Ultrasound imaging for the rheumatologist XXXVII. Sonographic assessment of the hip in ankylosing spondylitis patients

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ABSTRACT

Objectives. *To investigate the prevalence of ultrasound (US) detectable inflammation in hips of patients with ankylosing spondylitis (AS) and the relationship between US and measures of disease activity and severity.*

Methods. *Consecutive patients with AS attending the rheumatology units involved in this study were enrolled. Clinical and demographical data were recorded. US examination of bilateral hips was performed at the same time, evaluating anterior longitudinal scan to search for synovial hypertrophy (SH), joint effusion (JE) or power Doppler (PD) positive synovitis.*

Results. *A total of 56 patients were included, median age (interquartile range, IQR) 49 (39, 59.5), median disease duration 98 (72, 204) months, 80.3% were treated with TNF-α inhibitors, median BASDAI 2.65 (1.96, 3.95), 30.3% had hip tenderness. US JE was found in 26.7% of patients, US SH in 16%, no patient had detectable PD. The concordance between clinical findings and US abnormalities was moderate, with a kappa of 0.44. Patients with detectable US abnormalities had higher median visual analogue scale (VAS) pain and C-reactive protein (CRP), while there was no significant association with other measures of disease activity and disability. In the subgroup of patients with no hip tenderness, US alterations were still significantly related to higher CRP levels, while in patients with hip tenderness and no US abnormalities CRP was not higher than in the asymptomatic patients.*

Conclusions. *US assessment of hip joint in AS patients can be considered of value, as suggested by the correlation with relevant clinical and laboratory measures. In asymptomatic patients, US examination might provide further information on subclinical involvement.*

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that implies inflammatory involvement of joints and entheses. Its prevalence is similar to that of rheumatoid arthritis (0.5%) (1, 2); the disease has a slightly higher prevalence in males and is genetically related to the HLA B27 allele (3-5). The natural history of the disease implies persistent inflammation of the sacroiliac joints and the spine, leading to ankylosis of the areas involved and disability (6). The musculoskeletal manifestations of the disease include mainly inflammatory back pain, even if enthesal involvement and peripheral arthritis can also be detected. In most cases, arthritis asymmetrically involves the lower limbs (6). In this context, hip involvement is far from rare: up to 36% of patients experience hip involvement during the course of the disease, with 8% of subjects undergoing hip replacement, which is bilateral in 47% of cases, especially in patients with longer disease duration (7, 8). Among all possible peripheral joint involvement, clinical reports indicate that hip involvement increases the burden of the disease, leading to a reduction in physical function and an increase in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores (7, 9). Moreover, the involvement of the hip concerns a subset of patients with more severe disease that will more like-

ly progress from a radiographic point of view at spine level (7).

Ultrasonography (US) has proven to be a useful tool in patients with AS (10). In particular, US has been mainly applied to detect peripheral enthesitis (11-13) and sacroiliac joint involvement (14) proving to be more sensitive than clinical examination. US has also been used to assess the posterior sacroiliac ligaments (15), and to make US-guided injections in refractory enthesitis (16). To our knowledge, no specific studies have investigated the role of US hip examination in patients with AS. US has proven to be useful in the evaluation of the hip in patients with rheumatoid arthritis, and to be more sensitive than physical examination in the detection of inflammatory abnormalities in this site (17). Compared to magnetic resonance imaging (MRI) as reference standard, grey-scale (GS) examination on US showed a lower specificity in the detection of synovitis in patients with rheumatic diseases, but a good sensitivity (18). Moreover, based on the findings of a histopathological study, the qualitative assessment of increased synovial vascularity using power Doppler (PD) is considered reliable in the hip (19).

The aim of the present study was to assess the hip joints in patients with AS using US, in order to detect the frequency of joint abnormalities on GS and PD examination, and to cross-sectionally evaluate their relationship with clinical measures of disease activity and severity.

