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Prevalence and Radiographic Progression of Hip Involvement in Patients With Ankylosing Spondylitis Treated With Tumor Necrosis Factor Inhibitors

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ABSTRACT. ***Objective.*** To examine the prevalence of hip involvement between sexes in patients with ankylosing spondylitis (AS) treated with tumor necrosis factor inhibitors (TNFi) and to estimate the effect of TNFi on radiographic progression of hip involvement compared to the spine.

Methods. Two hundred ninety-nine patients with AS treated with TNFi (215 men; median age: 43 yrs [IQR 36-52], median disease duration: 7.6 yrs [IQR 2-15]) were evaluated for hip involvement, defined radiographically as Bath AS Radiological Hip Index (BASRI-hip) score ≥ 2. Those who received TNFi for ≥ 2 years (263/299) were assessed for radiographic progression. Radiographs of the pelvis and spine, obtained at baseline (ie, before TNFi initiation), were compared retrospectively to those obtained after 2.5 (SD 0.7) years and 7.0 (SD 2.3) years of TNFi treatment. Both hips were scored by BASRI-hip score and mean joint space width (MJSW). Spinal radiographs were scored by modified Stoke AS Spinal Score (mSASSS).

Results. The prevalence of hip involvement at baseline was 113/299 (38%) patients, of whom 87/215 (41%) were male and 26/84 (31%) were female ($P = 0.10$). In both sexes with hip involvement at baseline, BASRI-hip score and MJSW did not change significantly during follow-up. In males and females without baseline hip involvement, the BASRI-hip score remained unchanged after 2.5 (SD 0.7) years but increased significantly after 7.0 (SD 2.3) years, without reaching the cut-off of 2. In contrast, the MJSW slightly decreased at the 2 follow-up timepoints (ie, after 2.5 and 7.0 yrs). The mSASSS increased significantly during the follow-up in both sexes, regardless of hip involvement.

Conclusion. In our study, approximately one-third of patients with AS had hip involvement, which seemed to stabilize with TNFi treatment. No sex differences in the prevalence or progression of this manifestation were found.

Key Indexing Terms: ankylosing spondylitis, radiography, tumor necrosis factor inhibitors

Hip involvement is the most frequent extraspinal manifestation of ankylosing spondylitis (AS) and a common cause of disability. According to data derived from the ASPECT (Belgium), REGISPONSER (Spain), and RESPONDIA (Ibero-America) working groups, hip involvement is present in 24% to 36% of patients with AS, with 5% of them needing a total hip replacement (THR).[1] Hip involvement, older age, high Bath AS Disease Activity Index (BASDAI) scores, and spinal changes contributed significantly to functional impairment, as assessed by the Bath AS Functional Index (BASFI).[2] Moreover, a significant association between symptom duration and hip involvement has been described, indicating that patients with hip involvement were more likely to have severe spinal changes when disease duration increased.[2-4] Moreover, several studies reported an association between hip involvement and disease duration.[5,6]

According to the Prospective Study of Outcomes in AS (PSOAS) cohort, women with AS may have more peripheral arthritis (including hip and shoulder), but there was no evidence of more radiographic damage in these areas compared to men.[7,8] In contrast, many studies show that males with AS have more radiographic damage of the spine compared with females, but the differences in radiographic hip involvement is less well studied.[9,10]

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The authors declare no conflicts of interest relevant to this article.

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Further, sustained treatment with tumor necrosis factor inhibitors (TNFi) seems to inhibit the progression of radiographical hip involvement. Nevertheless, the relevant studies are scarce, observational, and include a relatively small number of patients.[11-15] Out of the total population of patients with AS, it has been estimated that 49% (ranging from 37% to 78%) are eligible for TNFi treatment. The latter are those with high disease activity, high levels of acute-phase reactants, worse spinal mobility, worse function, and more frequent hip involvement.[16]

Therefore, the aim of this study was to examine the prevalence of hip involvement in patients with AS eligible for TNFi, to evaluate patient characteristics and clinical assessments associated with the presence of this manifestation, and to identify possible sex differences. Moreover, we sought to estimate the effect of long-term TNFi (ie, > 2 years) treatment on radiographic progression of hip involvement in AS compared to spinal changes.

METHODS

Study population. All patients with AS included in this retrospective study were derived from the Amsterdam Spondyloarthritis (AmSpA) cohort in Amsterdam, the Netherlands, and the Rheumatology Departments of the Veterans Administration Hospital and First Propaedeutic Internal Medicine of National and Kapodistrian University in Athens, Greece. Patients fulfilled the modified New York criteria,[17] were ≥ 18 years old, and were eligible for TNFi treatment according to the Assessment of Spondyloarthritis international Society guidelines.[18] The patients started TNFi (infliximab [IFX], etanercept [ETN], adalimumab, or golimumab) treatment between January 2000 and March 2013. The study complied with the Declaration of Helsinki, was approved by the Medical Ethics committee of the Slotervaart Hospital and Reade, Amsterdam, the Netherlands (approval no. NL13486.029.06), and by Laikon Hospital Institutional Review Board, Athens, Greece, and have been described previously by Konsta et al.[19] Written informed consent was obtained from all participants before inclusion.

