Subclinical enthesopathy of the midfoot: could it be a peculiar feature in early psoriatic arthritis?

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Abstract

Objective

Bone scintigraphy (BS) is a sensitive tool that provides functional imaging to evaluate bone abnormalities in psoriatic arthritis (PsA). Our aims were to analyse the prevalence of increased BS uptake in the midfoot of PsA patients and to evaluate whether BS midfoot abnormalities could herald ultrasonography (US) and x-ray lesions in the same site.

Methods

Out of 88 consecutive BS performed in patients with early musculoskeletal symptoms (January-December 2010) and retrospectively analysed, 32 exams were carried out on subjects 3 months after being diagnosed with PsA. These patients were included in a retrospective study and analysed for BS feet uptake. Their baseline x-rays of the feet were also retrieved. Five years after BS (January-December 2015) all 32 PsA patients underwent clinical evaluation, x-rays and US of the feet. Frequency and percentage of each imaging abnormality of the midfoot were analysed. Clinical, functional and laboratory indexes were collected and correlations between clinical and imaging parameters were studied.

Results

Of all 32 PsA patients, 21 (65.6%) had an increased BS uptake in the midfoot, without any baseline x-ray abnormalities. After 5 years, the x-rays and US were able to detect ≥1 lesion in the midfoot of 14/32 (43.8%) and 28/32 (87.5%) patients, respectively. A high prevalence of enthesophytes in all 64 midfeet was shown by both x-rays (40.6%) and US (81.6%). We found a higher prevalence of structural lesions in the subgroup with BS positive midfoot compared with BS negative patients: x-rays [10/21 (47.6%) vs. 4/11 (36.4%); p=0.04] and US [19/21 (90.5%) vs. 8/11 (72.7%); p=0.04].

Conclusion

Midfoot involvement is frequent in PsA. BS increased uptake in the midfoot seems to be an early sign of the disease.

Key words

midfoot involvement, psoriatic arthritis, subclinical enthesitis, bone scintigraphy, x-rays, ultrasonography

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Introduction

Psoriatic arthritis (PsA) is a chronic multifactorial immune-mediated inflammatory disease included in the spondyloarthritis (SpA) spectrum (1). Enthesitis is a common clinical manifestation of PsA. About 60–80% of patients develop enthesitis (2), characterised by inflammation at the insertion site of tendons and ligaments, with a significant impact on function and quality of life (QoL) (3). It is a very specific manifestation of spondyloarthritides, setting them apart from other rheumatic diseases. In fact, the enthesis often represents the first site of involvement in SpA, usually followed by synovial inflammation of the adjacent joint and tendon sheaths, ultimately resulting in bone erosion and joint destruction (3, 4). Due to its importance, enthesitis is included in the "ClASsification criteria for Psoriatic Arthritis -CASPAR", and in core disease domains for PsA (5), according to Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) (6). The relevance of enthesitis is additionally pointed out by its inclusion in the Outcome Measures in Rheumatology (OMERACT) PsA core domain set, for inclusion in clinical trials and observational studies of PsA (6, 7). However, clinical assessment of enthesitis can be quite challenging, owing to the frequent absence of overt clinical signs of inflammation or to the involvement of clinically inaccessible sites (9, 10). Therefore, imaging techniques such as x-rays, ultrasonography (US), magnetic resonance imaging (MRI) and conventional total-body bone scintigraphy (BS), are used to facilitate the assessment of enthesitis and prevent under-diagnosis (11-17). This also carries important epidemiological consequences as the estimated prevalence of enthesitis in SpA patients ranges from 10% to 60% according to the different diagnostic tools (18).

The feet, in particular, the forefoot, hind foot (including Achilles tendon), and plantar fascia are frequently affected in PsA (19, 20). It has been reported that the typical radiographic changes observed in PsA are more common in the foot than in the hand, suggesting that foot x-rays may be more useful to differentiate PsA from rheumatoid arthritis (RA) (12). A study carried out in 26 patients diagnosed with PsA who underwent clinical evaluation and MRI of the foot showed subclinical inflammation in 92% of cases (21). The most frequent manifestations observed on MRI were: Achilles tendinitis (57%), back-calcaneal bursitis (50%), joint effusion/synovitis (46%), soft oedema tissue (46%) and presence of para-articular enthesophytes (38%) (21). The frequency of the lesions was found in different areas of the foot: forefoot (34%), midfoot (50%) and hindfoot (73%) (21). The midfoot is an under-investigated area in PsA. Hence, our interest was to evaluate the prevalence of subclinical enthesitis of the midfoot by BS in PsA and its correlation with inflammatory or structural lesions by US and x-rays.

In particular, we aimed to:

1. analyse the prevalence of increased BS uptake in the midfoot of PsA patients in early phases;
2. evaluate whether midfoot BS uptake correlated with inflammatory or structural lesions at the same site in later phases, detectable by US and x-rays performed 5 years after BS;
3. compare clinical, laboratory and functional variables in two PsA subgroups, with or without a positive BS midfoot.