Patients and methods

Consecutive patients from five rheumatology units, with a diagnosis of AS according to the modified New York Criteria (20), were enrolled. On the same day, patients underwent clinical and US evaluations. From a clinical point of view, main demographic, clinical and laboratory findings were recorded. In particular, BASDAI (21), BASFI (22), Bath Ankylosing Spondylitis Metrology Index (BASMI)(23), Bath Ankylosing Spondylitis Global Score (BAS-G) (24), Visual analogue Scale (VAS) pain, VAS Global Health (VAS GH), VAS Patient's Global Assessment (VAS PGA) were calculated. The presence of hip tenderness on history or motion, the concomitant therapy, erythrocyte sedimentation rate (ESR)(<20 mm/h) and high sensitivity C-reactive protein (CRP)(<0.5 mg/dl) were recorded. Disability was also evaluated using the Health Assessment Questionnaire modified for spondyloarthropathies (HAQ-S) (25).

US was performed at each centre by a single experienced operator, who was blinded to the clinical and laboratory data, and involved bilateral hips. Before beginning the study, the scanning protocol and the scoring system were selected with an agreement of all the participating centres. The patients were placed in a supine position, with the hip joints in neutral position. US was performed with a Logiq 9 machine (General Electrics Medical Systems, Milwaukee, WI) with a 6–8 MHz multi-frequency linear array transducer. A standardised longitudinal anatomic section plane along the neck of the femur was used to visualise the anterior capsule, in order to detect joint effusion (JE) or synovial hypertrophy (SH), according to the European League Against Rheumatism guidelines (26). Synovial pathology was defined according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definitions (27). In particular, JE was defined as abnormal hypoechoic or anechoic, PD negative, intraarticular material that is displaceable and compressible; SH as abnormal hypoechoic intraarticular tissue non-displaceable and poorly compressible that might be PD positive. Both JE and SH were evaluated according to a dichotomic score, as present or absent. The limit for normal hip dimension was defined according to Koski *et al*., with values ≥7 mm and a difference of 1 or more mm is suggestive of intracapsular effusion (28). JE and SH were also considered together, as presence or absence of US abnormalities at GS examination.

Synovial PD was assessed including an area in the colour box that involved the joint and a variable view of the surrounding tissues. Pulse repetition frequency (PRF) was adjusted depending on the joint size at the lowest possible in order to maximise sensitivity, ranging from 750 to 1100 Hz. Doppler frequency was adjusted depending on patient's characteristics and joint depth. Colour gain was set just below the level that causes the appearance of noise artefacts. Flow was demonstrated in two perpendicular planes and confirmed by pulsed wave Doppler spectrum to avoid artefacts. Synovial PD was evaluated as present or absent.

Statistical analysis

Descriptive results are reported as absolute and relative frequency for categorical data, and as median (IQR) or mean (SD) according to their distribution.

Concordance between clinical and US hip involvement was calculated by overall agreement (percentage of observed exact agreement), and un-weighted kappa-statistics.

The association between US involvement and clinical variables was systematically investigated. Categorical variables was analysed using chi-squared tests, quantitative variables were analysed using the unpaired *t*-test for normally distributed, and Mann-Whitney U-test for non-normally distributed variables.

The association between US and clinical variables was also investigated in the subgroup of patients without clinical hip involvement.

All analyses were conducted using Stata, version 10 (StataCorp).

Results

A total of 56 patients were enrolled with a mean age (SD) of 49, of whom 35.7% were female and the median disease duration (interquartile range, IQR) was 98 months (72–204). NSAIDs were used by 57.1% of the patients, while 10.7% were taking steroids, however all of them at a low dose (≤5 mg/day). DMARDs were given to 33.9% of patients, in particular 26.8% were taking methotrexate (MTX) and 10.7% sulphasalazine (SSZ). A large proportion of patients (80.3%) were also treated with TNF-α inhibitors. Median BASDAI (IQR) was 2.65 (1.96, 3.95), median BASMI (IQR) was 2 (1, 3), median BASFI (IQR) was 1.95 (0.72, 3.15), median BAS-G (IQR) 2.55 (1.5, 3.6). The median HAQ-S (IQR) was 0.7