Patients who had bilateral THR surgery, as well as those who have received TNFi for a period of less than 2 years, were included only in the prevalence and sex analysis.

At baseline (ie, before TNFi initiation), medical history, laboratory assessment, and radiographs of the spine and pelvis were obtained from all patients with AS. The following data were collected: demographics (ie, sex and age), family history of AS (in first-degree relatives), symptom duration, disease duration (time since disease diagnosis), and presence of peripheral arthritis (other than hip), inflammatory bowel disease (IBD), psoriasis, and uveitis. The BASDAI and AS Disease Activity Score (ASDAS) based on C-reactive protein (ASDAS-CRP)/erythrocyte sedimentation rate (ASDAS-ESR) recorded disease activity at baseline. The functional capacity was evaluated by BASFI and the Bath AS Metrology Index.

Laboratory assessment included HLA-B27, ESR, and CRP. Clinical assessment of hip involvement was based on pain, limited motion, and a history of THR.

Radiographic assessment. Radiographs of the pelvis and cervical and lumbar spine were obtained at baseline (ie, before TNFi initiation) and compared retrospectively to those obtained after 2.5 (SD 0.7; range: 1.8-5.8) years and 7.0 (SD 2.3; range: 2.7-12.7) years of TNFi treatment. In the case that these radiographs were not available within 2 years after TNFi initiation, the first available radiographs after that period were scored.

The radiographs were scored by 2 independent readers, blindly but with known chronology, as this is the most sensitive method.[20] Average scores of the 2 readers were used. In case of reader disagreement, no adjudication was implemented, due to good interobserver reliability.

Hip radiographic assessment. Two trained assessors (MK and AI) scored both hips separately in 2 ways: the Bath AS radiology hip (BASRI-hip) scoring system[21] and the mean joint space width (MJSW).[13] The latter is a quantitative scoring method, based on published methods,[22,23] applied for the estimation of hip joint space width in patients with osteoarthritis (OA). Joint space width was assessed by the average of measurements between the acetabulum and femoral head at 3 distinct sites (Figure 1). For each patient, the MJSW of the left and right hip joint (average of 3 measurements in each joint) was assessed.

Definite hip involvement was defined radiographically as mean BASRI-hip score ≥ 2 (ie, right and left hip) at baseline anteroposterior pelvis radiographs,[21] since there are no cut-offs for the MJSW in AS.

Interobserver reliability for the BASRI-hip score (intraclass correlation coefficient [ICC] 0.93, 95% CI 0.91-0.94) and the MJSW (ICC 0.973, 95% CI 0.97-0.98) were satisfactory. In each patient, there was an absolute agreement between both readers regarding the assessment of definite radiographic hip involvement.

Spinal and sacroiliac radiographic assessment. Radiographic progression was assessed by the modified Stoke AS Spine Score (mSASSS).[24] Two trained assessors (IEvdHB and MK) scored radiographs independently with good interobserver reliability (ICC 0.92, 95% CI 0.85-0.99). The mean mSASSS of both readers were used for analysis. Sacroiliitis on the anteroposterior pelvic radiographs was graded according to the New York scale[17] (0-4; ICC 0.99, 95% CI 0.98-0.99).

Statistical analysis. Reliability between the 2 readers was assessed by ICC. Categorical variables were expressed as frequencies or percentages, and quantitative ones as mean (SD) or median (IQR) according to data normality. Group differences were evaluated by 2-sample *t* test for normally distributed variables, Mann-Whitney *U* test for skewed variables, and Pearson chi-squared test for dichotomous variables. Univariable and multivariable logistic regression analysis were applied for the assessment of hip involvement risk factors. Mixed models with time as the covariate tested the significance of radiographical changes in the hip and spine. A P value < 0.05 was considered statistically significant. All analyses were performed by Stata 12 software (StataCorp).

RESULTS

Prevalence and risk factors of hip involvement. In total, 526 patients with AS were eligible, of whom 299 patients (241 from the AmSpA cohort in the Netherlands and 58 from Greece) were included with complete radiograph sets before TNFi initiation (Figure 2). The baseline characteristics, stratified by sex, are summarized in Table 1. Most patients were males (215/299, 72%) and 80% were HLA-B27 positive. The median age was 43 (IQR 36-52) years and the median disease duration was 7.6 (IQR 2-15) years with a median symptom duration of 18 (IQR 10-26) years.

Most disease outcome measures were comparable between sexes (ie, ESR, peripheral arthritis [other than hip], psoriasis, and IBD). Nevertheless, women showed a significantly higher frequency of uveitis compared to men. Additionally, at baseline, female patients scored significantly worse on patient-reported disease activity (ie, BASDAI), whereas significantly higher baseline CRP levels were observed in male patients, and no sex difference was observed for the ASDAS-CRP. Male patients showed significantly more spinal radiographic damage (sacroiliitis grade, mSASSS, and syndesmophytes) at baseline (Table 1).

