

Ultrasound detects occult enthesal involvement in early psoriatic arthritis independently of clinical features and psoriasis severity

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Abstract

Objectives

Enthesal involvement is a frequent and distinctive feature of psoriatic arthritis (PsA), and is often under-diagnosed. The aim of the present study is to investigate using ultrasound (US), lower limb enthesal abnormalities in patients with early psoriatic arthritis (ePsA) and to evaluate their correlation with ePsA clinical characteristics.

Methods

Ninety-two ePsA patients (with duration of symptoms less than 1 year), diagnosed according to CASPAR criteria, were consecutively scored with Glasgow Ultrasound Enthesitis Scoring System (GUESS) and Power Doppler (PD) US (My Lab 70 Esaote) of lower limbs entheses (quadriceps, patellar, achilles tendons and plantar fascia). Patients were clinically examined by palpation of lower limbs entheses, Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) and total Psoriasis Area and Severity Index (PASI). Correlations were investigated between GUESS and PD with other ePsA clinical characteristics (duration of symptoms and morning stiffness, pain and fatigue visual analogue scale [VAS], Health Assessment Questionnaire SpA-modified [S-HAQ]).

Results

All patients had GUESS>1 and 40.2% showed positive PD signal on entheses, at a higher percentage than tenderness revealed by clinical examination (29.3%). GUESS and PD did not correlate with MASES, PASI and other clinical characteristics. No significant differences in GUESS and PD were detected between positive or negative findings of MASES and PASI.

Conclusions

US detects subclinical enthesal involvement in ePsA, independently of ePsA clinical examination and symptoms.

Key words

early psoriatic arthritis, entheses, ultrasound

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Introduction

Psoriatic arthritis (PsA) is a heterogeneous and complex disease characterised by different subsets with varying degree of severity.

Enthesal involvement is a frequent and distinctive feature of PsA, often under diagnosed, caused by the inflammation of tendon, fascia, ligament and joint capsule attachment to bone (1–3) and characterised by oedema, inflammatory infiltrate, microlesions of fibrocartilage, and vascular proliferation, enthesophytosis and bone erosions at bone insertion (1).

Ultrasonography (US) is a valid non-invasive tool (4–7), essential to evaluate entheses thickness, enthesophytes, bursitis and erosions (5) and to disclose vascularisation on tendons through Power Doppler (PD) assessment (5, 6). Furthermore, recent studies have shown that US is highly sensitive to detect subclinical “occult” enthesal abnormalities (7–12) and its use in clinical practice was largely promoted by the development of high frequency probes useful to assess structural and blood flow changes (10–12).

Although there is a growing body of evidence on the validity of US in early spondyloarthritis (SpA) (13) and recent studies have focused on ePsA clinical spectrum (14), studies on US of entheses in the early phase (within the first year of disease) of PsA (ePsA) are still lacking.

The aim of the present study was to evaluate US entheses abnormalities in ePsA and their correlation with clinical characteristics.

Patients and methods

One hundred and nineteen consecutive PsA patients diagnosed with CASPAR criteria (15), with onset of rheumatologic inflammatory symptoms lower than 1 year, with and without actual psoriasis, referred to the ePsA Clinic of the Division of Rheumatology of the University of Florence, Italy.

Exclusion criteria were as follows: age under 18 years, BMI higher than 30, isolated suspect enthesal symptom before onset of disease (>1 year), previous agonistic sport, history of severe trauma or surgery or corticosteroid injection at entheses scanned,

dismetabolic syndrome (increase of cholesterol, diabetes, hyperuricaemia), other diagnosis of rheumatologic disorders (fibromyalgia, connective disease, condrocalcinosis or gout), cancer, concomitant infection, previous treatment with retinoids.

Twenty-seven patients were excluded from the study: 4 because of an isolated enthesal symptom in previous years, 4 previously performing agonistic sports, 9 with dismetabolic syndrome (increase in cholesterol, diabetes, increase in uric acid levels), 1 for previous joint and entheses surgery, 1 with recent trauma, 11 with other previous diagnoses of rheumatologic disease (2 condrocalcinosis, 6 fibromyalgia, 3 connective disease), 4 with concomitant genital-urinary infections and 2 with a previous diagnosis of cancer (bowel and lymphoma). Finally, 92 (51 female and 41 male, 51 ± 15 years old, in 69/92 [75%] of cases with actual psoriasis) patients underwent clinical and US examination and were compared to 40 healthy controls (out of 60 subjects, 20 were excluded: 10 for dismetabolic syndrome and 10 for agonistic sport), with a number near to previous data published in analogous studies, conducted on psoriasis patients (9–10), matched for age, sex, BMI, without present or past psoriasis, or familiarity for psoriasis/SpA/inflammatory bowel disease (as shown in Table I).