Table I. Demographical and clinical characteristics of the cohort.

n.		56
Age (median, IQR)		49 (39, 59.5)
Male/female (n)		36/20
Disease duration (months)		98 (72, 204)
NSAIDs (n, %)		32 (57.14)
Steroids (n, %)		6 (10.71)
DMARDs (n, %)		19 (33.93)
	MTX (n, %)	15 (26.79)
	SSZ (n, %)	6 (10.71)
TNF-α inhibitors (n, %)		45 (80.36)
	Infliximab (n, %)	28 (50)
	Etanercept (n, %)	11 (19.64)
	Adalimumab (n, %)	6 (10.71)
	Golimumab (n, %)	2 (3.57)
ESR mm/h		18 (9.5, 24)
CRP mg/dl		0.3 (0.1, 0.66)
BASDAI		2.65 (1.96, 3.95)
BASFI		1.95 (0.72, 3.15)
BASMI		2 (1, 3)
BAS-G		2.55 (1.5, 3.6)
HAQ-S		0.7 (0.2, 1.2)
VAS pain (mm)		20 (3, 33.5)
VAS GH (mm)		65 (50, 88)
VAS PGA (mm)		10 (4, 45)
Swollen joint count		0 (0, 0)
Tender joint count		0 (0, 4)
Hip tenderness (n,%)		17 (30. 3)
US JE (n,%)		15 (26.78)
	Right hip (n,%)	13 (23.21)
	Left hip (n,%)	9 (16.07)
US SH (n,%)		9 (16.07)
	Right hip (n,%)	6 (10.71)
	Left hip (n,%)	6 (10.71)
US PD (n,%)		0 (0)

NSAIDs: non-steroidal anti-inflammatory drugs; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BAS-G: Bath Ankylosing Spondylitis Global Health; HAQ-S: Health assessment Questionnaire modified for spondyloarthropathies; VAS: visual analogue scale; GH: global health; PGA: patient's global assessment; US JE: ultrasonographic joint effusion; US SH: ultrasonographic synovial hypertrophy; US PD: ultrasonographic power Doppler.
Values are expressed as median (IQR) unless otherwise specified.

(0.2, 1.8). Hip tenderness as revealed from the patient's history or motion was reported by 17 (30.3%) patients. The demographical and clinical features are summarised in Table I.

US examination demonstrated pathological findings in 20 (37.5%) patients. In particular, JE was evident in 15 (26.7%) subjects, while synovial hypertrophy was found in 9 (16%) patients. Synovial PD was not detected in any patient.

The concordance between clinical findings (hip tenderness) and the detection by US of any hip abnormality measured by the kappa statistic, was moderate, with a kappa of 0.44.

Afterwards, we investigated the relationship between clinical and demographical variables and US findings (Table II). Patients with US detectable hip involvement did not differ significantly in terms of gender, age, disease duration, and ESR from patients with normal US findings. Nevertheless, CRP was higher in patients with US hip involvement, with a median (IQR) of 0.48 (0.2, 1.3) *vs*. 0.2 (0.1, 0.5) in patients with no US abnormalities (p=0.04). No differences were found between patients with US alterations in terms of BASDAI, BASFI, BASMI, BAS-G, HAQ-S, VAS GH, VAS PGA, while VAS pain (mm) was significantly higher in patients with US hip involvement: a median (IQR) of 27 (4, 50) *vs*. 10 (2, 30), p=0.03. There was no difference in the number of tender and swollen joints.

To evaluate the additional value of US examination in asymptomatic patients, we then evaluated the data from patients who had no signs or symptoms of hip involvement. In this subgroup of patients, all the analysed variables did not significantly differ, except for CRP, which was still significantly higher in patients with US hip alterations (Table II). To further confirm the relevance of this finding, we performed the same analysis in patients with hip tenderness but no US alterations, and CRP was not higher in comparison with the patients with no symptoms (data not shown).