Materials and methods

Subjects

Out of 88 consecutive BS performed for unexplained musculoskeletal symptoms (*i.e.* arthralgia without a definite diagnosis) between January 2010 and December 2010, 32 exams were carried out on subjects who were diagnosed as having PsA within three months of BS. All patients fulfilled CASPAR criteria for peripheral PsA (5) and were included in this retrospective study. Their BS was analysed retrospectively for the presence of increased uptake in the midfoot. As part of baseline PsA standard imaging assessment, all 32 PsA patients also underwent x-rays of the feet. We then collected data about clinical evaluation, x-rays and US of the feet five years after BS, in order to detect inflammatory or structural lesions in the midfoot. At time of BS, all patients were on non-steroi-

dal anti-inflammatory drugs (NSAIDs) or paracetamol for the control of joint symptoms. Thereafter, patients were treated according the current recommendations for the management of PsA, without any limitation on pharmacological treatments, physical therapies or other treatments (6, 22-24). Patients with a history of trauma and midfoot fractures, diabetes, gout, familial hypercholesterolaemia, thyroid diseases and use of retinoids were excluded due to possible confounding causes of enthesopathy. The study was approved by the local ethics committee, (Padova University Hospital [approval no. 52723]) and all subjects gave written informed consent, in compliance with the Declaration of Helsinki.

Scintigraphy

BS was performed at the Nuclear Medicine Unit of Padova Medical Center. All subjects received a 740-MBq injection of 99m-Tc-methylene diphosphonate, a bone/seeking radiotracer. Whole body images were acquired in anterior and posterior projections, three hours after radionuclide administration, using a computerised gamma-camera fitted with a high-resolution collimator. Foot details were also acquired in latero-medial position. The articular 99mTc-MDP uptake images were read and scored as positive or negative when areas of increased uptake were observed in the midfoot (Fig. 1). The intensity of articular 99mTc-MDP uptake in midfoot joints was graded 0 to 4: 0=normal uptake, 1=mild uptake, 2=moderate uptake, 3=marked uptake (13).

The review of BS images was performed by two nuclear medicine physicians trained in musculoskeletal disorders and double-blinded to clinic rheumatologists, sonographers with expertise in rheumatology and radiologists.

X-rays

In our study, foot x-rays were performed at baseline and after 5 years. X-rays were obtained with Philips vertical bucky in antero-posterior and latero-lateral projections at the Radiology Unit of Padova University Hospital. All images were evaluated by double-blinded radiologists trained in the identification of midfoot lesions, which have been defined as structural lesions and scored as 1 if present and 0 if absent. The following radiographic findings were analysed: a) enthesophyte, b) joint space narrowing, c) erosion, d) cortical bone irregularity (Fig. 2).

Ultrasonography

The US was performed in B-mode and PwD mode, using the ESAOTE MyLab70 equipped with 18.6 MHz and 13.5 MHz multifrequency linear probe, by two rheumatology sonographers with expertise in musculoskeletal US and double-blinded to patient's clinical data. All digital copies of US scans were evaluated using the OMERACT-EULAR global synovitis and enthesitis definition (25). A bilateral examination of the midfoot was conducted transversally and longitudinally according to a standard protocol to evaluate the following: Chopart talo-navicular and calcaneal-cuboid joint, wedge-navicular joint and Lisfranc joint. In B-mode and PwD-mode assessment, all abnormal findings were recorded and scored as 1 if present and 0 if absent. The following findings were evaluated: a) joint effusion, b) capsule distention, c) synovial hypertrophy, d) enthesophyte, e) erosion, f) cortical bone irregularity, g) positive PwD signal (Fig. 3). These US lesions were subdivided in: inflammatory lesions (joint effusion; capsule distention; synovial hypertrophy and positive PwD signal) and structural lesions (enthesophyte; erosion; cortical bone irregularity).

