Purpose of review
Hip disease occurs in about one-third of patients with ankylosing spondylitis (AS) and can often be disabling, necessitating total hip replacement in young adults. There have been recent articles on a number of aspects of this problem, including the epidemiology and pathology. The most recent studies on diagnosis, prognosis and therapeutic management are reviewed here.

Recent findings
Several large studies have evaluated the prevalence and outcome of hip involvement in AS. Hip involvement can be diagnosed clinically, radiologically, by MRI or by ultrasonography. These examinations highlight different aspects of hip disease in AS. Hip disease is more prevalent in patients with a younger disease onset and seems to be associated with more severe axial disease. Antitumour necrosis factor (TNF) agents are helpful for pain relief and improvement of function in patients with active axial and active hip disease. However, it is not clear whether this treatment option can prevent progression of structural damage. In case of end-stage hip disease, total hip replacement should be considered.

Summary
In patients with AS, the hips should be routinely assessed, at least by clinical examination. Anti-TNF therapy should be considered in patients with NSAID-resistant active axial disease who have concomitant hip disease.

Keywords
ankylosing spondylitis, antitumour necrosis factor, hip, review

INTRODUCTION
Ankylosing spondylitis (AS) is the prototype of spondyloarthritis (SpA) characterized by inflammation of the sacroiliac joints and spine [1]. This spinal inflammation may lead to a completely ankylosed spine. Several clinical reports indicate that hip involvement increases the burden of AS and negatively impacts its prognosis [2–6]. Also, hip arthritis seems to be associated with more severe spinal involvement [6–8]. Due to the important and central function of the hip, impairment of hip-function is clearly related to functional impairment in patients with AS [6,9]. Data on the effectiveness of treatment strategies are scarce. A specific treatment option in patients with end-stage hip disease is hip replacement surgery [10]. Hip prostheses have a limited life-span, and revision surgery is often needed. Ideally, when new systemic treatment strategies are explored in reducing signs and symptoms in AS, the prevention of hip damage should also be evaluated. This article gives an update on the prevalence, imaging, prognostic features and treatment of hip involvement in AS.

EPIDEMIOLOGY OF HIP INVOLVEMENT
The reported prevalence of hip disease in AS varies from 19 to 36% [6,11]. This wide range can be explained by the different definitions that are used to describe the investigated population and by different definitions of hip involvement.

It should be noted that the articles referred hereafter describe mostly patients who fulfil the modified New York criteria for AS [1]. These patients may differ from patients classified as axial spondyloarthritis according to the more recently validated Assessment of SpondyloArthritis international Society criteria [12].
How to define hip involvement in ankylosing spondylitis

Hip involvement can be defined by clinical examination and by specific imaging techniques.

Clinical definition of hip involvement

Several structures in the anatomic region of the hip can be affected by AS. We will focus on the coxofemoral joint. This joint can be affected by synovitis [13], enthesial inflammation [14], bone marrow involvement [15] and other as yet incompletely defined mechanisms, finally leading to degeneration of the hip joint. Pain can be generated by the acute inflammation or by changes in the capsular and synovial hip nerves as seen in patients with chronic hip disease [16]. The clinical pattern of coxofemoral disease includes typical inguinal pain with impaired and painful movement of the hip [17].

A careful clinical examination may help to distinguish pain caused by coxofemoral joint from pain originated by other sites that are also typically involved in AS: trochanteric bursitis, adductor enthesitis, enthesitis of the fascia lata, ostiitis pubis or referred pain from sacro-iliacal or axial involvement.

On the contrary, one should also take into account that hips of patients with AS can be involved by other processes clinically indistinguishable from coxitis, for example osteoarthritis, osteonecrosis or idiopathic chondrolysis.

Most articles describing ‘clinical’ hip involvement refer to the physician’s clinical opinion. Further work should be done to standardize this definition [6,18**]. It is still a matter of debate whether hip involvement can clinically best be evaluated by symptoms, measurement of the intermalleolar distance, or assessment of internal rotation, or a combination of these such as the Harris hip score [19], www.orthopaedicscore.com/scorepages/harris_hip_score.html is still a matter of discussion [20].

In daily clinical practice, assessment of hip mobility should be part of the regular clinical examination of a patient with AS.

Histological findings in ankylosing spondylitis related hip involvement

In contrast to the knee, the coxofemoral joint is more difficult to approach by needle arthroscopy [21]. Nevertheless, histological data from biopsies and arthroplasty specimens suggest involvement by two processes, also described for the axial disease in AS: inflammation and pathological new bone formation [13,22–24]. Inflammation seems to be driven by cytokines, mainly tumour necrosis factor (TNF)-alpha and interleukin (IL)-6 and by specific cell–cell interaction in which HLA-B27 could play a role [24]. Pathological bone formation seems to be driven by WNT and bone morphogenic proteins [24]. However, the histological characteristics of this hip involvement may differ from what is seen in the sacroiliac joints or spine [22].

