding and renal failure might ensue. In a study of 158 patients with renal AL (84) or AA (68) amyloidosis a majority (84.6 %) had glomerular deposits, while vascular (9.4 %) and tubulointerstitial (6 %) deposits were less frequent. The glomerular deposits initially showed a focal segmental distribution, but gradually developed into diffuse and global deposits, while the biochemical type of amyloid had no influence on the distribution pattern. The level of serum creatinine correlated to tubular atrophy and interstitial fibrosis, whereas proteinuria correlated to glomerular amyloid load[114]. Amyloid deposits are detected by staining of tissue samples with Congo red. In a German study from 1998, it is suggested that 10 % of AS patients develop renal disease, and as many as 6 % develop secondary renal amyloidosis[115]. However, in a recent study from Finland, it was reported that the incidence of renal replacement due to amyloidosis in patients with rheumatic diseases had fallen dramatically after 2002, probably as a result of improved therapy[116].

The presence of amyloidosis can be determined through tissue samples from whatever organ is affected, but for screening purposes subcutaneous fat tissue is considered to be well suited. In such a screening of AS patients, amyloid deposits were found in 6-7 % of patients, mostly without previously recognised amyloidosis[117, 118]. On clinical suspicion, rectal biopsies are also performed.

Due to the involvement of the spine in AS, it is not surprising that neurological complications occur. As in RA, atlantoaxial subluxation may take place, but it appears to be a rare complication[119]. The cervical cord is particularly vulnerable to traumatic stress if there is a fusion of the vertebrae, and level C5-C6 is most frequently affected. The lifetime risk of a spine fracture in AS is reported to be 14 % (range 4-18 %) and consequential cord damage is estimated to be 53-83 %. A rare neurological complication is the cauda equina syndrome, which can occur after longstanding disease, possibly related to arachnoiditis with meningeal changes and formation of cysts[120].
10. OUTCOME MEASURES IN AS

In general, outcome measures are necessary tools in every discipline of medicine. In its simplest form this may be the personal evaluation by the physician of an individual patient to establish the success or failure of a chosen treatment strategy, or it may be the objective and definite outcome of death in patient groups. Regardless of its definition, outcome measures are the cornerstone in the evolution of every part of medicine. In rheumatology, the level of inflammation, function and pain, radiographic progression or damage evaluation, quality of life, cost of the disease, work impairment or disability and mortality are all examples of such outcome measures.

ASAS/OMERACT has recommended guidelines for the assessment of outcome in AS/SpA patients\[121\], which differ according to the purpose of the assessment; when evaluating symptom modifying therapy or physiotherapy, focus is set on changes in stiffness, mobility, pain, fatigue and patient global assessment; in clinical record keeping, acute phase reactants and evaluation of peripheral joints and enthesis should be added; in the setting of evaluating disease modifying therapy, radiographic evaluation should be added. In general, patient questionnaires, based on VAS or NRS, are used, unless the outcome is given as a result of the physical or laboratory examination.

Stiffness, mobility and function can be evaluated with distinct clinical examinations or by composite scores. Spinal mobility, for instance, can be evaluated using chest expansion, modified Schober's test, occiput to wall distance, cervical rotation, lateral lumbar flexion and intermalleolar distance as isolated measurements, even though the latter is a measure of hip mobility. Alternatively, these items can be combined in BASMI (0-10), a composite score, see appendix [122]. Dunham's spondylometry, which measures, in degrees, the maximum flexion and extension in the spine is still in use in some rheumatology departments [123]. While several composite scores evaluating level of function has also been used in AS, BASFI is the most frequently used and is recommended by ASAS, see appendix[124].

It has also been suggested to use single item questions to evaluate specifically pain, fatigue and patient global assessment in AS; pain at night in the spine due to AS; pain
overall in the spine due to AS; level of fatigue/tiredness experienced; activity of spondylitis last week[121].

The peripheral joint evaluation is usually given as the number of swollen joints (44-joint count) while enthesitis is usually given as a score of tenderness at specific sites. Because of the vast number of entheses these scores can be very cumbersome, such as the Mander Enthesis Index[125] which involves 66 different entheses. A simplified version is the Maastricht Enthesis index, which involves only 13 different enthesis and has shown both feasibility and validity in clinical practice and research [126], see appendix.

Systemic inflammation can be evaluated through laboratory tests such as CRP or ESR. However, in AS the level of CRP or ESR does not adequately reflect disease activity by BASDAI, which has been the most frequently employed composite score to evaluate inflammation. When CRP is elevated, this usually a coincides with increased activity of AS, although a normal test does not preclude active disease according to BASDAI[127]. BASDAI evaluates clinical characteristics typical of active AS, i.e. fatigue, axial pain, peripheral pain, enthesitis related pain and duration and intensity of morning stiffness[128], see appendix. It has been a tool in evaluating disease activity and treatment efficacy[129], and a BASDAI score > 4.0 indicate a high level of activity. However, BASDAI does not take into account objective measures, e.g. ESR, CRP or a platelet count, as it basically is a self-evaluation by the patient. To improve disease activity scoring, the AS Disease Activity Score (ASDAS) was introduced by the ASAS group. This score is partially based on the BASDAI score and includes CRP or ESR, as well as the VAS/NRS for back pain, duration of morning stiffness, peripheral pain/swelling and the patient’s global assessment of health [130]. ASDAS scores for defined activity states are: inactive (<1.3), moderate (<2.1), high (≤3.5) and very high (>3.5), and ASDAS reduction ≥1.1 is considered clinically important and major improvement is at a reduction by ≥2.0[131]. This scoring system has recently been endorsed by OMERACT[132].

