

Clinical utility and evaluation of radiology in diagnosing sacroiliitis

Mats Geijer



UNIVERSITY OF GOTHENBURG

The Sahlgrenska Academy
at the University of Gothenburg

Department of Radiology

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To Birgitta,

Erika, Anna, Cecilia and Kristina

"The diagnosis of ankylosing spondylitis depends on radiologic evidence of sacroiliitis, and the underrecognition of this disease primarily relates to the failure to make this radiographic diagnosis" *Andrei Calin* [40]

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Abstract

Background: Radiographic confirmation of diagnosis is important in all diagnostic and classification criteria for spondyloarthropathy. The aim was to evaluate computed tomography (CT) and to compare it to radiography.

Methods: A pilot study compared radiography and CT in 40 patients with spondyloarthropathy. A study on 1425 patients examined with CT, 910 of which also with radiography, was reported in four papers. All CT examinations were reviewed and scored by two observers. The original outcomes from the radiography and CT examinations were obtained from the radiology reports.

Results: CT had a higher sensitivity for sacroiliitis than radiography, especially in early sacroiliitis. Radiography had a high rate of false negative and false positive outcomes.

The observer agreement between two observers in a large material was good, while the observer agreements between each of the observers and the original radiology reports were moderate. Intraobserver agreement for a smaller part of the material for one of the observers was moderate.

There was a change in diagnosis in three of 126 patients (2.4%) examined more than once from normal or equivocal to unilateral or bilateral sacroiliitis. Ten normal cases had changed to equivocal (7.9%). In further six patients (4.8%) the diagnosis advanced from unilateral to bilateral sacroiliitis. Four equivocal cases were classified as normal on the second study, and one case of unilateral sacroiliitis was classified as equivocal on the second study.

Mainly multiple or large erosions seem to be a valid solitary diagnostic sign. Small solitary or few erosions need supplemental evidence from other inflammatory signs such as sclerosis. Inflammatory sclerosis can frequently be distinguished from degenerative sclerosis, and can sometimes support an early diagnosis, when erosions are not apparent. A practical CT classification for sacroiliitis consisting of no disease, suspect disease, and disease is proposed.

Conclusions: The clinical utility of conventional radiography for evaluation of sacroiliitis is low with a high rate of insufficient and false reports, making radiography unsuitable for clinical use or use in population studies. CT is a robust imaging method for suspected sacroiliitis with good observer agreement, with higher rate of detection of sacroiliitis than radiography; also for early changes. There is no use for repeat CT examinations for suspected sacroiliitis. The New York criteria are unsuitable for use with CT and a new grading system for CT of sacroiliitis is proposed.

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Original papers

This thesis is based on the following papers.

- I. Geijer M, Sihlbom H, Göthlin J.H. and Nordborg E.: The role of CT in the diagnosis of sacro-iliitis. *Acta Radiol* 1998;39: 265-268*.
- II. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: The clinical utility of computed tomography compared to conventional radiography in diagnosing sacroiliitis. A retrospective study on 910 patients and literature review. *J Rheumatol* 2007;34: 1561-1565**.
- III. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: Observer variation in computed tomography of the sacroiliac joints: a retrospective analysis of 1383 cases. *Acta Radiol* 2007;48: 665-671*.
- IV. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: Clinical utility of repeated CT examinations in diagnosing sacroiliitis. (Manuscript)
- V. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: The validity of the New York radiological grading criteria in diagnosing sacroiliitis by CT. (Submitted, under revision, *Acta Radiol*)

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Abbreviations

AP	Anteroposterior
AS	Ankylosing spondylitis
BASMI	Bath ankylosing spondylitis metrology index
CT	Computed tomography
DISH	Diffuse idiopathic skeletal hyperostosis
DMARD	Disease-modifying antirheumatic drug
HLA-B27	Human leukocyte antigen B27
IBD	Inflammatory bowel disease
MDCT	Multi-detector computed tomography
MPR	Multi-planar reformation
MRI	Magnetic resonance imaging
NSAID	Non-steroid anti-inflammatory drug
NY	New York
OCI	Osteitis condensans ilii
PACS	Picture archiving and communications system
PA	Posteroanterior
RA	Rheumatoid arthritis
RIS	Radiology information system
SpA	Spondyloarthropathy
THI	Triangular hyperostosis of the ilium

Background

The sacroiliac joint in the spondyloarthropathies

The SpAs are a group of disorders characterized by involvement of the sacroiliac joints and the spine, by peripheral inflammatory arthropathy and by insertional enthesitis (Table 1). There is a clinical overlap between the entities among the SpAs, there is a tendency towards familial aggregation, and there is an association with the HLA-B27 antigen [41]. AS is the oldest, most well-known and probably most common of these entities. Sacroiliitis is the hallmark of AS and is common in the rest of the SpAs.

Clinical diagnosis of the SpAs is difficult. Two sets of clinical criteria for AS have been reported [43, 167]. Radiological methods such as radiography, CT, MRI, ultrasonography and scintigraphy help in diagnosis.

Diagnostic and classification criteria placing greater or lesser emphasis on radiography have been presented [7, 23, 64, 72, 193]. It has been proposed that the underrecognition of AS primarily relates to the failure in making a correct radiographic diagnosis [40]. High-quality radiologic examinations of the sacroiliac joints are therefore necessary. Furthermore, it has recently been suggested that AS without radiographic confirmation and radiographically confirmed AS be treated as the same disease [31].

Ankylosing spondylitis
Reactive arthropathy (<i>Campylobacter</i> , <i>Shigella</i> , <i>Chlamydia</i> spp.)
Enteropathic spondylitis (Crohn's disease and ulcerative colitis)
Psoriatic arthropathy
Uveitis
Juvenile ankylosing spondylitis
Seronegative enthesopathic arthropathy syndrome
Undifferentiated spondylitis (i.e. subset of patients who have spondylarthropathic features but who fail to meet criteria for ankylosing spondylitis, Reiter's syndrome, or other conditions, e.g. dactylitis, uveitis plus unilateral sacroiliitis)
Pustulotic arthro-osteitis (considered by the Japanese to be part of the spondylarthropathy spectrum (rare in USA and Europe))
Behçet's disease (argument exists as to whether this should be considered as part of the group)
? Remitting seronegative symmetrical synovitis with pitting edema (RS3PE)

Table 1: Individual conditions that overlap to form the spondyloarthropathies. From [41].

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Anatomy

The sacroiliac joints connect the sacrum to the innominate bones to form the bony pelvis (Figure 1). The load from the entire upper body is transmitted to the legs over the sacroiliac joints when standing. At birth, the sacroiliac joints are practically straight, parallel to the long axis of the body. The greatest possibility for passive motion is at birth, which rapidly declines soon after [172]. Growth and development, and the mechanical forces from man's upright posture and bipedal gait, cause the joints to enlarge and to curve in a caudodorsal direction [21]. Epiphyseal secondary ossification centers appear in late adolescence [86] (Figure 4). In adults, there is great variation in size and shape [30, 172].

The sacroiliac joint has two compartments, one posterior-superior which is ligamentous, and one anterior-inferior, which is the true "synovial" joint. The joint is supported by strong ligamentous tissues, both the anterior capsular complex and the posterior ligamentous apparatus (Figure 2). The joint has an auricular shape (C-shape), with convex iliac surfaces articulating with concave sacral surfaces (Figure 3). The sacral hyaline cartilage in the "synovial" compartment has been reported to be about 4 mm thick in anatomical studies, often remaining largely unaltered into old age [30, 106]. The iliac cartilage, consisting of a fibrillar network of collagen bundles in the newborn, becomes hyaline in the adult with a maximal thickness of

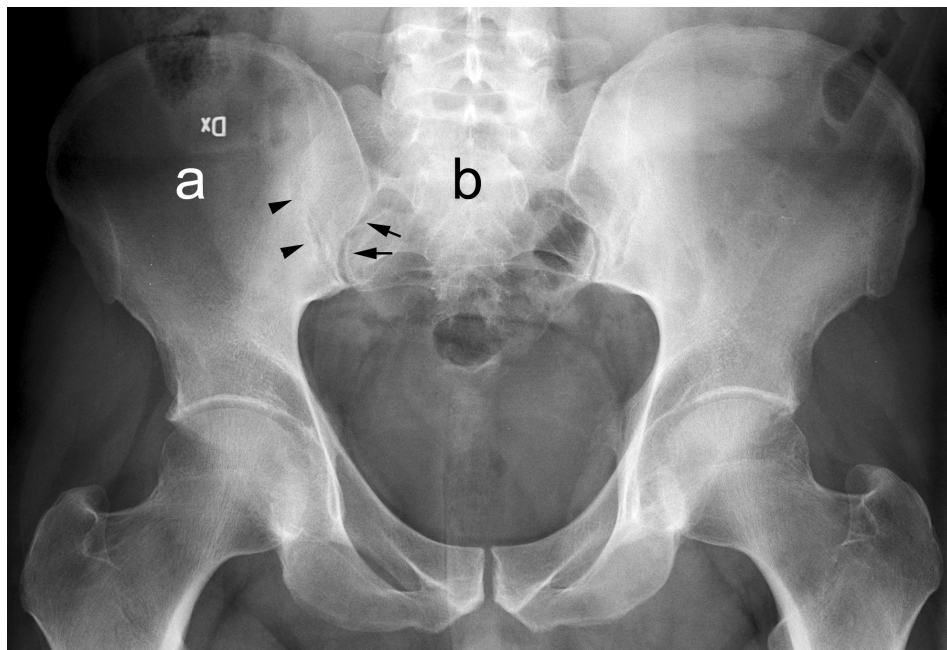


Figure 1: A radiograph of a pelvis showing a) the ilium and b) the sacrum. The sacroiliac joints are visible in the AP projection, with arrowheads indicating the anterior border and arrows indicating the posterior border.

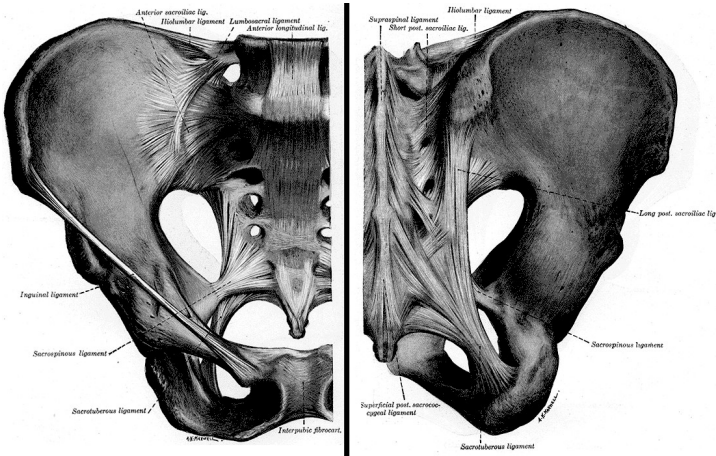


Figure 2: The right hemipelvis from anterior and posterior, showing the strong anterior and posterior sacroiliac ligaments. From [85].

1-2 mm. Degenerative changes appear early, with sometimes fibrous tissue filling up superficial defects and fissures [106]. The sacroiliac joint has been regarded as a synovial joint bordered by a dorsal and superior syndesmosis before the report by Puhakka et al [155], where it was been demonstrated that the sacroiliac joint should

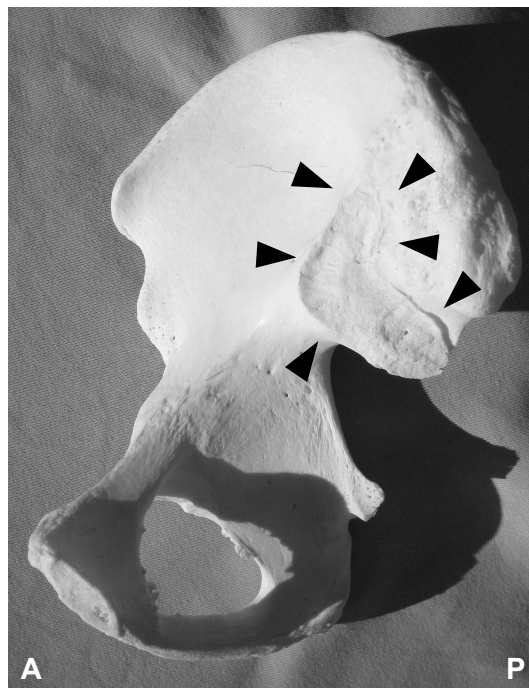


Figure 3: Photograph of the medial side of the right hemipelvis, showing the auricular or C-shape of the synovial part of the sacroiliac joint (arrowheads). (A=anterior, P=posterior).

be regarded as a symphysis [155] (a cartilaginous joint consisting of a fibrocartilaginous fusion between two bones): the joint surfaces are covered with hyaline cartilage, and the joint is connected through strong fibrous tissue, which blends with the hyaline cartilage through a transition zone of fibrocartilage. There is some resemblance of a synovial joint only in the distal third on the iliac side in ventral and dorsal transition zones [155].

There is a large variation in the morphology of the sacroiliac joint. Normally in women, the long axis of the “C” is oriented more anteroposterior than in men, where the craniocaudal orientation predominates [104]. The lumbosacral nerve plexus traverses directly anterior to the anterior capsule and may be involved in disease.

Dysfunction of the sacroiliac joints is a cornerstone in diagnosis and treatment in the fields of manual medicine, physiotherapy, and chiropractics. Terms such as locking, hypomobility, hypermobility and even dislocation are used. However, the movement of the sacroiliac joint in various loading positions has been found to be very low by using radiostereophotogrammetry [68, 184-186]. Between extreme positions in 25 patients, a mean rotation of 2.5 degrees and a mean translation of 0.7 mm was reported (the direction of translation was not stated) [184].

Normal variants and dysplasias

Normal variants

The sacroiliac joints are surrounded by several structures which may be radiologically confusing. One of these is the paragenoid sulcus (Figure 34), a variable sulcus immediately lateral to the inferior border of the joint, mostly appearing in multiparous women. The sulcus is considered to be an area of bone resorption at the insertion of the anterior sacroiliac ligament in response to stress, both from pregnancy and posture. The authors state that there also may be a relation between paragenoid sulci and THI (also known as OCI) [171]. Several normal

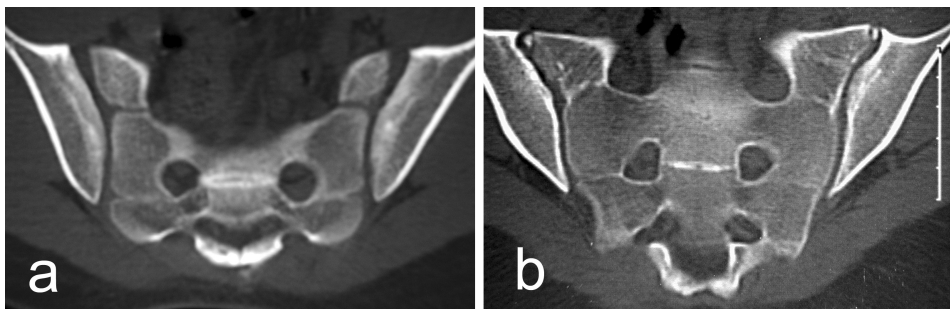


Figure 4: CT of the sacroiliac joints in two adolescents. a) Normal immature sacroiliac joints in a 13-year old girl, b) epiphyseal accessory ossification centers in a 17-year old girl.



Figure 5: A 36-year old female with a lumbosacral transitional vertebra, resulting in an anatomic variant of the left sacroiliac joint. The joints are otherwise normal.

variants can be seen when evaluating radiologic studies of the sacroiliac joints, and these may or may not be involved in the patient's symptoms and disease. Among these are the lumbosacral transitional vertebra, where in some cases the transverse process of the vertebra articulates directly with the ilium over a separate synovial joint to form part of the sacroiliac joint (Figure 5). The transverse process of a transitional vertebra may occasionally form a pseudo-articulation with the lateral mass of the sacrum which may be associated with subchondral sclerosis and eburnation, and possibly a cause of mechanical back pain. The sacroiliac joint itself presents in a variety of shapes [74], sometimes with accessory sacroiliac joints [69] (Figure 6). A number of variants have been described on CT [56, 151].

Dysplasias

Dysplasias such as myelomeningoceles, sacral dysplasias and arachnoid cysts (Tarlov cysts) may be noticed at imaging of the sacroiliac joints. Sacral dysplasias may affect the appearance of the sacroiliac joints, and can lead to early degenerative disease.



Figure 6: A 44-year old female with bilateral accessory sacroiliac joints (arrowhead) showing degenerative changes.

Diseases of the sacroiliac joints

Degenerative changes are very common, starting at an early age. In the spectrum of arthritis the inflammatory arthritides are most common, followed by septic arthritis. Secondary changes from metabolic disease such as hyperparathyroidism and other diseases can lead to arthritic changes.

Inflammatory arthritis

Seronegative arthritis

The seronegative arthritides are interchangeably known as spondylarthropathies, spondyloarthropathies, or spondylarthritides. They are a group of diseases which have a number of features in common, with sometimes substantial clinical overlap. Inflammatory arthritis of the sacroiliac joint is characteristic in AS [112], and in the other entities in the SpA group inflammatory sacroiliitis is also common, though with lower incidence. In clinical practice it is not always possible to differentiate between the subgroups of SpA, especially in the early stage of disease. This overlap can also make radiologic diagnosis difficult. The diseases are described in several textbooks, e.g. by Calin and Taurog [44] (Table 1).

Classification of spondyloarthropathies

Several diagnostic or classification criteria have been described [41, 141]. The first set of internationally agreed criteria for population studies were the Rome criteria [109] (Table 2), which dealt only with AS. The NY criteria (also for the diagnosis of AS) were first published in 1968 [23, 24, 142] (Table 3), with a

Clinical criteria

1. Low back pain and stiffness for more than three months which are not relieved by rest.
2. Pain and stiffness in the thoracic region.
3. Limited motion in the lumbar spine.
4. Limited chest expansion.
5. History or evidence of iritis or its sequelae.

Radiological criterion

X-ray showing bilateral sacroiliac changes, characteristic of ankylosing spondylitis (this excludes bilateral osteoarthritis of the sacroiliac joints).

Table 2: The Rome criteria for diagnosing AS. Four clinical criteria or one clinical criterion and one radiological criterion fulfilled are needed for the diagnosis of sacroiliitis. From [141].

modification published in 1984 [193] (Table 4). There are also criteria for reactive arthropathy [41] while those for psoriatic arthropathy [95] are under debate. With the wide variation in the disease spectrum many patients will not be included in such specific classifications. Therefore, two separate co-existing classification criteria have been developed for SpAs: the European Spondylarthropathy Study Group (ESSG) criteria [64] (Table 5) and the Amor criteria [7] (Table 6).

Ankylosing spondylitis

Historical perspectives

It is unclear how old AS is as a disease. It existed in ancient Egypt with high probability. The famous Florentine family di Medici was the first to be studied with AS [180]. Many previously described ancient cases are, however, cases with DISH or degenerative changes [49, 180]. The recognition of AS and the other SpAs as a group of overlapping complex diseases has slowly emerged during the last three centuries. The first description of a case of AS is probably by Bernard Connor in 1691 [164]:

“... the Body of this Perfon muft have benn immoveable, that he could neither bend or fretch himself out, rife up nor lye down, nor tun upon his

Radiologic criteria of sacroiliitis

X-ray grading:

- 0 normal
- 1 suspicious
- 2 abnormal with erosions or sclerosis
- 3 unequivocal abnormal, moderate, or advanced sacro-iliitis showing one or more of: erosions, sclerosis, widening, narrowing, partial ankylosis
- 4 total ankylosis

Clinical criteria

- 1 Major limitation of the lumbar spine in three planes, anterior flexion, lateral flexion and extension
- 2 A history of, or presence of pain at the dorso-lumbar junction or in the lumbar spine
- 3 Limited chest expansion of one inch or less (measured at the 4th intercostal space)

Definition for prevalence studies

Definite AS:

Grade 3 or 4 bilateral sacro-iliitis and one clinical criterion

Grade 2 bilateral or grade 3 or 4 unilateral sacro-iliitis plus either clinical criterion #1 or both #2 and #3

Probable AS:

Grade 3 or 4 bilateral sacro-iliitis without a clinical criterion

Table 3: The NY criteria for diagnosing AS. From [23].