Neither patients nor controls were treated with retinoids.

The local ethics committee approved the study and an informed consensus (according to the Declaration of Helsinki) was signed by patients and controls.

Clinical assessment

Lower limbs entheses (quadriceps, patellar, achilleon tendons and plantar fascia) and the other entheses comprised in Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) (16) were assessed with palpation to elicit tenderness by an expert rheumatologist (FBar).

All patients were classified for duration of rheumatologic symptoms (<3 months, ≥ 3 and <6 months, ≥ 6 and <12 months) and morning stiffness,

Competing interests: none declared.

pain and fatigue visual analogue scale (VAS, 0–100) and Health Assessment Questionnaire modified for SpA (S-HAQ) (17).

The extent and severity of psoriasis were measured with Psoriasis Area and Severity Index (PASI) (18) by an expert dermatologist (FP) with a score from 0 (no psoriasis) to 72 (very severe psoriasis).

The healthy controls did not refer inflammatory pain at entheses, joint and spine actually and in the past, answered negatively to S-HAQ and did not show pain at clinical examination (lower limbs entheses tenderness, MASES, 68/66 joint count, sacral sulcus tenderness, Bath Ankylosing Spondylitis Metrology Index, PASI).

US assessment

An experienced rheumatologist (FB), blind to rheumatologic clinical examination, examined all subjects using a My Lab 70 XVG US machine (Esaote Biomedical, Genoa, Italy, 6–18 MHz linear probe), according to Balint *et al.* (4), quadriceps and proximal patellar tendons insertion at the patella and patellar distal insertion at the tibial tuberosity (with patient in the supine position and knee flexed at 30°) and achilles and plantar fascia entheses at heel (with patient lying prone and feet hanging over the edge of the examination table at 90° of flexion). The exact position was confirmed using a goniometer.

Abnormalities were scored using the 0–36 Glasgow Ultrasound Enthesitis Scoring System (GUESS) (thickness, enthesophytes, bursitis, bony erosions) (4): thickness was measured at the point of the maximal thickness proximal to the bone insertion; enthesophytes and bone erosions were defined, as an ossification of entheses with irregularity of cortical bone insertion and as a cortical break with a step down defect of bone contour (visible in the longitudinal and transversal axis), respectively; bursitis was considered as a well circumscribed, localised anechoic or hypoechoic area at the site of an anatomical bursa, compressible by the transducer, with short axis >2 mm (4).

Entheses thickness was expressed in millimetres (mm) and was also scored

as pathologic (following Balint cut-off [4]): quadriceps ≥ 6.1 mm, proximal and distal patellar ≥ 4 mm, Achilles ≥ 5.29 mm and plantar fascia ≥ 4.4 .

PD was standardised with pulse repetition frequency of 750 Hz and gain of 53 dB and the temperature of the room was set to 20°C (5). Vascularity, studied at insertion of enthesis at the cortical bone, was scored as a binary item (positive if any signal was present and negative if absent) and was also semi-quantitatively graded (no flow (grade 0); only one spot detected (mild or grade 1); 2 spots (moderate or grade 2); >3 spots (severe or grade 3)), as was validated by D'Agostino (6). Finally, a total PD (tPD) was calculated by summing semiquantitative PD scores of each tendon (19).

Intra-reader reliability was established by recording the 10 entheses US of all patients and controls in a digital archiving computer system. The saved images were re-measured by the same rheumatologist who performed US examination (FB) 2 months after the initial scanning, blind to the previous results and the identity of the patients was mixed with that of the controls.

Statistical analysis

All values were given as mean (standard deviation (SD)) and percentage. A p -value <0.05 was deemed significant. US differences between patients and controls were calculated with Mann-Whitney test; US differences between different values of clinical characteristics (positive or negative findings of pain and fatigue VAS, MASES and PASI; duration of symptoms <3, <6, <12 months; PASI <10 and >10) were analysed with Mann-Whitney test and analysis gamma of frequency.