Discussion

US examination has proven to play an important role in the detection of many alterations in spondyloarthritides, with a greater sensitivity over clinical examination especially when applied to the investigation of sacroiliac joints and entheses (11, 14). The impact of US in the study of hip joints has not been specifically investigated so far.

Hip inflammation was reported to be a common manifestation in patients with AS (7, 29), with a large proportion of patients experiencing this kind of involvement at least once during the course of the disease (6) In our population, one third of patients reported symptoms that were compatible with joint inflammation, and US alterations were demonstrated in a similar proportion of subjects, which is substantially consistent with the prevalence reported in the literature. In previous studies, hip involvement appeared to be more common in patients with longer disease duration, and its occurrence individuated a subgroup of patients with more severe disease, as suggested by the association with more extended axial involvement, and with worse BASDAI and BASFI scores (7). Nevertheless, the relationship between US hip involvement and disease activity or physical function was not evident in the cohort we examined. It must be underlined that our population was mainly

Table II. Correlation between US and clinical features.

	All patients (n=56)			Patients with no hip tenderness (n=39)		
	US neg	US pos	*p*-value	US neg	US pos	*p*-value
Age (years)	46 (38, 60)	53 (41, 59)	0.53	42 (36, 59)	43.5 (38.5, 48.5)	0.56
Disease duration (months)	102 (72, 192)	84 (72, 216)	0.52	96 (72, 148)	110 (78, 240)	0.43
ESR (mm/h)	18 (8,21)	19 (15, 32)	0.06	18 (6, 21)	18 (14, 20)	0.63
CRP (mg/dl)	0.2 (0.1, 0.5)	0.48 (0.2, 1.3)	0.04	0.2 (0.1, 0.4)	0.39 (0.3, 0.9)	0.02
BASDAI	2.6 (2.08, 3.8)	3 (1.6, 5.1)	0.40	2.7 (1.5, 3.8)	1.76 (0.79, 2.29)	0.18
BASFI	1.91 (0.6, 2.63)	2 (1, 3.9)	0.13	2 (0.55, 3)	1.17 (0.52, 1.67)	0.25
BASMI	2 (1,3)	3 (0,4)	0.27	1 (1, 2)	1 (1, 4)	0.92
BAS-G	2.6 (1.5, 3.5)	2.5 (1.5, 5.2)	0.30	2.1 (0.75, 3)	2 (0, 2.87)	0.61
HAQ-S	0.5 (0,1)	1 (0.25, 2.15)	0.13	0.4 (0, 1)	0.2 (0.2, 0.4)	0.90
VAS pain (mm)	10 (2, 30)	27 (4, 50)	0.03	10 (1, 30)	26 (17, 34)	0.11
VAS GH (mm)	70 (52, 90)	55 (40,70)	0.12	80 (65, 91)	69 (60, 92)	0.59
VAS PGA (mm)	10 (6, 35)	29 (4, 45)	0.68	10 (4, 30)	29 (5, 31)	0.48
Swollen joints	0 (0, 0)	0 (0, 0)	0.52	0 (0, 0)	0 (0, 0)	n.a.
Tender joints	0 (0, 1)	2 (0, 4)	0.07	0 (0, 0)	0 (0, 2)	0.71

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BAS-G: Bath Ankylosing Spondylitis Global Health; HAQ-S: Health assessment Questionnaire modified for spondyloarthropathies; VAS: visual analogue scale; GH: global health; PGA: patient's global assessment.
Values are expressed as median (IQR) unless otherwise specified.