A. Diagnosis

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

B. Grading

1. Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion
2. Probable ankylosing spondylitis if:
 - a) Three clinical criteria are present
 - b) The radiologic criterion is present without any signs or symptoms satisfying the clinical criteria. (Other causes of sacroiliitis should be considered)

Table 4: The modified NY criteria. From [193].

Side, having only the Head, Feet, and Hands moveable ... and it is likely this Perfon breathed very fhort ...

An Extract of al Letter from Bernard Connor, M.D. to Sir Charles Walgrave, Publifhed in French at Paris: Giving an Account of an Extraordinary Humane Sceleton, whofe Vertebrae of the Back, the Ribs, and feveral Bones downb to the Os Sacrum, were all firmly united into on folid Bone, without Joyinting or Cartilage.

Philosophical Transactions. Royal Society (1695) London Vol 19, p 21."

The historical aspects have been extensively described by Bywaters and Spencer et al [37-39, 180]. The first clinical description was by Benjamin Travers in 1824, and the first clinical and pathological correlations were drawn by Charles Fagge from Guy's Hospital in London in 1877 [164]. Soon afterwards, the disease was described by three physicians, whose names remain associated with AS: Vladimir Bechterew in Russia [18] (reprinted in [19]), Pierre Marie in France [25, 83], and Adolf Strümpell in Germany [1, 25, 108]. Even though Bechterew recognized cases of AS in his practice, his initial reports from 1892 and 1893 are about a disorder clearly separated from the one reported by Marie and Strümpell – deformity of the spine associated with cervical cord affection [125]. Bechterew himself was aware of this fact, even if his contemporaries had difficulties in seeing the differences, and studies of his original reports have corroborated this [124].

According to Bywaters [39], AS is still known as Morbus Bechterew in Scandinavia, Germany, Austria, Russia, and Russia's former satellite countries. The similarity between rheumatoid arthritis and AS led most North American observers

Inflammatory spinal pain

OR

Synovitis (Asymmetric or predominantly in the lower limbs)

AND

One or more of the following

- Positive family history
- Psoriasis
- Inflammatory bowel disease
- Urethritis, cervicitis, or acute diarrhea within one month before arthritis
- Buttock pain alternating between right and left gluteal areas
- Enthesopathy
- Sacroiliitis

Bilateral grade 2-4 or unilateral grade 3-4, according to the following radiographic grading system

0	Normal
1	Possible
2	Minimal
3	Moderate
4	Ankylosis

Table 5: The ESSG criteria. From [64].

to equate the two, calling AS “rheumatoid spondylitis” largely because of the histological resemblances in peripheral joints [39]. The use of the term did not cease until 1974 when Wright et al initiated the use of the term of seronegative spondylarthritis [164].

Epidemiology and pathogenesis

AS is a disease of the adolescent or young adult. The average age of onset is 25 years, and onset after the age of 45 is very uncommon [112]. In a questionnaire survey to 3000 members of a national patient self-help group in the United Kingdom, the male/female ratio was reported to be 2.4/1 [201]. It seems to develop more slowly in women.

The SpAs are closely linked to HLA-B27, but the strength of disease association with HLA-B27 varies markedly both among the disease entities and among genetic populations. The prevalence of AS and other SpAs seem to correlate with that of HLA-B27. The highest prevalences of both HLA-B27 and AS have been found among the Haida Indians living on the Queen Charlotte Islands in British Columbia, on the west coast of Canada, west of Vancouver. They show a 50% prevalence of HLA-B27 and a prevalence of AS of 4% among the male population [111]. The prevalence of HLA-B27 is between 10 and 16% among northern Swedes and northern Norwegians, who have a prevalence of AS of 1.4%. Samis have a 24% prevalence of HLA-B27, with a prevalence of AS of 1.8% In

A. Clinical symptoms for past history of:	Points
1. Lumbar or dorsal pain during the night or morning stiffness of the lumbar or dorsal spine	1
2. Asymmetrical oligoarthritis	2
3. Buttock pain – if affecting alternatively the right or the left buttock	1 or 2
4. Sausage-like toe or digit	2
5. Heel pain or other well-defined enthesopathic pain	2
6. Iritis	2
7. Non-gonococcal urethritis or cervicitis accompanying or within 1 month before onset of arthritis	1
8. Acute diarrhea accompanying or within 1 month before onset of arthritis	1
9. Presence or history of psoriasis and/or balanitis and/or inflammatory bowel ulcerative colitis, Crohn's disease	2
B. Radiological finding	
10. Sacroiliitis (grade ≥ 2 if bilateral, grade ≥ 3 if unilateral)	3
C. Genetic background	
11. Presence of HLA-B27 and/or familial history of ankylosing spondylitis, Reiter's syndrome, uveitis, psoriasis, or chronic enterocolopathies	2
D. Response to treatment	
12. Clear-cut improvement of rheumatic complaints with non-steroidal anti-inflammatory drugs (dramatic improvement) or relapse of pain if NSAIDs discontinued	2

Table 6: The Amor criteria. Patients with a total score of 6 points or more are classified as having a spondylarthropathy. From [7].

contrast, western Europeans have a HLA-B27 prevalence of 8% and a prevalence of AS of 0.2% [111].

In the industrialized world, juvenile onset is rare [112] but is much more common in developing countries such as Mexico, China, and Thailand [121]. The distribution of SpAs among the major groups is slightly different from western Europe and North America, and even though the disease conforms well with the ESSG criteria, response to treatment may not be identical due to different genetic and environmental factors [121].

The cause of AS is not fully understood. The disease sometimes occurs in association with reactive arthritis, psoriasis, ulcerative colitis, or Crohn's disease, in which case it is called secondary AS. Most cases of AS show no such association.

AS does not have a Mendelian pattern of inheritance (dominant or recessive). Recurrence risk in families has been shown to differ between the gender of the probands, with increased risk for relatives among young female probands. There is a strong genetic predisposition in association with the histocompatibility complex

antigen HLA-B27. Histocompatibility is the property of having the same, or mostly the same, alleles of a set of genes called the major histocompatibility complex. These genes are expressed in most tissues as antigens to help the immune system recognize foreign substances and are found in all higher vertebrates. In humans the complex is also called the human leukocyte antigen (HLA) system. Besides the well-known association with HLA-B27, recent studies have identified two major AS candidate genes outside the major histocompatibility complex region [156].

With inheritance of HLA-B27 the risk of developing AS is 20% for first-degree relatives of probands with AS [194]. The inheritance is, however, complex. The SpAs should be regarded as a group of phenotypically similar, but multifactorial diseases, with heterogeneity of the genetic predisposing factors and with an environmental trigger [111]. Bacterial infection and HIV infection have been suggested as possible underlying causes for differences in prevalence and age [121]. The disease probably starts when an antigen or other trigger activates an inflammatory response in the synovium and/or subchondral bone. The inflammatory response includes activated lymphocytes, which produce cytokines, including TNF α , leading to tissue destruction. Other cytokines are produced in the subchondral bone, which leads to new bone formation via chondroid metaplasia, eventually progressing to ankylosis [22].

Natural history

The natural history of AS and the other SpAs is in a worst-case scenario severe. Rapid progression to complete bony ankylosis of the entire spine, as well as of the sacroiliac joints and sometimes hip joints is the end result, with severe restrictive lung disease. Evidence of this has been presented in the early literature from skeletal remains [164] and with photographic illustrations [37]. Most cases do not progress that far at such a rapid pace. In a study initially on 150 English veterans from World War II [46], 67 were interviewed with a mean disease duration of 38 years. The results suggested that a predictable pattern of AS emerges within the first 10 years of the disease, where a mild form of disease does not progress to a more advanced form.

In a study on the natural history of AS [35], serial radiographs obtained at the start of disease, at 10 years, and at 20 years were scored according to the Bath AS radiology index (BASRI). It was found that the change in radiographic score increased about 35% per 10 years. The authors concluded that radiographic changes increase at a linear rate, and that spinal involvement largely is an effect of disease duration. In about 25% of the patients there was involvement of the hip joints which may predict a more severe outcome for the cervical spine [35]. The disease will almost never enter long-term remission spontaneously, and many patients with spontaneous remission will develop active disease again after a few years. Active disease seems to continue to be active, even after several decades of disease [110].

Diagnosis

Detection of sacroiliitis by radiography, CT, or MRI in the presence of clinical symptoms is diagnostic for AS. However, the presence of inflammatory back pain together with at least two other typical features of SpA such as uveitis and enthesitis is highly predictive of early AS [177].

Clinical manifestations

Two sets of clinical criteria to diagnose AS have been reported [43, 167] (Table 7). The patient experiences an often insidious onset of low back pain in the gluteal or sacroiliac region, which improves with exercise and worsens with rest. The gluteal pain may initially be unilateral or alternating, and may radiate down to the mid-posterior thigh. Nightly awakenings due to pain are typical. The pain improves with heat such as a hot shower or a stay in warm climate. Cold climate has the opposite effect. After a couple of months or even longer the pain and restriction in movements leads the patient to seek medical attention. This patient's delay together with a doctor's delay due to often very diffuse symptoms leads to a late diagnosis, according to two reports occurring at 8.5-11.4 to 9 years after onset of symptoms [76, 134]. It has recently been recommended that specific components of the medical history should be identified to better define and document the concept of disease duration. At the moment, different reports apply different ways of estimating disease duration, and the lack of standardization leads to reduced comparability between studies, including those on efficacy of modern therapy. Specifically, time of onset of first sign of axial manifestation, time of onset of each additional manifestation such as peripheral arthritis or enthesitis, time of onset of associated diseases such as anterior uveitis, IBD, or psoriasis, and time since diagnosis by a physician should be recorded [54]. In a study to facilitate earlier diagnosis, early referral from primary-care physicians and orthopedic surgeons was initiated. Patients below age 45 having chronic low back pain for shorter duration than three months and with either symptoms of inflammatory back pain or positive HLA-B27, or sacroiliitis detected by imaging, were referred to a specialist clinic, with 45.4% of all referred patients having SpA [31].

Age at onset < 40 years	Chronic back pain with onset < 50 years of age
Duration > 3 months	Morning stiffness > 30 minutes
Insidious onset	Improvement with exercise, but not with rest
Improvement with exercise	Awakening during the second half of the night
Morning stiffness	Alternating buttock pain
Calin et al, 1977 [43]	Rudwaleit et al, 2006 [167]

Table 7: Comparison of criteria for inflammatory back pain

Sciatica may be associated with sacroiliitis, especially infectious sacroiliitis [206]. Sciatica due to inflammatory sacroiliitis has also been reported [204].

Skeletal manifestations

AS is a chronic inflammatory rheumatic disease of the axial skeleton. The disease, as opposed to rheumatoid arthritis, involves the entheses (insertions of ligaments and capsular structures in the skeleton) producing an inflammatory response, enthesitis [12]. In synovial joints it also produces synovitis with pannus formation and resulting cartilage destruction. The destructive synovitis together with myxoid subchondral bone marrow were the earliest changes seen in AS in a histopathologic study [79]. However, an alternative pathologic mechanism has been proposed, with primary autoimmunity to cartilage, especially fibrocartilage, which would lead to the development of underlying subchondral osteitis [130].

Sacroiliitis is the hallmark of the disease, and all diagnostic and classification criteria incorporate that, with sacroiliitis almost invariably being the initial physical presentation of AS. The classic sacroiliac joint involvement in AS is bilateral and symmetric [160]. In about 10% of cases, however, unilateral sacroiliitis is the initial presentation, eventually progressing to bilateral involvement [59], and involvement of the spine.

The classic involvement of the spine is a cranially progressive ankylosis, which, when untreated, leads to a characteristic stoop. The inflammatory changes start as inflammation in the entheses of the apophyses in the anterior corners of the vertebrae. Ossification of the anulus fibrosus develops around an otherwise healthy intervertebral disk with progressive ankylosis. The longitudinal ligaments also ossify, as well as the posterior ligaments and the intervertebral joints. The early signs of apophysitis, with initially mild sclerosis at the anterior corners of the vertebral bodies (so called “shining corners”) later replaced by bone resorption, eventually replaced by bony ligamentous ankylosis, together with ankylosis of the intervertebral joints.

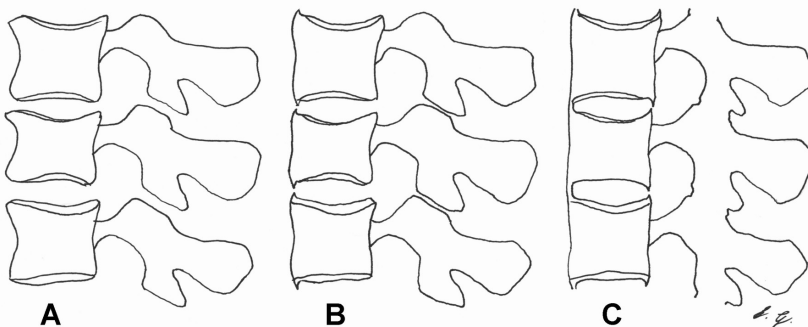


Figure 7: The stages of spinal ankylosis. A) Initially, enthesitis and reactive sclerosis gives rise to shining corners. B) Eventually, the vertebrae flatten due to inflammatory bone resorption and syndesmophytes arise. C) Finally, bony ligamentous ankylosis occur, together with ankylosis of the intervertebral joints.

have been called Romanus lesions [165], leading to flattening of the normally concave anterior border of the vertebra. Simultaneously, there is development of syndesmophytes (ossification of the insertions of the anterior longitudinal ligament). Eventually bony ankylosis along the circumference of the joint capsule will develop, as well as ankylosis of the posterior elements including the intervertebral joints (Figure 7). Rarely, another more serious disk destructive lesion develops, referred to as spondylo-discitis (so called Andersson lesion [8]). This was initially thought to represent local aggressive inflammatory disease, but has later come to be seen as a post-traumatic change after a non-displaced transverse stress fracture in an otherwise ankylotic spine [4, 12, 89]. These fractures involve the posterior neural arch and almost invariably involve the bone-disc interface in the vertebral column.

The entire spine need not be involved, but if so there will commonly be the appearance of a “bamboo” spine. If there is ankylosis along the superficial interspinous ligament, AP radiographs will show a typical “dagger sign”. Commonly, the largest spinal involvement is in the cervical spine.

A multitude of different physical measurements have been evaluated in AS. Lately, several of these have been examined for interobserver reliability. The suggested best measurements have been cervical spine rotation [149], thoracolumbar spine rotation [103, 197], cervical spine lateral flexion [149], lateral spinal flexion [103], finger-to-floor distance [149, 197], the Schober or modified Schober test [103, 149, 197], lumbar skin contraction in three consecutive 10 cm segments [140], C7 to iliac crest distraction [149], thoracolumbar flexion [197], occiput-to-wall or tragus-to-wall distance [103, 149, 197], and intermalleolar distance [103]. Of these, five clinical measurements have been combined into a composite index, the Bath AS metrology index (BASMI; cervical rotation, tragus to wall distance, lateral flexion, modified Schober test, intermalleolar distance) [103] to provide disease status information in AS. The BASMI has been reported to be quick (7 minutes), reproducible, and sensitive to change across the disease spectrum [103].

A number of clinical tests for evaluation of sacroiliac joint dysfunction have been evaluated and described by Stureson et al [183].

Pain and eventually ankylosis in the costovertebral and costotransverse joints lead to reduction in chest expansion, and almost all breathing is done with the diaphragm.

In the peripheral skeleton, involvement of the large joints in the girdles (i.e. shoulder and hip joints) is most common. Involvement of small joints is fairly uncommon. There may also be enthesitis in the peripheral skeleton, such as at the insertion of the Achilles tendon in the calcaneus.

Extraskkeletal manifestations

Acute anterior uveitis (acute iritis, iridocyclitis) is the most common extraskkeletal involvement in AS, occurring in up to 30% of the patients. It is more common in HLA-B27 positive patients. Occasionally it may be the presenting symptom [112]. In combination with positive HLA-B27 titer, the chance of the patient having AS is about 90% [168].

There may be cardiac involvement in some patients, usually after long-standing severe disease. Dilatation of the aortic ring and aortic valve incompetence may result after aortitis of the ascending aorta. Cardiac conduction anomalies can result from involvement of the bundle of His' or the atrioventricular node. Very rarely it may progress to mitral valve incompetence [112].

There are also, in rare cases, asymptomatic inflammatory mucosal lesions in the terminal ileum and colon, and some patients experience a slowly progressive apical pulmonary fibrosis [112].

Laboratory findings

There is no serum indicator for seronegative arthritides such as in rheumatoid arthritis, where the rheumatoid (RF) factor is an indicator of disease. Laboratory testing mainly serves to help rule out other diseases. The association between HLA-B27 and AS has been known since the mid-1970's. However, not all with positive HLA-B27 titer develop ankylosing spondylitis, neither do all patients with AS have a positive titer, and HLA-B27 testing makes sense as long as it is used in combination with relevant clinical, laboratory, or imaging parameters [168]. Based on the results from a study on blood donors in Berlin [33], it was calculated that the frequency of HLA-B27 was 9.3% among the population, with a prevalence of SpA of 1.9% (AS 0.86%, undifferentiated SpA 0.67%, and psoriatic arthritis 0.29%). SpA was diagnosed in 13.6% of the HLA-B27 positive group and in 0.7% of the negative group.

Histologic findings

John Ball [11] stated that enthesitis was the hallmark of AS, something that has often been repeated [10, 79]; a statement which over time has proven not completely true. It has been suggested that bone marrow inflammation, rather than enthesopathy, may be the primary component of the early pathology of SpA [130]. The microscopic features of sacroiliitis in AS have been evaluated in biopsies and autopsies [79], where destructive synovitis and myxoid subchondral bone marrow were found, which offers an explanation for the widespread joint destruction, and an unusual form of chondroid metaplasia which contributes to ankylosis. The authors of that report concluded that initially lesions in the synovium and the subchondral bone appear, which progressively destroy cartilage and subchondral bone by granulation tissue, and subsequently, destroy cartilage and subchondral

bone by a proliferative process of cartilage metaplasia and endochondral ossification, fibrosis, and formation of woven bone [79]. The microscopic pathology of sacroiliitis and AS is thus complex, and has not yet been completely elucidated.

Treatment

The pain and the debilitating effects of the ankylosis of AS have been treated in many different ways. Initially, bed rest or plaster immobilization was applied [164], up to the middle of the 20th century. During World War II, many drafted British soldiers with AS were referred to civilian physicians. Several of the soldiers expressed their wish to be free from their plaster “prisons”, and were further referred to military physiotherapists. The improvement in mobility was apparent, and thus a new approach to treatment was born. Several other different treatments have been tried, from liver sandwiches and mud baths to deep X-ray therapy [39], the latter being abandoned first after many cases of leukemia and aplastic anemia had come to be associated with the treatment in the late 1950's and early 1960's [38].

Until recently treatment was thus mostly symptomatic, consisting of pain relief with NSAIDs and long-term treatment with physiotherapy to postpone or avoid ankylosis [117]. This is facilitated by using heat, either in warm swimming-pools or by using physiotherapy facilities in places with a suitable climate, such as the Canary Islands, Spain, or Israel.