Correlation between US and all clinical parameters was assessed with Rho correlation coefficient of Spearman.

Intra-reader reliability for US was established with intraclass correlation coefficient (ICC) with interval confidence of 95%.

Results

Patient and control demographic characteristics and US assessment comparison to clinical examination of lower limbs entheses are reported in Table I.

Intra-reader (ICC 0.99, 0.98–1 for GUESS and 0.97, 0.90–1 for binary PD) reliability of US was significantly high.

US assessment

All patients had GUESS >1, with mean 7.1 ± 3.3 (range 1–14).

Thickness of tendons was higher in ePsA than in controls ($p < 0.001$) and was found in 87/92 (94.5%) of patients. Enthesophytes, bursitis and erosions were discovered in 76/92 (82.6%), 20/92 (21.7%) and 10/92 (10.8%), respectively and only enthesophytes were present in healthy controls – only 2/40 (5%).

Thickness was more frequent at the proximal patellar (69/92, 85.8%), enthesophytes at the Achilles (48/92, 52.1%), bursitis at the distal patellar (14/92, 15.2%), bone erosions at the quadriceps, achilles and plantar insertions (2/92, 2%) (Table I).

PD was positive in 37/92 patients (40.2%) and more common in the Achilles and quadriceps entheses (12/37; 32.4%), while no signal was found in controls (Table I). The semi-quantitative score was mild in 28/92 (30.4%), moderate in 9/92 (9.7%) and severe (Fig. 1) in 7/92 (7.6%), with a mean t-PDUS 2.4 ± 2.1 (range 0–6).

Clinical assessment

In ePsA patients, the frequency of tenderness of entheses was low (27/92 patients, 29.3%), if compared to US findings (Table I).

Only 8/37 (21.6%) PD positive ePsA patients had PD in the same entheses painful at clinical examination.

GUESS and PD were not different between ePsA patients with positive and negative findings of pain and fatigue VAS, morning stiffness, MASES, PASI (shown in Table II).

US scores did not correlate with duration of symptoms, pain and fatigue VAS, morning stiffness, MASES, S-HAQ, PASI. No significant difference were found between ePsA duration of symptoms <3, <6 and <12 months, with and without psoriasis and between PASI <10 and >10 (Table II).

Discussion

To the best of our knowledge, this is the first study that comprehensively evalu-

Table I. Percentage of clinical and US entheses abnormalities of tendons in ePsA patients (P) and healthy controls (C). Demographic characteristics of ePsA patients and healthy controls.

Percentage of tenderness, components of GUESS (thickness expressed in mm with mean \pm SD and range) and PD in ePsA patients (P) and healthy controls (C)											
Tenderness: 31.5% P vs. 0% C		Thickness: 94.5% P vs. 0% C ($p>0.001$)		Enthesophytes: 82.6% P vs. 5% C		Bursitis: 21.7% P vs. 0% C		Erosions: 10.8% P vs. 0% C		PD: 40.2% P vs. 0% C	
Right P	Left P	Right P vs. C	Left P vs. C	Right P vs. C	Left P vs. C	Right P vs. C	Left P vs. C	Right P vs. C	Left P vs. C	Right P vs. C	Left P vs. C
QUADRICEPS											
6.5%	4.3%	41.3% (6.2 \pm 1.2, 4.5–11.1 mm) vs. 0% (5 \pm 0.4, 4.2–5.8 mm,)	45.6% (6.2 \pm 1.2, 4–10.2 mm) vs. 0% (4.8 \pm 0.5 mm)	43.5% vs. 0%	43.5% vs. 0%	0% vs. 0%	0% vs. 0%	2% vs. 0%	1% vs. 0%	16.3% vs. 0%	4.3% vs. 0%
PROXIMAL PATELLAR											
3.2%	3.2%	85.8% (4.7 \pm 0.9 mm, 2.7–6.1 mm) vs. 0% (3.3 \pm 0.3, 3.1–3.9 mm)	69.5% (4.5 \pm 0.9, 3.8–8.2 mm) vs. 0% (3.4 \pm 0.4 mm)	2% 0%	2% 0%	0% 0%	0% 0%	0% 0%	0% 0%	4.3% 0%	4.3% 0%
DISTAL PATELLAR											
3.2%	2.1%	59.8% (4.5 \pm 1, 3–7.8 mm) vs. 0% (3.4 \pm 0.4 mm)	63% (4.6 \pm 0.9, 3–8 mm) vs. 0% (3.2 \pm 0.01 mm)	4.3% vs. 0%	6.5% vs. 0%	10.8% vs. 0%	15.2% vs. 0%	0% vs. 0%	0% vs. 0%	12% vs. 0%	6.5% vs. 0%
ACHILLES											
14.1%	19.5%	38% (5 \pm 1.1, 4–8.5 mm) vs. 0% (3.7 \pm 0.4 mm)	29.3% (4.9 \pm 1, 4–10.1 mm) vs. 0% (3.8 \pm 0.5 mm)	52.1% vs. 5%	55.4% vs. 0%	5.4% vs. 0%	7.6% vs. 0%	2% vs. 0%	1% vs. 0%	14.1% vs. 0%	18.5% vs. 0%
PLANTAR FASCIA											
3.2%	2.1%	14.1% (3.8 \pm 0.8, 3–6.4 mm) vs. 0% (2.9 \pm 0.7 mm)	15.2% (3.7 \pm 0.8, 2–7.1 mm) vs. 0% (2.9 \pm 0.5 mm)	3% vs. 0%	5.4% vs. 0%	0% vs. 0%	0% vs. 0%	2% vs. 0%	1% vs. 0%	0% vs. 0%	0% vs. 0%