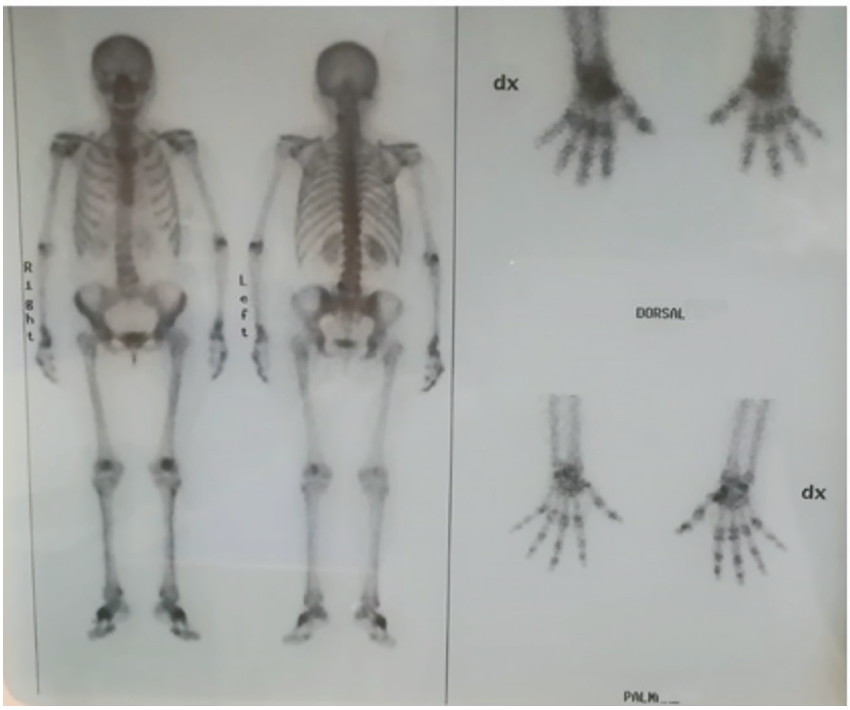
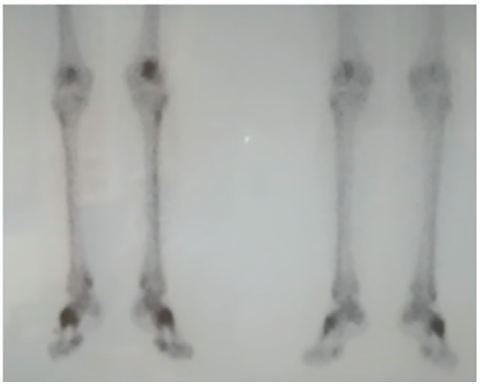


Fig. 1. Bone scintigraphy: Polyarticular increased uptake with detail of the midfoot.
Written informed consent was obtained from the patient for the publication of this image.



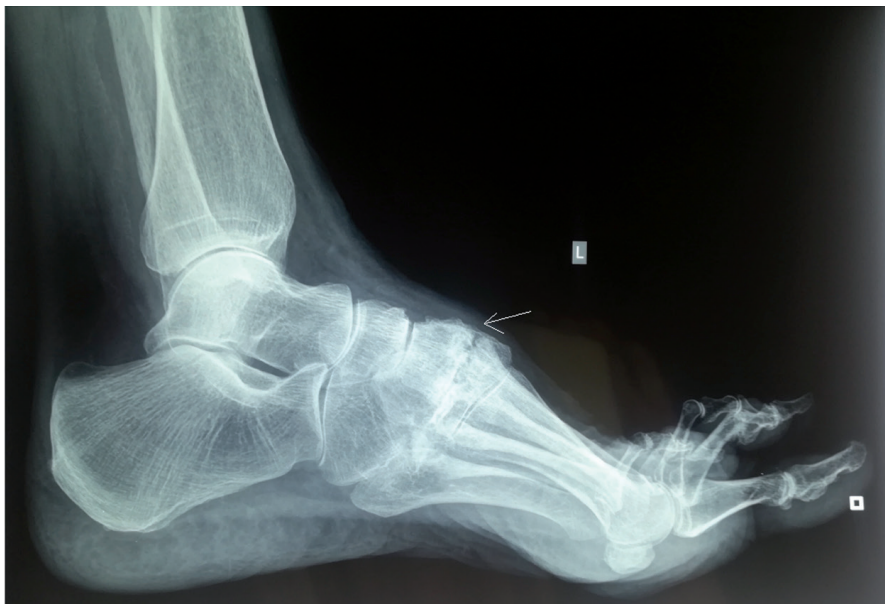


Fig. 2. X-rays: detail of left foot with enthesophyte on the dorsal surface of the midfoot, in the presence of irregularities and erosive aspects of bone cortical margin (see thin white arrow).
Written informed consent was obtained from the patient for the publication of this image.

Clinical and laboratory data

Clinical data of PsA patients including demographics, lifestyle, age of disease onset and diagnosis, joint symptoms, site of pain or discomfort, comorbidities, and ongoing therapies were collected. Two trained rheumatologists conducted double-blind assessment of each patient's medical history and a clinical examination. This choice was made in view of the fact that tenderness over an entheseal area can also be documented in conditions that mimick enthesitis, such as tendinitis or mechanical injury, overweight, exposing a suspected clinical diagnosis to false-positive conclusion (26). Clinical examination consisted of joint count (66/68 joints for swelling and tenderness) and of Bath Ankylosing Spondylitis Metrology Index (BASMI). The enthesis' evaluation was performed using the LEI (10) and the following parameters were considered: a) spontaneous pain; b) tenderness; c) swelling; d) skin redness. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI), the visual analog scale (VAS) for pain, the VAS for patient global health, and the Health Assessment Questionnaire (HAQ) were administered to all patients. Disease activity was measured by the Disease Activity in Psoriatic Arthritis (DAPSA) and Ankylosing Spondylitis disease activity score (ASDAS). Psoriasis Area Severity Index (PASI) was used to assess skin involvement. In addition to clinical data, C-reactive protein (CRP) [normal range 0–6 mg/L] and erythrocyte sedimentation rate (ESR) [normal range 0-15 mm/h] levels were measured, along with Human-Leukocyte Antigen (HLA)-A, B, and C (genotyping assay).