With disease-modifying antirheumatic drugs (DMARD), there are a few small open studies with methotrexate that report a potential effect on AS [176]. There are no studies beyond case reports for DMARDs such as gold, azathioprine, cyclosporine A, or leflunomide which are effective in the treatment of rheumatoid arthritis [176].

Tumor necrosis factor alpha (TNF α) is a cytokine involved in systemic inflammation and is a member of a group of cytokines that all stimulate the acute phase reaction. In modern-day treatment, the symptomatic treatment is assisted by TNF blocking agents, which have the ability to induce remission of inflammatory disease. Recently, several studies have reported on the use of infliximab on AS [32, 34, 131, 133, 175, 190]. The results are very promising with prompt and strong effects on almost all features of AS. In one study, using clinical parameters and MRI to evaluate response [145], there was an almost immediate relief of pain and stiffness, and the inflammatory edema surrounding the sacroiliac joints before treatment was absent at MRI at 16 weeks in nearly all patients, with the findings being stable at one year. Other agents such as etanercept [14] and adalimumab [120] have also been evaluated.

Risks and complications of disease

The most severe medical complications of AS are vertebral column fractures which may lead to some early deaths among patients with AS. In the ankylotic “bamboo” spine every fracture is complete, transverse, and by definition unstable. They are most common in the cervical region [100]. Even minor trauma can produce an unstable injury as a result of disruption of the ossified supporting ligaments [89, 100]. These fractures can be completely overlooked at radiography or even CT, or their severity can be underestimated. Correctly treated, most fractures after minor trauma heal without complications. After a high-velocity trauma, an unstable cervical spine fracture often leads to paraplegia or even tetraparesis. Epidural hematoma is a complicating factor, especially of cervical spine trauma. In patients with advanced AS and cervical spine trauma initial assessment with a lateral radiograph of the cervical spine, MDCT with MPR images and MRI have been recommended [146].

The most important long-term complication for the patient in general is probably the socio-economic impact and work disability. Recent studies have suggested that the burden of disease is similar to that of advanced adult rheumatoid arthritis, which, however, has a higher mean age of onset [176].

Psoriatic arthritis

Psoriatic arthritis is a disease both of peripheral joints, typically the distal interphalangeal joints of hands and feet, and of the axial skeleton, with sacroiliitis and spinal ankylosis as typical findings (Figure 8). The male/female ratio has been

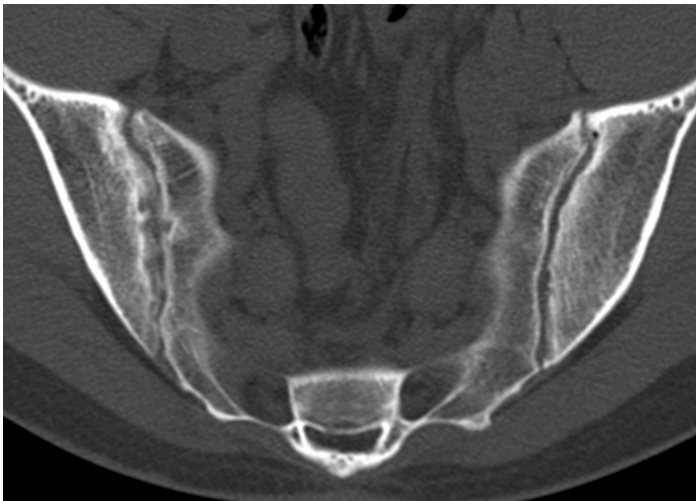


Figure 8: A 41-year old male with clinical psoriatic arthritis. The sacroiliitis is bilateral but highly asymmetrical.

estimated to 3.5/1 [201]. The arthritis usually appears after the typical skin lesions, sometimes decades after. It may occasionally appear before the skin lesions.

Sacroiliitis in psoriatic arthritis is not uncommon. In one study, about 50% of patients were found to have sacroiliitis, usually bilateral and asymmetric [91]. In another study, there was no difference in the rate of sacroiliitis between the four major groups in the SpA complex; however, the rate of asymmetry was higher for psoriatic arthritis than for both AS and enteropathic arthritis [94]. In a further study on 221 patients with psoriatic arthritis 78% had sacroiliitis NY grade 2 or higher; 55% grade 3 or 4, but the degree of symmetry was not reported [17].

There may be two forms of spinal arthritis in patients with psoriasis. One in patients who are HLA-B27-positive but lack peripheral arthritis, and probably have a coincidental more or less classic AS. The other form is seen in patients with characteristic psoriatic arthritis with or without HLA-B27, who have an often asymptomatic and nearly always asymmetrical sacroiliitis and spinal disease [188].

Psoriatic arthritis differs from the other major SpA groups in that there are no validated classification criteria such as for RA or AS. Despite clinical, radiological, and familial evidence supporting psoriatic arthritis as a distinct disease entity, controversy still exists about which patients to include within this disease group [95].

Reactive arthritis

Reactive arthropathy (including Reiter's syndrome) is defined as an inflammatory arthropathy distant in time and place from the original inciting infection [42]. The arthritis is seronegative, often asymmetric, and predominantly of the lower extremity. The infection is often in the bowel or genitourinary tract, but also

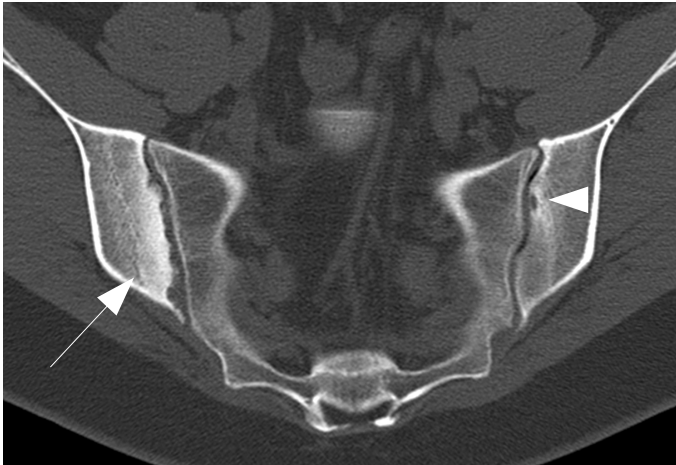


Figure 9: Reactive arthritis in a 20-year old female. On the right, erosions are covering 3/4 of the iliac joint surface with surrounding inflammatory sclerosis (arrow). On the left, there is a small area with a suspicious erosion (arrowhead).

respiratory pathogens have been implicated. The classic triad of Reiter's syndrome consists of urethritis, arthritis, and conjunctivitis or iritis. There is a striking relationship between an infective trigger (*Salmonella* spp., *Shigella* spp.), HLA-B27, and a clearly defined acute or chronic natural history [42]. In reactive arthritis, sacroiliitis was observed in 37% of patients followed for 15 years or more and is associated with axial lesions of AS in 15% of the cases [6]. It is often asymmetric or unilateral [137] (Figure 9). The disease may be self-limiting in some individuals, but chronic with frequent relapses in others [42]. Spontaneous remission of mild radiographic changes may occur in reactive arthritis.

Enteropathic arthritis

The connection between IBD and arthritis has been known since the 1920's. There is a tendency for the arthritis to flare with exacerbation of the colitis. Peripheral arthritis with a prevalence of 10-25% of the patients, more common with Crohn's disease, is the most common extraintestinal manifestation of IBD [139]. Sacroiliitis eventually appears in 23% of patients with IBD [182] and it is indistinguishable from sacroiliitis of AS [107]. The male/female ratio has been estimated to be 1/1 [201]. The prevalence of AS in patients with ulcerative colitis is over 40%, and the clinical picture is indistinguishable from uncomplicated AS [139]. In IBD, both AS and sacroiliitis is linked to HLA-B27, but to a lesser degree than in uncomplicated AS. The prevalence of HLA-B27 ranges between 50 and 70% [139].

Juvenile arthritis

When AS, reactive arthritis, psoriatic arthritis, or enteropathic arthritis present in patients younger than 16 years they are called juvenile SpAs. They must be distinguished from juvenile RA, but the distinction is not always obvious. Peripheral joint involvement as well as sacroiliitis is common [9].

Undifferentiated spondyloarthropathy

Patients with SpA may be classified or diagnosed according to classification criteria [7, 64] into the subgroups AS, psoriatic arthritis, reactive arthritis, and enteropathic arthritis. Those patients who do not fulfill any such classification remain unclassified and comprise the subgroup of undifferentiated SpA [36]. Two forms of undifferentiated SpA may be identified: early AS before erosive or inflammatory changes are apparent [31], and definite undifferentiated SpA. Undifferentiated SpA as an early form of AS is of interest because of new treatment options which have the possibility to influence erosive changes, ankylosis, and disease progression.

Undifferentiated SpA *per se* is mostly characterized by peripheral enthesitis and arthritis, and in a small proportion by axial symptom and a lower incidence of HLA-B27 [36]. It accounts for a significant but variable proportion of SpA patients in various studies [36]. In most cases undifferentiated SpA does not mean early or recent AS. Mean age of onset is later than for AS, there is a female predominance, and there is a low prevalence of HLA-B27. Since undifferentiated SpA does not fit into any defined subcategory of SpA, it has largely been ignored in earlier population studies. It may in some populations be as frequent as AS or reactive arthritis [114].

Seropositive arthritis

Rheumatoid arthritis

Involvement of the sacroiliac joint in RA is unusual, appearing late in the disease, if at all. The involvement of the sacroiliac joints may be unilateral or bilateral, but symmetric destruction is unusual. The erosions are usually superficial, without prominent sclerosis, and there is very seldom progression to ankylosis or ligamentous ossification [162]. In a study comparing psoriatic arthritis with RA, radiographic sacroiliitis was found in 10% of patients with RA and in 38% of patients with psoriatic arthritis. There was no significant difference in the rate of unilateral sacroiliitis [205]. In a study on 56 patients from northern Sweden with classical seropositive RA, half of which were positive and half negative for HLA-B27, radiographic sacroiliitis was found in 82% of the HLA-B27 positive patients and 57% in the HLA-B27 negative patients. The difference was statistically significant. The authors suggest that differences in sacroiliitis prevalence in RA in different studies may be attributed not only to patient selection and criteria, but also to genetic differences, where the presence of HLA-B27 increases the risk for more severe sacroiliac joint involvement [157].

Infectious arthritis

The most common agents causing septic sacroiliitis are *Mycobacterium tuberculosis*, *Staphylococcus* spp., and *Streptococcus* spp. There is usually significant soft tissue involvement around the joint, sometimes with abscess formation. Symptoms may be indistinct, such as abdominal pain, pain leading to limping, buttock pain, hip pain, or even radiating pain mimicking sciatica [13, 84, 123, 187]. The infection is always unilateral.

Degenerative joint disease

Degenerative changes in the sacroiliac joints appear in early adult life [30, 170, 199]. Resnick et al have compared the radiographic findings in degenerative disease with those of inflammatory sacroiliitis [160]. At radiography, joint space loss, subchondral sclerosis, and osteophytes are common findings. Erosions, subchondral cysts, ligament calcifications, and ligament ossifications are infrequently encountered [160]. In a CT evaluation of asymptomatic subjects [198], degenerative changes were seen fairly frequently over age 30, making CT diagnosis of sacroiliitis more difficult with increasing age. The degenerative changes at CT include ill-defined and non-uniform areas of subchondral sclerosis, particularly on the iliac side, and focal joint space narrowing. The authors proposed that the infrequent findings in the asymptomatic population were better indicators of inflammatory disease, such as increased sacral subchondral sclerosis in subjects under the age of 40, bilateral or unilateral uniform joint space of less than 2 mm, erosions, and intraarticular ankylosis [198]. Degeneration tends to progress more rapidly in women than men, presumed to be caused by the first (but not subsequent) pregnancy [174].

Diffuse idiopathic skeletal hyperostosis

With advancing age, para-articular bridging osteophytes or para-articular ankylosis are not uncommon. These are probably in many cases a manifestation of DISH, and not purely of degenerative origin [65]. DISH was initially described by Forestier (Forestier's disease) and others during the first half of the 20th century, and is a disease of middle-aged and older patients, presenting as idiopathic hyperostosis along primarily the anterior longitudinal ligament of the spine, but also in extraaxial locations. The historical, clinical, radiographic, and pathologic findings have been summarized by Resnick [161]. In DISH, sacroiliac joint abnormalities may include osteophytes and coexistent degenerative joint disease, particularly in older patients. These changes are associated with sacroiliac joint space narrowing and paraarticular bridging osteophytes, but should not be confused with AS. In DISH, there are no signs of erosions, inflammatory sclerosis, or intraarticular ankylosis [161]. In a study of spinal and pelvic changes in DISH compared to spondylosis deformans [88] ossification of the ligamentous superior, but not the inferior, portion of the sacroiliac joints was statistically significant for DISH. Dar et al have shown that sacroiliac joint bridging, i.e. para-articular ankylosis, is a phenomenon of enthesal proliferation, very similar to DISH in terms of genetics, age, and distribution [52, 53]. They suggest that the definition of DISH requiring hyperostosis along four consecutive vertebrae only accounts for 1/4 of the prevalence of DISH.

Other conditions

Primary or secondary hyperparathyroidism can result in subchondral bone resorption also in the sacroiliac joints, resulting in pseudowidening with ill-defined subchondral bone, practically indistinguishable from that of inflammatory sacroiliitis at radiography [62] and at CT [98]. Ankylosis does not occur.

The SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) includes skin conditions such as palmoplantar pustulosis and acne conglobata, osteoarticular manifestations of synovitis, hyperostosis and osteitis in particular target sites, and a clinical course with relapses and remissions [66]. Changes in the sacroiliac joints (Figure 10) are frequent [105, 135], usually unilateral in a high number of cases [92], with unusual sclerosis and hyperostosis predominantly on the iliac side, which may extend further into the iliac bone. The combination of moderate sacroiliitis and extensive sclerosis in the ilium is suggestive of SAPHO [66].

In calcium pyrophosphate deposition disease (CPPD) there may be sacroiliac involvement in 50% of the patients, with joint erosions, sclerosis, and joint space narrowing. These changes tend to be bilateral. Often there are anterior osteophytes. The chondrocalcinosis of CPPD is difficult to detect using radiographs but may be seen with CT [192].

Sacroiliac joint involvement by gout is rare, and when it occurs it is often unilateral [192].

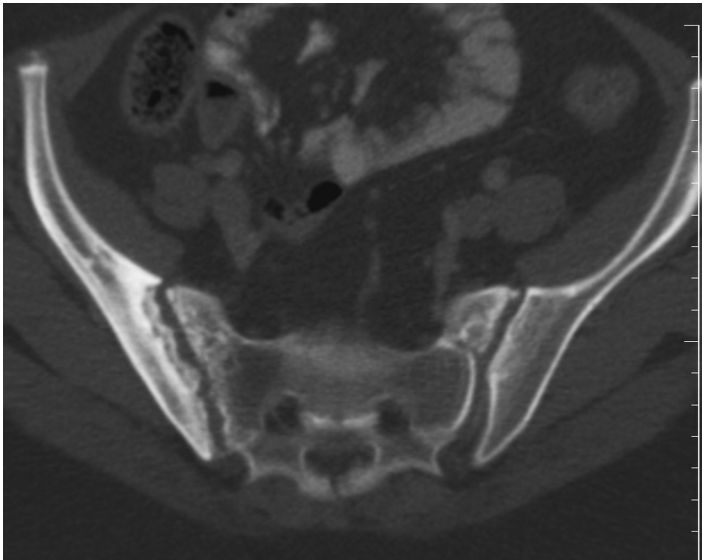


Figure 10: An 18-year old female with SAPHO. There are widespread arthritic changes in the right sacroiliac joint with extensive osteitis in the adjacent ilium. There were associated changes in two lumbar vertebrae.

Prior radiation therapy can cause widening and irregularity of the sacroiliac joints, and the weakened adjacent bone may be the site of osteonecrosis or insufficiency fractures [192].

In athletes, particularly long-distance runners or soccer players, erosions and sclerosis in the sacroiliac joints may be found due to shearing stress [192]. The reason for the development of these changes is unknown.

Multiple other conditions cause imaging abnormalities of the sacroiliac joints, such as immobilization or paralysis [192], familial Mediterranean fever [101, 208], multicentric reticulohistiocytosis, and Whipple's disease [192].

Diseases of the sacrum

A number of sacral traumatic and pathologic lesions may at times affect the sacroiliac joints, and may be detected on sacroiliac joint imaging.

Trauma

Fatigue fractures and osteoporotic fractures

Para-sagittal osteoporotic fractures of the sacrum are common. They do not directly involve the sacroiliac joints, but traverse more or less in the para-sagittal plane subcortically in the lateral mass of the sacrum. The fracture may be unilateral. When bilateral, they are often associated with a transverse fatigue fracture at the S2-S3 level. This gives rise to the classical H-sign or Honda sign at bone scintigraphy. At CT, the appearance is unmistakable, with an incomplete or minimally displaced fracture in the superior anterior part of the lateral mass of the sacrum (Figure 11). At MRI there is extensive bone marrow edema seen as low signal on T1-weighted images and high signal on T2-weighted or STIR images. There is often a fracture line visible on the T1-weighted images. The fractures are sometimes mistaken for metastasis [119]. Bilateral metastases in the lateral mass of the sacrum should not be diagnosed on MRI of the spine unless the entire sacrum has been examined with coronal images.

High-velocity trauma

The pelvis, sacrum and sacroiliac joints may all be involved in high-velocity trauma. The sacroiliac joints are commonly involved in more severe pelvic fractures. The anterior capsule of one or both sacroiliac joints may be disrupted in anterior compression trauma, and the posterior capsule may be disrupted in lateral compression trauma [99]. With vertical shearing fractures several lumbar transverse processes may be affected as well as the lateral mass of the sacrum and the sacroiliac joint. A posterior column acetabular fracture may sometimes affect the inferior part of the sacroiliac joint [81].

Tumors

Benign and malignant tumors of the sacrum are not uncommon, and in different age groups various tumors are more common than others. The patient has often had mild symptoms for a long time since the weight load from the upper body is distributed over a wide area in the lumbosacral junction, and the destruction is often large at presentation. The symptoms are frequently diffuse, and may be

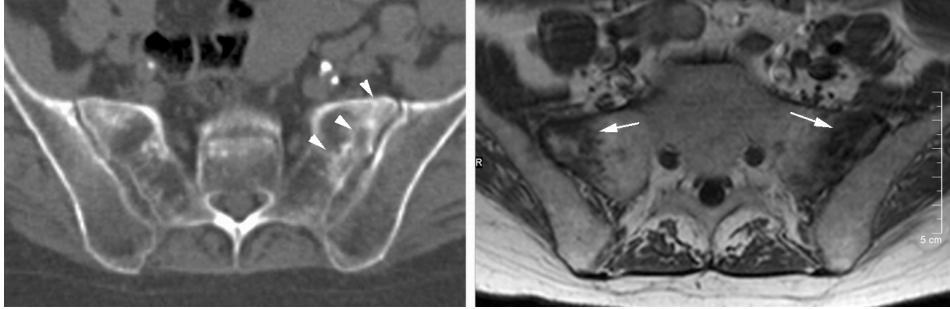


Figure 11: A 70-year old female with lung cancer. The MRI was misinterpreted as showing bilateral sacral metastases (arrows). CT confirmed the correct diagnosis of bilateral stress fractures in the sacrum (arrowheads).

attributed to the lumbar spine as well as the hip joints. Destructions in the sacrum or ilium adjacent to the sacroiliac joints are notoriously difficult to detect at radiography due to superimposed soft tissue and the complex bony anatomy, which is not the case with CT.