As far as hip involvement was concerned, 19 out of 299 (6.3%) patients underwent THR (unilateral or bilateral). More precisely, bilateral THR was evident in 10/299 (3.3%)

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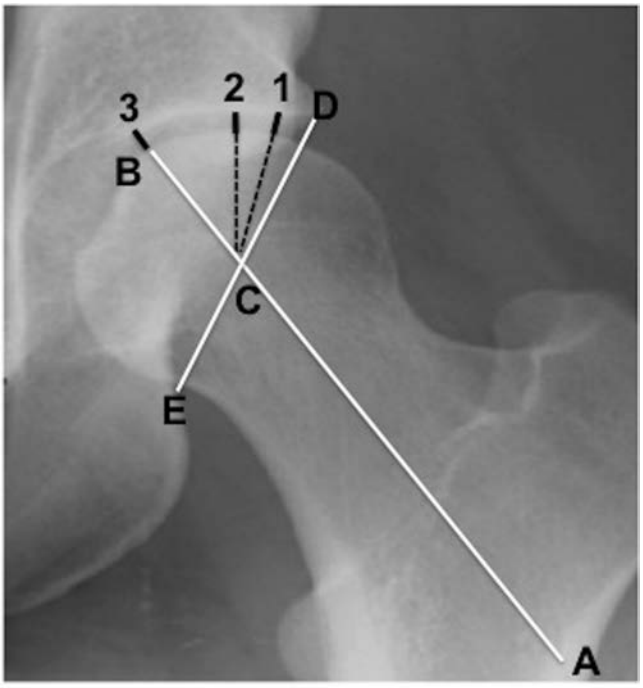

Figure 1. Three distinct sites of interbone distance in anteroposterior radiographs of the pelvis: (1) 2 mm inner of the external end of the acetabulum; (2) vertical line through femoral head center; and (3) head-neck center line. AB: head-neck center line; C: center of the femoral head; DE: line connecting the outer edge of acetabulum and the inner edge of the femoral head where head loses sphericity.

patients, all males, and unilateral THR in 9/299 (3%) patients, 2 of them were females. A trend of higher THR was observed in males (17/215 males vs 2/84 females, $P = 0.06$). Moreover, the BASRI-hip score was significantly higher in men, but the quantitative estimation with MJSW showed no sex difference (Table 1). Additionally, no sex difference was observed in MJSW in either the lower (grade 0-1) or higher (grade 2-4) BASRI-hip categories (Table 2).

Definite hip involvement was detected in 113/299 (38%) patients, 87/215 (41%) men and 26/84 (31%) women ($P = 0.1$; Table 3). Thus, regarding the frequency of hip involvement between sexes, no difference was observed. In patients with hip involvement, the MJSW was significantly lower both in males (3.6 [3.2-4.0] vs 4.5 [4.1-4.9], $P < 0.001$) and females (3.5 [3.3-3.7] vs 4.4 [3.9-4.9], $P < 0.001$) compared to those without (Table 2).

Patients with AS with hip involvement had significantly higher disease activity scores (ie, BASDAI, ASDAS-CRP/ESR, CRP, ESR). Additionally, patients with hip involvement were significantly older, had a longer disease duration, had significantly higher spinal damage scores (ie, higher sacroiliitis grade and mSASSS scores, higher percentage of syndesmophytes), and had a higher frequency of peripheral arthritis (ie, other than hips; Table 3).

According to multivariable logistic regression analysis, after adjusting for sex and age, concomitant factors for hip involvement were raised CRP (odds ratio [OR] 1.01, 95% CI 1.001-1.02), raised BASFI (OR 1.3, 95% CI 1.1-1.5), presence of syndesmophytes (OR 2.8, 95% CI 1.4-5.6), and peripheral arthritis (OR 1.9, 95% CI 1.06-3.6; Supplementary Table, available from the authors upon request).

Radiographic progression of hip involvement. Out of the 299 initial patients, 10 patients were excluded because of bilateral THR and 26 because they received TNFi for < 2 years. Thus, 263 patients with AS (189 men) under sustained TNFi for > 2 years, were included for the assessment of radiographic progression of hip involvement during TNFi treatment (Figure 2). The median age was 43 (IQR 36-52) years and the median disease duration was 7.3 (IQR 2-15) years, similar to the initial patient group. After 2.5 (SD 0.7; range 1.8-5.8) and 7.0 (SD 2.3; range 2.7-12.7) years of TNFi treatment, 226 and 210 patients' radiograph sets were assessed, respectively.

Definite hip involvement at baseline (ie, prior to TNFi treatment), according to the aforementioned criteria, was detected in 95/263 (36%) patients. These patients had significantly higher BASRI-hip scores (2 [2-2.5] vs 0.5 [0-1], $P < 0.001$) and lower MJSW (3.6 [SD 0.7] vs 4.5 [SD 0.7], $P < 0.001$) compared to those without.

The incidence of THR during the follow-up period was 8/263 (3%) patients. More specifically, after 2.5 (SD 0.7) years of TNFi treatment, 2 male patients with unilateral THR and definite hip involvement of the contralateral hip (BASRI-hip = 4) at baseline underwent THR to the other hip. In the same timeframe, a female patient with bilateral hip involvement at baseline (BASRI-hip = 3) proceeded to bilateral THR. After 7.0 (SD 2.3) years, another 4 patients underwent THR. In particular, 1 male and 1 female patient with unilateral hip involvement at baseline (BASRI-hip of 3 and 4 respectively) proceeded to THR of the involved joint. Two females with bilateral hip involvement at baseline (BASRI-hip = 3) proceeded to bilateral THR. Additionally, 1 male patient without hip arthritis prior to TNFi underwent unilateral THR because of a hip fracture.