Statistical analysis

Frequency and percentage of each distinct abnormality of the midfoot were

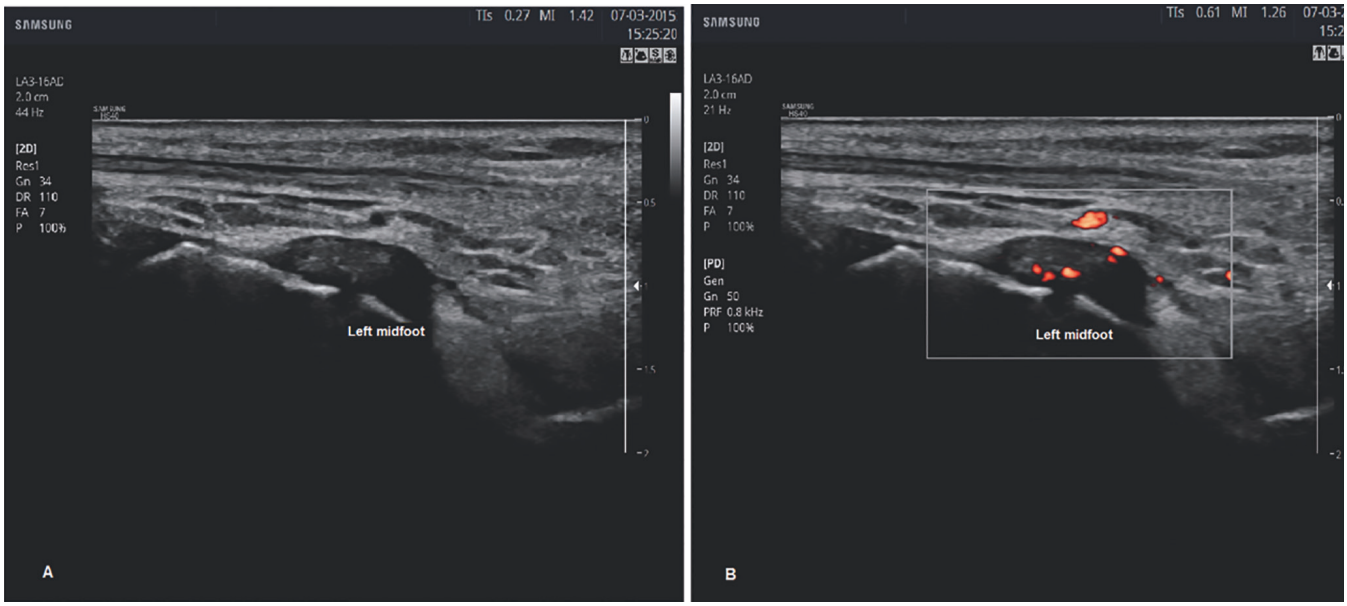


Fig. 3. Ultrasonography:
A: B-mode assessment: wedge-navicular joint of left midfoot with capsule distention, joint effusion and signs of synovial hypertrophy in longitudinal view;
B: PwD-mode assessment: wedge-navicular joint of left midfoot with positive PwD signal as sign of synovitis in longitudinal view. B-mode assessment: two-dimensional ultrasound image obtained in greyscale; PwD-mode assessment: two-dimensional ultrasound image obtained with Power-Doppler signal.
Written informed consent was obtained from the patient for the publication of this image.

Table I. Baseline characteristics and scintigraphic data in 32 PsA patients.