Osteolytic and osteoblastic metastases are the most common lesions in age groups above 50. After metastasis, myeloma and plasmocytoma are probably the most common sacral tumors. Chordoma is an uncommon primary tumor of the spine which typically appears in the distal sacrum, and may rarely be found elsewhere in the spine and in the clivus. In all adult age groups tumors such as chondrosarcoma, Schwannoma and ependymoma may occur.

In adolescents and young adults a number of primary tumors and tumor-like conditions may affect the sacrum. Among these, osteogenic sarcoma, Ewing's sarcoma, aneurysmal bone cyst, and giant cell tumor are probably the most common.

Imaging of the sacroiliac joints

Radiography

The living spine was first imaged with radiography by Schlayer in 1906 [37]. In the 1930's, radiography of the sacroiliac joints for evaluation of sacroiliitis was performed by Krebs and Bachman in 1930, and Charles Buckley in 1931 [37]. The evolution of radiographic techniques has been eminently described by Romanus and Ydén [166] and by Dihlmann [58].

Technique

Several projections for radiography of the sacroiliac joints have been described over the years [58]. The techniques mostly used today are probably a prone straight PA view using the fact that the sacroiliac joints are angled outwards towards the front and thus appearing more parallel to the X-rays; the Ferguson view (an AP view angled 20 degrees cranial); oblique AP views of each sacroiliac joint separately with the pelvis rotated about 20 degrees around the long axis of the body in order to align the sacroiliac joints parallel with the X-rays; and a straight AP view of the sacroiliac joints or the entire pelvis (Figure 1).

The outline of the joint on radiographic films has been demonstrated with the help of solder wires and radiopaque paint on cadaveric specimens [67].

In a comparison between an AP pelvis view and detailed oblique sacroiliac joint views no significant difference in severity score of sacroiliitis was reported [16], and the authors concluded that in most circumstances the AP pelvis film will yield the diagnosis of sacroiliitis without the additional expense and radiation exposure from specific sacroiliac joint radiographs. In another comparison between AP pelvis and AP lumbar spine radiographs and prone PA sacroiliac joint radiographs on 100 patients there was no change in diagnostic outcome [163].

Complex motion tomography has been evaluated [55] and compared to CT [63, 78] in evaluation of sacroiliitis. Recently, digital multislice tomography (tomosynthesis) using a flat-panel detector has become commercially available, but has not yet been evaluated in diagnosing sacroiliitis.

Radiation dose

For well collimated views with a skin area of 14x10 cm a Ferguson view results in an effective dose of 39 μ Sv for men using effective lead protection for the gonads and 255 μ Sv for women. Two oblique oblique projections with a skin area of 6x11 cm similarly results in an effective dose of 12 and 69 μ Sv, respectively [104].

Radiographic signs of sacroiliitis

Dihlmann [58] has in great detail described the polymorphism of radiographic signs of sacroiliitis, which may be divided into signs of destruction, sclerosis, and ankylosis (Figure 12). The signs are A) loss of sharpness of the contours of the joint; B) unsharp periarticular structures due to atrophy and remodeling as well as resorption of the subchondral bone; C) pseudo-widening of the joint due to demineralization of the subchondral bone, often in the shape of a garland or shallow scalloping; D) pseudowidening of the joint due to resorption of the subchondral bone, parallel to the joint; E, F and G) erosions of the joint, earlier on the iliac than on the sacral side with E) erosions seen as lucencies like a “string-of-pearls” in an otherwise well delineated joint, F) continuous erosions at the joint border, looking like a saw-blade or perforations of a postage stamp, or G) larger circumscribed erosions, dissection-like destructions and para-articular osteolysis; H) smaller spotted sclerotic changes, called *aspect tigré* by Forestier [58] or larger bulleted areas of sclerosis more than 5 mm wide (*aspect pommelé*); I) subchondral band-like sclerosis, not unlike that of degenerative joint disease; J) triangular-shaped sclerosis at the inferior border of the sacroiliac joint, somewhat similar to that of THI (Figure 13); K and L) ankylosis of the joint which may start as L) ossification of the

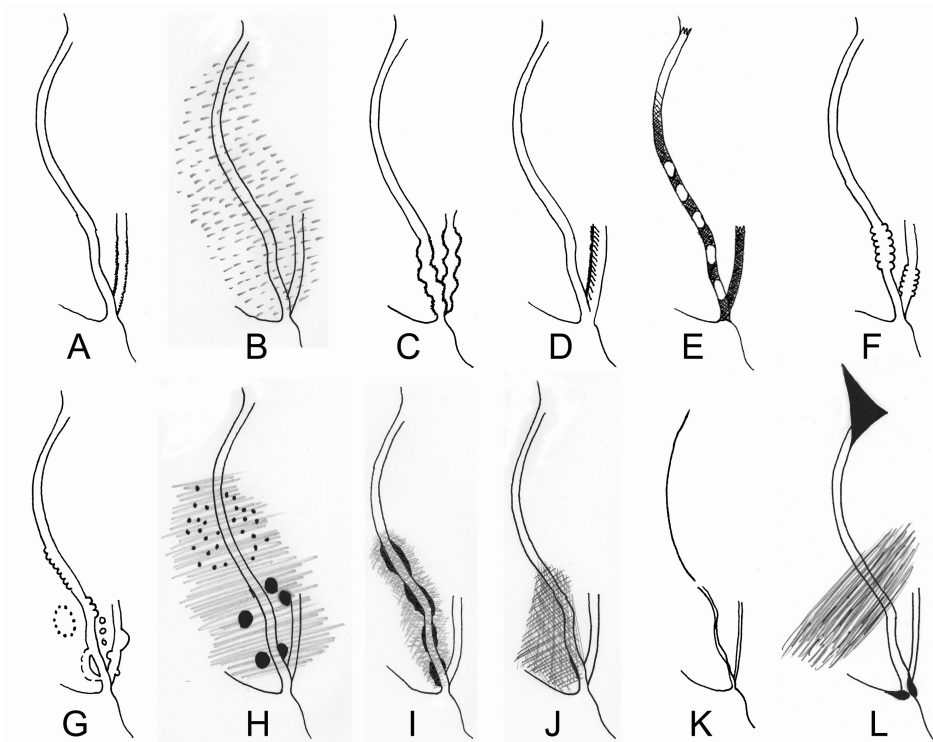


Figure 12: The polymorphism of radiographic changes in sacroiliitis. For explanation see text. Adapted from [58].

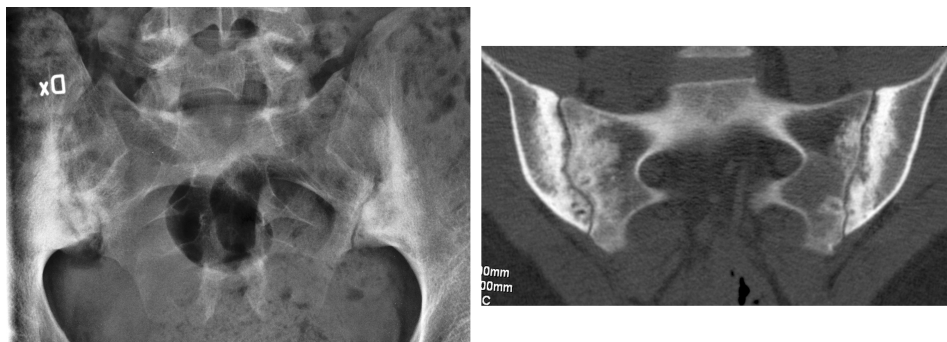


Figure 13: A 45-year old female with bilateral sacroiliitis. The triangular dense sclerosis on the plain radiograph might be suggestive of THI but the diagnosis of sacroiliitis is supplemented by widespread erosions and irregular joint space narrowing. The findings are more evident on CT.

anterior joint capsule and ligaments, or as ossification of the posterior ligamentous structures. Signs of ankylosis are also the ghost joint sign where the anterior joint border is sharply delineated despite a completely ankylotic joint, and the star sign, where dense ankylosis at the superior joint border may have a star-like appearance [58].

Diagnostic criteria

The diagnostic and classification criteria used are presented above under *Diseases of the sacroiliac joints, Classification of spondyloarthropathies* (Page 15). In all criteria, radiography of the sacroiliac joints is a key point, even though CT and/or MRI in many previous reports has been proven superior to radiography. Strangely enough, conventional radiography of the sacroiliac joints continues to be used, both in clinical practice and in scientific studies [17, 195]. In scientific studies, this may sometimes be warranted in order to keep the detectability of disease at the same level as in previous studies. If a new, better, diagnostic method such as CT of the sacroiliac joints is introduced there may be an overestimation of disease prevalence due to the improved detectability [27].

Scintigraphy

Quantitative sacroiliac scintigraphy, which is sensitive but has a low specificity for sacroiliitis, has been used to supplement the diagnosis of sacroiliitis [50, 57]. The method evaluates changes in sacroiliac/sacral (SI/S) ratio after injection of technetium-99m-methylenediphosphonate which are related to age and gender. The SI/S ratios decline with increasing age and there are differences in ratios between the genders in certain age groups. It has been suggested that each department should establish its own values for SI/S ratios based on gender and age

[127]. More importantly, in a recent meta-analysis on 25 papers after exclusion, the authors concluded that scintigraphy is “at the most of limited diagnostic value for the diagnosis of established AS as well as for diagnosis of probable or suspected sacroiliitis” [179].

Computed tomography

CT of the sacroiliac joints for evaluation of inflammatory changes was first described by Dihlmann et al in 1979 [60], a paper that is not often cited. The reason for this is probably that it is in German, but maybe also because the English translation of the title in Medline was wrong until 2006. In 1981, three papers [29, 48, 116] and one abstract [113] were published on CT of the sacroiliac joints. Two of those papers [48, 116], one published in 1982 [122] and one in 1983 [169] have mainly the same authors, and seem to share some of the same patient material. Later, several articles and abstracts have compared CT to radiography for evaluation of sacroiliitis in association with various diseases [45, 75, 77, 102, 123, 138, 152, 153, 158, 189, 209], to scintigraphy [75, 113, 1384], and to MRI in inflammatory as well as infectious sacroiliitis [2, 15, 123, 144, 154, 158, 187, 203, 209]. One recent study has evaluated the use of multidetector computed tomography (MDCT) [126].

Most of the cited studies above are favorable to CT as compared to radiography. One study could find no improved diagnosis with CT compared to radiography [29]. Another study on adolescents and young adults [102] concluded that the CT images provided no additional information for an experienced reader but that sensitivity was greater than for radiography; 91.2% compared to 71.6%.

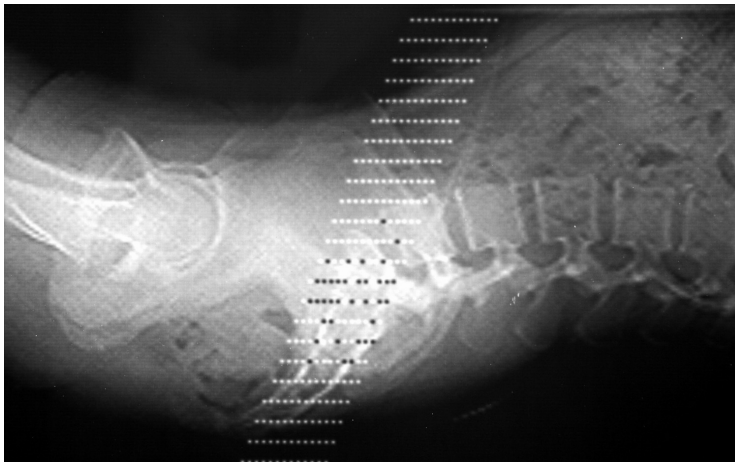


Figure 14: CT of the sacroiliac joints. The gantry tilt is similar in both supine and prone positions. The scans are acquired in a semicoronal plane to image the joints with the fewest number of scans and to avoid direct radiation of the ovaries.

This advantage was canceled out, however, by the large number of false-positive CT studies for a less experienced reader, mostly on immature joints. There were some non-favorable opinions on early CT of the sacroiliac joints [40]. One study has evaluated CT in orthopedic patients with sacroiliac pain. The authors found that a sacroiliac injection test was more reliable for localizing the source of pain [71]. No specific clinical diagnoses were reported.

Technique

CT of the sacroiliac joints, before the advent of MDCT, could theoretically be done in three different anatomic orientations; transverse to the anatomic long axis of the body, transverse to the long axis of the sacrum, and in a semicoronal plane, parallel to the long axis of the sacrum. From 1981, it has been recommended that CT be performed with the semicoronal technique, that is, coronal to the long axis of the sacrum and parallel to the anterior border of the sacrum through the synovial portion of the joints [47, 122]. This way, the least number of slices are used to image the synovial part of the sacroiliac joints, and the direction of the main beam also avoids the ovaries in females [104] (Figure 14). In older CT scanners with a gantry tilt possibility of 20 degrees, this was usually done prone with a pillow under the hips to increase lumbar lordosis. Today, CT is done supine as the gantry tilt of more recent CT scanners is 30 degrees. Thin slices of about 3 mm are used, with an image matrix of 512x512 pixels (in older scanners the highest possible, about 320x320 pixels) (Figure 15). It is of course also possible to evaluate the sacroiliac joints on pelvic studies on axial scans [73]. A high-resolution algorithm should be used. The quality may be reduced if thicker slices are used.



Figure 15: A 29-year old female with normal sacroiliac joints. The symmetric joint spaces have an even width, the subchondral bone plate is well defined, and there are no signs of sclerosis or erosions.

MDCT of the sacroiliac joints would theoretically result in higher dose for the same image quality, since a larger body volume has to be included in the scan field. This may be compensated by the improved beam geometry for MDCT compared to single-slice scanning. If semicoronal reconstructions comparable to direct semicoronal CT are desired scanning an even larger body volume is needed. In one study on MDCT of the sacroiliac joints [126] no report on the effective dose was given. In the author's experience, MDCT sometimes results in poor image quality due to the patient's body composition and insufficient dose (Figure 16), and MDCT seems to offer no benefits in dedicated CT of the sacroiliac joints. MDCT does offer, however, the ability to reconstruct thin slices in the semicoronal plane as well as other arbitrarily chosen planes to evaluate the sacroiliac joints. This can be done also on abdominal CT, provided that the dose is sufficient.

The scan time has decreased from 30 seconds in the early eighties to less than one second, which has reduced the risk of motion artifacts to virtually nil. The images are viewed at bone window setting with a window width of 1600-2000 Hounsfield units and a window level of 400-600 Hounsfield units.

Radiation dose

CT is a high-dose technique, and it is vital to use optimal settings for good diagnostic image quality and at the same time minimize the radiation dose to the patient. However, dose measurements, especially for CT, are fraught with technical difficulties and possibilities of errors [104].

The entrance skin dose for CT has been measured to be about twice that of a routine AP radiograph of the sacroiliac joints [29], which means that the dose from a full series of three sacroiliac radiographs is more or less equal to the dose from one CT examination. Also, one diagnostic CT examination will have less entrance skin dose than repeated radiographic examinations. Friedman et al have suggested a limited, low-dose, three-slice protocol [80] as an alternative to radiography in primary radiologic investigation for sacroiliitis. It is claimed to give a 2-fold to 4-fold reduction in radiation exposure relative to radiography and a 20-fold to 30-fold

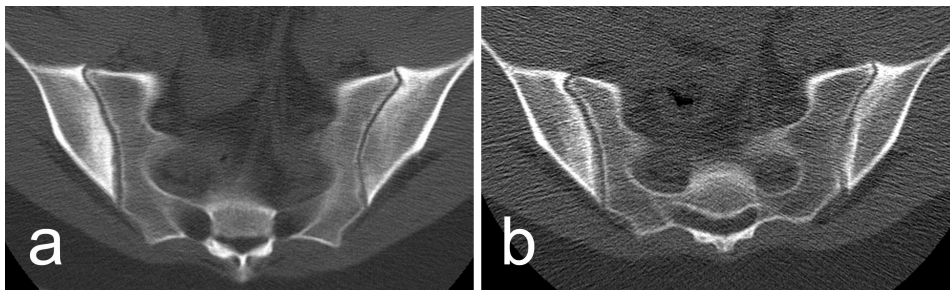


Figure 16: a) CT with contiguous slices on a 23-year old female with unilateral right-sided sacroiliitis. b) Follow-up with MDCT 2 years later is difficult to interpret due to insufficient dose.

reduction relative to a full CT series. Damilakis et al [51] studied different technical factors, and concluded that settings of 120 kVp and 508 mAs were optimal for evaluation of the sacroiliac joints on the scanner used, with 1.5 mm thick axial slices and 5 mm increment using a high-resolution algorithm. This resulted in a two-fold reduction in abdominal surface dose compared to a 4-image radiography series as well as a 5-image conventional tomography series, with equal doses for CT and radiography reported for the 8.5 cm depth, at the level of a fetus during early gestation. In a study by Jurik et al [104] measuring the effective dose, the dose to female gonads was reported to be 2.5 times lower for a semicoronal CT examination (102 μ Sv) than for a single AP radiograph (255 μ Sv) and more than six times lower than for axial CT (678 μ Sv). However, the effective semicoronal CT dose for men (100 μ Sv) was more than twice that of an AP radiography (39 μ Sv), using effective lead shielding of the male gonads at radiography and CT. The dose from semicoronal CT was about four times lower than for axial CT (410 μ Sv) also for men.

The results from these studies, where different measurements and measurement techniques have been used, are almost impossible to compare. Differences in results can be attributed to the use of different radiographic techniques, using measurements from different CT scanners, and using different calibration and reading of thermoluminescence dosimeters. The reports all point in the same direction, though: CT of the sacroiliac joints can without serious image degradation be done with significantly lower dose than abdominal CT, since mainly bony details are evaluated. The number of images should be kept to a minimum, and semicoronal imaging should be used to reduce the number of images and avoid direct targeting of the female gonads. The effective radiation dose to women is significantly less for CT than for radiography. In men, the use of lead shielding on the gonads at radiography significantly reduces the effective radiation dose, and the CT dose is somewhat higher. There are different opinions on which slice thickness is best for diagnostic purposes, 1.5 mm [51], 3 mm [209], or 5 mm [104].

Magnetic resonance imaging

MRI of the sacroiliac joints was first reported in 1990 [2]. MRI has a similar capacity to CT to detect manifest disease in the sacroiliac joints but has better capability to detect early disease [153], due to its ability to detect bone marrow edema [132] and inflammatory enhancement after intravenous contrast injection before morphologic changes can be detected by CT. Thus, MRI has the capacity to monitor response to treatment. Several follow-up studies have evaluated MRI changes over time [28, 147, 153, 154].

Technique

In routine clinical practice, a quick examination protocol consists of heavily fluid-sensitive sequences such as STIR or fat-suppressed T2 sequences to detect active changes such as bone marrow edema and erosions filled with fluid or granulation tissue, and T1-weighted sequences to detect chronic changes such as fatty replacement of bone marrow after inflammation and sclerosis [2]. The scans are obtained in the semicoronal plane comparable to CT of the sacroiliac joints, and in a semi-axial plane perpendicular to the previous. A minimum protocol consists of semicoronal STIR and T1 sequences and a semi-axial STIR sequence.

Intravenous contrast enhancement using gadolinium has been shown to show inflammatory changes well [153], and previous studies have shown that contrast-enhanced fat-suppressed T1-weighted imaging may show slightly larger areas of inflammatory changes in the bone marrow [143], but it has not been shown that this will detect more cases of active sacroiliitis than MRI without contrast enhancement. It has been suggested that about 10% less area of inflammatory changes are seen when using STIR imaging, compared to contrast-enhanced imaging [143]. There seems to be no clear consensus on whether contrast enhancement is necessary in clinical practice or not, and there has been no blinded study comparing STIR imaging with post-contrast imaging. STIR imaging is cost- and time saving [143], and STIR imaging and contrast-enhanced imaging are almost, but not exactly, equal for the detailed evaluation of active sacroiliitis [143].

