

Ultrasound assessment of enthesis thickness in psoriasis and psoriatic arthritis: A cross-sectional study

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Abstract

Background: The inflammatory involvement of the enthesis in the course of psoriasis is accompanied by structural abnormalities detectable by ultrasound. The most common of these abnormalities is the thickening of the tendon at the insertion site.

Aims: The aim of the present study was to compare the thickness of entheses of patients with psoriatic arthritis, only skin psoriasis, and healthy controls.

Methods: A cross-sectional study was conducted in a cohort of patients affected with either only skin psoriasis or psoriatic arthritis as well as in a control group. Eight entheses sites were scanned by ultrasound bilaterally. The following enthesal characteristics were collected and recorded in a predefined database: enthesal thickness, bone erosions, enthesis calcifications (enthesophytes), presence of blood flow, and presence of bursitis. All the detected enthesal changes were scored, and the data was statistically analyzed.

Results: The major differences in enthesis thickness between only skin psoriasis and psoriatic arthritis patients were found at the following sites: (i) olecranon tuberosity, (ii) superior pole of the patella, and (iii) medial epicondyle of femur. The thickness of the medial collateral ligament at the site of the femoral origin was increased in psoriatic arthritis, but not in both only skin psoriasis and healthy controls. The score obtained by adding the thickness of all the 8 examined entheses for each patient showed significant differences among the three groups (psoriatic arthritis: 81.3; only skin psoriasis 74.4; Controls: 67.6; $P < 0.0001$). Interestingly, we found that in psoriatic arthritis patients, the highest enthesis thickening was seen in entheses affected by bone erosions.

Limitations: The small sample of patients studied is a limiting factor in this study.

Conclusions: Our data demonstrated that the ultrasound measurement of the enthesis thickness enables a distinction between patients with psoriatic arthritis from those with only skin psoriasis. It is a useful method to improve diagnostic accuracy, especially in patients without clear clinical signs of enthesitis.

Key words: Enthesis, psoriasis, psoriatic arthritis, ultrasound

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Introduction

Enthesitis is an inflammation at the insertion of ligaments, tendons, or joint capsules to bone. It is a typical feature of spondyloarthritis (SpA), a family of inflammatory rheumatic diseases including psoriatic arthritis that share common clinical features as dactylitis, peripheral arthritis, and involvement of spine joints.^{1,2}

Enthesitis is the earliest event in the course of psoriatic arthritis and could be the only clinical manifestation of the disease.¹ Enthesitis has been hypothesized to be the result of an exaggerated innate immunity response that plays a pivotal role in directing the subsequent adaptive immune response.³ The clinical assessment of enthesitis is predominantly performed by eliciting tenderness at the entheses' sites. Specific clinical tools have been validated to assess enthesitis such as the Leeds Enthesitis Index (LEI) and the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).^{4,5}

However, an enthesal involvement is often misdiagnosed and undertreated in many psoriasis patients.⁶

Musculoskeletal ultrasound in combination with power Doppler is a valid and reliable technique for the diagnosis and follow-up of patients with psoriatic arthritis with enthesal involvement.⁷⁻⁹

In the past decades, different ultrasound enthesitis scores have been developed. The most used are: (i) Glasgow Ultrasound Enthesitis Scoring System (GUESS) which examines posterior and inferior pole of the calcaneus, superior and inferior pole of patella; and (ii) Madrid Sonographic Enthesis Index (MASEI) which assesses posterior and inferior pole of the calcaneus, superior and inferior pole of patella, tibial tuberosity and olecranon tuberosity.^{7,9,10}

Methodological complexity and inter-observer variability are the main factors that limit the use of the above cited scores in clinical practice. Furthermore there is no clarity on the meaning to be attributed to each elemental lesion, and which of these best discriminate between inflammatory and degenerative processes affecting the osteotendinous junction.^{7,9,11-13}

In our experience, the ultrasound measurement of the enthesal thickness represents the best tool for the assessment of enthesitis for several reasons: (i) the thickening may be considered an early sign of inflammation compared to the presence of hypervascularization, calcifications, and erosions; (ii) it is an operator-independent method; and (iii) finally it is reliable and easy to use.^{14,15}

Aim of the study

The aim of the present study was to compare the ultrasound measurement of the thickness of 8 enthesal sites between