		Total PsA patients n=32	BS positive midfoot + n=21	BS negative midfoot - n=11	*p*-value
Demographics	Male, n (%)	17 (53.1%)	11 (52.4%)	6 (54.5%)	0.45
	Age, mean (±SD)	37.9 (±9.1)	35.9 (±8.2)	38.8 (±10.7)	0.33
Anamnestic Data	Age onset of PsA (yrs), mean (±SD)	25.4 (±6.8)	26.5 (±6.2)	24.3 (±6.7)	0.21
	Psoriasis, n (%)	26 (81.3%)	17 (80.9%)	9 (81.8%)	0.09
	Age onset of psoriasis (yrs), mean (±SD)	25.4 (±6.8)	26.5 (±6.2)	24.3 (±6.7)	0.17
	Onicopathy, n (%)	13 (40.6%)	9 (43%)	4 (36.3%)	0.08
	Familiar history for arthritis, n (%)	8 (25%)	5 (23.8%)	3 (27.3%)	0.27
	Familiar history for psoriasis, n (%)	12 (37.5%)	8 (38.1%)	4 (36.3%)	0.38
	Poli/oligo-articular pattern, n (%)	30 (93.8%)	20 (95.2%)	10 (90.9%)	0.17
	Mono-articular pattern, n (%)	2 (6.3%)	1 (4.8%)	1 (9.1%)	0.26
	Dactylitis, n (%)	6 (18.8%)	5 (23.8%)	1 (9.1%)	0.09
	Enthesitis, n (%)	23 (71.9%)	16 (76.2%)	7 (63.6%)	0.23
	Axial involvement, n (%)	16 (50%)	10 (47.6%)	6 (54.5%)	0.19
Clinical, functional and disease activity indices	TJ [0-68], mean (SD)	7.4 (±6.3)	8.9 (±7.1)	6.5 (±5.3)	0.15
	SJ [0-66], mean (SD)	2.7 (±1.2)	2.9 (±1.4)	2.5 (±1.6)	0.73
	LEI [0-6], mean (SD)	1.5 (±0.7)	1.6 (±1.2)	1.4 (±1.7)	0.95
	VASGh [0-10], mean (SD)	68.3 (±22.4)	65.3 (±24.2)	69.4 (±25.4)	0.81
	VASp [0-10], mean (SD)	69.7 (±21.4)	62.6 (±27.3)	60 (±25.8)	0.55
	HAQ [0-8], mean (SD)	1.6 (±0.9)	1.4 (±0.6)	1.4 (±0.8)	0.97
	DAPSA [0-164], mean (SD)	37.9 (±10.1)	38.5 (±10.5)	36.4 (±10.4)	0.72
	ASDAS-PCR [0-6], mean (SD)	3.6 (±1.9)	3.9 (±1.4)	3.2 (±1.7)	0.44
	ESR [0-25] (mm/h), mean (SD)	23.2 (±14.7)	25.4 (±12.6)	22.6 (±14.1)	0.37
	CRP [0-6] (mg/L), mean (SD)	6 (± 4.2)	5.6 (±4.1)	6.4 (±3.8)	0.28
Increased Uptake at baseline total BS	Midfeet, n (%)	21 (62.6%)	12 (57.1%)	0 (0%)	NA
	Right midfoot, n (%)	13 (40.6%)	13 (61.9%)	0 (0%)	NA
	Left midfoot, n (%)	20 (62.5%)	20 (95.2%)	0 (0%)	NA
	lateral epicondyle, n (%)	8 (25%)	6 (28.6%)	2 (18.2%)	0.11
	medial femoral condyle, n (%)	9 (28.1%)	6 (28.6%)	3 (27.3%)	0.45
	Achilles tendon, n (%)	4 (12%)	3 (14.3%)	1 (9%)	0.37
	Sterno-clavear joint, n (%)	14 (43.8%)	9 (42.9%)	5 (45.5%)	0.19
	Sacroiliac joints, n (%)	8 (25%)	4 (19.1%)	4 (36.3%)	0.09
	Peritrochanteric regions, n (%)	10 (%)	7 (33.3%)	3 (27.3%)	0.14
Score uptake at baseline BS midfoot	Normal uptake, n (%)	11 (34.4%)	11 (52.4%)	-	NA
	Mild uptake,n (%)	8 (25%)	8 (38.1%)	-	NA
	Moderate uptake, n (%)	8 (25%)	8 (38.1%)	-	NA
	Marked uptake, n (%)	5 (15.6%)	5 (23.8%)	-	NA

n: absolute frequency; %: percentage; SD: standard deviation; HLA: human leucocyte antigen; BS: bone scintigraphy; yrs: years; PsA: Psoriatic Arthritis; TJ: tender joints; SJ: swollen joints; LEI: Leeds Enthesitis Index; HAQ: Health Assessment Questionnaire; VASGh: Visual Analogue scale Global health; VASp: Visual Analogue Scale pain; DAPSA, Disease Activity Index for Psoriatic Arthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C Reactive Protein; ESR: erythrocyte sedimentation rate; CPR: C-reactive protein. p§Anova (Kruskal Wallis) non-parametric test was performed at t0: $p<0.05$; ns: not statistically significant; NA: not applicable.

analysed. The Mann Whitney and Anova (Kruskal Wallis) non-parametric tests were performed to compare the prevalence of clinical, laboratory and instrumental data in the PsA groups with positive or negative midfoot BS. Spearman test was performed to examine possible correlations between BS variables and clinical, x-rays and US data of the midfoot. The Cohen's Kappa test was used to assess the intra- and inter-observational reliability between 2 nuclear medicine physicians, 2 clinical rheumatologists, 2 sonographers with expertise in rheumatology and the 2 radiologists. Statistical tests were considered significant for $p<0.05$.

Results

Among 32 PsA patients, 53.1% were males, the mean age was 37.9±9.1 years [range 23–65], the mean age onset of PsA was 25.4±6.8 years. All PsA patients showed a peripheral involvement: poli/oligo-articular pattern in 30 (93.8%) subjects and mono-articular pattern in 2 (6.3%) subjects. The enthesitis was the second most frequent manifestation (71.9%), followed by axial involvement (50%) and dactylitis (18.8%) (Table I). At baseline, the midfoot was frequently involved in PsA with an increased BS uptake in 21 (65.6%) patients. Thirteen (40.6%) had increased uptake in the right midfoot and 20 (62.5%) in the left midfoot, respectively. Twelve patients (57%) had bilateral increased uptake in the midfoot and 9 (43%) patients in only one. There was no significant difference in the prevalence of other sites of increased uptake BS enthesitis between PsA patients with or without midfoot uptake (Table I). No differences in the prevalence of clinical, functional and/

Table II. Clinical, serological, functional data in 32 PsA patients observed 5 years after the baseline BS.