Quality of life (QOL) is also an important aspect when considering the patient’s burden of disease, and a test evaluating this in AS has also been developed. The ASQOL consists of 18 questions regarding everyday activities and state of mind[133]. Similarly, a
Disease-specific score exist also for work productivity and activity impairment (WPAI) in SpA [134]. However, these tests are not yet included in the ASAS/OMERACT recommendations.

Radiographic damage development is a vital aspect in the long-term management of AS patients. With the uncertainty about the importance of inflammation as a risk factor for radiographic damage, radiographic evaluation of the axial skeleton is still important. While several different radiographic scoring methods have been proposed in AS, the mSASSS is most sensitive to change [135]. However, when it comes to feasibility the BASRI[136] is actually easier/faster to perform, but its sensitivity to change is inferior to mSASSS, which is therefore recommended by ASAS for radiographic evaluation in long term follow-up or clinical studies of AS[137].

MRI has proven to be a useful tool in diagnosis of SpA[138] and a method of evaluating ongoing inflammation in AS. MRI findings correlate to markers of inflammation such as CRP or BASDAI and is also a useful method to evaluate treatment efficacy, as it is sensitive to change[139]. A method for scoring both active inflammation and chronic changes was initially proposed by a group from Berlin[140]. Subsequently, two different scoring methods for MRI in SpA have been proposed, one of which is an alteration of the scoring system proposed by the Berlin group (ASspiMRI-a)[141], and the other a proposal by the Canadian SPARCC group[142]. The common feature in all MRI scoring schemes is the assessment of the extent of inflammation in defined discovertebral units (DVU). A DVU consists of the adjacent endplates of two vertebrae with underlying bone marrow and the intervertebral disc separating them[139]. However, while the Berlin score evaluates all of the 23 vertebral units, the SPARCC evaluates the 6 most affected DVUs. There are no OMERACT recommendations as to which score should be preferred. Regarding the evaluation of sacroiliitis by MRI, there are currently 5 separate scoring systems under consideration by OMERACT[143].

The ability to remain employed can also serve as a long-term outcome measure in a lifelong disease like AS. Several groups have reported on work disability (WD), and regional differences can naturally be expected due to differences in the structure of the welfare system. The reported WD in Argentina was 9.4%, while the rate of
unemployment among AS patients was 26 %[144]. This should not be interpreted as a sign that Argentinian AS patients have a milder disease than Czech AS patients, although 30 % of AS patients there are disabled[145], but it illustrates that comparing such outcomes across regions can be difficult. Other groups have also showed that the distribution of other variables in a population will influence WD, e.g. level of education[146]. It is therefore likely that variations in level of education, proportion of workers employed in manual labour, unemployment and socioeconomic status will influence differences observed across regions as well. Another factor likely to influence the risk of developing disability is the extent and quality of health care provision in a region. It has been documented that a patient’s coping strategy is an important predictor for the long-term risk of becoming disabled[147]. One could argue that having a broad approach in patient care, giving them the best possible medical treatment combined with patient education, would reduce the risk of WD.

In every discipline of medicine, mortality is the ultimate outcome measure. To establish that a certain condition carries a reduced expectancy in lifespan is an essential finding that should be an important factor in the allocation of resources for treatment and research. Some conditions carry a very high mortality rate after a short disease course, such as pulmonary carcinoma. Outcome research for a disease with such short life expectancy can be performed on relatively small cohorts and with limited time of follow-up. However, when evaluating a less rapidly progressive condition like AS, that already starts early in life, outcome research must be based upon longer periods of observation, larger cohorts and a larger variety of outcome measures. Although such research is more time and resource consuming, several groups have reported estimates of mortality in AS. The first indication of a reduced life expectancy came in the middle of the 20th century, with a two-fold increase of mortality in AS patients having undergone radiation therapy[107]. However, it soon became clear that also patients who had never been exposed to radiotherapy were at significantly increased risk of reduced survival. In a relatively large study of 836 patients, Radford et al reported a SMR of 1.6, and Khan et al found similar mortality in a smaller study [148, 149]. Both groups showed that circulatory disease, rather than malignancy, was the leading cause of death. Lehtinen et al[150] reported a similar SMR (1.5), and found circulatory disorders to the most prevalent cause of death. While Radford and Khan’s groups
reported 5 % of deaths to be caused by violence and accidents and no deaths due to amyloidosis, Lehtinen reported 11 % and 13 % of deaths to be caused by these conditions. In a more recent Finnish study alcohol-related deaths due to violence and accidents were found to be 2.6 times more likely to occur in AS patients compared to the normal population[151]. Comparing cause of death in studies across different populations is complicated as uncertainty about accuracy of registered cause of death poses a problem. When comparing Khan's/Radford's findings with Lehtinen's, one would expect to find some cases of death due to amyloidosis in all groups, even though cultural differences could explain variations in other causes of death. In a review of mortality in AS, SMR of 1.3-1.8 were reported[152], which is comparable to e.g. RA mortality. The review could, however, not report any other studies with the same association to alcohol-related mortality in AS.

With increasing possibilities in treatment of AS, and increasing cost of this treatment, it is paramount to justify both the allocation of resources to a potentially debilitating and life-shortening disease as well as documenting positive results of the chosen therapy. In a longer perspective, it is essential to demonstrate that a presumed efficient and very costly treatment is beneficial not only with regards to symptom reduction, but also contributes to improved outcome in terms of reduced disability and mortality. Outcome research continues to evolve in medicine, and it is likely our best possibility to document and justify our use of resources. It is also necessary if we are going to be able to adapt treatment to the individual patients. Genetic profiling of AS patients is not common yet, bar HLA B27-testing, but can presumably be an important part of outcome research in years to come in addition to the methods described here.
11. OBJECTIVES OF THE STUDY

The university and its affiliated hospital in Tromsø, Northern Norway, have a longstanding interest in AS treatment and research. This is due to the relatively high number of patients seen, and the scope of scientific interest of doctors involved with the hospital and university since the foundation of the department of Rheumatology in 1978. Epidemiology and outcome research have been areas of particular interest in the past, and it appeared like a natural continuation, bridging the research efforts of the past and the present in this project.