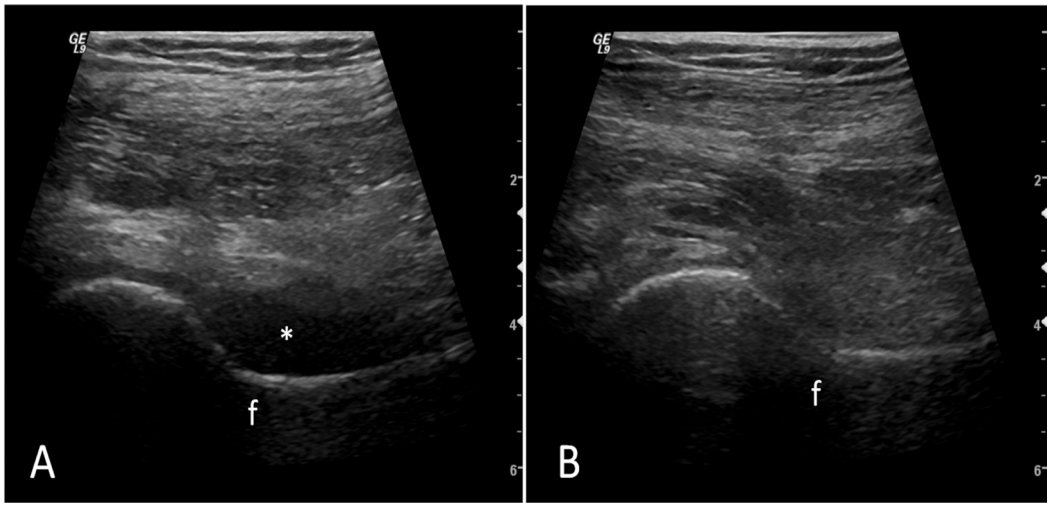

Fig. 1. Ultrasound images obtained using anterior longitudinal view in a patient with ankylosing spondylitis. **A.** Representative example of sonographic evidence of hip joint effusion (*). **B.** Contralateral side showing no signs of hip joint inflammation. **f** = femur.

composed of patients with a long median disease duration, with the majority of subjects receiving active treatment such as TNF-α inhibitors, and low median BASDAI and BASFI. In this kind of population the prevalence of US abnormalities could be lower than in patients with active disease, and a larger sample size might have been necessary to detect a correlation with disease activity and functional disability. In line with this supposition, in our patients increased synovial vascularity detected by PD was not found in any patient. This is consistent with the results from a study on the effect of TNF-α blockers on synovial histology in patients with AS, which demonstrated a reduction in vascularity during treatment (30).

The detection of hip US abnormalities on GS examination was related to a higher overall median VAS pain, which is, however, a relevant indicator of overall disease burden. Besides this patient-reported outcome, SH and/or JE were also related to an objective measure of disease activity, such as CRP that was higher in patients with US-detectable pathology. This latter finding supports the validity of US hip examination in AS patients. Moreover, this is in keeping with results of previous studies, indicating higher CRP levels in case of large joint involvement (31).

US alterations, detectable on GS examination, had only a moderate concordance with clinical manifestations suggestive of inflammatory hip involvement, as determined with kappa statistics. For this reason, a higher prevalence of US abnormalities in symptomatic patients should not be expected.

However, to explore the additional value of US examination in patients with no clinical signs and symptoms of inflammatory hip involvement, we performed a separate analysis in this subgroup. While US findings were not significantly related to clinical features, disease activity or disability, CRP was still significantly higher in subjects with US abnormalities, despite the small sample size, thus providing a further confirmation of the robustness of this finding. On the other hand, patients with hip tenderness and no US detectable involvement did not show higher levels of

CRP. Applied in a clinical setting, these results indicate that performing hip US in asymptomatic patients, especially when CRP is higher, might be helpful to detect local subclinical disease activity. Isolated hip tenderness seems to be a non-specific symptom that might also be due to consequences of past disease activity, such as secondary osteoarthritis, more than to disease activity.

This study carries some limitations. The small sample size affects the power of the estimates, and the cross-sectional design does not allow an evaluation of the impact of US findings on relevant outcomes. Univariate analysis does not allow correction for possible confounders. However, to our knowledge, this was the first study that specifically investigated the role of hip US in AS patients. Studies on larger populations and with longitudinal design will be helpful to clarify the role of this technique to detect a potentially severe manifestation of AS.

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