New bone formation can also be seen in patients with osteoarthritis, which makes it difficult to distinguish whether the process can be attributed to AS or degenerative joint disease.

Radiological hip involvement

Both of these processes produce changes that can be seen on conventional radiographs by two typical features: concentric osteoproliferation with osteophytes around the femoral neck and erosions of the acetabulum (Fig. 1).

The most widely used and best validated index to evaluate severity and evolution of hip involvement is the bath ankylosing spondylitis radiology index [25]. In this score, the hips are graded on a scale of 0–4 (0, no change; 1, suspicious: focal joint space narrowing; 2, mild: circumferential joint space narrowing >2 mm; 3, moderate: circumferential joint space narrowing ≤2 mm or bone-on-bone apposition of <2 cm; and 4, severe: bone deformity or bone-on-bone apposition of ≥2 cm) [26]. This score shows a reasonable sensitivity to change and therefore can be used in clinical trials and observational studies [27,28].

Computed tomography (CT) can detect erosions and can be combined with isotope scanning techniques such as PET [29]. However, CT scanning is evaluated by symptoms, measurement of the intermalleolar distance, or assessment of internal rotation, or a combination of these such as the Harris hip score [19], www.orthopaedicscore.com/scorepages/harris_hip_score.html is still a matter of discussion [20].

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Computed tomography (CT) can detect erosions and can be combined with isotope scanning techniques such as PET [29]. However, CT scanning is
not recommended as a standard screening tool is AS. It is recommended that conventional spinal radiographs should not be repeated more frequently than every 2 years unless clearly indicated in individual cases [10]. This probably holds true also for radiographs of the hips.

**Ultrasound hip involvement**

Similarly to other inflammatory involvement of peripheral joints, ultrasound of the hip joints can reveal synovial hypertrophy and hypervascularization as signs of inflammation [30,31].

The concordance between clinical findings and ultrasound abnormalities is only moderate, but correlates better with C-reactive protein than clinical hip tenderness [31].

Ultrasound is especially recommended to evaluate hip joint effusions in children. A capsular-synovial thickness of more than 5 and more than 2 mm difference compared with the asymptomatic contralateral hip are the sonographic criteria described for hip joint effusion in children. In children, hip effusion can be the first symptom of (juvenile onset) SpA, but other diseases should be excluded, including transient synovitis of the hip and septic arthritis [32,33].

Ultrasound is also an excellent tool to identify enthesitis of the great trochanter. Ultrasound findings of enthesopathy include thickening, calcification, bone erosions, enthesophytes, bursitis, and power Doppler signal: compared with controls, subclinical enthesitis of the great trochanter is found more frequently in patients with AS. Enthesitis of the anterior insertion of gluteus medius is the most prevalent finding in AS [34].

**MRI hip involvement**

About half of the patients with juvenile AS show enthesitis and osteitis in the coxofemoral area (Fig. 2) [15,35]. In contrast with juveniles, whole-body MRI was able to detect active hip lesions in only a limited number of adult patients with AS [36]. It should also be noted that bone marrow oedema of the hip is a nonspecific finding that can be seen in a variety of diseases. An arthropathy due to infection may be indistinguishable from noninfective inflammatory causes [37]. In routine clinical practice, MRI examinations should be performed in patients with AS with painful hips if clinical examination, plain radiographs and ultrasound are not helpful in making a diagnosis of the origin of the problem.

**Single photon emission computed tomography and PET**

Single photon emission computed tomography and PET can be used to demonstrate active

**FIGURE 1.** Typical radiographic features of hip involvement in a patient with ankylosing spondylitis: concentric ‘necklace-like’ osteoproliferation with osteophytes at the femoral head (black arrows) and erosions (white arrow).

**FIGURE 2.** The image is an STIR sequence obtained in the coronal plane in a 14-year-old boy with ERA (HLA-B27 positive). Fluid and disease appear bright, as does spinal fluid. Increased signal abnormality is observed around bilateral triradiate cartilages and greater trochanteric apophyses (arrowhead), frequent areas of involvement for ERA. Also, signal abnormality appears on the iliac side of the sacroiliac joints bilaterally around more curvilinear dark sclerotic subchondral areas representing erosions and sacroiliitis (arrows). ERA, enthesitis-related arthritis; SpA, spondyloarthritis; STIR, short T1 inversion recovery. Adapted from [35].
inflammation, but are not be recommended in the routine assessment of a patient with AS. It may have an added value in the assessment of patients to narrow the differential diagnosis, for example vs. septic arthritis.