In the total group, the BASRI-hip score increased significantly at follow-up end (1.14 [SD 1] vs 1.1 [SD 1] vs 1.2 [SD 1]), whereas the MJSW was slightly decreased (4.2 [SD 0.8] vs 4.2 [SD 0.8] vs 4.1 [SD 0.8]). Indeed, in patients with hip involvement at baseline, regardless of sex, both BASRI-hip score and MJSW did not change during the follow-up (Table 4). In those without hip involvement, the BASRI-hip score remained unchanged after 2.5 (SD 0.7) years. However, it increased significantly after 7.0 (SD 2.3) years compared to baseline, both in males and females, without reaching the cut-off of 2 for definite radiographic hip involvement. Indeed, the MJSW of those without hip involvement at baseline was slightly, but nonsignificantly, reduced at the 2 follow-up timepoints. Overall, none of the patients with AS without baseline hip involvement developed this manifestation after 7.0 (SD 2.3) years of TNFi treatment. The mSASSS was raised significantly during the follow-up period in both sexes, regardless of hip involvement (Table 4).

DISCUSSION

Hip involvement in AS is less studied compared to spinal. In the present retrospective study of patients with AS with high disease

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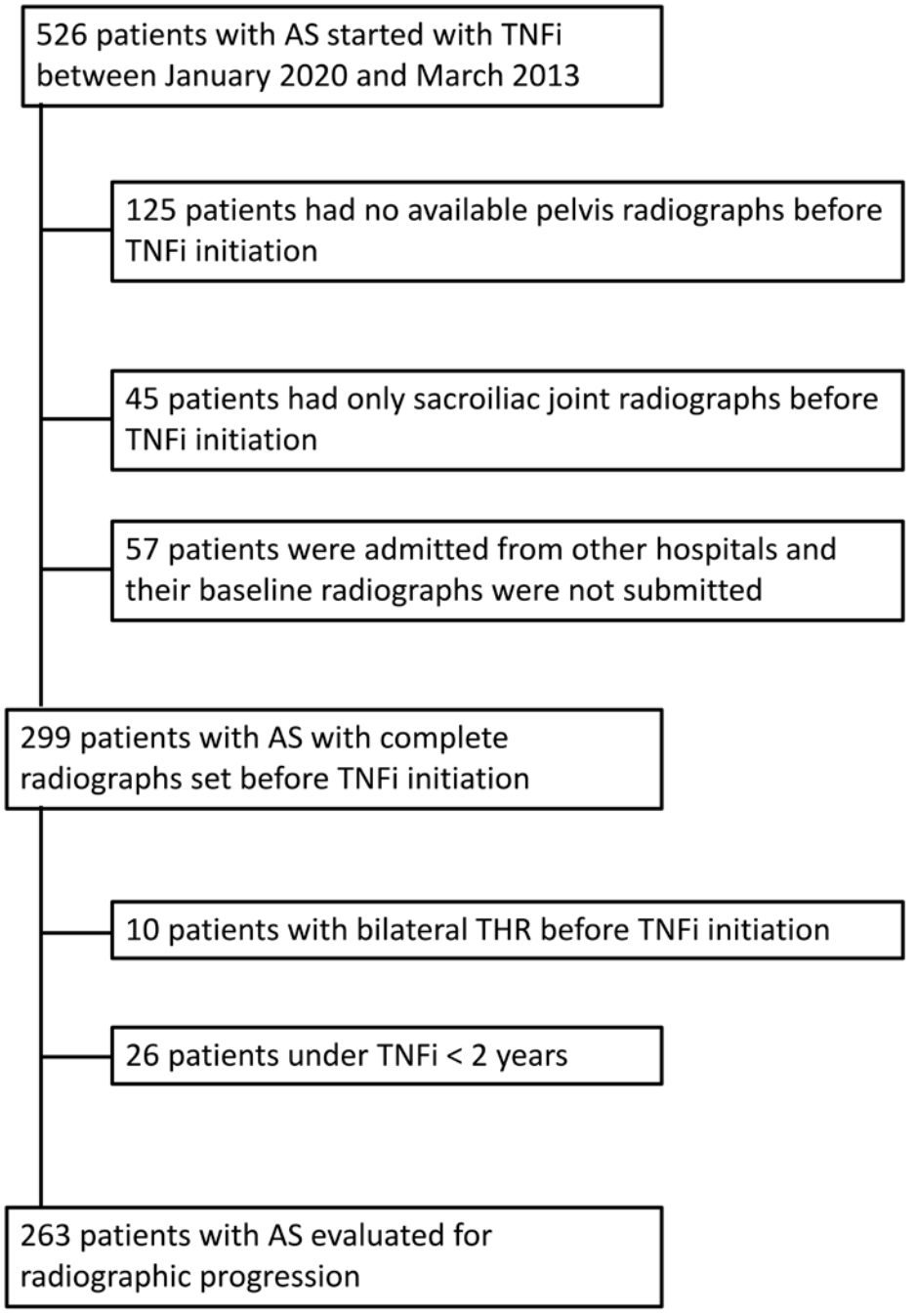

Figure 2. Flowchart of patients with AS included in the analysis.AS: ankylosing spondylitis. THR: total hip replacement; TNFi: tumor necrosis factor inhibitors.

activity, hip involvement was evident in approximately one-third (38%), including patients with THR. Long-term TNFi treatment (ie, > 2 years) appeared to stabilize hip radiographic changes; no sex differences regarding both prevalence and radiographic progression of hip involvement were observed. To the best of our knowledge, this is the first multicenter study with a relatively high number of patients that clearly demonstrates the impact of TNFi on hip radiographic progression.