11.1 Paper I

The aim of paper I was to describe the prevalence and incidence of AS in this region. While the prevalence of AS had been estimated previously, this was done by a very different approach, and we wanted to compare the results when using a different method. Estimates of the incidence rate of AS had not previously been performed in this region and were scarce for any other regions at the time of study. Our objective was to calculate estimations for the incidence rate over a long observation period to evaluate whether the incidence was stable over time or increasing with any trends to be found. To achieve this, we evaluated every patient registered at our hospital since the foundation of the Department of Rheumatology and verified a correct diagnosis of AS according to the modified New York criteria. At this time, our department was the sole provider of medical service to patients with rheumatic diseases in this region, hence, most patients who had ever been in contact with a rheumatologist would be included in our database. Prevalence and incidence rates were then calculated using the national statistics database to establish the size and structure of the total population.

11.2 Paper II

The aim of paper II was to evaluate the extent of work disability among AS patients in this region and to clarify which clinical or demographic characteristics carry an increased risk for work disability. We included also complications that had occurred due to AS and any concomitant comorbidity. We used the database that had been established in our epidemiologic study and invited all patients still living in this region to an outpatient research visit. Work status was among the many variables registered in this cross-sectional observation study that
included a retrospective longitudinal analysis arm to define risk factors for work disability.

### 11.3 Paper III

In paper III, the aim was to compare survival between AS patients and a control population matched for age, gender and area of residence. AS patients were recruited from the same database used in earlier studies, but with the added advantage of follow-up observations after the research visit. Thus we could prospectively analyse risk factors for reduced survival in AS patients in a subset of the total AS cohort.

### 12. METHODS

#### 12.1 Ethics

This study has been focused on three related areas of a clinical-epidemiologic approach to AS, and the study protocol was approved by the local ethics committee in the northern region (REK Nord).

#### 12.2 Study design

Paper I was performed as a retrospective cohort study of patients with AS, where cross-sectional analysis was performed on different points in time.

Paper II was performed as a cross-sectional retrospective longitudinal study.

Paper III is in part designed as a retrospective cohort study, but a subset of patients has been followed as a prospective longitudinal study.

#### 12.3 Study participation and data collection

All patients have been recruited using the hospital’s patient record system. In Paper I, the data collection was performed as an identification of patients with a confirmed diagnosis of AS, and did not require any additional information given by the patient. In Paper II and the prospective arm of Paper III we retrieved the patient’s informed consent before collecting and storing any data, and the ethics committee approved this approach.
After identifying patients with suspected AS, the basis for the clinical diagnosis was re-evaluated and in case of insufficient supportive data (which in most cases turned out to be ambiguous results on SIJ radiography), a further diagnostic work up was performed. Thus, we feel confident that patients included in the database satisfy the modified New York criteria.

The time of onset of the first symptoms attributable to AS was defined as the time of disease onset, and the date of confirmed sacroiliitis was chosen as the time of diagnosis. In Paper I, data on population size were extracted from the governmental Statistics Norway database (www.ssb.no). In Paper II and III we used a predefined data sheet for each consultation with patients, collecting demographic and clinical data. This data included information about family members with SpA features, work status, educational status and use of NSAIDs or DMARDs. The patient’s health status would be obtained through information from the patient and from the patient’s records. The clinical investigation would focus on level of function, both as composite scores (BASFI and Dougados Functional Index) and single item measures such as modified Schober’s test, chest expansion, occiput-to-wall distance, finger-to-floor distance, lateral flexion and the Dunham’s spondylometry. In connection with the visit, blood samples were taken and evaluated at the department of clinical chemistry (CRP, ESR, Haemoglobin, Leukocytes, Thrombocytes, AST, ALT, ALP, Creatinine and TSH), and a radiologic work-up was performed. All data were initially stored in Epi-Info v 6.01, and later entered into an Access database for completion before being transferred to SPSS 15 for further analysis.

12.4 Data analysis and statistics
In general, p-values < 0.05 were considered statistically significant.
In Paper I, all data were presented as median or mean values. Continuous data were analysed by Mann-Whitney U test and contingency tables analysed by χ² analyses or Fischers exact test in case of low number. All incidence rates were given as cases per 100.000 person years. The survival analysis in this paper was calculated using the Kaplan-Meier method and SMR. As a control group, we used data from an earlier case-control study of mortality in Rheumatoid Arthritis in the same region.
In Paper II we performed a survival analysis using the Kaplan-Meier method to evaluate differences in development of WD between male and female patients. Comparative analyses between groups were performed using \( \chi^2 \) analyses for categorical data and Mann-Whitney U test for continuous data. The multivariate analysis was performed as a logistic regression analysis, and variables were selected on the bases of p-values <0.2 in the univariate analysis. We encountered a total of 104 cases with missing values. This would typically be one item in a composite score, total years of education or similar to this. We decided to replace missing variables using median or mean value, depending on whether the variable in question was skewed or not, as recommended by Katz[153].

In Paper III we performed the comparative analyses between groups using \( \chi^2 \) analyses for categorical data and Mann-Whitney U test for continuous data. Survival curves were estimated using Kaplan-Meier analysis, and compared using Mantel-Cox log rank test. Variables yielding p<0.2 in a univariate analysis were later included in a multivariate analysis to establish which variables were associated to reduced survival. We decided to improve the matching of controls to patients compared to the mortality analysis we had performed in the first paper. Consequently, each patient was assigned three controls from the background population matched for gender, age and postal area of residence. We very carefully considered the patients age at disease onset in matching controls. Thus, if a patient had a disease onset at the age of 20 years in 1980, three controls aged 20 years in 1980 would be selected and retrospectively followed for the occurrence of death from 1980 onwards.