**CHARACTERISTICS OF PATIENTS WITH ANKYLOSING SPONDYLITIS WITH HIP INVOLVEMENT**

A variety of factors associated with hip involvement can be defined.

**Juvenile onset**

It is consistent in all datasets and analyses that early age at disease onset is associated with hip involvement \([6,38**,39**]\). Patients with juvenile onset (age at disease onset <16 years) of AS are at the highest risk of developing hip disease and the subsequent need for hip replacement surgery. In juvenile patients, one should recognize that the number of potential differential diagnoses of coxitis is large and that an aggressive coxitis can be seen in patients with systemic onset juvenile idiopathic arthritis in whom it is clearly associated with polyarthritis and more systemic inflammation \([40]\). The classification of juvenile onset spondyloarthritis is reviewed elsewhere \([35]\).

**More severe axial disease**

The observation that hip disease can be found more frequently with more severe axial disease led to the hypothesis that hips, together with the shoulders, can be considered ‘root joints’, which behave more similarly to the spine than to other peripheral joints \([11]\).

Children with SpA are at a risk for sacroiliitis, which may be present in the absence of suggestive symptoms or physical examination findings. The major risk factor for sacroiliitis is hip arthritis \([41]\). Also, in a recent series of 769 adults with AS, a strong correlation was seen between hip involvement and the severity of spinal involvement \([27]\).

However, it seems that the effect of age at onset and disease duration is somewhat different for the hip disease compared with axial disease: patients with juvenile onset have more hip involvement \([11,25,42,43**]\), but less severe axial disease \([42]\).

**Enthesial disease, arthritic disease**

Hip involvement is also associated with other peripheral manifestations of AS, including enthesitis and arthritis in other joints \([6]\).

**Genetic background, sex, ethnicity and social background**

In the ASPECT-REGISPONSER study \([6]\), HLA-B27 positivity was not associated with hip involvement or hip prosthesis surgery. In a Brazilian study \([44**]\), Africans had more hip involvement than white patients, but, in a British study \([45]\), African patients had less frequently hip pain. In another study \([46]\), hip involvement was more common in patients with familial AS, in whom it was also associated with HLA-B27. In a recent Moroccan study \([47]\), hip involvement was more prevalent in men than in women, but this was not found in other recent studies \([6,48]\). An older study \([49]\) comparing patients with AS in Morocco and France found hip involvement to be three times as common in the Moroccan patients.

**FUNCTIONAL IMPAIRMENT**

The most commonly used functional outcome measure in SpA is the Bath Ankylosing Spondylitis Functional Index (BASFI) \([50]\). Patients with hip involvement (clinical or radiological) have worse BASFI scores than patients without hip involvement \([6,43***,51,52**,53]\). These higher BASFI scores seem to be associated with all BASFI questions of which many appear to be directly related to the hip (e.g. difficulty with getting up off the floor or out of a chair, tying shoes, climbing stairs). However, they are associated with functions that are independent of the hip (e.g. question 8 of the BASFI: looking over the shoulder without turning your body) \([6,52**]\). This could indicate that a patient’s judgement of functional impairment is not necessarily only reflecting range of motion in the joints. Perhaps hip involvement also hampers other activities related to spinal mobility. An alternative explanation could involve the association of hip involvement with more severe axial disease in terms of ankylosis progression, as noted above.

An alternative functional measurement, the health assessment questionnaire (HAQ) modified for the Spondyloarthopathies (HAQ-S), was designed to enhance the validity of the HAQ for the assessment of functional limitations in patients with SpA by adding five items related to axial function \([54]\). In this questionnaire, limited hip rotation is reflected in the questions concerning dressing, walking stairs and hygiene \([52**]\).

**THERAPY**

Ideally, a systemic therapy for AS should also be able to prevent AS-related damage. However, as stated earlier, current definitions of hip involvement in AS
which emphasize early detection) make it difficult to differentiate hip involvement by inflammation from degenerative hip involvement.