Currently there is no standard definition of hip involvement in AS. Most often, patient-reported symptoms, physical examination (ie, internal hip rotation, intermalleolar distance), and radiographs of the hip joints are used.[1,6] The absence of consensus may lead to heterogeneous results and thus variable prevalence rates. In the present study, for a more objective assessment we defined hip involvement as a radiographical score of BASRI-hip ≥ 2. In our study, the patients included were eligible for TNFi and none of them had mild disease. Thus, the percentage of hip involvement was higher than in previous studies, which included patients with varying disease status and treatment regimes.

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Table 1. Baseline characteristics of 299 patients with AS stratified by sex.

	All, N = 299	Male, n = 215	Female, n = 84	*P*
Demographic variables				
Age, yrs, median (IQR)	43 (36-52)	44 (36-52)	43 (33-51)	NS
Disease-related variables				
Age at disease onset, yrs, median (IQR)	23 (19-30)	23 (19-30)	24 (18-30)	NS
Time since diagnosis, yrs, median (IQR)	7.6 (2-15)	8 (2-16)	7 (2-13)	NS
Symptom duration, yrs, median (IQR)	18 (10-26)	18 (10-27)	17 (9-26)	NS
HLA-B27 positive, n (%)	211/264 (80)	149/185 (80.5)	62/79 (78.5)	NS
AS in a first-degree relative, n (%)	38/295 (13)	25/212 (12)	13/83 (15.7)	NS
Peripheral arthritis (other than hip), n (%)	123/296 (41.6)	86/213 (40.4)	37/83 (44.6)	NS
PsO, n (%)	33 (11)	24 (11)	9 (10.7)	NS
IBD, n (%)	25 (8.4)	15 (7)	10 (12)	NS
Uveitis (ever), n (%)	87 (29)	54 (25)	33 (39.3)	**0.02**
Smoker (current), n (%)	124/292 (42.5)	93/208 (44.7)	31 (37)	NS
ESR, mm/h, median (IQR)	19 (8-35)	21 (8-37)	18 (8-32)	NS
CRP, mg/L, median (IQR)	10 (3.2-24)	13 (4-26)	7 (2.5-19)	**0.002**
BASDAI, median (IQR)	5.9 (4.7-7)	5.7 (4.6-6.7)	6.4 (5.4-7.4)	**0.01**
BASFI, mean (SD)	5.3 (2.3)	5.4 (2.3)	5.3 (2.3)	NS
ASDAS-ESR, mean (SD)	3.4 (0.9)	3.3 (0.9)	3.5 (0.8)	NS
ASDAS-CRP, mean (SD)	3.6 (0.9)	3.6 (0.9)	3.6 (0.8)	NS
BASMI, median (IQR)	3.95 (2-6)	4 (2.6-6)	3 (1.6-4.7)	NS
Intermalleolar distance, cm, median (IQR)	103 (89-115)	105 (92-116)	97 (80-113)	NS
Radiographic damage				
Sacroiliitis (range 0-4), median (IQR)	3 (2.5-4)	3.5 (2.5-4)	2.5 (2-3.5)	**< 0.001**
mSASSS (range 0-72), median (IQR)	6 (1-24.5)	13 (3-33)	2 (0-4)	**< 0.001**
Presence of syndesmophytes (yes/no), n (%)	151/289 (52)	134/205 (65.4)	17 (20)	**< 0.001**
THR (unilateral or bilateral), n (%)	19 (6.3)	17 (8)	2 (2.4)	NS
BASRI-hip (range 0-4), median (IQR)	1 (0-2)	1 (0.5-2)	0.5 (0-2)	**< 0.001**
BASRI-hip total score ≥ 2, n (%)	113 (38)	87 (40.5)	26 (31)	NS
MJSW, mm, median (IQR)	4.2 (3.7-4.7)	4.2 (3.7-4.7)	4.2 (3.6-4.7)	NS
Medications, n (%)				
Concurrent use of NSAIDs	184/276 (66.7)	126/198 (63.6)	58/78 (74.4)	NS
Concurrent use of DMARDs	53/293 (18)	34/212 (16)	19/81 (23)	NS

Values in bold are statistically significant. AS: ankylosing spondylitis; ASDAS: AS Disease Activity Score; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; BASMI: Bath AS Metrology Index; BASRI-hip: Bath AS Radiology Hip Index; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease; MJSW: mean joint space width; mSASSS: modified Stoke AS Spinal Score; NS: nonsignificant; NSAID: nonsteroidal antiinflammatory drug; PsO: psoriasis; THR: total hip replacement.