13. SUMMARY OF RESULTS


We identified 687 AS patients in the hospital records, of which 49 were residing outside our catchment area at the time of diagnosis. We included only patients with onset of AS between 1960 and 1993, leaving 534 patients for further analyses. There was no significant difference regarding gender distribution, age at disease onset or frequency of HLA B27 between the included and excluded patients. Age at onset of
disease was 24.2 years (SD 8.5), male: female ratio was 3.1:1, 93.0 % were HLA B27 positive, diagnostic delay was 8.0 years (range 0-33 years) and 18.1 % of patients had psoriasis or IBD. We observed that the gender ratio declined during the period of observation, and for patients diagnosed later than 1990 it was 1.5:1. Patients with IBD or psoriasis had a significantly lower frequency of HLA B27 (82.2 % v. 94.9 %; p=0.0005), but were not different with regards to age at onset, diagnostic delay or gender distribution. HLA B 27 negative patients were significantly older at disease onset than HLA B27 positive patients (29.0 v. 23.6 years, p=0.01).

We defined the disease as being Primary AS when not associated to IBD or psoriasis and, conversely Secondary AS. The incidence rate over a 34 years period for primary and secondary AS was 7.26 (95% CI 6.38 to 11.04) and 8.71 per 100,000 person years, respectively. When the observation period was divided in three, the incidence rate was somewhat lower during the first period, but was actually peaking during the second period (6.52 – 10.64 – 8.59, all secondary AS).

The overall prevalence of AS in this period was 0.26 % for primary AS and 0.31 % for secondary AS. The point prevalence at the end of the observation period was 0.41 % in the municipality of Tromsø and 0.22 % in the remainder of the region, p<0.0001.

Survival in AS patients was compared to the expected survival in this region based on national statistical data, and we found no evidence of reduced survival in AS patients.

13.2 Paper II: Work Disability in Patients with Ankylosing Spondylitis in Norway

In total, 585 patients were identified as potential subjects in this study. Of these, 360 accepted our invitation, which yields a response rate of 62 %. No significant differences existed regarding gender or age distribution among those who accepted and declined our invitation. With work disability (WD) defined as ≥ 50% disability pension, patients were categorised as WD+ (n=157) or WD- (n=203); 43.6 % of the patients were WD at the time of follow up, and on average, patients became WD 18.7 years after onset of disease. WD+ were likely to be older at onset (24.0 v. 22.1 years, p=0.02), younger at time of study (40.6 v. 51.6 years, p<0.001), have a longer diagnostic delay (11.4 v. 8.0 years, p<0.001), be female (34.4 % v. 21.7 %, p=0.009), have children with SpA (18.5 % v. 3.9 %, p<0.001) and less likely to have college or university education (12.7 % v. 33.5 %, p<0.001). Also, we found significant differences in the level of physical function; WD+ were likely to have higher BASFI (4.3 v. 2.9, p<0.001), lower modified Schober's
(3.2 v. 3.7 cm, p=0.004), increased occiput-wall distance (4.7 v. 2.1 cm, p<0.001) and floor-to-finger distance (19.2 v. 13.8 cm, p<0.001), reduced chest expansion (3.8 v. 5.0 cm, p<0.001) and forward spinal flexion (34.1 v. 38.8 degrees, p=0.008). Interestingly, men scored lower on spinal mobility tests, but not on BASFI, compared to women. In a subsequent multivariate analysis, the following demographic and clinical variables were found to be significantly associated to WD, presented as odds ratios (OR); Female gender (3.36), age at follow up (1.05), level of education (0.72), having a child with SpA (2.91), presence of coronary heart disease (7.84), past or present polyarthritis (9.61), changing profession (2.82), higher BASFI score (1.16) and increased finger-to-floor distance (1.02).

We also studied the occurrence and influence of extra-spinal AS complications, as well as comorbidities. More than half (55.8 %) of all patients had experienced some extra-spinal complication. Uveitis was the most frequent problem (41.9 %), followed by peripheral arthritis (16.9 %), psoriasis (11.1 %) and IBD (8.1 %). Cardiac involvement (conduction disorder or aortic insufficiency) was observed in 6.7 %, and lung involvement and amyloidosis in 0.6 % each. In this study, we confirmed that Norwegian AS patients are at substantial risk of becoming work disabled 18 years after disease onset as a consequence of physical limitations. As there are considerable differences between countries regarding work disability benefits, work disability studies should always be interpreted in such a context.

13.3 Paper III: Increased mortality in Ankylosing Spondylitis is related to disease activity

In this study, we included 677 patients with AS identified in the hospital’s patient record system. Each patient was assigned three controls matched for gender, age and postal area of residence, in total 2031 controls. There was a male preponderance in AS patients (3.1:1), mean age at symptom onset was 23.2 years and median diagnostic delay was 7.0 years. The crude mortality rate at the end of follow up was 14.5 % (n=98). Among the case fatalities there was a male dominance (9.9:1), and interestingly, the male non-survivors were significantly older at disease onset (28.5 years) than both female non-survivors (23.3 years, p=0.002) and male survivors (22.4, p<0.001). The diagnostic delay among male non-survivors was also significantly longer than among
male survivors (11.2 v. 8.3 years, p=0.012). The mortality rate in the AS cohort was increased (SMR=1.61, 95 % CI 1.29 to 1.93), but when mortality was broken down to gender, only male patients had significantly increased mortality (SMR 1.63). A cause of death was established in 84 % of cases, and circulatory disease was the leading cause of death (40 %), followed by malignant disease (27 %) and infectious disease (23%).