The current investigation – aims and hypothesis

The aim of the study was to evaluate the performance of CT of the sacroiliac joints in diagnosis of sacroiliitis in a large patient material, by 1) comparing its performance to radiographs, 2) by evaluating the observer variation inherent in the method, 3) by evaluating the clinical utility of repeat CT, and 4) attempting to validate the diagnostic CT criteria for sacroiliitis.

The hypotheses were that a) CT is superior to radiography in primary radiologic diagnosis of sacroiliitis, b) there is good observer agreement for CT in a study environment but lower agreement in routine clinical practice, c) repeat CT is a good tool to investigate for sacroiliitis not detected on the primary CT, and d) the NY criteria are not valid for CT grading.

Aims of individual papers

I. Geijer M, Sihlbom H, Göthlin J.H. and Nordborg E.: The role of CT in the diagnosis of sacro-iliitis. *Acta Radiol* 1998;39: 265-268.

In a pilot study on 53 consecutive patients with low back pain admitted to the department of Rheumatology, the purpose was to correlate the findings at radiography with those at CT, and also to correlate the duration of clinical symptoms with the degree radiological changes.

II. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: The clinical utility of computed tomography compared to conventional radiography in diagnosing sacroiliitis. A retrospective study on 910 patients and literature review. *J Rheumatol* 2007;34: 1561-1565.

The clinical information delivered to the referring physician in suspected sacroiliitis was studied on 910 patients, examined with radiography and subsequently by CT within two years.

III. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: Observer variation in computed tomography of the sacroiliac joints: a retrospective analysis of 1383 cases. *Acta Radiol* 2007;48: 665-671.

The purpose was to evaluate the interobserver variation in 1383 CT examinations of the sacroiliac joints for possible sacroiliitis, and to evaluate the intraobserver variation in 122 of these cases.

IV. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: Clinical utility of repeated CT examinations in diagnosing sacroiliitis. Manuscript.

The purpose was to a) assess to which extent normal or equivocal findings turned into pathologic changes, and b) assess the occurrence of progression of changes characteristic for sacroiliitis at repeated CT.

V. Geijer M, Gadeholt Göthlin G. and Göthlin J.H.: The validity of the New York radiological grading criteria in diagnosing sacroiliitis by CT. Submitted, under revision, *Acta Radiol.*

The purpose was to validate the NY criteria grading for CT in 1304 CT studies of the sacroiliac joints by correlating the amount, structure and extension of erosions, sclerosis, ankylosis and other changes to the CT diagnoses.

Errata

Paper I

Page 265, first paragraph: The citation from reference 14 should be from reference 13.

Paper III

Page 667, Interobserver variation between A or B and C, line 6: “had originally been reported” should be “were scored by observer A”.

Page 668, Interobserver variation between A and C for patients during the first 2 and the last 2 years of the study, last line: “0.6724” should be “0.4651.”

Material and methods

Overview

In **paper I**, a pilot study, the performance of CT in diagnosing sacroiliitis compared to radiography was evaluated by two observers who scored the studies according to the NY criteria. This was followed by **papers II – V**, where the performance of CT was evaluated from different angles.

In **paper II**, again the performance of CT was compared to that of radiography. This was now done on a large number of patients in a retrospective analysis, using the clinical information delivered in the radiology reports while no radiographs were scored in a review. The amount of false positive, false negative, and false equivocal radiography reports was calculated.

In **paper III**, two observers independently scored a large number of CT examinations, which was the basis for an observer variation analysis in a study situation. The information from the original reports was categorized for an observer variation analysis between the observers in a study situation and the originally reporting radiologists working in a daily practice. A number of studies had been read by one of the observers previously in clinical practice, and this material was used for an intra-observer analysis.

Paper IV evaluated whether it is useful to repeat a negative CT study or not.

In **paper V**, the validity of the NY criteria in grading CT of the sacroiliac joints for evaluation of sacroiliitis was examined by evaluating a number of inflammatory and other changes such as erosions, sclerosis, ankylosis, joint space width and shape, osteophytes, subchondral cysts and pneumatocysts, vacuum phenomenon and other changes, and relating them to the radiological diagnosis.

Patients

Paper I

Forty patients admitted to the Department of Rheumatology at Sahlgrenska University Hospital, Göteborg, Sweden (28 male, 12 female, mean age 31.5 years, range 17-50) with symptoms of sacroiliitis and a control group of 13 patients (six male, seven female, mean age 35.5 years, range 22-47) without symptoms of sacroiliitis were compared. In the 40 patients with clinical sacroiliitis, 18 had AS, the rest had other forms of SpA. In all, 25 of 40 patients were HLA-B27 positive; 17 of which had AS.

Papers II – V

CT of the sacroiliac joints has been a routine examination method at Sahlgrenska University Hospital since 1980. Photocopies of all CT reports were prospectively archived for research purposes during 1981 – 1992, and from 1991 all radiology reports are accessible in the radiology information system (RIS).

The reports and the referral forms for all CT examinations of the sacroiliac joints, performed between 1981 and 1997 were retrieved. Totally, 1477 records of examinations were located.

Two of these 1477 records were false registrations of examinations not performed. In 23 cases the patients were excluded from the current study for being under age 18 years. In 17 cases the examination was performed for evaluation of tumor, in five cases for evaluation of fracture, and in two cases for evaluation of post-operative pain after spine surgery. These cases were also excluded, since the examinations were not targeted on the sacroiliac joints. In three cases, the films as well as the request form and the radiology report were missing. Fifty-two examinations were thus excluded, and 1425 examinations remained as the basis for the four papers.

In **papers II, III, and V** an additional three cases were excluded from the 1425 examinations, where it was impossible to locate referral forms or radiology reports.

For **paper II** radiography of the sacroiliac joints had been done in 1150 patients. The reports and referral forms for radiography were retrieved. Seventy patients were excluded where the radiography reports were missing. Of the remaining 1080 patients who had been examined with both CT and radiography and where radiology reports for both examinations were available, 910 patients had been examined with radiography either on the same day as the CT examination or

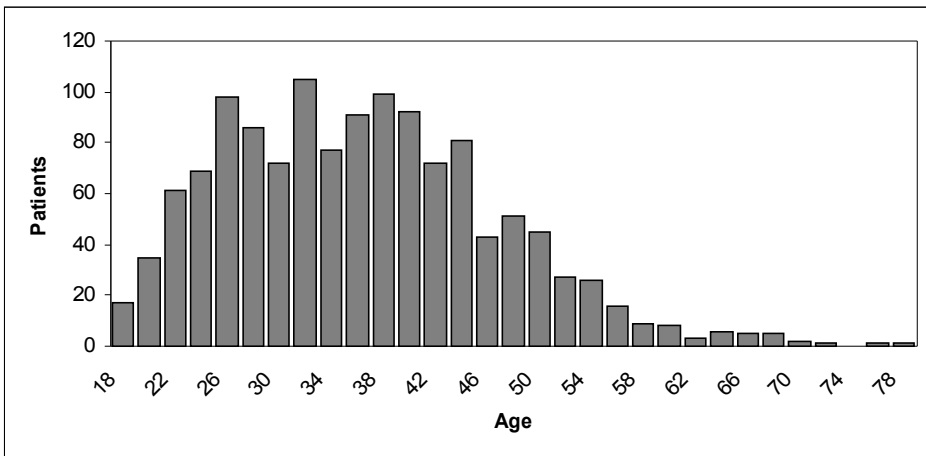


Figure 17: Age distribution of 1304 patients referred for CT of the sacroiliac joints.

within 2 years before the CT examination. Patients with radiography either after CT or more than 730 days before CT were excluded.

For **papers III and V** further 36 cases had films missing, and in three cases so much of the film material was missing that review was impossible. Totally 1383 cases were included in **paper III**.

In **paper IV** the same 39 cases as in paper III were excluded where all or most of the films were missing and 1386 cases remained. From the years 1998 – 2007 1517 cases were added after exclusion of 5 patients younger than 18 years. Among the resulting 2903 available CT examinations there were 492 examinations on 228 patients where the patient had been examined with CT more than once and the films from all examinations were available for review. After exclusion of 61 patients where the symptoms were suggestive of mechanical low back pain or sciatica, four patients with hypermotility symptoms, and 37 patients where the indications were not clearly stated, there remained 126 patients where the indications were inflammatory back pain (83 women and 43 men, f/m ratio 1.93). The median age was 31 years (34 at the second examination), age range 18-54 (19-58) years.

In **paper V** an additional 79 cases were excluded, since the calipers were missing on the films, thus making evaluation impossible. Totally, 1304 cases remained. The age distribution and duration of symptoms for **paper V** are shown in Figure 17 and Figure 18.

Radiographic examinations

In **paper I** radiographs of the sacroiliac joints were obtained in AP projection of the pelvis, and in oblique projection of each joint with a 20 degrees from caudal

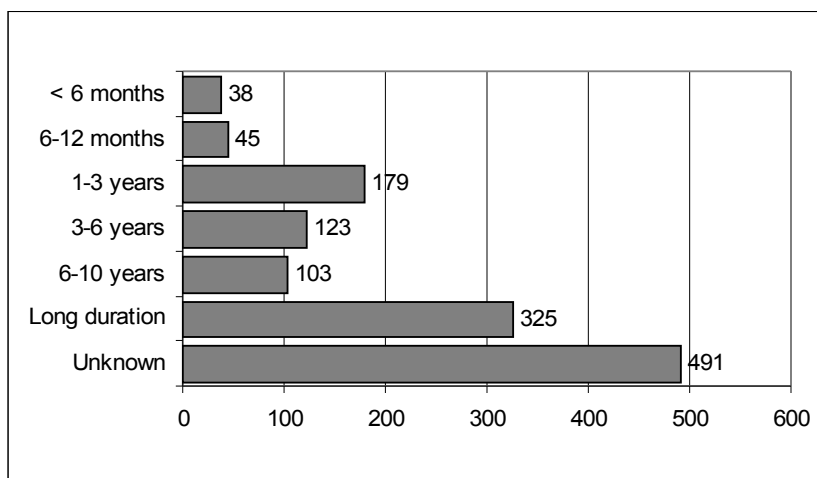


Figure 18: Duration of symptoms in 1304 patients referred for CT of the sacroiliac joints. In the group with long duration several patients had symptoms explicitly over 10 years.

tube angle within three months of the clinical examination. All examinations had been done at Sahlgrenska University Hospital, and the images were independently interpreted by two radiologists on film.

In **paper II**, only the reports were used and the films were not scored. The films were retrieved when possible for review of the radiographic techniques which varied. Specific examinations of the sacroiliac joints at Sahlgrenska University Hospital, as well as at most other hospitals, were done using a Ferguson view and one additional AP oblique view of each joint. Other examinations such as an AP pelvis examination, an AP radiograph of the sacrum, or a PA view of the SI joints were also included if the originally reporting radiologist had commented on the status of the SI joints in the report done at the time of the examination.

CT examinations

In **paper I**, CT was performed with the patient prone with a pillow under the hips, with a gantry tilt of 20 degrees to obtain angled coronal images of the sacroiliac joints, within three months of the clinical examination. Three-millimeter thick contiguous slices were obtained through the synovial part of the sacroiliac joints, using a high-resolution reconstruction algorithm at usually 120 kV and 200 mA. The studies were independently reviewed on film by two radiologists. All studies were made at Sahlgrenska University Hospital.

In **papers II – V** the same CT technique was initially used as for paper I. When more recent CT scanners became available with 30 degrees gantry tilt, the studies were made with the patient in the supine position, otherwise with the same technical settings. For a number of studies in paper IV performed after 2005 an MDCT volume was obtained with secondary reconstructions in the same angled coronal plane as described above. All studies were made at Sahlgrenska University Hospital.

Scoring and measurements

In **paper I**, both radiographs and CT films were scored according to the NY criteria [23] (Table 3). A narrow, irregular joint space, reactive sclerosis, erosions, pseudo-widening of the sacroiliac joint, and ankylosis were regarded as signs of sacroiliitis. Each joint was scored separately.

In **paper III** two reviewers interpreted all available studies using hard copy films, independently from each other, and blinded to the original report and all clinical data. The reviews were performed sequentially, not in random order. The same review technique was used for **papers IV and V**. For **paper IV**, studies made during 2004 – 2007 were evaluated and scored as soft-copies, using the normal PACS (General Electric RA 600).

Each sacroiliac joint was scored separately. Two scoring systems were used; a) the NY criteria [23] assigning points for each joint (0 = normal, 1 = suspicious for sacroiliitis, 2 = abnormal with erosions or sclerosis, 3 = unequivocally abnormal, moderate, or advanced sacroiliitis showing one or more of: erosions, sclerosis, widening, narrowing, partial ankylosis, 4 = total ankylosis), b) a grading assessing the reviewers confidence in a radiologic diagnosis of sacroiliitis (0 = no sacroiliitis, 1 = possible sacroiliitis, 2 = doubtful sacroiliitis, 3 = probable sacroiliitis, 4 = definite sacroiliitis). The second scoring system was used because the NY criteria only uses one degree of equivocality, while the second scoring system gives a wider scale from normal to pathologic with three levels of equivocal findings, which was presumed to be more useful for CT than the NY criteria.

Changes specific for sacroiliitis were evaluated thoroughly. The extent, density and homogeneity of subchondral sclerosis were assessed using pre-defined scales. The transition zone from sclerosis to normal medullary bone was defined as sharp or indistinct. The homogeneity of sclerosis (i.e. if all sclerosis had the same appearance) was defined as homogeneous, intermediate, or inhomogeneous. The density of sclerosis was defined as high, intermediate, or low. The distribution of erosions as well as the presence of ankylosis was recorded. The joint space width was measured on the slice with the longest synovial joint; in the middle and about 1 cm from the cranial and caudal borders, from bone-cartilage interface to cartilage-bone interface, using a magnifying loupe with a 0.1 mm graded caliper. The locations of the measurement points are indicated by circles at the left sacroiliac joint in Figure 32a. The mean value of the three measurements was used for further calculations. Other changes were also recorded, such as three levels of degenerative changes, the presence of THI, incidental findings such as tumors or fractures, or post-operative changes such as sites of bone graft harvesting for spinal fusion, and other changes. The presence of vacuum phenomenon, subchondral cysts, pneumatocysts, and accessory sacroiliac joints was recorded.

The clinical information was obtained from the request forms. Information about the exact or estimated duration of symptoms, and type of symptoms was recorded. The symptoms were classified as 1) inflammatory back pain with symptoms such as morning stiffness and nightly awakening due to pain, and improvement with physical exercise; 2) low back pain of suspected noninflammatory origin, such as sciatica or diffuse lumbago; 3) hypermotility symptoms after pregnancy; and 4) other symptoms or clinical history such as tumor or trauma.

For **papers II** and **III** the initially reported outcomes from CT and, in **paper II**, radiography were classified as 1) normal or normal with degenerative changes, 2) equivocal for sacroiliitis, 3) pathologic, thus uni- or bilateral sacroiliitis, and 4) other findings such as post-operative changes, fractures, or THI.

Statistics

In **paper I** Fisher's exact test was used for comparisons between groups. Fisher's permutation test was used with regard to age and low back pain. In **papers II, III and IV** the degree of observer agreement was evaluated using the unweighted kappa statistic (κ), with the value of kappa converted to the strength of agreement [5]. A kappa value less than 0.20 constitutes poor agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate; 0.61-0.80 good; and 0.81-1.00 very good agreement. The use of unweighted kappa was required by journal referees.

Results

Paper I compared the findings between radiography and CT in suspected sacroiliitis. Thirty of 40 patients had sacroiliitis at CT, ten of them also at radiography. Radiography gave a false negative result in 20 cases using CT as gold standard. Generally a higher score (the combined NY criteria grading for both joints) was registered at CT (mean 4.75, range 0-8) than at radiography (mean 2.8, range 0-6), and all changes seen on conventional radiographs were visualized equally well or better at CT.

Only CT demonstrated changes in ten patients, especially erosions and ankylosis. No changes were seen in the control patients, thus no false positive diagnoses were registered at conventional radiography or at CT. CT was positive in 20 of the 26 patients with more than two years' duration of symptoms. Radiography was positive in eight of those 20. CT was positive in three patients with clinical sacroiliitis for more than 10 years and negative radiography. CT was positive in 10 of 14 patients with symptoms of sacroiliitis for less than two years, radiography in two of these 10.

The four patients with negative CT all had diagnoses associated with SpAs: psoriasis, chronic IBD, and reactive arthritis. Both conventional radiography and CT had 100% specificity. CT had a 75% sensitivity for radiographic sacroiliitis in patients with clinically suspected sacroiliitis independent of the duration of symptoms. Conventional radiography, with a total sensitivity of 25%, had 14% sensitivity for sacroiliitis of less than two years' duration, and 31% sensitivity for clinical sacroiliitis with more than two years' duration.

Paper II compared the reported findings for radiography and CT. Preliminary results had been reported earlier [82]. Pathological diagnoses were 2.3 times more frequent with CT than with radiography. At radiography, equivocal findings were 2.5 times more frequent (250/100) than definitive pathological diagnoses (Table 8) while at CT, pathologic findings were about 2.6 times more frequent (230/87) than equivocal findings (Table 9).

Comparing the reported diagnoses at radiography and CT, only 65/100 (65.0%) radiographic examinations with reported sacroiliitis could be confirmed

Outcome	Number (%)
Sacroiliitis	100 (11.0)
Equivocal findings	250 (27.5)
Normal or degenerative changes	554 (60.9)
Other diagnoses	6 (0.7)
Total	910 (100.0)

Table 8: Paper II: Outcome of 910 sacroiliac joint radiographs.

Diagnosis	Number	Sum	%
Sacroiliitis, bilateral	187		
Sacroiliitis, unilateral	43	230	25.3
Equivocal	35		
Follow-up recommended	52	87	9.6
Severe degenerative changes	2		
Moderate degenerative changes	23		
Mild degenerative changes	194	219	24.1
Osteitis condensans ilii	31		
Normal	335	366	40.2
Tumor	1		
Fracture	1		
Post-operative findings	4		
Miscellaneous	2	8	0.9
Total	910	910	100.0

Table 9: Paper II: CT diagnoses in 910 examinations of the sacroiliac joints.

with CT (Table 10). The kappa value for these comparisons was 0.2418 (standard error 0.0265), indicating only fair agreement. Equivocal radiographic findings were reported as pathological on CT in 88/250 cases (35.2%), and as normal in 127 cases (51.0%). The CT result was pathological in 77/560 (13.8%) radiographic examinations assessed as normal.

Radiography was thus true-positive in 65.0% of the 100 examinations reported as pathologic (Table 11), with CT confirming the positive diagnoses. Radiography was true-negative in 77.5% of the 580 normal radiographic examinations. Considering all the data for 910 patients, 41.3% of the radiographs were incorrectly diagnosed or the results were equivocal (Figure 19). Uni- or bilateral sacroiliitis diagnosed by radiography thus showed a high rate of false-positives, as only 65.0% could be confirmed with CT. Radiography also yielded 22.5% false negative

		Radiography							
		Pathologic		Equivocal		Normal		Total	
		n	%	n	%	n	%	n	%
CT	Pathologic	65	7.1	88	9.7	77	8.5	230	25.3
	Equivocal	3	0.3	35	3.8	49	5.4	87	9.6
	Normal	32	3.5	127	14.0	434	47.7	593	65.2
	Total	100	11.0	250	27.5	560	61.5	910	100.0

Table 10: Paper II: Differences in reported outcome for radiography and CT in patients referred for suspected sacroiliitis. Percentages are of whole material.