		Total PsA patients n=32	BS positive midfoot + n=21	BS negative midfoot - n=11	*p*-value
Genetic typing	HLA B-27 +, n (%)	2 (6.3%)	1 (5%)	1 (9%)	0.81
	HLA B-38 +, n (%)	4 (12.5%)	2 (10%)	2 (18%)	0.93
	HLA B-39 +, n (%)	1 (3.1%)	0 (0%)	1 (9%)	0.75
	HLA Cw6 +, n (%)	4 (12.5%)	3 (14%)	1 (9%)	0.08
	HLA Cw7 +, n (%)	2 (6.3%)	2 (10%)	0 (0%)	0.71
Clinimetric and functional indices	TJ [0-68], mean (SD)	4.4 (±8.1)	6 (±9.7)	1.5 (±1.3)	0.06
	SJ [0-66], mean (SD)	0.7 (±1.5)	0.9 (±1.7)	0.5 (±1)	0.14
	LEI [0-6], mean (SD)	0.5 (±0.9)	0.6 (±1)	0.4 (±0.7)	0.55
	BASMI [0-10], mean (SD)	0.9 (±1.6)	0.6 (±1.3)	1.5 (±1.9)	0.08
	BASDAI [0-10], mean (SD)	5.2 (±1.9)	5.3 (±1.8)	5 (±2.1)	0.12
	BASFI [0-10], mean (SD)	2.6 (±2.3)	2.7 (±2.5)	2.3 (±2)	0.31
	HAQ [0-8], mean (SD)	0.4 (±0.5)	0.4 (±0.4)	0.4 (±0.5)	0.77
	VASGh [0-10], mean (SD)	43.4 (±26.3)	45.7 (±25.8)	39.1 (±28.1)	0.09
	VASp [0-10], mean (SD)	39.1 (±28.6)	43.8 (±28)	30 (±28.6)	0.08
Disease activity and laboratory indices	DAPSA [0-164], mean (SD)	27.6 (±12.1)	28.8 (±11.5)	26.3 (±10.8)	0.11
	ASDAS-PCR [0-6], mean (SD)	2.2 (±0.9)	2.3 (±1)	2 (±0.7)	0.34
	PASI [0-72] mean (SD)	0.9 (±2.2)	1.1 (±2.7)	0.6 (±0.9)	0.08
	ESR [0-25] (mm/h), mean (SD)	18.2 (±12.9)	16.3 (±12.3)	21.9 (±13.6)	0.07
	CRP [0-6] (mg/L), mean (SD)	4 (± 5.1)	4.6 (±6.1)	2.9 (±1.8)	0.06

n: absolute frequency; %, percentage; SD: standard deviation; HLA: human leucocyte antigen; BS: bone scintigraphy; yrs: years¸ HLA: Human Leucocyte Antigen TJ: tender joints; SJ: swollen joints; LEI: Leeds Enthesitis Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HAQ: Health Assessment Questionnaire; VASGh: Visual Analogue scale Global health; VASp: Visual Analogue Scale pain; DAPSA, Disease Activity Index for Psoriatic Arthritis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C Reactive Protein; PASI: Psoriasis Area Severity Index; ESR: erythrocyte sedimentation rate; CPR: C-reactive protein; p§Anova (Kruskal Wallis) non-parametric test was performed at t0: $p<0.05$; ns: not statistically significant; NA: not applicable.

or laboratory data were found between the two PsA groups with or without increased BS uptake at the midfoot, respectively (Table II). X-rays performed at baseline resulted negative for bone irregularity or entheseal involvement at the midfoot. No patients were lost during the follow-up and there were no missing data at baseline or at 5 years. After 5 years, at least one typical sign of enthesopathy of the midfoot was detected by x-rays in 14/32 (43.8%) PsA patients and by US in 28/32 (87.5%) of PsA patients. We found a higher prevalence of structural lesions at x-ray [10/21 (47.6%) *vs*. 4/11 (36.4%); $p=0.004$] and at US [19/21 (90.5%) *vs*. 8/11 (72.7%); $p=0.04$] in subgroup with positive BS midfoot than those with negative BS. At least one inflammatory lesion was observed in 76.2% of patients with positive BS midfoot, while in 63.6% of those with negative BS.