In a subset analysis of 360 patients who had attended the follow-up visit, we identified four risk factors for reduced survival. In a multivariate analysis controlling for age, gender, disease duration and pre-existing cardiovascular disease, we found increasing levels of CRP (OR 2.68), diagnostic delay (OR 1.05), work disability (OR 3.65) and not using any NSAIDs (OR 4.35) to be independent predictors of reduced survival. These findings indicate that intensity of inflammation and duration of inflammation should be considered as risk factors for reduced survival in AS, and this may have implications for the diagnostic process as well as treatment of the disease.
14. GENERAL DISCUSSION

The investigations in this study have been focused on three separate, albeit interrelated clinical-epidemiological topics in AS, namely incidence/prevalence, disability and mortality. While the aims for each study were clearly defined, the methodologies applied in each paper have their own limitations. This is important when considering the results and evaluating the findings in the light of similar studies.

14.1 Paper I

In Paper 1, we performed a retrospective analysis, based on patients being registered in the hospital record system, of incidence and prevalence of AS in the two northernmost counties in Norway in a limited period of time, 1960 to 1993. The reason for this limitation was the fact that observations earlier than 1960 were likely to be too incomplete for firm conclusions. The data collection began in 1998, and although we continuously included newly diagnosed patients in our database during the period of data collection, we decided that the diagnostic delay would be a problem if we tried to include patients with symptom onset later than 1993.

The incidence rate was relatively stable over a 34 years observation period, and the minor variation we did discover, we presume is a consequence of the increased awareness of rheumatic diseases in general after the foundation of our department in 1978, and not a decline in the incidence rate during the last period of observation. Our data confirm that this region has a relatively high prevalence and incidence of AS compared to other Caucasian populations, as would be expected in given the high prevalence of HLA B27 previously reported. Our estimates of prevalence are considerably lower than Gran et al reported in a study twenty years previously[80]. While we reported an AS prevalence of 0.4 % Gran et al reported 1.1-1.4 %. The main reason for this discrepancy is likely the different methods used in the two studies. Our study was completely based on hospital records, and the assumption that all patients at some point are in contact with the hospital, where the ICD diagnosis of M45 or 720 have been registered. This assumption is probably flawed, as some of the AS patients with a mild disease or a better self-coping strategy will not necessarily demand the services of a rheumatologist, and hence would not be included in our studies. It is unclear how large this proportion of AS patients has been, whether this is related to the regional
characteristics that may impede access to medical care and whether this potential flaw is currently as important as several decades ago. We know that the prevalence of HLA B27 in parts of Finnmark county is estimated to be 24 %[79]. This is about 50 % higher than observed in Tromsø, and would suggest that the prevalence of AS should be considerably higher in Finnmark than in the municipality of Tromsø. We do, however, regularly receive patients at our out-patient clinic who have clearly had AS for many years and who may or may not be aware of their precise medical condition, but for different reasons have not previously been referred to a rheumatologist. Thus, there are likely to be cases of AS in our region that remain unidentified by us.

The method applied by Gran et al was based on the Tromsø study, which is a population-based study of health performed every 6 to 7 year in Tromsø since 1974[154]. In their study, individuals with low back pain and or back stiffness were identified through a questionnaire used in the survey, and a selection of respondents was then examined to determine AS status. This method also allows for selection bias, but while the results in this study must be evaluated in light of the method chosen, we must conclude that our finding of prevalence 0.4 % in Tromsø is a very conservative estimate.

It was also a striking feature, that the prevalence in the region outside Tromsø was significantly lower (0.22 % v. 0.41 %, p<0.0001). The same was observed regarding incidence rates, where the incidence rate in Tromsø was nearly three times that of the region beyond Tromsø. We have no indication that there is any major genetic difference in the population of the region, apart from HLA B27 distribution, and we expect that there are many cases of undiagnosed AS in the rural area. A similar phenomenon has been observed in RA patients in Spain, where RA prevalence in urban and rural areas was 0.6 % and 0.2 %, respectively, and may reflect a higher threshold for the population in rural areas to seek medical attention[155].

Few publications on AS incidence are available, but recently a Czech study estimated a prevalence of 0.09 % and an incidence rate of 6.4 per 100,000 person years. Assuming that the HLA B27 frequency is around 10 %, the authors conclude that their data is as expected compared to previous studies[156].

As previously mentioned, a study from Finland reported an AS incidence of 6.9 per 100,000 person years [87] and a study from Rochester, Minnesota, USA, found the incidence rate of primary and secondary AS to be 6.3 and 7.3 per 100 000 person years,
respectively[86]. Overall, our results are largely in agreement with these findings, despite some methodological differences. The Finnish study is based upon a national register of patients entitled to receive specially reimbursed medication for AS, but a similar registry does not exist in Norway. AS patients who were not requiring such disease specific pharmacological treatment would not be registered in the Finnish material, and could reflect a potential underestimate of AS incidence. The Rochester study, on the other hand, is based on hospital records, and is more similar to our study in that sense.

Even though our data seems reasonable compared to these publications, we still expect that this is a conservative estimation of the incidence rate, based on the selection bias recruitment from the hospital records inflicts.

We reported that there was no reduced survival among AS patients in this study, while the results from Paper III contradicted this observation. There are probably two significant factors contributing to this observation; Firstly, we improved the process of matching controls to each case. Secondly, and perhaps more significantly, the time of observation was nearly ten years longer. Given the nature of the disease course of AS and many rheumatic diseases, with a prolonged duration and mortality correlated to comorbidity, one would expect that an extended period of observation is necessary to verify a reduced survival. In this process, the size of the study population is also of essence.

14.2 Paper II

This study was performed as a cross sectional study, where demographic -, work - and clinical status was recorded. Some of the recorded data were retrospectively scored, such as age at onset and diagnosis, development of complications and comorbidities, history of employment status and changes of profession.