Table 2. Sex difference in baseline BASRI and MJSW scores, stratified by BASRI-hip categories.

		BASRI-hip Score < 2	*P*	BASRI-hip Score ≥ 2	*P*
BASRI-hip, median (IQR)	Males	0.5 (0-1)	**0.001**	2 (2-3)	**0.003**
	Females	0 (0-0.5)		2 (2-2)	
MJSW, mm, median (IQR)	Males	4.5 (4.1-4.9)	NS	3.6 (3.2-4)	NS
	Females	4.4 (3.9-4.9)		3.5 (3.3-3.7)	

Values in bold are statistically significant. BASRI: Bath Ankylosing Spondylitis Radiological Index; BASRI-hip: Bath Ankylosing Spondylitis Radiological Hip Index; MJSW: mean joint space width; NS: nonsignificant.

A more comprehensive approach to the estimation of hip involvement prevalence was conducted by the Groningen Leeuwarden Axial SpA cohort. Out of 111 patients with AS eligible for TNFi, 22 (20%) reported a history of hip involvement and 25 (23%) had 1 or more tender hip joints. Structural radiographic damage (ie, BASRI-hip score ≥ 2), was evident in 11 (10%) patients.[25]

In the multicohort study of Vander Cruyssen et al,[1] which included 847 Belgian (ASPECT), 1405 Spanish (REGISPONSER), and 466 Ibero-American (RESPONDIA) patients with AS, the prevalence rates of clinical hip involvement were 27%, 24%, and 36%, respectively.[1] There was no uniform definition for hip involvement among those cohorts. Moreover, the prevalence rate of THR was 5%, which is very close to the corresponding percentage of 6.3% in our study.

A lower prevalence of hip involvement, 49 out of 275 (18%)

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Table 3. Comparison of baseline clinical, laboratory, and radiographic characteristics of patients with AS without vs with hip involvement.

	Without Hip Involvement, n = 186	Hip Involvement, n = 113	*P*
Male, n = 215, n (%)	128 (59.5)	87 (41)	NS
Female, n = 84, n (%)	58 (69)	26 (31)	NS
Age, yrs, median (IQR)	43 (36-49)	46 (37-56)	**0.02**
Age at disease onset, yrs, median (IQR)	23 (18-30)	23 (19-29)	NS
Symptom duration, yrs, median (IQR)	17 (9-25)	18 (10-27)	**0.002**
Time since diagnosis, yrs, median (IQR)	7 (2-13)	8 (2-16)	**0.04**
Uveitis (ever), n (%)	52 (28)	35 (31)	NS
PsO, n (%)	20 (10.8)	13 (11.5)	NS
Peripheral arthritis, n (%)	68 (37)[a]	55 (49.6)[b]	**0.03**
IBD, n (%)	14 (7.5)	11 (10)	NS
BASDAI, median (IQR)	5.7 (4.5-6.7)	5 (3.5-6.3)	**0.01**
ASDAS-CRP, mean (SD)	3.4 (0.9)	3.9 (0.8)	**< 0.001**
ASDAS-ESR, mean (SD)	3.2 (0.9)	3.6 (0.9)	**< 0.001**
CRP, mg/L, median (IQR)	7 (2.9-22)	16 (7.7-32)	**< 0.001**
ESR, mm/h, median (IQR)	16 (7-33)	26 (10-42)	**0.004**
BASFI, mean (SD)	4.8 (2.3)	6.3 (2)	**< 0.001**
BASMI, median (IQR)	3 (2-5)	5.6 (3-7)	**< 0.001**
Intermalleolar distance, cm, median (IQR)	107.5 (94.5-118)	92.5 (73.5-106)	**< 0.001**
Radiographic damage			
BASRI-hip, median (IQR)	0.5 (0-1)	2 (2-2)	**< 0.001**
MJSW, median (IQR)	4.4 (4.1-4.9)	3.6 (3.2-4.0)	**< 0.001**
mSASSS, median (IQR)	4 (0-16)	15 (3-39)	**< 0.001**
Presence of syndesmophytes, n (%)	76 (41)[c]	75 (70)[d]	**< 0.001**
Sacroiliitis, median (IQR)	3 (2-4)	4 (3-4)	**< 0.001**

Values in bold are statistically significant. For variables with missing values, denominators are as follows: [a] n = 185. [b] n = 111. [c] n = 182. [d] n = 107. AS: ankylosing spondylitis; ASDAS: AS Disease Activity Score; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; BASMI: Bath AS Metrology Index; BASRI-hip: Bath AS Radiological Hip Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease; MJSW: mean joint space width; mSASSS: modified Stoke AS Spinal Score; NS: nonsignificant; PsO: psoriasis.

patients, was derived from a retrospective study from France, which included patients with peripheral spondyloarthritis (SpA) on various treatment regimens.[6] In a study from Korea, hip arthritis, defined both clinically and radiographically, was evident in 60 out of 488 (12.3%) patients with AS with undefined treatment status.[15] Moreover, in a study from Taiwan 48/531 (9%) TNFi-naïve patients with AS had radiographic evidence of hip involvement.[4] In a cross-sectional study of 655 patients with AS with undefined treatment regimes from China, 168 (25%) had early stage hip involvement, based on MRI, and 103 (16%) had advanced hip involvement, defined as BASRI-hip score ≥ 2.[26]