ePsA and healthy controls matched demographic characteristics:

ePsA: 51.6 \pm 15.4 (years), 51 F: 41 M, BMI 22 \pm 2.6; CONTROLS: 49.6 \pm 11.1 (years), 22 F: 18 M, BMI 24 \pm 2

ated the lower limb entheses in ePsA and demonstrated that enthesal abnormalities are common and frequently subclinical in these patients.

In our study, the thickness of entheses was the most relevant finding in ePsA patients, probably secondary to the initial oedema of tendons described by McGonagle *et al.* in SpA (1), even if until now a direct comparison between US and histological data has never been performed in humans.

In the literature, the presence of thickness (7–11) enthesophytes, bursitis (9–10), erosions (10) and PD signal (11) had been previously demonstrated in psoriasis patients. Otherwise, in ePsA patients, we found PD signal in a more impressive percentage in comparison

to psoriasis patients data shown in the study of Naredo *et al.* (40.2% in ePsA versus 7.4% in psoriasis) (11). This result was confirmed by the previous definition of PD signal as the most distinctive feature of enthesitis in Spa (20) and was supported by the histological studies of McGonagle *et al.* that defined that the increase of vessels and cell infiltration were the main entheses abnormalities in early phases of Spa (21). Future other studies might compare psoriasis and ePsA patients to better understand if PD in psoriasis might be interpreted as a subclinical pathological feature of PsA and prospectively analysed to better understand if PD is predictive of ePsA.

The presence of thickness, erosions and

enthesophytes in early phase of disease were demonstrated in our study, in accordance to previous US evidences of McGonagle *et al.* that detected these abnormalities in fibrocartilage of Achilles tendon entheses in early Spa patients, with erosions in lower percentage than thickness and bony spurs (22).

Furthermore, we demonstrated that the most affected tendon was the patellar tendon as previously shown by other US evidences of Balint *et al.* who showed that thickness of distal patellar (39/69 (56.5%)) was the most frequent sign of enthesopathy in SpA subjects, followed by plantar fascia (4), confirmed also by other issues in psoriasis (9, 10) and inflammatory bowel disease (23) patients.