The limitations including a retrospective arm in this study design need to be appreciated, and it would always be preferable to perform the study in a prospective manner. Whereas the time of diagnosis can be determined relatively accurately using for instance the date of positive SIJ radiology, there will be more uncertainty related to information such as time of disease onset, change of profession and information about SpA-features in family members. We tried to standardise the process of obtaining
information by using predefined questionnaires and reducing the number of people involved in the process, and thus minimize this potential bias.

In our study, in which the mean disease duration was 22.6 years at the time of follow up, we found that 44 % of patients were WD, and an additional 9 % were not participating in the labour force. Compared to the 9.8 % in the general population who were receiving disabled benefits, this would give an OR=7.1 for AS patients to become work disabled compared to the general population.

In studies comparing WD across different regions, it is important to be aware of the potential influence the structure of a country’s benefit system might have on the results. In the Norwegian social benefits system at the time of this survey, individuals were considered WD if their ability to participate in the labour force was reduced by at least 50 % as a consequence of a recognised illness. With this regulatory framework, Norwegian AS patients are not considered unemployed if their medical condition renders them unable to work, as they would be granted work disability support. This is clearly different to reports from other countries. In Argentina[144], Spain[157], USA[146] and the Czech republic[145], the rate of WD among AS patients are considerable lower than our results indicate for Norwegian AS patients. At the same time, AS patients in Argentina are five times more likely to be unemployed than the normal population, with 9.4 % of AS patients in the survey being WD and 26 % unemployed. The Dutch social benefit system has greater resemblance to the Norwegian system, and in a study by Boonen et al they reported that 63 % of male patients and 47 % of female patients were employed at the time of the survey, a significantly lower rate of employment than the normal population, whereas only 24 % and 22 %, respectively, were receiving disability benefits[158].

In a multivariate regression analysis we identified nine variables independently associated with disability, presented as OR; Female gender (3.36), age at follow up (1.05), level of education (0.72), having a child with SpA (2.91), presence of coronary heart disease (7.84), past or present polyarthritis (9.61), changing profession (2.82), higher BASFI score (1.16) and increased finger-to-floor distance (1.02).

These risk factors are quite similar to the variables Boonen et al found in their prospective analysis of withdrawal from the labour force among AS patients, where age,
less than 12 years of formal education, manual profession, comorbidity, peripheral arthritis and total hip replacement were independently associated with WD[147]. We found gender to be important in our survey, with an increased likeliness of WD among women. This is in line with the findings of Ward[146] *et al*, but is not supported by Forejtová[145] or Ariza-Ariza [157]. We find it unlikely that this dissimilar gender association is a product of a more aggressive course of disease among female AS patients in Norway compared to female patients in the Czech republic or Spain. However, there are some methodological differences in these studies. While we were recruiting patients strictly using the hospital records, Forejtová *et al* was recruiting patients from the national AS association, and thus might possibly have included patients without AS according to the modified New York criteria. The proportion of female patients in their study (40 %) is certainly higher than what we observed, but on the other hand, this was lower in the Spanish study (23 %). Another possible explanation could be intrinsic in the national benefit system, as there is a general tendency of a higher proportion of WD among women compared to men in Norway. However, a German study demonstrated that female AS and RA patients have a significantly worse evaluation of their own disability than male patients do[159], and it is possible that this difference in the patient’s perception of disability is contributing to the higher degree of WD we observed in our study. Total hip replacement was unfortunately not an individual variable on our material. However, we did find polyarthritis, change of profession, education and the presence of a specific comorbidity to be important variables. In addition, physical function, represented by BASFI and finger-to-floor distance, came out as independently associated to WD. The overlap between our retrospective and Boonen’s prospective approach suggests that our method can be a valid alternative. The variables associated with WD seem to reflect the combined effects of a genetic predisposition and the ensuing pathological processes in AS, and not so much a psychological effect of suffering from a chronic disease.

The finding that has not been reported by any other group, to our knowledge, is the association of having children with AS and being WD after adjusting for factors like age, disease duration, inflammatory activity and comorbidities. We have no reason to believe that children with AS is an additional liability to the patients *per se*. It is,
however, possible that being several members in a family with the same illness changes the coping strategies of those patients, and adds to a ‘social burden’. Boonen et al demonstrated in their study that coping strategies are important for patients to be able to stay in the labour force [147]. Alternatively, these patients might have a different genetic profile that would portray a greater risk of having a more aggressive disease course. One could speculate that some families have a different subtype of HLA B27 (B2705 v. B2702) or an accumulation of genetic variants associated with AS or a more aggressive course of AS, but this remains to be demonstrated.

In this paper, we also described the development of complications associated with AS. We found that, in all, 55.8% of the patients had one or more acknowledged extraspinal complications to AS. These were AAU (41.9%), history of peripheral arthritis (16.9%), psoriasis (11.1%), IBD (8.1%), cardiac involvement (6.7%), lung involvement (0.6%) and amyloidosis (0.6%). The prevalence of AAU, peripheral arthritis, psoriasis and IBD is as would be expected in a population of AS patients. These are all features that would be readily detected in the outpatient clinic, and the patients would be likely to know whether they have ever experienced any of these complications. By their nature, cardiac involvement, lung involvement and amyloidosis on the other hand, would be difficult to ascertain without more extensive procedures. Our approach would therefore simply identify patients where these complications already inflict symptoms. While lung involvement and amyloidosis rarely poses a clinical problem, one should probably consider whether AS patients should be screened by echocardiogram to identify this potentially serious complications.