The most common imaging method to evaluate hip involvement in AS is by using a pelvis radiograph, which the BASRI-hip score is based on. In our study, the interpretation of pelvis radiographs was enriched by MJSW. MJSW is a quantitative measurement of hip joint space, in contrast to BASRI-hip score, which is qualitative, consists only of 4 categories, and is rather subjective. In general, the MJSW might be a useful radiographic method for the assessment of hip involvement in various inflammatory and degenerative disorders.[27] Moreover, it might be more sensitive to change over certain time periods.[28] Therefore, it has been applied for the longitudinal quantification of hip joint space narrowing rate in OA.[29-31] For the assessment of hip arthritis in OA there is a MJSW threshold of ≤ 2.5 mm,[32] in contrast to the AS-related one, in which there is no established cut-off.

No sex differences in AS-related hip involvement were detected in our study. This finding was reinforced not only by the relatively high percentage of women who were included (ie, approximately a third of the total patients with AS), but also by the implementation of MJSW, which did not vary significantly between sexes in both BASRI-hip cut-off categories. In Table 2, it is shown that although women had smaller mean scores both in MJSW and BASRI-hip compared with men, this difference was statistically significant only for BASRI-hip. The latter is an ordinal rating (range 0-4), in contrast to MJSW, which is measured within a decimal range.

Further, the PSOAS cohort[7] and Hawley et al demonstrated that the incidence rate of THR in AS did not change with regard to sex.[33] Also, in accordance with our findings, the aforementioned studies from Taiwan,[4] China,[26] Korea,[15] and Vander Cruyssen et al[1] did not demonstrate a gender difference regarding the frequency of hip involvement. Only 1 study showed a higher percentage of hip involvement in men with AS.[6]

The relation between disease activity and severity and hip involvement in AS was confirmed by our study. Although all patients with AS eligible for TNFi have moderate to high disease burden, according to our findings, those with hip involvement seem to be even worse in terms of disease activity, levels of acute-phase reactants, spinal mobility, and function. In accordance with previous studies,[4,34] we found that disease activity variables, such as increased CRP, correlated significantly with

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Table 4. Hip and spinal radiographic progression after 2.5 (SD 0.7) years and 7.0 (SD 2.3) years of TNFi treatment.

Baseline Patients, n		Baseline	After 2.5 (SD 0.7) Yrs	After 7.0 (SD 2.3) Yrs	*P*
All patients, N = 263	BASRI-hip, median (IQR)/mean (SD)	1 (0-2)/1.1 (1)	1 (0-2)/1.1 (1)	1 (0-2)/1.2 (1)	**< 0.001**
	MJSW, mm, mean (SD)	4.2 (0.8)	4.2 (0.8)	4.1 (0.8)	NS
	mSASSS, median (IQR)	6.0 (1-24)	8.5 (1.5-29.5)	11.0 (2-32)	**< 0.001**
Patients with hip involvement, n = 95	BASRI-hip, median (IQR)/mean (SD)	2 (2-2.5)/ 2.3 (0.5)	2 (2-2.5)/ 2.3 (0.6)	2 (2-2.5)/ 2.3 (0.6)	NS
	MJSW, mm, mean (SD)	3.6 (0.7)	3.6 (0.7)	3.5 (0.7)	NS
	mSASSS, median (IQR)	12.0 (2.5-36)	17 (3-40.5)	15.5 (3-37.5)	**< 0.001**
Patients without hip involvement, n = 168	BASRI-hip, median (IQR)/mean (SD)	0.5 (0-1)/0.5 (0.5)	0.5 (0-1)/0.5 (0.53)	0.5 (0-1)/0.6 (0.57)	**0.003**
	MJSW, mm, mean (SD)	4.5 (0.7)	4.5 (0.6)	4.4 (0.6)	NS
	mSASSS, median (IQR)	4.0 (0-18)	7.0 (1-25)	9.0 (2-27)	**< 0.001**
Males with hip involvement, n = 71	BASRI-hip, median (IQR)/mean (SD)	2.0 (2-2.5)/ 2.4 (0.5)	2.0 (2-2.5)/ 2.4 (0.6)	2.0 (2-2.5)/ 2.4 (0.6)	NS
	MJSW, mm, mean (SD)	3.6 (0.75)	3.6 (0.76)	3.57 (0.7)	NS
	mSASSS, median (IQR)	16.5 (4-43)	23.0 (7-49)	20.0 (9-43)	**< 0.001**
Females with hip involvement, n = 24	BASRI-hip, median (IQR)/mean (SD)	2.0 (2-2)/ 2.2 (0.4)	2.0 (2-2)/ 2.2 (0.5)	2.0 (2-2)/ 2.2 (0.5)	NS
	MJSW, mm, mean (SD)	3.5 (0.5)	3.5 (0.6)	3.4 (0.6)	NS
	mSASSS, median (IQR)	2.5 (1-19)	4.5 (1-26.5)	3.0 (1-27)	**< 0.001**
Males without hip involvement, n = 118	BASRI-hip, median (IQR)/mean (SD)	0.5 (0-1)/0.6 (0.52)	0.5 (0-1)/0.6 (0.54)	0.5 (0-1)/0.6 (0.5)	**0.045**
	MJSW, mm, mean (SD)	4.5 (0.7)	4.5 (0.66)	4.5 (0.6)	NS
	mSASSS, median (IQR)	9.0 (2-25)	12.0 (4-34)	15.0 (5-38)	**< 0.001**
Females without hip involvement, n = 50	BASRI-hip, median (IQR)	0 (0-0.5)	0 (0-1)	0 (0-1)	**0.04**
	MJSW, mm, mean (SD)	4.4 (0.6)	4.4 (0.6)	4.4 (0.6)	NS
	mSASSS, median (IQR)	1.0 (0-3)	1.5 (0-4)	2.0 (0-7)	**< 0.001**