Table 1: Characteristics of the study population

Variables	PsA (n=57)	PsO (n=45)	HC (n=50)	P
Age	48±9.2	46.3±13.4	43.9±12.1	0.31
Sex (female/male)	25/32	17/28	23/27	0.7
Height (cm)	173.7±8.7	172±8.5	173.2±8.1	0.61
Weight (kg)	80.4±20.2	74.3±15.6	76.3±18.6	<0.001
BMI	22.9±7.1	24.9±3.2	24.3±3.6	0.7
Age of onset of PsO	32.4±13.6	24.2±10.2	-	0.01
Age of onset of PsA	43.5±9.4	-	-	-
PASI	6.5±8.2	12.5±9.6	-	<0.001
DLQI	5.7±6.5	9.8±6.8	-	<0.001
VAS pain	20.3±6.5	-	-	-
Nails involvement (%)	33/50 (66)	24/50 (48)	-	<0.001
TJC	3.1±4.8	-	-	-
SJC	1.4±2.6	-	-	-
HAQ	0.5±0.7	-	-	-
Use of TNF-α blocker	40 (70)	8 (18)	-	<0.0001
Use of DMARDs	11 (19)	12 (27)	-	0.47
Use of NSAIDs	6 (10)	-	-	-

Data expressed as mean±SD. PsA: Psoriatic arthritis, PsO: Skin psoriasis alone, HC: Healthy controls, PASI: Psoriasis Area and Severity Index, DLQI: Dermatology Life Quality Index, VAS: Visual analog scale, TJC: 66/68 American College of Rheumatology tender joint count, SJC: 66/68 American College of Rheumatology swollen joint count, HAQ: Health Assessment Questionnaire, TNF: Tumor necrosis factor, DMARDs: Disease-modifying antirheumatic drugs, BMI: Body mass index, NSAIDs: Nonsteroidal anti-inflammatory drugs, SD: Standard deviation

patients with psoriatic arthritis, only skin psoriasis, and healthy controls, to verify if it is an effective and reliable tool for improving diagnostic accuracy, especially in patients without clear clinical signs of enthesitis. Our ultrasound assessment included the evaluation of two sites never considered so far: (i) the lateral epicondyle of the elbow and (ii) the medial epicondyle of femur.

Methods

This was a cross-sectional study conducted in a cohort of patients attending our outpatient dermatology clinic for psoriasis in Rome.

The study was approved by the local ethics committee and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Demographical, clinical, and treatment-related characteristics of the study population are shown in Table 1.

Forty-five consecutive patients with only skin psoriasis and 57 with psoriatic arthritis (without clinical signs of active enthesitis) were examined between December 2014 and December 2015. The diagnosis of inflammatory arthritis was made by the consultant rheumatologists (GD and CMS) based on detailed history and physical examination. Patients were classified as affected by psoriatic arthritis in agreement with CASPAR criteria.¹⁶ The diagnosis of skin psoriasis was confirmed by a trained dermatologist (BC).

All patients with psoriatic arthritis were under systemic therapy at the time of ultrasound examination – 40 with biologic DMARDs, 11 with conventional DMARDs, and 6 with NSAIDs.

Twenty of 45 only skin psoriasis patients were under systemic treatment, and the others were treated only with topical medications or UVB.

Patients with clinically active enthesitis (defined as tenderness and/or swelling at the site of an enthesis) were excluded to better explore subclinical enthesal involvement.

Fifty age and sex-matched individuals selected from the hospital staff served as healthy controls. All participants gave their signed informed consent before inclusion in the study.

All ultrasound examinations and entheses thickness measurements were performed by a rheumatologist, blinded to clinical diagnosis, (DG) using a MyLab70 (EsaoteSpA, Genoa, Italy) equipped with a 6–18 MHz broadband linear transducer.

The following 8 entheses sites were scanned bilaterally: lateral epicondyle, olecranon tuberosity, superior pole of the patella, inferior pole of the patella, tibial tuberosity, medial epicondyle of femur (origin of the medial collateral ligament), superior pole of the calcaneus, and inferior pole of the calcaneus. The sonographer examined morphological and structural abnormalities in B mode, as well as the vascularization with power doppler at bony insertions in both longitudinal and transverse planes; the scan images were stored.

The following enthesal characteristics were collected and recorded in a predefined database: enthesal thickness, bone erosions, enthesis calcifications (enthesophytes), presence of blood flow, and presence of bursitis.