	True		False		Total
	n	%	n	%	n
Positive	65	65.0	35	35.0	100
Negative	434	77.5	126	22.5	560
Equivocal	35	14.0	215	86.0	250
Total	534	58.7	376	41.3	910

Table 11: Paper II: True and false positive, negative, or equivocal radiography studies compared to CT in 910 patients suspected for sacroiliitis. The CT diagnoses are regarded as correct. Percentages of each diagnosis.

examinations. Normal radiography, where CT showed equivocal changes, was encountered in 5.4% of the patients. There were no obvious differences between the entire group and a subset of patients where the interval between radiography and CT was 90 days or less.

Paper III evaluated the observer agreement in CT of the sacroiliac joints. The observer agreement between observers A and B was good (κ 0.6724, Table 12). There was excellent agreement on cases of bilateral sacroiliitis, with agreement in 168 of a total of 201 cases scored as bilateral sacroiliitis by any of the observers. Observer A had an additional nine cases (5.4%) where B had scored these as unilateral sacroiliitis (six cases), equivocal (two cases), and normal (one case). Observer B had an additional 24 cases (14.3%) where A had scored these as unilateral sacroiliitis (11 cases), equivocal (10 cases), and normal (three cases). There was moderate agreement on cases of unilateral sacroiliitis, with agreement in 53 of a total of 107 cases scored as unilateral sacroiliitis. A had an additional 16 cases (30.2%) where B scored these as bilateral sacroiliitis (11 cases), equivocal (three cases), and normal (two cases). B had an additional 38 cases (71.7%) where

		A				
		Bilateral sacroiliitis	Unilateral sacroiliitis	Equivocal	Normal	
B	Bilateral sacroiliitis	168	11	10	3	192
	Unilateral sacroiliitis	6	53	26	6	2
	Equivocal	2	3	80	71	156
	Normal	1	2	86	855	944
		177	69	202	935	1383

Table 12: Paper III: Interobserver agreement between A and B in 1383 CT examinations of the sacroiliac joints for evaluation of sacroiliitis; agreement is good, κ 0.6724.

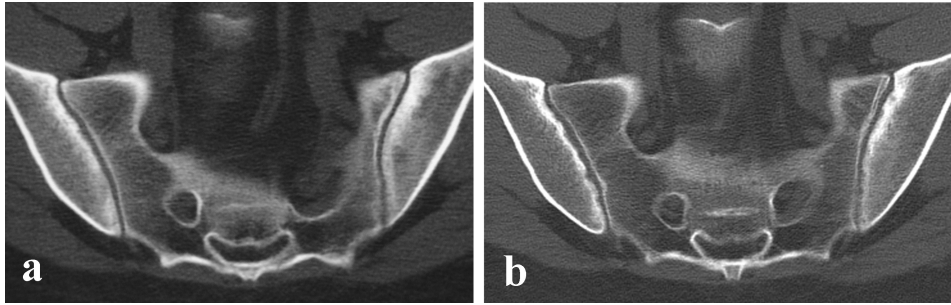


Figure 19: A case with subtle changes initially interpreted as normal showing progression to evident sacroiliitis. a. A 32-year old male with 3-6 years history of suspected SpA. A previous CT one year earlier had been reported as normal. The CT shows bilateral iliac very subtle cortical erosions in the sacroiliac joints, with ill-defined dense subcortical sclerosis of inflammatory origin. b. 6 ½ years later, there is progression to definite but mild bilateral sacroiliitis.

A had scored these as bilateral sacroiliitis (six cases), equivocal (26 cases), and normal (six cases). Excellent agreement was also reached in 865 normal cases of a total of 1034 cases scored as normal by any of the observers. A had an additional 80 cases (9.4%) and B 89 cases (10.4%). There was poor agreement in classifying equivocal findings. Unanimous agreement was reached in only 80 out of a total of 278 cases scored as equivocal by any of the observers. A had an additional 122 cases and B an additional 76 scored as equivocal.

Moderate agreement was found between the original reports (C) and the findings of observers A and B (κ 0.4651 and κ 0.4481, respectively, Figure 19). Observer A agreed on 160 of 264 cases originally reported as bilateral sacroiliitis (60.6%) by observer A, who scored the remaining 104 cases as unilateral sacroiliitis (26 cases), equivocal findings (37 cases), and normal (41 cases). In cases of unilateral sacroiliitis, there was agreement in 22 of 55 cases (40.0%) and in equivocal cases 35 out of 136 (25.7%). There was agreement in 792 of 928 normal cases (85.3%).

To evaluate the possible influence by degenerative changes on the reliability of CT, the data for observer A were compared to the data from the original reports for patients aged 30 or below, and for patients aged 51 and above, respectively. There was moderate observer agreement (κ 0.5347) for the younger patients, but a lower kappa value (0.393) and fair agreement for the older patient group.

To evaluate the possible influence of symptom duration and possibly easier diagnosis with longer duration, the data for observer A were also compared to the original data for patients with symptom duration less than 3 years, and for patients with symptom duration more than 6 years. The kappa values were moderate for both groups; for shorter duration 0.4804, for longer duration 0.467.

To evaluate the influence from improved CT scanner technology and learning curve, the data for observer A were compared to the original data for the

examinations from the first 2 years and the last 2 years of the study. The kappa value for the first 2 years was 0.3275 (fair agreement), and for the last two years 0.4542 (moderate agreement).

To further assess the importance of experience and possible learning curve, the original reports by the radiologist with the most readings (395 cases) and by the radiologist with the highest number of readings under 100 (53 cases) were compared to the scoring by observer A. The interobserver agreement was good in both cases, with κ 0.5782 for the radiologist with 395 cases and κ 0.6187 for the radiologist with 51 cases.

For A, there were data available for intraobserver analysis in 122 cases, showing moderate intraobserver agreement (κ 0.4785).

Paper IV analyzed the clinical utility of repeat CT examinations in suspected sacroiliitis. In 126 patients where the indications were inflammatory back pain two CT examinations had been made, in 16 women and 3 men a third examination, and in three women a fourth CT examination had been made.

The mean time between examination one and two was 41 months (range 1-254 months) for 126 patients. The duration of symptoms before the initial CT were approximated to shorter than one year in 11 cases, 1-3 years in 27 cases, 3-6 years in 13 cases, 6-10 years in 10 cases, more than 10 years in 7 cases, to unspecified long duration in 8 cases, and could not be deduced in 50 cases (40%). Thus a symptom duration up to 3 years was encountered in 38 of 76 cases (30% of whole material) and longer duration in 38 of 76 cases (30% of whole material).

From the first to the second study one normal and one equivocal case had advanced to bilateral sacroiliitis, and one equivocal case to unilateral sacroiliitis.

Sex	Age at CT 1	Duration of symptoms at CT 1	CT 1	Interval 1 (years)	CT 2	Interval 2 (years)	CT 3
M	37	3-6 years	Normal	21	Bilateral		
M	38	1-3 years	Equivocal	5	Bilateral		
F	29	1-3 years	Equivocal	2	Unilateral	11	Bilateral
M	21	1-3 years	Unilateral	4	Bilateral		
F	30	Unspecified long duration	Unilateral	9	Bilateral		
F	34	1-3 years	Unilateral	9	Bilateral		
M	31	> 10 years	Unilateral	2	Bilateral		
F	20	< 1 year	Unilateral	8	Bilateral		
M	25	1-3 years	Unilateral	7	Bilateral		

Table 13: Patients with advance in diagnosis at repeated CT of the sacroiliac joints. Of 126 patients, three advanced from normal or equivocal to unilateral or bilateral sacroiliitis. In six additional patients unilateral sacroiliitis advanced to bilateral sacroiliitis at the repeated study.

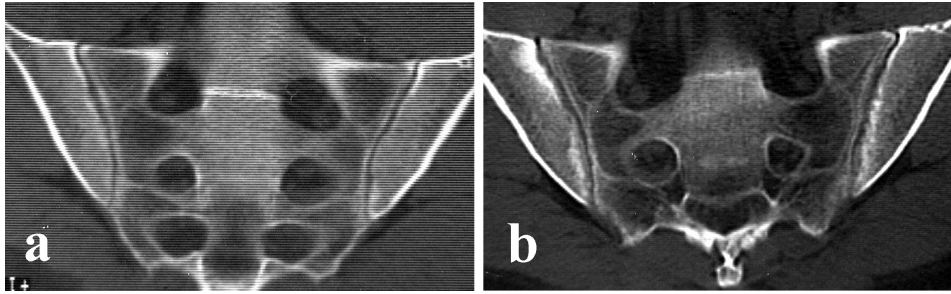


Figure 20: A patient with equivocal changes progressing to sacroiliitis. a. A 37-year old male with 1-3 years duration of inflammatory low back pain. The initial CT, reported as equivocal with recommendation for follow-up, shows subtle but definite erosions on the iliac side of the right sacroiliac joint. b. After 5 ½ years, there is progression to bilateral moderately advanced sacroiliitis.

Six cases had advanced from unilateral to bilateral sacroiliitis (Table 13, Figure 20, Figure 21). Ten normal cases had advanced to equivocal.

The patients changing from normal or equivocal to unilateral or bilateral sacroiliitis were 26, 37, and 37 years old at the first study. At the second, they were 28, 42, and 58 years old. The six patients changing from unilateral to bilateral sacroiliitis at the second CT had a mean age of 37 years at CT one, and 43.5 years at CT two.

Four equivocal cases were classified as normal on the second study, and one case of unilateral sacroiliitis was classified as equivocal on the second study.

At examination three only one case had advanced from unilateral to bilateral sacroiliitis (Figure 22). This patient had advanced from equivocal to unilateral sacroiliitis at the second study (Table 13). Two patients had remained equivocal at all three examinations, and three equivocal patients at examinations one and two were graded as normal at the third study. Two normal patients were graded as

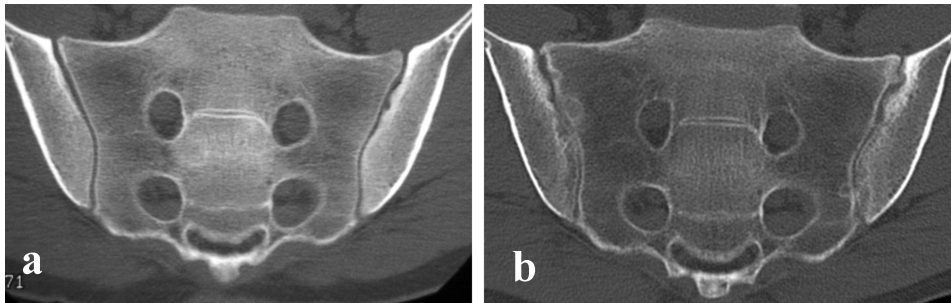


Figure 21: A case with subtle changes initially interpreted as normal showing progression to evident sacroiliitis. a. A 25-year old male with 1-3 years history of suspected SpA. The initial CT, reported as normal, shows subtle iliac erosions in the left sacroiliac joint, with mild inflammatory sclerosis. On the right, there is poor definition of the subchondral cortical bone. b. Seven years later, there is progression to definite bilateral sacroiliitis.

equivocal at the second examination and remained stable at the third examination. In 11 patients, the grading was normal at all three examinations.

At the fourth examination two patients were unchanged normal 9 and 11 years after the first examination, respectively. One had changed from normal to equivocal at the first repeat CT, and remained equivocal after 12 years.

Totally, three patients of 126 (2.4%) had changed from normal or equivocal to unilateral or bilateral sacroiliitis. Ten normal studies changed to equivocal (7.9%) Four equivocal studies turned normal at the second CT and one case of unilateral sacroiliitis was classified as equivocal on the second study.

Paper V addressed the validity of the NY criteria grading for CT. A NY criteria grade 0 was assigned in 1703 of 2608 joints, grades 1 and 2 in 485, grade 3 in 374, and grade 4 in 46 joints. The diagnosis sacroiliitis was thus unequivocal in 420 joints in 251 patients (grades 3 and 4). The grading was symmetrical in 1028 patients (2056 joints). Inflammatory changes were never located exclusively in the sacrum. In joints grade 3 and 4, more than 2/3 of the joint was involved in 71.0%.

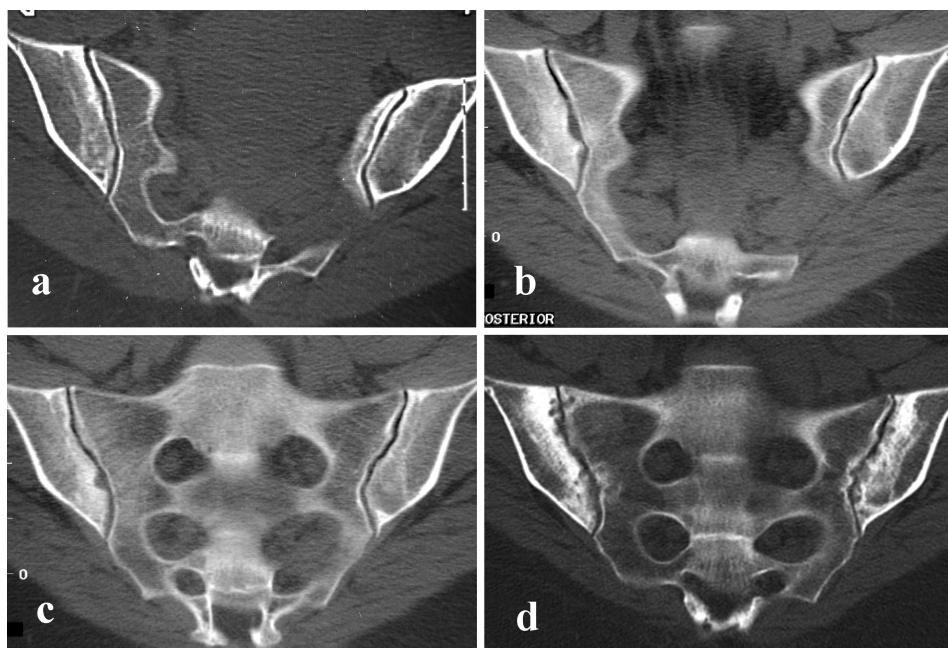


Figure 22: Three studies on a female patient showing progression from equivocal to unilateral to advanced bilateral sacroiliitis. a. The initial CT at age 26 was reported as equivocal, with recommendations for follow-up. There is a mild asymmetric sclerosis on the iliac side of the right sacroiliac joint, with a suggestion of a single erosion and slightly poor definition of the iliac subchondral cortex. b, c. At age 29, the suspected changes have progressed to definite unilateral sacroiliitis, with broad erosions and dense inflammatory sclerosis surrounding the right sacroiliac joint. d. At age 39, the disease has progressed into bilateral advanced sacroiliitis, with widespread erosions and inflammatory sclerosis affecting both the sacral and iliac sides of the joints.

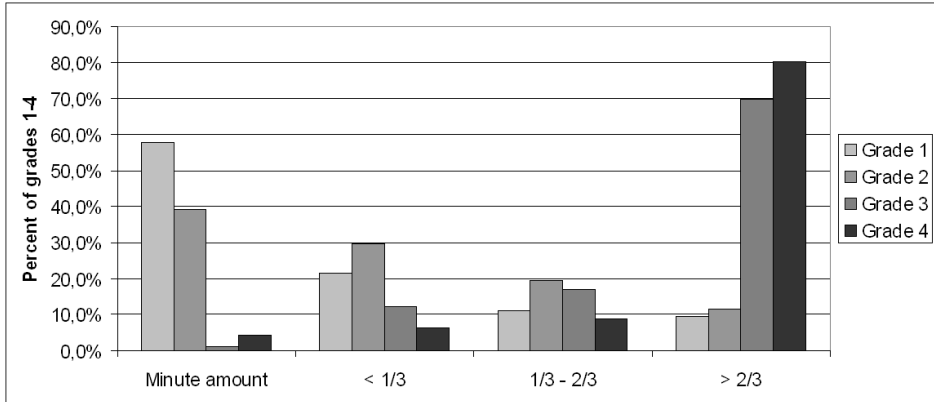


Figure 23: Degree of involvement of suspect inflammatory changes in 905 synovial joints.

Less than 1/3 of the joint was involved in 68.8% of grade 2 joints, and 79.3% in grade 1 joints (Figure 23).

Median age for the 146 patients with bilateral grade 3 sacroiliitis was 31.5 years (range 19-65) (32 years for 96 males, range 19-65, 31 years for 50 females, range 22-57).

Erosions were present in the ilium in all grade 3 joints (Figure 24). There were 23 grade 2 joints with contiguous erosions, 331 grade 3 joints and 20 grade 4 joints. In the sacrum, there was one joint grade 2 joint with erosions, 86 grade 3 joints and nine grade 4 joints.

Sclerosis in the ilium was recorded in 52.4% of grade 1 joints, 63.8% of grade 2 joints, and 97.4% of grade 3 joints. Iliac sclerosis was much more prevalent than sacral sclerosis (32.6%) in grade 3 joints. In grade 1 joints there was 8.9% sacral

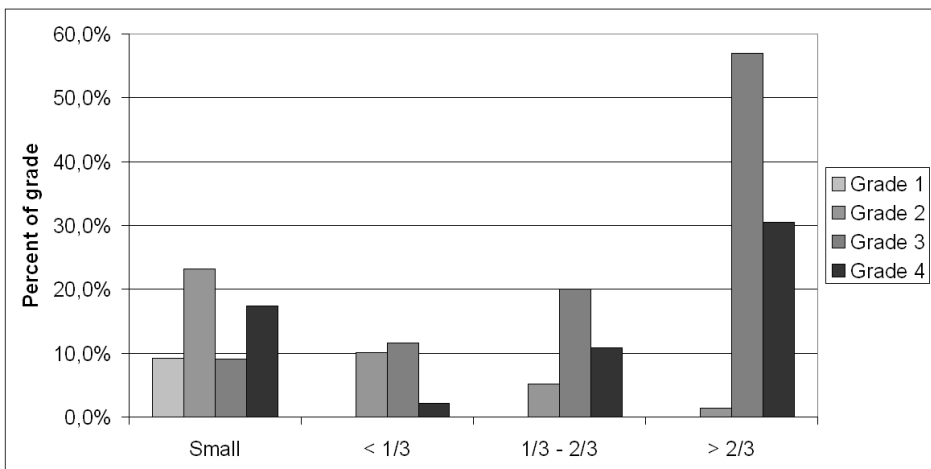


Figure 24: Iliac erosions in 754 joints. A joint could have one or more small erosions.

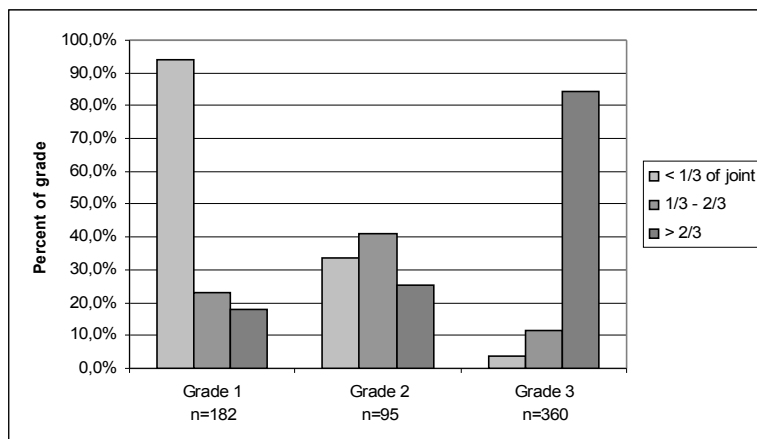


Figure 25: Extent of iliac sclerosis in 637 joints with New York grades 1 – 3.

sclerosis, in grade 2 joints 6.5%. In no case did sclerosis appear on the sacral side only. With higher grading the extent of iliac sclerosis increased markedly (Figure 25). The mean width of sclerosis increased from 4.2 mm (range 0-18.2 mm) in NY grade 1 joints to mean 5.1 mm (range 0-19.1 mm) in grade 2 and reached mean 8.2 mm (range 0-19.1 mm) in grade 3 joints. In 57% of grade 1 – 3 joints the sclerosis in the ilium was of the same width along the entire joint.