The clinical, US and x-ray data collected for all 64 midfeet of PsA patients are outlined in Table III. A significantly higher prevalence of the following lesions was detected by US in the patients with positive BS midfoot compared with those with negative BS: synovial hypertrophy (31.3% *vs*. 17.2%), enthesophytes (39.1% *vs*. 20.3%), cortical bone irregularities (43.8% *vs*. 23.4%) (Table III). We also found that radiographic structural damage was more frequent in PsA patients with positive BS midfoot compared to those of negative BS: enthesophytes (20.3% *vs*. 10.9%); joint space narrowing (18.8% *vs*. 6.3%); erosions (15.6% *vs*. 0%). An increased prevalence of spontaneous pain and tenderness was observed in positive BS patients than those with negative BS (4.7% and 32.8% *vs*. 1.6% and 15.6%) (Table III). No significant differences in the prevalence of clinical, US and x-ray abnormalities between right or left side were observed.

Uptake of BS midfoot correlated with the tenderness at clinical evaluation ($r=0.25$; $p=0.040$). Interestingly, a correlation between x-rays and US was also described in relation to the presence of the following findings: erosive lesions ($r=0.44$; $p=0.0002$) and enthesophytes ($r=0.42$; $p=0.0005$). The tenderness correlated with the positive PwD sign at US ($r=0.261$; $p=0.037$), such as erosive lesions at US correlated with positive PwD sign ($r=0.261$; $p=0.008$). Among 64 midfeet, 38 (59.4%) had enthesophytes at US and 20 (31.3%) at x-ray.

The inter-observer reliability for all x-ray images between two radiologists was good ($\kappa=0.78$). The inter-observer reliability between two sonographer rheumatologists and between two clinical rheumatologists was good ($\kappa=0.81$ and $\kappa=0.79$, respectively). The inter-observer reliability between two nuclear medicine physicians was good ($\kappa=0.80$). Moreover, intra-observer reliability was good for all images on BS, on x-rays and on-US (respectively, $\kappa=0.82$ for BS, $\kappa=0.78$ for x-rays and $\kappa=0.80$ for US) and for clinical evaluation ($\kappa=0.77$).

Discussion

Enthesitis is an important clinical domain of PsA that may be detected early in disease progression and serve as an indicator of disease severity (27, 28). Nevertheless, there is currently no gold standard technique to detect enthesitis.

Table III. Clinical and imaging data of all 64 midfeet (in total PsA patients; in those with positive or negative BS for the midfoot; in right and left sites).

Midfeet =64		Total PsA patients	Baseline BS positive midfoot +	Baseline BS negative midfoot -	*p*-value	Right midfoot	Left midfoot	*p*-value
Clinical Exam	Spontaneous pain, n (%)	4 (6.3%)	3 (4.7%)	1 (1.6%)	<0.05	2 (3.1%)	2 (3.1%)	0.23
	Tenderness, n (%)	31 (48.4%)	21 (32.8%)	10 (15.6%)	<0.05	15 (23.4%)	16 (25%)	0.10
	Swelling, n (%)	2 (3.1%)	1 (1.6%)	1 (1.6%)	0.11	1 (1.6%)	1 (1.6%)	0.34
	Skin redness, n (%)	0 (0%)	0 (0%)	0 (0%)	0.73	0 (0%)	0 (0%)	0.46
US	Joint effusion, n (%)	6 (9.4%)	4 (6.3%)	2 (3.1%)	0.06	2 (3.1%)	4 (6.3%)	0.55
	Capsule distention, n(%	31 (48.4%)	18 (28.1%)	13 (20.3%)	0.08	17 (26.6%)	14 (21.9%)	0.19
	Synovial hypertrophy, n (%)	31 (48.4%)	20 (31.3%)	11 (17.2%)	<0.05	16 (25%)	15 (23.4%)	0.78
	Enthesophyte, n (%)	38 (59.4%)	25 (39.1%)	13 (20.3%)	<0.05	18 (28.1%)	20 (31.3%)	0.61
	Erosion, n (%)	19 (29.7%)	12 (18.8%)	7 (10.9%)	0.06	7 (10.9%)	12 (18.8%)	0.13
	Cortical bone irregularity, n (%)	43 (67.2%)	28 (43.8%)	15 (23.4%)	<0.05	21 (32.8%)	22 (34.4%)	0.26
	Positive PwD signal, n (%)	7 (10.9%)	5 (7.8%)	2 (3.1%)	0.07	3 (4.7%)	4 (6.3%)	0.58
X-rays	Enthesophyte, n (%)	20 (31.3%)	13 (20.3%)	7 (10.9%)	<0.05	10 (15.6%)	10 (15.6%)	0.84
	Joint space narrowing, n (%)	16 (25%)	12 (18.8%)	4 (6.3%)	<0.05	8 (12.5%)	8 (12.5%)	0.63
	Erosion, n (%)	10 (15.6%)	10 (15.6%)	0 (0%)	<0.05	5 (7.8%)	5 (7.8%)	0.72
	Cortical bone irregularity, n (%)	10 (15.6%)	8 (12.5%)	2 (3.1%)	0.06	5 (7.8%)	5 (7.8%)	0.81

n: absolute frequency; ns: non-statistical significance; US: ultrasonography; x-rays: radiography; SD: standard deviation; BS: bone scintigraphy; PwD: power Doppler; PsA: psoriatic arthritis. p§ Mann Whitney and Anova (Kruskal Wallis) non-parametric test was performed at t0: $p<0.05$; ns: not statistically significant.