Enthesal thickness was measured at the point of maximal thickness, 2 mm proximal to the bone insertion, and the sum of the thickness of the 8 entheses of each patient was calculated and stored (thickness total score).

The presence of enthesophytes was assessed using a semi-quantitative score from 1 to 3 for each enthesis according to previous studies and the total obtained for each patient yielded a calcification score.^{6,9}

Bone erosion was defined as an interruption of the cortical bone assessed in both longitudinal and transverse planes.

The normal ultrasound features and thickness of the entheses examined have been previously described.^{7,9,17,18}

Power Doppler settings were standardized with a Doppler frequency of 8 MHz and pulse repetition frequency of 0.5 kHz.

The sample was not sized for a powerful statistical analysis so, results should be interpreted cautiously. Continuous variables were described as median (range) or mean \pm SD according to the distribution. Comparisons among different groups were carried out using Kruskal Wallis analysis (KW), the Mann–Whitney *U*-test and Pearson's Chi-square as necessary. Pearson coefficient was used for correlations. In all statistical analyses, significance was defined as $P < 0.05$. Statistical analyses were performed using the GraphPad Prism 5.02 version (GraphPad software Inc, La Jolla, CA, USA).

Results

Differences in enthesis thickness across the groups

The respective differences in enthesis thickness have been summarized in Table 2.

- a. Elbow: Ultrasound examination of the lateral epicondyle showed a significant difference in the enthesis thickness bilaterally across the three groups (KW: $P < 0.0001$). In particular, we found the highest difference comparing the right lateral epicondyle of psoriatic arthritis patients with the healthy controls group [psoriatic arthritis: 5.2 mm (3.9–7.1); healthy controls: 4.1 mm (3.1–5.9); $P < 0.0001$]. A difference of approximately 0.7 mm at the lateral epicondyle bilaterally was found between only skin psoriasis group and healthy controls ($P = 0.003$). Only slight differences emerged comparing only skin psoriasis and psoriatic arthritis. The olecranon tuberosity enthesis thickness was bilaterally higher in psoriatic arthritis group compared to only skin psoriasis and healthy controls [psoriatic arthritis: 4.3 mm (3–5,8); only skin psoriasis: 3.8 mm (2.8–5.2); healthy controls: 3.5 mm (3–4.6)]. The following significances were found when comparisons among the different groups were performed: Psoriatic arthritis vs healthy controls $P < 0.0001$; psoriatic arthritis vs only skin psoriasis $P = 0.001$, only skin psoriasis vs healthy controls $P = 0.0085$
- b. Knee: At the four knee entheses examined, we found relevant differences across the three groups. The highest thickness difference was between the right superior pole of the patella of psoriatic arthritis patients and healthy controls [psoriatic arthritis: 7.8 mm (5.3–10.5); healthy controls: 5.4 mm (4.6–7.6); $P < 0.0001$]. psoriatic arthritis group differed from only skin psoriasis at approximately 1.3 mm bilaterally ($P < 0.0001$). At the medial epicondyle of femur, there was bilaterally a significant difference between psoriatic arthritis and healthy controls and between psoriatic arthritis and only skin psoriasis, respectively, but not between only skin psoriasis and healthy controls [significance: Psoriatic arthritis vs healthy controls, $P = 0.0003$; psoriatic arthritis vs only skin psoriasis, $P = 0.0022$; only skin psoriasis vs