The transition zone from sclerosis to normal medullary bone in the ilium was indistinct in 8.8% of grade 1 joints, in 22.7% of grade 2 joints, and in 31.4% of grade 3 joints. The structure of sclerosis was inhomogeneous in most grade 3 joints and mainly homogeneous or intermediate in grade 1 joints (Figure 26). The sclerosis in most grade 1 joints had high density. With increasing grade, the density decreased (Figure 27). In 38% of both grade 2 and 3 joints the sclerosis had a low, almost lace-like density.

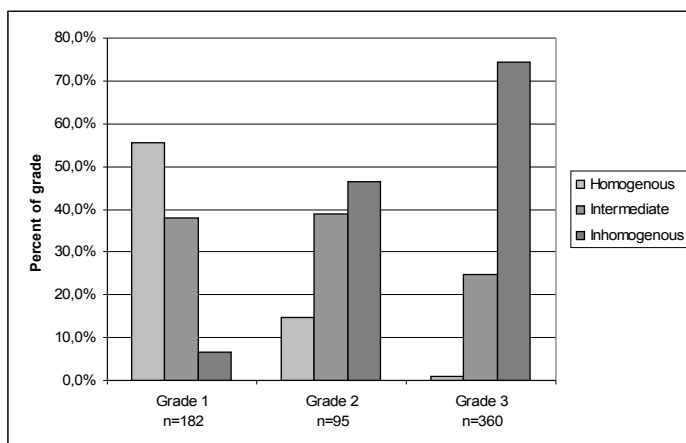


Figure 26: Structure of sclerosis in the ilium for 637 joints with New York grades 1 – 3.

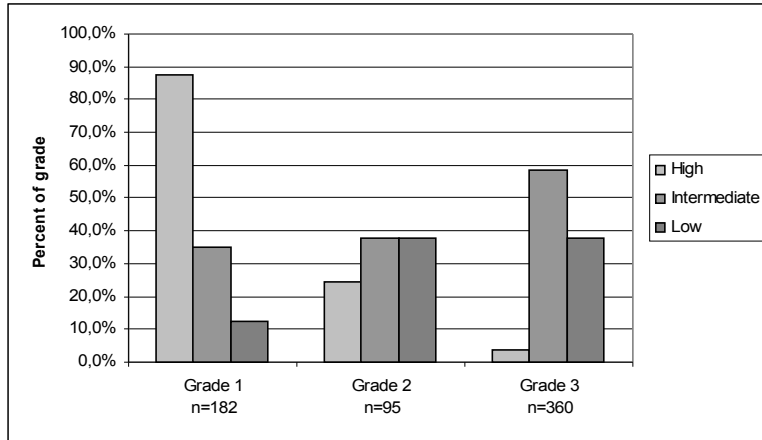


Figure 27: Density of iliac sclerosis for 637 joints with New York grades 1 – 3.

In the sacrum 122 (32.6%) of the joints assigned NY criteria grade 3 had subchondral sclerosis. This sclerosis was in 85.2% limited to less than 1/3 of the length of the joint.

Ankylosis varied from partial to complete ankylosis. The structure was variable, from fibrosis-appearing to completely remodeled mature bone. Joints assigned NY classification grade 4 had contiguous ankylosis over at least 1/3 of the joint space in 87.0%. Small focal points of ankylosis were present in 34.0% of grade 3 joints.

Ligamentous ossification was seen in 33 joints assigned a NY criterion grade 4. With lower grading the frequency sank from 18.7% in grade 3 joints to 2.8% in grade 0 joints. In all groups there were between 1.3% and 3.2% equivocal cases due to difficulties in distinguishing normal cortical irregularities from early new bone formation in the ligamentous part of the joint.

Bone mineral content was evaluated visually for density and distribution. In all examinations decreased bone mineral content was found in 7.2% in the ilium and in 8.4% in the sacrum. There was no difference between the NY grades, thus there was no correlation with sacroiliitis.

To summarize the inflammatory changes, in grade 3 joints the inflammatory changes were located in the entire joint in 75.2%. In 18.7% there was ligamentous ossification. In 96.3% there was inflammatory sclerosis in the ilium, in 32.6% in the sacrum, and the extent of the iliac sclerosis was more than 2/3 of the joint in 81.3%. There was an indistinct transition from sclerosis to normal medullary bone in 31.4%, and the sclerosis had the same width in 57%. All grade 3 joints had erosions on the iliac side, 23.0% on the sacral side, and there was partial ankylosis in 34.0% of the joints.

Anatomical changes such as joint space width, THI (in the literature mainly called osteitis condensans ilii), and accessory sacroiliac joints were evaluated. The

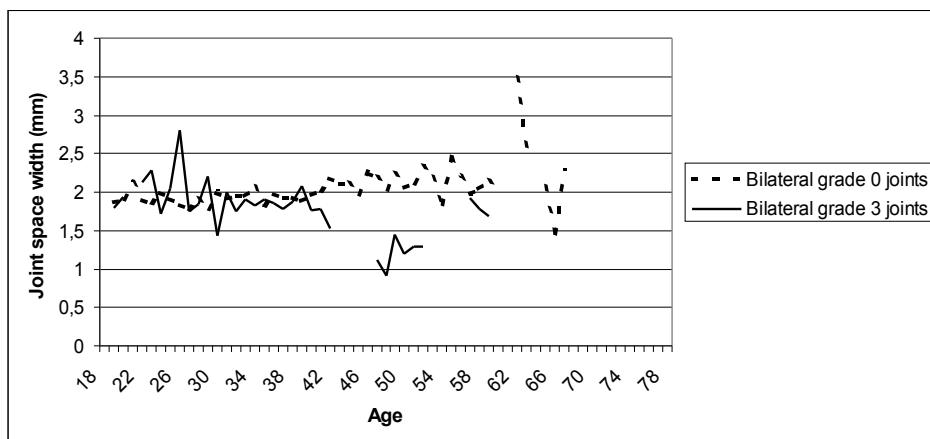


Figure 28: Mean joint space width for 754 patients with bilateral New York criteria grade 0, and for 146 patients with bilateral New York criteria grade 3.

mean joint space width was 1.950 mm (standard deviation 0.571) in 2608 joints. In the 754 patients with bilateral NY criteria grade 0 the mean joint space width was 2.004 mm (standard deviation 0.460) (Figure 28). There was no significant difference between patients examined prone or supine in NY grade 0 joints; in 283 patients examined supine the mean joint space width was 1.974 mm (standard deviation 0.458); in 471 patients examined prone 2.023 mm (standard deviation 0.461). For both scan positions in the 754 patients assigned bilateral grade 0 the joints were slightly wider cranial than caudal (supine: cranial 2.130 mm SD 0.604, middle 1.928 SD 0.589, caudal 1.856 SD 0.565; prone: cranial 2.160 mm SD 0.584, middle 2.012 SD 0.562, caudal 1.957 SD 0.551). In 146 patients with bilateral grade 3 sacroiliitis, the mean joint space width was 1.848 mm (Figure 28).

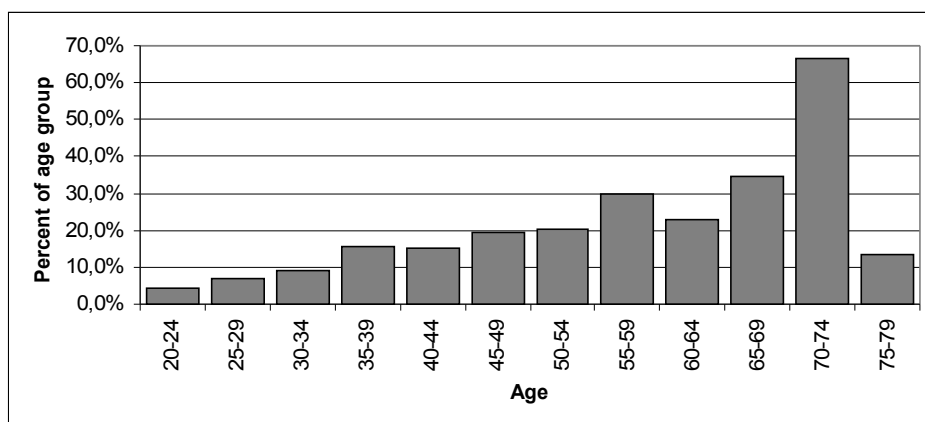


Figure 29: Prevalence of 344 accessory sacroiliac joints in 217 patients in different age groups.

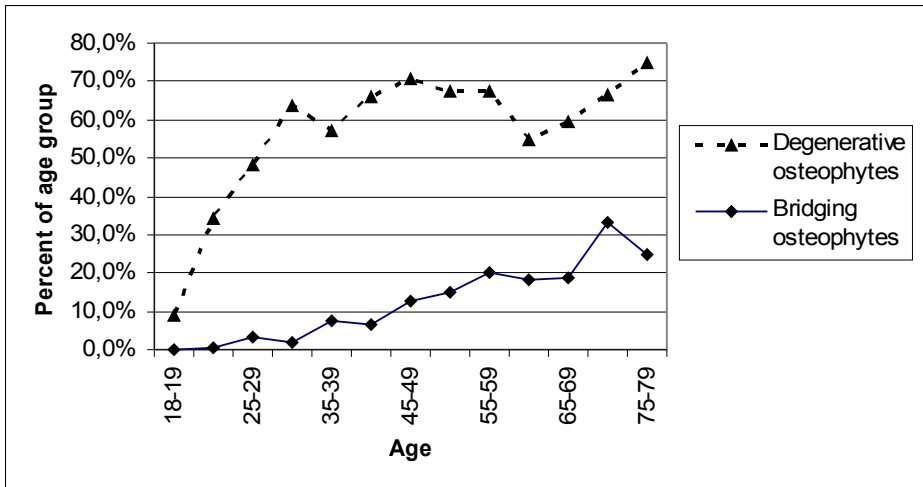


Figure 30: Prevalence of degenerative and bridging osteophytes in 2608 joints.

THI was found in 92 female and 4 male joints. The median age of the patient was 34 years, range 22-55. In joints assigned NY criteria grade 0 THI was found in 0.8% of the joints, grade 1 in 19.3%, grade 2 in 5.1%, and grade 3 in 2.4%.

Accessory sacroiliac joints were noted bilaterally in 127 cases and unilaterally in 90 cases (totally 344 joints), of which 137 were male and 207 female. The prevalence was identical 13.2% in both sexes (Figure 29). Seven accessory joints were ankylotic and 162 showed degenerative changes (Figure 6). Only six joints showed inflammatory changes, and in these cases there were inflammatory changes also in the proper sacroiliac joints.

Degenerative changes such as osteophytes, subchondral cysts, and pneumatocysts were recorded. Osteophytes were seen in more than 60% of the joints by age 35 (Figure 30), first seen as only paraarticular degenerative osteophytes. From age 50 there was a slow, steady increase of paraarticular ankylosis (or bridging osteophytes), which reached a prevalence of almost 20% in the age group 50-59 years, and continued to increase with age. Paraarticular ankylosis was seen in 170 of 2608 joints (6.5%; Figure 30).

Vacuum phenomena in the synovial part of the sacroiliac joints were common and highly dependent on body position. In 833 patients scanned in the prone position, a vacuum phenomenon appeared in 7.7% of the joints. In 471 patients scanned supine, it was noted in 65.2% of the joints. The vacuum phenomenon was symmetrical in 90%. In the 942 joints on 471 patients scanned supine, there was between 58.8% and 76.3% vacuum phenomenon in the age groups 20-54 years. In all patients, a vacuum phenomenon was more common in joints grade 0-2 than in joints grade 3, and increased with age above age 40 (Figure 31). The frequency decreased from 31.8% in NY grade 0 to 14.2% in grade 3.

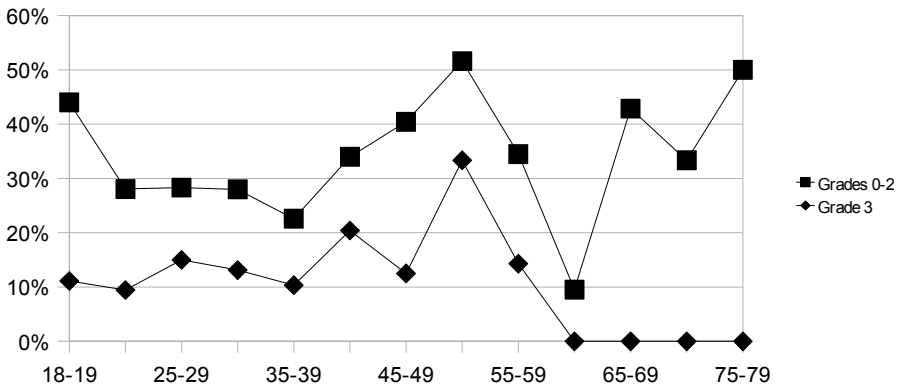


Figure 31: Vacuum phenomenon was more common in joints grade 0-2 than in grade 3, and increased with age above age 40.

Subchondral cysts in the ilium or sacrum were seen in 347 of 2608 joints. They were present in young age groups, but the number increased distinctly with age. There was no correlation between subchondral cysts and sacroiliitis. Normal joints had subchondral cysts in 14.0%. Grade 3 joints had 10.2% subchondral cysts.

Pneumatocysts (Figure 32) were few, with only 91 detected totally. Forty-two of these patients had been examined prone, 41 supine. The pneumatocysts were three times as common on the iliac side as on the sacral side. There was no correlation with sacroiliitis. Normal joints had pneumatocysts in 4.0% while grade 3 joints had them in 1.1%. There was a higher prevalence of pneumatocysts in joints with a vacuum phenomenon (5.4%) than in joints without (2.7%).

Over the years, several CT scanners were used. Fifty-seven percent of the studies in **paper V** had been filmed using a display field of view between 140 mm and 199 mm, 42% using a display field of view between 200 and 259 mm. Eighty percent were archived on film at a window width/level setting between 1500-1600/400-430, or at 2000/400. Tube voltage was set at 120 kV for 86% of the studies, while tube current was set at 200 mA for 76%. The annotation on the films

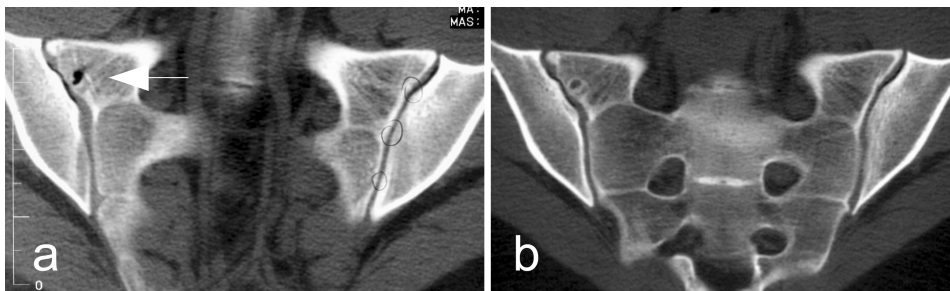


Figure 32: A 19-year old female with a gas-filled pneumatocyst in the sacrum on the right (arrow). Six years later the appearance is that of a subchondral cyst with sclerotic borders.

contained no information about scan time, so the total mAs could not be calculated. The median number of slices passing through the synovial joint was 15 (range 8-25).

Discussion

CT for diagnosis of sacroiliitis was first reported in 1979 [60]. It rapidly gained acceptance [45, 48, 75, 77, 123, 152, 158, 189], with few negative reports or opinions [3, 29, 40, 102, 113]. The current study was performed to investigate the clinical utility of CT in diagnosing sacroiliitis.

The patient material was limited to studies on patients aged 18 and above. This was done partly for practical reasons, since children in Göteborg, Sweden, are usually seen at the Children's Hospital. There are also diagnostic difficulties in assessing CT of the sacroiliac joints in children, as these joints mature late in adulthood, and adolescents 16-18 years old may or may not have fully developed joints. Immature joints are a cause of false positive diagnoses [102], such as in one case where a study on a 17 year-old girl (not included in the current study) was read as bilateral sacroiliitis but where the joints 10 years later were perfectly healthy (Figure 33). However, juvenile SpAs may be diagnosed with CT [90], provided that the radiologist has sufficient experience.

The distinction between unilateral and bilateral sacroiliitis in the current study was done to permit evaluation of each sacroiliac joint separately. Seen in the perspective of the single patient, the difference between unilateral and bilateral sacroiliitis in most cases represents different stages of disease, as most SpA patients eventually develop bilateral sacroiliitis. Thus the distinction is important in the setting of a clinical study, but not for the single patient.

In the current study using CT, the ratio bilateral/unilateral sacroiliitis was 169/82 for patients with sacroiliitis, thus with a much higher rate of unilateral sacroiliitis than reported for radiography. Sacroiliitis in AS is almost always symmetrical [160] while it may be unilateral or asymmetric bilateral in the other subgroups of SpA [136]. In about 10% of the cases of AS, however, unilateral radiographic sacroiliitis is the initial presentation, eventually progressing to bilateral involvement [59]. In psoriatic arthritis, about 50% of the patients have sacroiliitis,



Figure 33: A 17-year old female falsely diagnosed with bilateral sacroiliitis (a). Ten years later, the sacroiliac joints are completely normal (b).

which is usually bilateral and asymmetric [91]. In reactive arthritis, sacroiliitis is reported to occur in about 40% of the patients [137], often asymmetric or unilateral.

In a CT study on sacroiliitis in Crohn's disease [182] 23% had sacroiliitis. It has been stated that sacroiliitis in IBD is indistinguishable from that of AS [107]. Obviously, there is a significant overlap of the radiographic appearance, and probably also of the CT appearance, of sacroiliitis between the different subgroups of SpA.

The CT studies were read and scored in sequential order to detect subtle signs of progression within the same grading, and comparison was possible for repeat studies. It has been shown for radiography of the sacroiliac joints that chronological reading of films improves the detection of subtle progression, compared to reading each patient's films in random order [200].

It is difficult to compare kappa values for observer agreement from different studies, as the value is influenced by a number of factors such as the prevalence of disease or findings, the number of categories used, and the chosen weighting [178]. Unweighted kappa is unsuitable for ordinal data, where linear or quadratic weighted kappa is more suitable. Unweighted kappa treats all disagreements equally, whereas weighted kappa penalizes disagreements according to their seriousness. Unweighted kappa was used for calculation of observer agreement in the present study. It can be debated whether the scale used of no sacroiliitis – equivocal sacroiliitis – unilateral sacroiliitis – bilateral sacroiliitis represents nominal or ordinal data. The referees for paper II demanded that the data be treated as nominal data, and that unweighted kappa be used. For the sake of consistency unweighted kappa was used also in papers III and IV, even though weighted kappa would have given figures of better agreement.

Only erosions were considered to be purely inflammatory while sclerosis may also be reactive. The sclerosis was mostly very dense, homogeneous and well defined in grade 1 joints. In grade 2 joints there were equal amounts of intermediate and low density, and in grade 3 more joints had sclerosis with intermediate than low density. There was a marked decrease in sclerosis density from grade 1 to grade 3.

Various amounts of ankylosis were present in a high number of grade 3 joints. The changes were mostly small focal areas (bony bridges, spiculation, bony buds) of intraarticular ankylosis or "near-ankylosis" – it was sometimes difficult to determine visually whether there actually was ankylosis or merely a minute area of bilateral sclerotic bone interdigitating over a diseased joint with destroyed cartilage. In the current study, ankylosis in grade 4 joints represented obvious contiguous ankylosis of a part or the entire joint.