Moreover, studies of therapy in AS have been mainly focused on the spine and axial radiology and to some extent on peripheral arthritis or enthesitis. Little is known regarding the effects of either classical disease modifying antirheumatic drugs (DMARDs) or biological treatments on the hip and the need for hip replacement surgery. For example, the classic DMARDs, sulphasalazine and methotrexate (MTX), have demonstrated little or no effect on axial disease and are recommended only in patients with peripheral arthritis [8,55]. However, their effect on hip involvement is uncertain. Similarly, although TNF-inhibitors have been shown to be highly effective in controlling axial inflammation, their ability to reduce the incidence and activity of coxitis, and their effect on the long-term need for hip surgery has yet to be investigated systematically. As TNF-inhibitors in rheumatoid arthritis reduce progression of erosive disease, and as the chronic morphological changes that are seen in AS-related hip involvement are frequently of the erosive/destructive type, there are grounds to anticipate that anti-TNF may help reverse hip disease in AS [22,56,57]. Anecdotal case reports seem to support this (Fig. 3).

On the contrary, a recent Chinese study [19] of combination therapy with etanercept with MTX showed a significant improvement in the Harris hip score after 1 year, but had no significant effect on the radiological scores [58*]. Another Chinese study [59], using etanercept as monotherapy, showed a significant improvement of the Harris hip score. Whether this improvement reflects changes in the coxofemoral joint, the periaricular entheses or the spine requires further investigation.

**FIGURE 3.** Chondroprotection and regeneration of articular cartilage by cytokine blockers. (a) Hip joint of a patient with ankylosing spondylitis before (left) and after 1 year of treatment with the TNF-α blocking mAb infliximab. Erosive progression has been ended and joint space reappeared. TNF-α, tumour necrosis factor-alpha. Adapted from [57].

Similarly, persisting low bath ankylosing spondylitis disease activity index and BASFI scores under continuous long-term anti-TNF therapy might suggest a protective effect on hip involvement.

Hip involvement has also been reported as an independent factor associated with prescription of anti-TNF agents in AS patients [60,61].

Whether NSAIDs should be combined with anti-TNF treatment to reduce radiological progression of axial disease is still a matter of debate. Nevertheless, NSAIDs are efficient in controlling signs and symptoms in many patients, and have shown to contribute to reduction of axial radiographic progression [62].

An alternative therapeutic option to systemic treatment of the hip is local intraarticular infiltration of corticosteroids. Although this is a commonly used strategy in cases of active coxofemoral synovitis, with a rapid effect, it remains unclear whether this can prevent damage in the long term.

In the case of end-stage hip disease, hip replacement is the final treatment option. As noted above, a number of factors are associated with the end-stage hip disease, including early age at onset, disease duration, enthesial disease, arthritic disease and severity of axial disease [6,51].

Beyond these factors, Hamdi et al. [63] showed that a limited flexion/extension of the hip and a destructive radiological pattern (mimicking the osteoarthritis radiological pattern) may be risk factors for hip replacement surgery.

The survival of hip prostheses in patients with AS seems to be similar to that of patients with osteoarthritis [64] and could be estimated at 98.5, 96.8 and 66.3% at the 5-year, 10-year and 15-year intervals [65].

Some complications, specific to AS, are well documented, including ectopic calcification and pelvic hyperextension due to the characteristic spinal deformity of AS (i.e. excessive thoracic kyphosis and loss of lumbar lordosis) [65]. Also, ectopic ossification seems to be prevalent in patients with AS [65]. Specific precautions can be taken such as minimal invasive techniques, perioperative use of NSAIDS and quick mobilization. In some cases, bilateral arthroplasty in the same session may be required [64,66,67].

**CONCLUSION**

Hip involvement is a common disease manifestation of AS, reflecting more severe disease that is associated with a functional impairment. Hip involvement should be assessed routinely in clinical practice, but further international consensus is needed on how this should be done.
long-term studies are needed to evaluate the effect of therapeutic strategies that can prevent hip involvement and the need for hip replacement surgery, especially in patients with younger onset of disease. At present, TNF inhibitors seem to offer the best treatment, perhaps in combination with NSAIDs.

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Conflicts of interest

B.V.C. and E.C. have no conflict of interest declared in the context of this article. N.V. is an employee of Merck company.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 555).


A key article concerning ultrasound examination of the hip in AS.


A detailed description of the ultrasound examination of the different entheses of the hip.


Whole-body MRI is a new technique that evaluates the patient with AS beyond the SI joints.


39. A large cohort of South-American patients with AS.


This study highlights the differential phenotype of AS in function of age at onset of AS.


Spondyloarthropathies


A large study on the radiological aspects of AS and its relation with age at onset and disease duration.


45. Roussou E, Sultana S. Early spondyloarthropathy in a multiracial society: differences between gender, race, and disease subgroups with regard to first symptom at presentation, main problem that the disease is causing to patient, and employment status. Rheumatol Int 2012; 32:1597–1604. An interesting study describing the social context of AS.


This study compares BASDAI with HAQ-s.