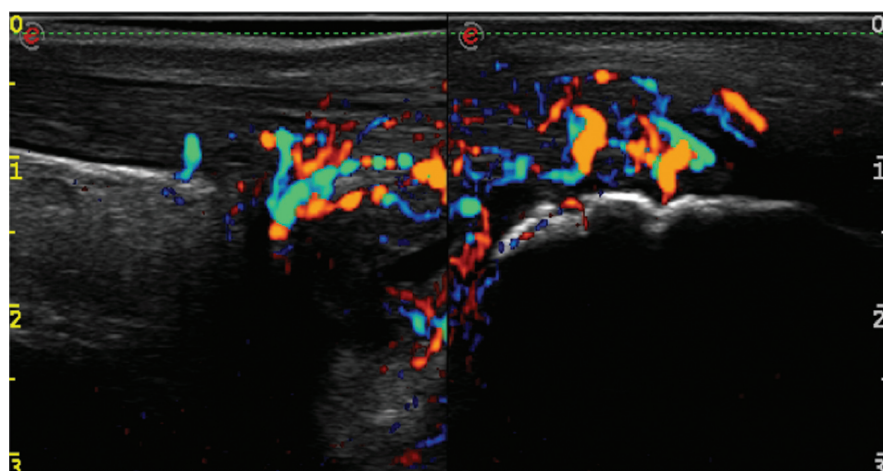


Fig. 1. Achilles tendon enthesitis in a PsA patient (within 3 weeks since onset of symptoms): US revealed thickness, marked enlargement of retroachillean bursae, bone erosions at heel and PD (bi-directional PD) signal.

Table II. Clinical parameters of ePsA patients (expressed in percentage, mean \pm SD and range).

	Mean	Standard deviation	Score >0 (percentage)	Minimum	Maximum
Duration of symptoms (months)	7.4	4	<3 months: 28.2% <6: 25% <12: 46.7%	1 (3 weeks)	12
Pain VAS (0–100)	62	31	90.2%	0	100
Fatigue VAS (0–100)	47	37	68.5%	0	100
Morning stiffness	34	39	77.2%	0	180 minutes
Pasi (0–72)	4.1	7.3	>0: 75% >10: 9.8%	0	53
Mases (0–13)	2	2.4	59.8%	0	10
S-HAQ (0–3)	0.5	0.6	84%	0	3

These data were only in disagreement with studies limited to clinical presentation of symptomatic enthesitis on a small number of SpA patients, which considered the Achilles to be the most frequent clinically affected tendon, followed by proximal and distal patellar (24).

Furthermore, the most relevant result of our study was to exhibit in ePsA patients, with US, thickness, bursitis, enthesophytes and erosions (enthesopathy) and vascularisation of entheses (enthesitis), as defined by McGonagle *et al.* (25), in asymptomatic sites.

While the under-diagnosis of enthesopathy in SpA patients was previously shown in other issues (4, 5, 26, 27), first of all Balint *et al.* had demonstrated that clinical assessment had a lower sensitive (22.6%) than US assessment

(57%) in SpA patients (4), the discrepancy between PD positive enthesitis and clinical evidence was the most surprising element and was in contrast with previous published data.

In fact, both Kiris *et al.* on SpA (19) and Delle Sedie *et al.* on PsA (26) patients (with longer duration of disease), demonstrated a correlation between PD signal and tenderness at clinical examination (19, 26)

Otherwise, we might hypothesize that the clinical assessment might be also falsely positive and influenced by other soft tissue diseases associated (*e.g.* oedema perimalleolar very frequent in PsA), more frequent in late disease.

This hypothesis is supported by the evidences of Delle Sedie *et al.* (26) and Spadaro *et al.* (28) that showed that apparently affected entheses at medical

visit might be negative at PD, with a high percentage of false positivity.

Probably a comparison between late and early stages and a more specific tenderness score for lower limbs entheses might clarify better this datum in the future.

Finally, we confirmed that enthesal involvement did not correlate with the presence of psoriasis and its severity, analogously to other studies that documented enthesal abnormalities in patients with psoriasis (9, 10), confirming that the two diseases might have a different natural course, even though associated.

Conclusions and take-home messages

- Our study showed in ePsA patients a high frequency of enthesopathy and enthesitis that, to date, was not deeply investigated in the early phase of disease.
- US discloses a high percentage of occult subclinical entheses abnormalities in ePsA patients, independent of rheumatologic symptoms and psoriasis, and demonstrated to be fundamental for a correct diagnosis at the beginning of the disease

Authors' contributions to this study

F. Bandinelli: conception of research project, patient selection, ultrasound images production, collecting data, statistical analysis, interpretation of data and writing manuscript; F. Prignano: patient selection and clinical assessment, revision of manuscript; D. Bonciani: clinical assessment and collecting data; F. Bartoli: clinical assessment and data collection; L. Collaku Ledio: ultrasound images reading, data collection; A. Candelieri: statistical analysis and interpretation of data; T. Lotti: revision of the manuscript; M. Matucci-Cerinic: conception of research project, patient selection, statistical analysis, interpretation of data and writing of the manuscript.

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