Values in bold are statistically significant. BASRI-hip: Bath Ankylosing Spondylitis Radiological Hip Index; MJSW: mean joint space width; mSASSS: modified Stoke Ankylosing Spinal Score; TNFi: tumor necrosis factor inhibitor.

hip involvement. Moreover, the patients with hip involvement had longer disease duration and a delayed diagnosis compared to those without, consistent with other studies.[4,15] Additionally, the spinal radiographic damage and the presence of arthritis in other peripheral joints were independent risk factors for hip involvement. Similar results were derived from the Cochin Spondyloarthritis (COSPA) study[6] and the aforementioned studies from Taiwan[4] and Korea.[15]

The influence of treatment with TNFi on radiographic progression of the hips in AS was clearly demonstrated in our study. To the best of our knowledge, this is the first multicenter study with a high number of patients and a long follow-up period that confirms the hypothesis of the favorable effect of TNFi on AS-related hip arthritis. We have demonstrated, by the implementation of both BASRI-hip score and MJSW, that there is no deterioration of baseline hip radiographic changes after 2.5 (SD 0.7) and 7.0 (SD 2.3) years of TNFi treatment. Moreover, we recorded the radiographic evolution of patients with no baseline hip involvement. In these patients, the BASRI-hip score increased significantly after 7.0 (SD 2.3) years, but remained below the grade 2, which is the cut-off for definite radiographic damage. In contrast, the MJSW was nonsignificantly decreased on follow-up. The aforementioned discrepancy between BASRI-hip and MJSW could be explained in similar manner to the one found in sex comparison. Moreover, the slight increase in BASRI-hip score and decrease in MJSW at the follow-up end in those patients could be attributed to age-related osteoarthritic changes. Nevertheless, the spinal changes have deteriorated significantly, regardless of hip involvement.

Wang et al[11] and Lian et al[12] reported that treatment with ETN combined with methotrexate significantly reduced disease activity and inhibited radiographic progression of, respectively, 56 and 97 patients with AS with hip involvement at baseline. However, these studies included a rather short follow-up period of 3 and 12 months, respectively, whereas in AS a timeframe of at least 2 years is required for radiographic changes to occur. In a previous study,[13] we demonstrated nonsignificant radiographic progression of hip involvement after 6 (SD 2.5) years of continuous IFX treatment in 23 patients with AS. Moreover, radiographic deterioration of hip involvement was observed in 3 patients after IFX discontinuation due to neoplasia. Song et al[14] found that BASRI-hip score decreased and MJSW increased in 6 patients with AS after 1.97 (SD 1.3) years of TNFi treatment.

Interestingly, Wink et al demonstrated the effect of TNFi on hip involvement by ultrasound examination. Overall, after 6 months of TNFi therapy, significant decrease was found in tender hip joints, total number of inflammatory ultrasound lesions and positive power Doppler.[25] Further, according to data derived from the Norwegian Arthroplasty Register, the initiation of TNFi reduced the need for THR surgery.[35]

According to our findings, the baseline inflammatory markers (ESR and CRP) were associated with hip involvement (Table 3). Even in the absence of relevant follow-up data, we might assume that the decline in inflamation by TNFi could limit the relevant radiographic progression.

This study has some limitations. Patients with high disease activity and long disease duration were primarily included, which could have increased the prevalence of hip involvement. Moreover, the effect of mechanical stress (expressed either as

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BMI or body weight) was not evaluated, because the relevant variables were not longitudinally recorded in patients' medical files.

The major study limitation is the lack of a TNFi-naive control group. In the era of biologic disease-modifying antirheumatic drugs, the majority of patients with AS with high disease activity, in which those with hip involvement are included, start therapy—mainly with TNFi—in a relatively short time period after the disease diagnosis.[16] Therefore, it is challenging to find a suitable control group.

Nevertheless, our long-term data suggest a positive effect of inflammation resolution due to TNFi treatment on hip radiographic changes in AS, which seems to be more prominent compared to the corresponding effect on spinal structural damage. The latter, in case it is confirmed in other cohorts, could possibly influence therapeutic strategies in AS. Moreover, the implementation of hip MJSW may reliably both quantify and follow-up longitudinally the structural lesions in pelvis radiographs.

In conclusion, the burden of hip involvement in AS is significantly high, regardless of sex. However, TNF inhibition seems to stabilize the radiographic damage in the hip, in contrast to concurrent spinal changes.

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