14.3 Paper III
The approach to our third paper was twofold; Firstly, in the process of identifying all AS patients who had been registered in the hospital record system, patients who had passed away were registered in our database as deceased. Secondly, surviving patients attending to our outpatient research visit would provide us with cross sectional data and the possibility to follow this subset of patients prospectively, which is the preferred method to evaluate risk factors. Establishing the cause of death also proved to be a challenge. We had not applied for permission to link our database to the Cause of Death registry at the start of the project,
and this was not possible at a later stage as it required a complete revision of the project plan and the potential loss of already gathered data. As the accuracy of death certificates for patients with rheumatic disease is also doubtful,[160], we decided to use the medical record system at the four hospitals in Troms and Finnmark to establish cause of death. For most patients we found that they died in hospital or had been in contact with the hospital shortly before their death. In this way we could ascertain the direct cause of death in 62 cases and a clear contributory cause in a further 20 cases. Also, we were not convinced that our survival analysis in the epidemiologic study was appropriate to detect the presumed moderate increased mortality in AS. Comparing summary mortality statistics for a regional patient cohort with mortality data for the general population gathered by the national bureau of statistics might have been too crude as a method to reliably measure this outcome. Therefore, we performed extended matching in this study and assigned each patient three controls matched for gender, age and area of residence.

SMR was calculated using the control group, and clearly showed that male AS patients in particular had reduced survival compared to the normal population. There was a tendency towards reduced survival in female patients that did not reach significance. In our study population of 677 patients there were only 166 women, which might be insufficient to demonstrate reduced survival. Previous studies of AS mortality have not reported any significant gender differences[161].

In the multivariate regression analysis, we identified increasing levels of CRP, diagnostic delay, being work disabled and not using NSAIDs as independent variables associated with increased risk of premature death. CRP has been associated to increased risk of cardiovascular events in general in previous publications[162, 163], and mortality in RA and AS has previously reported to be related to disease activity[150, 164]. Several publications have reported cardiovascular disease as an important contributor to increased mortality in other rheumatic diseases[165, 166].

The correlation to CRP in our study is therefore not an unexpected finding. One could argue, that WD may reflect the presence of high disease activity over time in AS patients, and thus the correlation to reduced survival is the load of inflammation, in the same way that CRP is a marker of inflammation. Alternatively, WD could reflect a
general reduced health status. However, in light of the publicity regarding the increased mortality of patients on Rofecoxib and later publications indicating increased mortality correlated to NSAIDs in general[167], it was very surprising to find that our data indicated reduced survival for patients not taking NSAIDs. There are, nevertheless, publications that support our results, as no increased mortality was found during use of NSAIDs in patients with polyarthritis[168]. The authors offer no concrete explanation for the effect of NSAIDs on mortality, but speculate whether it could be an effect on COX2 found in atherosclerotic plaques. A similar finding was reported by Mangoni et al, who found that use of NSAIDs within the last two years resulted in a modest reduction in mortality in a cohort of more than 83,000 Australian veterans[169].

The fourth variable independently associated with reduced survival was diagnostic delay. In the entire population of 677 patients, we observed that male non-survivors had a significantly higher age at onset of disease. This opens for speculation as to whether these patients could have been neglecting the symptoms, and that both the increased diagnostic delay and higher age at onset are related to this. In that case, increased mortality could of course also be related to a general neglect of symptoms of ill health. This would, however, not preclude the possibility that the observed reduced survival correlated to diagnostic delay, is also a consequence of continuous disease activity. It also raises awareness to the effort of improving the classification criteria in order to facilitate an earlier diagnosis in these patients, not as Ankylosing spondylitis, but rather axial spondyloarthritis[170]

14.4 Implications for future research

The present publications provide useful clinico-epidemiological information regarding AS. While we are the first group to report an estimate of AS incidence in this region, these data, as well as the prevalence data are based on patients fulfilling mNY criteria for AS. As new classification criteria for SpA have emerged it will be important to evaluate the MRI based operating characteristics of ASAS axial SpA versus modified New York criteria in this population.

All patients included in our outcome studies in AS were treated according to a conservative approach in the first years of disease. Since then, treatment for a good
number of these patients with longer standing disease has been converted to include TNF inhibiting biological therapies. This class of drugs has also become the second line therapy of choice in patients newly diagnosed with AS since then. It will be interesting to evaluate whether these new therapeutic possibilities will result in similar improved outcomes in both patients with longstanding and new onset disease. To strengthen conclusions, future outcome studies should preferably be performed in a prospective manner.

The progress that has been made in genetic studies of AS have to a large extent been based on genome-wide association scans (GWAS), and to determine the correlation with phenotype, clinical studies must be linked with known genetic determinants. Having a large AS/SpA population, we believe this is a field of research our department should pursue in future projects.

15. MAIN CONCLUSIONS

1. AS is a prevalent disease in Northern Norway and affects at least 0.4 % of the population; our method of investigation might have underestimated this prevalence.
2. The estimated incidence of AS is in Northern Norway is 7.3 to 8.7 per 100,000 person years.
3. In the time before TNF-inhibitors were available, patients with AS in Northern Norway had a high risk of becoming work disabled or unemployed.
4. AS increases long term mortality especially in men when compared to a matched normal population and can thus be considered a slow killer similar to arterial hypertension.
5. Mortality in AS is dependent on duration and intensity of inflammation, and is inversely related to use of NSAIDs. Diagnostic delay independently increases risk of reduced survival.
6. Comparing outcome research results across regions is complicated by differences in social benefit systems, socioeconomic structure and quality of public statistics.
7. The journals’ editors might have a different opinion regarding the originality of your paper than you have, but that should not discourage you from presenting your results in the most highly regarded journals. Many, but not all, reviewers give excellent constructive comments.

8. Health administrators, with some exceptions, do not seem to grasp the consequence of the chronicity in our patients’ diseases and the need for qualified and continuous medical care.

9. As in football, the ability to see the killer pass can open up a seemingly tight defence. So when struggling, pass the ball to your professor.
16. Reference List


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17. APPENDIX

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
(Norwegian version)

Spørsmålene nedenfor gjelder hvordan du følte deg den siste uken. Marker ditt svar med en loddrett strek på linjene.