Dihlmann and Hering [61] reported that in non-infectious sacroiliitis there is no distinct sequential order of the different changes, instead erosions, inflammatory sclerosis and signs of bony ankylosis seen as small transarticular bony bridges may appear simultaneously [61].

Ossification of ligaments in the posterior joint compartment was common in grade 4 joints. Ligamentous ossification was fairly frequent also in grade 3 joints (70/374; 18.7%), slightly lower than the rate 13/41 (32%) reported previously [153] but it can be explained by our larger material and differences in patient selection.

Triangular hyperostosis of the ilium (THI) [61], also known as OCI, is nowadays regarded as the result of a stress effect in pregnancy [61, 171]. In the current study, definite or possible THI was noted in 3.7% of the joints, symmetrically in over 95% of the cases. Possibly the prevalence was underestimated, since THI is seen differently with CT than with radiography (Figure 34). Instead of the densely sclerotic triangles bordering on the caudal borders of the sacroiliac joints on the iliac side at radiography it is seen as dense but not completely distinct sclerosis on CT, bordering on the middle of the joint in the most anterior slices, without erosions, but sometimes with mild degenerative changes.

At radiography, there may be an overlap in diagnosis between sacroiliitis and THI [202]. Due to the tomographic images at CT, this diagnostic overlap has practically been removed. The expression “osteitis” is not adequate for CT diagnosis and a descriptive expression such as “triangular hyperostosis of the ilium” is preferable [61]. Paraglenoid sulci, also reported to be the result after stress in pregnancy [171], were not systematically recorded when reviewing the CT studies. When comparing some cases with THI on both radiography and CT, however, they were seen as deep iliac incisures, corresponding to what has been previously been described as bipartite iliac bony plate on CT [151] (Figure 34).

The para-articular bridging osteophytes or para-articular ankylosis are probably in many cases a manifestation of DISH, and not of degenerative origin. We have, however, no correlating data or spinal imaging to support this hypothesis. DISH was initially described by Forestier (Forestier’s disease) and others during the first half of the 20th century, and is a disease of middle-aged and older patients, presenting as an idiopathic hyperostosis along primarily the anterior longitudinal ligament of the spine, but also in extra axial locations. The historical, clinical,

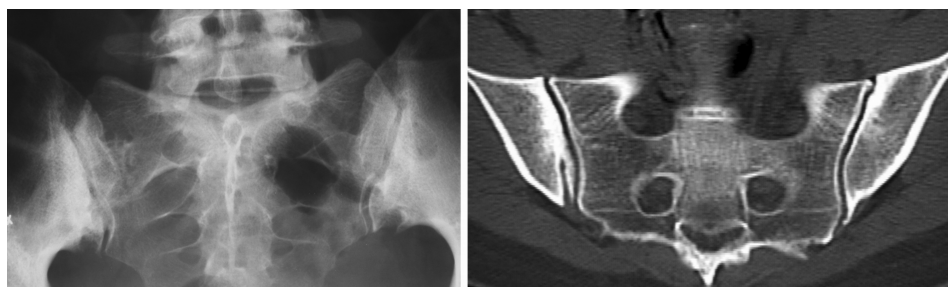


Figure 34: Radiography and CT of mild right-sided THI on a 41-year old female. At CT, there is a very dense anterior subchondral iliac sclerosis. There are bilateral paraglenoid sulci (arrowheads), which on the CT scan can be seen as a deep incisure on the right.

radiographic, and pathologic findings have been summarized by Resnick [161]. In DISH, sacroiliac joint abnormalities may include osteophytes and coexistent degenerative joint disease, particularly in older patients. These changes are associated with sacroiliac joint space narrowing and paraarticular bridging osteophytes, but should not be confused with ankylosing spondylitis. In DISH, there are no signs of erosions, inflammatory sclerosis, or intraarticular ankylosis [161]. In a study of spinal and pelvic changes in DISH compared to spondylosis deformans [88], ossification of the ligamentous superior, but not the inferior, portion of the sacroiliac joints was statistically significant for DISH.

The prevalence of degenerative osteophytes increased with age in the current study, as expected, and osteophytes were present in a high proportion of patients already in the age group 35-39 years. Several previous studies have remarked on early degenerative changes in the sacroiliac joints, including osteophyte formation [30, 159, 170, 172].

There were subchondral cysts in 347 of 2608 joints, with increasing prevalence with age. They were commonly bordered by a thin sclerotic rim, and the surrounding bone marrow was without inflammatory sclerosis, as opposed to erosions. The prevalence of pneumatocysts of 3.5% in the present study is lower than the 10.3% reported previously [150]. Presumably they are variants of subchondral cysts which communicate with the joint, but this has been debated in the literature [96]. In the current study there have been examples on repeat CT examinations where the same cyst has contained gas at one examination and fluid at the next (Figure 32). Previously, communication of a pneumatocyst with the sacroiliac joint has been described [26], and it seems reasonable to assume that pneumatocysts in general represent subchondral cyst where gas from a vacuum phenomenon has evacuated the joint fluid from the cyst. The prevalence of pneumatocysts in the current study was about twice as high in joints with vacuum phenomenon than in joints without, which indicates a correlation.

The appearance of the accessory sacroiliac joint at CT (Figure 6) has been described previously [60, 69, 151]. The prevalence of 16.6% in the current study is similar to previous figures in CT examinations of 13% [69] and 19.1% [151]. There is an increasing prevalence with age [191]. Inflammatory changes in the accessory joints have been mentioned earlier [87]. Other anatomical variants [151] such as the "iliosacral complex" and bipartite iliac bony plate were seen in a number of cases, but not systematically recorded. The bipartite bony plate may in fact represent the appearance of a paragenoid sulcus on CT (Figure 34).

In the current study, no correlation was found between decreased bone mineral content and sacroiliitis. The post-inflammatory fatty infiltration of periarticular bone marrow that can be seen with MRI cannot be reproduced at CT [153].

In patients without sacroiliitis there was no appreciable reduction of joint space width up to about 60 years of age in the current study, after which the samples

became too small to be reliable. The joint space width of 2 mm corresponds well with previous figures from CT [198]. The figures are close to those of a study done on 10 mm thick axial body CT slices [73], where a decrease in joint space width from 2.3 mm in patients aged 15-39 years to 1.9 mm in patients over 40 was seen. In a retrospective study on patients over 55 years of age, using abdominal CT, no further reduction in joint space width after age 55 was shown [207]. In the current study, patients with bilateral grade 3 sacroiliitis in general had slightly narrower joint spaces than patients with grade 0, with a tendency to progressive joint space reduction over the years. The changes were too small to verify joint space width as a diagnostic sign.

The explanation for the high prevalence of vacuum phenomenon in the supine position as opposed to very low prevalence in the prone position is unknown. No vacuum phenomenon was detected in the ligamentous part of the joint.

The NY criteria [23] (Table 3) or the modified NY criteria for ankylosing spondylitis [193] (Table 4) were originally devised for grading of sacroiliitis on radiographs. The grades are: 0=normal findings, 1=minimal changes suspicious for sacroiliitis, 2=minimum abnormality, defined as small localized areas with erosion or sclerosis without alteration in the joint width, 3=unequivocal abnormality, and 4=total ankylosis. In papers III, IV and V effort was made to evaluate and develop the NY grading to be more suitable for CT. In paper III, a new more differentiated grading system was evaluated where 0=normal, 1=low degree of suspicion for sacroiliitis, 2=moderate degree of suspicion, 3=high degree of suspicion, and 4=pathologic was evaluated. In the evaluation of observer agreement, bilateral grade 0 was considered as normal, bilateral grade 4 as bilateral sacroiliitis, unilateral grade 4 as unilateral sacroiliitis, and all other grades as equivocal. In paper V, the joints were scored according to the NY criteria. In the analysis NY grades 1-2 were considered as equivocal since all cases of definite sacroiliitis were graded as NY grades 3-4. A new grading system for CT was proposed, consisting of grades 0=normal, 1=suspect sacroiliitis, 2=definite sacroiliitis. Sectional imaging and high spatial resolution with CT makes the cut-off between disease and non-disease easier than with radiography. Having two equivocal grades 1 (maybe normal) and 2 (maybe diseased) is superfluous. Also, the distinction between sacroiliitis without and sacroiliitis with ankylosis has no meaning for certainty of diagnosis at CT.

It has been reported that detection and scoring of changes in CT appearance is possible after a follow-up period of only one year in a study group of patients with early SpA [154]. In the current study on a clinical material, paper IV reports on the progression of known sacroiliitis in a number of cases, but in most cases the progression was not evident as a change in score, but only when comparing the studies side-by-side, showing progressive changes such as increasing subchondral sclerosis or progression in size and number of erosions. The scoring system in the

present study differed from the one used by Puhakka et al [154], since the purpose in paper IV was to detect a change in radiologic diagnosis and not to register degree of progression *per se*. Only a few cases in the current study evolved from normal or equivocal to pathologic, thus the yield of the repeated examinations was low compared to the yield of primary sacroiliac joint CT.

There was good observer agreement between the two observers in paper III for normal cases and for cases with sacroiliitis, especially bilateral sacroiliitis. Agreement was lower for equivocal cases, corresponding to the outcome of other studies [195]. Agreement in general was also lower comparing the two observers' results with the outcome in the initial radiology report. In a study situation according to protocols or at reviews the participants tend to be more careful and concerned with accuracy and exactness. This is known as the Hawthorne effect, which means the phenomenon of altered behavior resulting from the awareness of being a part of an experimental study [148, 196], which is probably reflected in the higher observer agreement between the observers in the study and lower agreement between the observers and the original reports. Agreement was higher for younger patients than for older patients, probably reflecting the influence from superimposed degenerative changes, and was higher for later studies than for earlier studies, probably reflecting improvements in equipment and technique, and possibly in learning.

In the transition of classification from normal to unequivocal sacroiliitis a number of cases remains where the findings are not unequivocally normal, but on the other hand neither unequivocally pathologic; in the current study as well as in other studies. Different observers will have different cut-off levels between normal, equivocal and pathologic, leading to observer variation. In the evaluation of sacroiliitis confounding factors are young age (these patients were not included in the current study) and old age, where degenerative narrowing of the joint spaces, osteophytes, and dense degenerative subchondral sclerosis make it more difficult to make a distinct diagnosis of inflammatory sacroiliac changes. In the current study, problems sometimes arose with defining joint borders when measuring joint space width, due to variable anatomy and different scanning angles leading to partial volume effect, to variations in joint space width measurements due to selection of different parts of the joint for measurement, to non-uniform joints, or to difficulties in defining joint borders between synovial and ligamentous portions. There were also differences between the visual global assessment of joint uniformity and the 3-point measurements, as well as methodological difficulties in grading and measuring subchondral sclerosis. The technical factors were also contributing in confounding measurements (different CT scanners, different techniques, different filming techniques, different film partition, different field-of-view, etc).

There is a high degree of observer variation in evaluating sacroiliitis on radiographs [20, 97] and this has been suggested as the cause of "sacroiliitis"

reported in Behçet's syndrome and familial Mediterranean fever [208]. This factor may account for at least some of the variation in the frequencies of false positive and negative diagnoses in the current study. It has been argued that careful training and example films [129] can improve the results from population studies using radiographs, but the study situation diverges considerably from the normal clinical situation. Another report showed that training neither improves sensitivity nor specificity for sacroiliitis at radiography [195]. In paper I, a high rate of false negative radiographic studies was demonstrated (20/30), which was confirmed in a larger material in paper II, with the rate similar to that of previous studies, giving figures such as 6/17 [189] and 12/37 [77]. Paper II also demonstrated a high rate of false positive or falsely equivocal radiographs (35.0% false positive radiographic diagnoses). The figure cannot readily be compared with other reports as reliable frequency figures from other studies are lacking, and the focus in earlier reports has been on false negative results, not false positive findings. The possibility of false positive radiographs has been mentioned in single cases [29, 173], and in one study a result of 8% false positive findings in 140 readings on 35 patients by four observers was reported [169]. False-positive outcomes from CT on adolescents due to immature joints have also been reported [102].

Even though CT has a higher resolution than radiography, all CT diagnoses in the current study cannot be considered correct. In 9.6% of the 910 CT studies in paper II the report was equivocal or follow-up was recommended by the initially reporting radiologist. It is not unlikely that there are false negatives at CT in early sacroiliitis as the discrete inflammatory sclerosis that sometimes is the first sign of inflammatory disease may be overlooked. False positives may also be caused by inadequately interpreted synovial cysts or partial volume effect. In paper IV there were in all three normal or equivocal CT studies (2.4%), which became positive with unilateral or bilateral sacroiliitis at a later study, and only one false positive case which was downgraded from unilateral sacroiliitis to equivocal.

In paper III, there was a high rate of pathologic outcome at CT (17.8% bilateral or unilateral sacroiliitis for observer A; 32.4% if also non-normal equivocal cases are included, corresponding figures for observer B 20.5% and 31.4%, respectively). There is a low rate of sacroiliitis on repeat CT studies (2.4%) compared to primary CT (17.8%), indicating that there is high and sufficient yield from the primary CT. There is generally a slow progression of radiographic changes in SpA [35, 46, 115, 118, 128, 134, 181], and a higher rate of positive results at the follow-up examinations would have been expected if the patients with negative or equivocal primary CT had had inflammatory sacroiliitis at that time.

During the course of the study, two short abstracts on pilot studies involving MRI of the sacroiliac joints have been published. In one, age related changes in the sacroiliac joints were evaluated on 16 healthy volunteers [70]. In another, the possible influence on the MRI findings in sacroiliitis after treatment with NSAID

was evaluated [93]. No change in MRI findings could be found in nine patients with clinical SpA.

MRI is today generally regarded as the imaging method of choice for investigation of suspected sacroiliitis. However, in Sweden and elsewhere, the availability of CT may be greater than of MRI and the cost is lower, with in certain places more extensive use of CT than of MRI in primary investigation of suspected sacroiliitis. Also, the numbers of abdominal and trauma CT investigations continue to increase, with increasing numbers of incidental CT findings to report.

Summary and conclusions

Paper I: CT has a much higher sensitivity than conventional radiography in detecting subtle changes in the sacroiliac joints necessary to confirm a clinical diagnosis of sacroiliitis. CT is superior to radiography in detecting sacroiliitis of short duration. CT allows an early start of treatment with better prognosis. When a thorough case history and physical examination strongly points to sacroiliitis and a radiological confirmation is judged mandatory for starting treatment CT is the radiological examination of choice over radiography.

Paper II: The clinical utility of radiography for evaluation of sacroiliitis is limited. The number of insufficient radiographic diagnoses (false-positive, false-negative, and equivocal) is high. Several true radiographic diagnoses cannot be trusted because of the low accuracy rate. The use of radiography for evaluation of sacroiliitis is questioned, and the necessity of acquiring positive or negative imaging findings for a correct diagnosis of sacroiliitis speaks for sectional imaging such as CT as the method of choice.

Paper III: The interobserver variation for the diagnosis of sacroiliitis on CT in a study setting showed good agreement. The agreement between each of the observers and the original clinical report showed moderate agreement, comparable to the intraobserver agreement between the original report and subsequent image review for one of the reviewers. CT is a reliable method for evaluating the sacroiliac joints for changes of sacroiliitis.

Paper IV: CT is a valuable examination for diagnosis of sacroiliitis, with very few normal cases later progressing into sacroiliitis. The clinical utility of repeated CT of the sacroiliac joints is very low, and the use of repeated CT may be questioned.

Paper V: Only multiple or large erosions seem to be a valid solitary diagnostic sign. Small solitary or few erosions need supplemental evidence from other inflammatory signs such as sclerosis. Inflammatory sclerosis can frequently be distinguished from degenerative sclerosis, and can sometimes support an early diagnosis, when erosions are not apparent. Joint space width, joint shape, bone mineral content, or enthesopathy have no place in sacroiliitis diagnosis on CT. The

NY criteria grading is unsuitable for use with CT. A practical classification of sacroiliitis on CT is no disease, suspect disease, and disease.

General summary:

1. The clinical utility of conventional radiography for evaluation of sacroiliitis is low with a high rate of insufficient and false reports, making radiography unsuitable for clinical use or use in population studies.

2. CT is a robust imaging method for suspected sacroiliitis with good observer agreement, with higher rate of detection of sacroiliitis than radiography; also for early changes.

3. There is no use for repeated CT examinations for suspected sacroiliitis.

4. The NY criteria are unsuitable for use with CT and a new grading system for CT of sacroiliitis is proposed, consisting of the grades no disease, suspect disease, and definite disease.

5. Only multiple or large erosions seem to be a valid solitary diagnostic sign. Small solitary or few erosions need supplemental evidence from inflammatory sclerosis. Inflammatory sclerosis can frequently be distinguished from degenerative sclerosis, and can sometimes support an early diagnosis, when erosions are not apparent. Joint space width, joint shape, bone mineral content, or enthesopathy have no place in diagnosis of sacroiliitis on CT.

Sammanfattning på svenska

Bakgrund: Ankyloserande spondylit är en kronisk sjukdom där radiologisk bekräftelse av diagnosen är viktig i alla diagnos- och klassifikationskriterier för spondylartrit. Syftet med studien var att utvärdera datortomografi (CT) och jämföra den med konventionell röntgenundersökning.

Metoder: I en pilotstudie jämfördes CT och röntgenundersökning på 40 patienter med spondylartrit. En studie på 1425 patienter undersökta med CT, 910 av dem också med röntgenundersökning, rapporterades i fyra artiklar. Alla CT-undersökningar eftergranskades av två bedömare. Den ursprungliga diagnosen från CT och röntgenundersökning hämtades från röntgenutlåtandet.

Resultat: CT hade högre sensitivitet för sakroiliit än röntgenundersökning, speciellt vid kort sjukdomsduration. Röntgenundersökning hade en hög andel falskt negativa och falskt positiva utfall.

Överensstämmelsen mellan bedömarna (observer agreement) i ett stort material var god, medan överensstämmelsen mellan bedömarna var för sig och originalutlåtandet var måttlig. Överensstämmelsen mellan en av bedömarna och dennas tidigare originalutlåtanden (intraobserver variation) var måttlig.

CT-diagnosen förändrades hos tre av 126 patienter (2,4%) som hade undersökts mer än en gång, från normal eller tveksam till ensidig eller dubbelsidig sakroiliit. Tio normala fall hade ändrats till tveksamma. I ytterligare sex patienter (4,8%) hade diagnosen förvärrats från ensidig till dubbelsidig sakroiliit. Fyra tveksamma fall bedömdes som normala på den andra undersökningen, och ett fall av enkelsidig sakroiliit bedömdes som tveksam på CT två.

Huvudsakligen flera eller stora leddestruktioner verkar vara säkra enskilda diagnostiska förändringar för sakroiliit. Små enstaka eller få destruktioner behöver ytterligare stöd i form av andra inflammatoriska förändringar som skleros. Inflammatorisk skleros kan ofta skiljas från degenerativ skleros, och kan ibland stödja en tidig diagnos innan leddestruktioner blivit uppenbara. En praktiskt användbar CT-gradering bestående av ingen sakroiliit, misstänkt sakroiliit, och sakroiliit har föreslagits.

Sammanfattning: Den kliniska nyttan av konventionell röntgenundersökning vid misstänkt sakroiliit är låg, med en hög andel av oklara eller felaktiga svar, vilket gör metoden dålig för kliniskt bruk och för populationsstudier. CT är en robust diagnostisk metod vid misstänkt sakroiliit med god överensstämmelse mellan bedömare och högre känslighet än röntgenundersökning, också för tidiga förändringar. Det finns inget skäl att upprepa en CT-undersökning vid misstänkt sakroiliit. New York-kriterierna passar dåligt för CT-diagnostik och ett nytt graderingssystem har föreslagits.

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