Standardised imaging techniques and protocols are needed to better define enthesitis with validated scoring systems (12, 21, 29-33). Despite its usefulness in detecting several alterations – particularly in early stages of diseases – MRI presents many limitations, especially in the identification of peripheral enthesitis (34). In fact, the enthesitis visualisation is limited in absence of bone marrow oedema (31). However, in a study carried out in psoriatic patients, a high prevalence of subclinical enthesitis was detected by MRI and the foot emerged as the predominant site of involvement (93% of cases) (21). Moreover, MRI is less used than other techniques for costs, availability, and the time required to perform the procedure on each joint (31, 33). Conversely, US is widely used for economic reasons and accessibility; it allows real-time image acquisition and to collect structural data during clinical approach (26, 27). In fact, Naredo *et al*. conducted a study on patients with psoriasis and detected osteitis by US in 62.5% of cases and a positive PwD signal in 7.4% (35). Although BS is not a standardised practice in PsA, it was frequently used in the past before the advent of MRI and US. Hence, the reason why we opted to perform BS in 2010 was to define the diagnosis in the very early disease stages, for differential diagnosis because these patients presented only arthralgia at the begin of the study, and for prognostic value on the basis of the uptake. We observed that in patients with psoriasis and without joint symptoms, the isotope 99mTc-MDP is taken up by the periarticular zones which would suggest a link between psoriasis and osteitis (36). BS allowed to characterise PsA patients with early peripheral involvement owing to its ability to highlight subclinical enthesopathy. Our findings revealed that midfoot involvement was frequent and entheseal involvement may be detectable before the development of structural lesions (*i.e*. enthesophytes) by x-ray and US. Previous reports in the literature show that patients with psoriasis more frequently present imaging findings consistent with tendon dysfunction *versus* healthy controls and fibromyalgia patients (21, 35, 37, 38, 40-43). Entheseal involvement may also be assessed by BS, which is a useful and very sensitive exam, to discern PsA from other rheumatic or non-rheumatic diseases (29, 30, 38). In our study, we observed an increased uptake at the midfoot on BS of PsA patients (65.6%). Although midfoot is a poorly investigated site of involvement, our findings indicate that uptake at midfoot on BS may constitute an early indicator of entheseal lesion in PsA. During a 5-year follow-up, almost all PsA patients showed at least one typical sign of enthesopathy – detected by x-ray and/or US – as a manifestation of the disease. Erdem et al. conducted a study on 26 patients with PsA to assess foot involvement by MRI: they reported a high prevalence of midfoot lesions in 50% of patients, particularly para-articular enthesophytes (38%) (21). Furthermore, midfoot involvement might be a discriminating feature between PsA and RA (12, 18, 43, 44). In fact, Ezzidin *et al*. found that PsA patients showed an overall asymmetric joint involvement *versus* RA, and the intensity of uptake on BS was markedly higher in PsA patients *versus* RA (45). Therefore, BS represents a useful diagnostic tool for PsA with axial and/or peripheral involvement, as it scans the entire skeleton and is able to highlight areas of subclinical inflammation as x-rays are unable to detect early structural alterations (11, 13).

Our secondary outcome was to describe the clinical involvement and the inflammatory/structural lesions of the midfoot by x-rays and US in PsA patients with positive or negative midfoot BS at baseline. X-rays are not able to

detect inflammation in soft tissues, but only damage from chronic enthesitis (30, 31, 46). US is able to detect inflammatory lesions, expression of disease activity and inflammatory stage; thus, clinical examination has been coupled with x-rays and US to identify both inflammatory and structural lesions of the midfoot in the follow-up of our patients. We found a higher prevalence of structural lesions – detected by x-ray (absent at baseline) and by US – in PsA patients with positive midfoot BS vs. those with negative midfoot BS ($p<0.05$). Inflammatory lesions detected by US were also found more frequently in patients with positive BS midfoot. Upon evaluation of all 64 midfoot images, the most frequent structural abnormality observed both by x-ray and US was enthesophytes (31.3% and 59.4%, respectively), in line with previous reports in the literature (18, 21). Moreover, cortical bone irregularities were very frequent at US, but less frequent at x-ray, probably because x-rays detect only advanced structural damages. PwD was positive only in a small number of cases, as patients were treated with conventional therapy (DMARDs) and thus less likely to present active lesions.

The main limitation of our study is the relatively small sample size, given that BS is not a routine diagnostic imaging tool in patients with a suspicion of PsA. However, the thorough evaluation of US and x-ray findings by expert sonographers and radiologists represents a major strength.

In conclusion, BS may offer an effective complementary tool to identify patients with early peripheral involvement, particularly enthesitis. The subclinical entheseal involvement of the midfoot on BS may be considered an early predictive sign of future structural damage (*i.e.* enthesophyte of the midfoot), corroborated by x-ray and US.

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