1. Hvordan vil du beskrive den generelle graden av utmattelse/tretthet du har erfart?
   
   Ingen  Svært høy
   
2. Hvordan vil du beskrive den generelle graden av smerter i nakke-, rygg eller hofter i forbindelse med Bekhterev sykdom?
   
   Ingen  Svært høy
   
3. Hvordan vil du beskrive det generelle nivået av smerte/hevelse du har hatt i andre ledd enn nakken-, ryggen eller hoftene?
   
   Ingen  Svært høy
   
4. Hvordan vil du beskrive den generelle graden av ubehag du har hatt på eventuelle steder som gjør vondt ved berøring eller trykk?
   
   Ingen  Svært høy
   
5. Hvordan vil du beskrive den generelle graden av stivhet du har opplevd om morgenen fra det tidspunktet du våkner?
   
   Ingen  Svært høy
   
6. Hvor lenge varer morgenstivheten fra det tidspunktet du våkner?

   0 timer ½ time 1 time 11/2 time 2 timer el mer
Bath Ankylosing Spondylitis Functional Index (BASFI) (Norwegian version)

Sett en loddrett strek på linjene å markere hvordan du greide følgende aktiviteter den siste uken:

1. Ta på strømper eller strømpebukser uten assistanse eller ved bruk av hjelpemiddel (for eksempel strømpe påtrekker)
   
   lett       umulig

2. Bøy deg forover fra midjen for å plukke opp en penn fra gulvet uten å bruke et hjelpemiddel
   
   lett       umulig

3. Nå opp til en høythengende hylle uten bruk av hjelpemidler (for eksempel gripetang).
   
   lett       umulig

4. Reise deg fra en spisebordsstol uten armlener eller annen hjelp
   
   lett       umulig

5. Reise deg opp fra liggende stilling på gulvet uten hjelp
   
   lett       umulig
6. Stå oppreist uten støtte i 10 min. uten å få ubehag

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\begin{array}{c}
\text{litt} \\
\text{umulig}
\end{array}
\]


\[
\begin{array}{c}
\text{litt} \\
\text{umulig}
\end{array}
\]

8. Se deg over skulderen uten å vri kroppen

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\begin{array}{c}
\text{litt} \\
\text{umulig}
\end{array}
\]

9. Utføre fysisk krevende aktiviteter (for eksempel fysioterapiøvelser, hagearbeid eller sport).

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\begin{array}{c}
\text{litt} \\
\text{umulig}
\end{array}
\]

10. Utføre en hel dags aktiviteter enten hjemme eller på arbeid

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\begin{array}{c}
\text{litt} \\
\text{umulig}
\end{array}
\]
### Bath Ankylosing Spondylitis Metrology Index (Norwegian version)

#### SCORE

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tragus til vegg</td>
<td>&lt;15cm</td>
<td>15-30cm</td>
<td>&gt;30cm</td>
</tr>
<tr>
<td>Lumbal fleksjon</td>
<td>&gt;4cm</td>
<td>2-4cm</td>
<td>&lt;2cm</td>
</tr>
<tr>
<td>Cervical rotasjon</td>
<td>&gt;70°</td>
<td>20°-70°</td>
<td>&lt;20°</td>
</tr>
<tr>
<td>Lumbal sidebøy</td>
<td>&gt;10cm</td>
<td>5-10cm</td>
<td>&lt;5cm</td>
</tr>
<tr>
<td>Intermalleolær avstand</td>
<td>&gt;100cm</td>
<td>70-100cm</td>
<td>&lt;70cm</td>
</tr>
</tbody>
</table>

Mild sykdomsgrad: 0  
Moderat sykdomsgrad: 1  
Alvorlig sykdomsgrad: 2

Resultater for cervical rotasjon og lumbal sidebøy er gjennomsnitt av høyre og venstre mål.

Scoring range 0-10.

- **Tragus til vegg:** Pasienten står med helene inntil vegg, strake knær, skuldre tilbake, og plasserer hodet så langt tilbake som mulig.
- **Lumbal fleksjon:** Sett merke 5 cm under og 10 cm over en strek mellom SISP. Mål avstanden mellom de to merkene når pasienten er max. foroverbøyd med strake knær.
- **Cervical rotasjon:** Pas. ryggliggende, mål med Myrinometer
- **Lumbal sidebøy:** Måles ved FFD i full sidebøy uten og bøye forover eller i knærne. Merke ved midterste finger, forskjell mellom start og ende, snitt høyre og venstre.
- **Intermall. avstand:** Ryggliggende pasient, strake knær, tær peker rett opp. Pasienten abduserer, avstand måles mellem malleoler.
The ASDAS calculator[130]

The ASDAS formulas are as follows:

- ASDAS-CRP (the preferred version): $0.12 \times \text{Back Pain} + 0.06 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.07 \times \text{Peripheral Pain/Swelling} + 0.58 \times \ln(\text{CRP}+1)$

- ASDAS-ESR (the alternative version): $0.08 \times \text{Back Pain} + 0.07 \times \text{Duration of Morning Stiffness} + 0.11 \times \text{Patient Global} + 0.09 \times \text{Peripheral Pain/Swelling} + 0.29 \times \sqrt{\text{ESR}}$

CRP is in mg/litre, ESR is in mm/h; the range of other variables is from 0 to 10; Ln represents the natural logarithm; $\sqrt{}$ represents the square root.
The MASES index

Illustration of the MASES, with evaluation of 13 sites for enthesitis, each scored as tender or non-tender[126]. Courtesy of publisher.
Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)

Scoring of spinal radiography according to mSASS[138]. Courtesy of publisher.

The first MRI scoring system for AS: ASspiMRI-a

Illustration of the scoring of a DVU[138].
Figure 5. World map with an illustration of occurrence of malaria (shaded area) and known prevalence of HLA B27 subtype[42]. Courtesy of publisher.
18. PAPERS I-III