Table 2: Enthesis thickness

Enthesis site	PsA (n=57)	PsO (n=45)	HC (n=50)	P value
Lateral epicondyle right (elbow)	5.2 (3.9-7.1)	4.85 (3.2-7.2)	4.1 (3.1-5.9)	PsA versus HC: <0.0001 PsO versus HC: 0.003 PsA versus PsO: 0.017
Lateral epicondyle left (elbow)	5.1 (3.9-6.9)	5 (3.3-6.2)	4.35 (3.3-5.7)	PsA versus HC: <0.0001 PsO versus HC: 0.0017 PsA versus PsO: 0.04
Olecranon tuberosity right	4.35 (3-5.8)	3.8 (2.8-5.2)	3.55 (3-4.6)	PsA versus HC: <0.0001 PsO versus HC: 0.0085 PsA versus PsO: 0.001
Olecranon tuberosity left	4.3 (3.1-7.1)	3.8 (2.9-4.9)	3.55 (2.9-4.7)	PsA versus HC: <0.0001 PsO versus HC: 0.0069 PsA versus PsO: <0.0001
Superior pole of the calcaneus right	4.6 (3.4-6.5)	4.35 (3.4-8)	4.65 (3.7-5.6)	PsA versus HC: 0.37 PsO versus HC: 0.94 PsA versus PsO: 0.18
Superior pole of the calcaneus left	4.8 (3.6-7.9)	4.65 (3.6-6.4)	4.55 (3.4-5.5)	PsA versus HC: 0.19 PsO versus HC: 0.063 PsA versus PsO: 0.2
Superior pole of the patella right	7.8 (5.3-10.5)	6.5 (4.1-9.5)	5.45 (4.6-7.6)	PsA versus HC: <0.0001 PsO versus HC: 0.0004 PsA versus PsO: <0.0001
Superior pole of the patella left	7.3 (4.5-10.6)	6.25 (4.8-8.3)	5.3 (4.8-7.2)	PsA versus HC: <0.0001 PsO versus HC: 0.002 PsA versus PsO: <0.0001
Inferior pole of the patella right	4.8 (3.1-7.5)	4.8 (3.4-6.2)	4.45 (2.7-5.6)	PsA versus HC: 0.013 PsO versus HC: 0.05 PsA versus PsO: 0.64
Inferior pole of the patella left	4.7 (3.6-6.4)	4.7 (3.7-6.6)	4.5 (3.1-5.5)	PsA versus HC: 0.05 PsO versus HC: 0.21 PsA versus PsO: 0.56
Tibial tuberosity right	5 (3.5-7.5)	5 (3.3-6.5)	4.4 (3.6-5.8)	PsA versus HC: 0.008 PsO versus HC: 0.0065 PsA versus PsO: 0.47
Tibial tuberosity left	4.9 (3.2-7.8)	4.8 (3.3-6.9)	4.2 (3.6-5.5)	PsA versus HC: 0.0045 PsO versus HC: 0.0038 PsA versus PsO: 0.93
Medial epicondyle of femur (medial collateral ligament) right	4.3 (3.2-6.8)	3.85 (3.3-5.3)	3.9 (3-4.7)	PsA versus HC: 0.0003 PsO versus HC: 0.59 PsA versus PsO: 0.0022
Medial epicondyle of femur (medial collateral ligament) left	4.2 (3-6.1)	3.9 (3.2-5.3)	3.75 (3.2-5.2)	PsA versus HC: <0.0001 PsO versus HC: 0.51 PsA versus PsO: 0.0015

Thickness is expressed as median (range) in mm; significance was defined as $P \leq 0.05$. PsA: Psoriatic arthritis, PsO: Skin psoriasis alone, HC: Healthy controls

Table 3: Enthesis chronic abnormalities

Types of entheses abnormalities	PsA (n=57)	PsO (n=45)	HC (n=50)	P
Calcification score	22.5 (12-36)	18 (11-29)	11.5 (2-19)	<0.0001
Bone erosion count	3 (0-12)	1 (0-5)	0	<0.0001

Data are expressed as median (range), significance was defined as $P \leq 0.05$. PsA: Psoriatic arthritis, PsO: Skin psoriasis alone, HC: Healthy controls

healthy controls, $P = 0.59$]. The thickness differences detected at the origin and insertion of the patellar ligament emerged mainly by comparing the tibial tuberosity insertion of psoriatic arthritis and healthy controls [psoriatic arthritis: 5 mm (3.5–7.5); healthy controls: 4.4 (3.6–5.8); $P = 0.008$]

c. Heel: the analysis of the measurements carried out at the superior pole of the calcaneus showed only slight statistically not significant differences among the three groups (KW: $P = 0.4$). At the inferior pole of the calcaneus, we found a slight but statistically significant difference among the three groups (KW: $P < 0.0001$), with the most relevant difference between patients with psoriatic arthritis and controls (0, 8 mm; $P < 0.0001$).

Thickness total score

The comparative analysis of the score obtained by summing the thickness of the 8 entheses for each patient showed statistically significant difference among the three groups with a median

of 81.3 mm (66.7–98.5) for psoriatic arthritis patients and respectively of 74.4 mm (63.6–87.6), and 67.6 mm (60.6–80.7) for only skin psoriasis group and controls (KW: $P < 0.0001$).

The thickness total score correlates with the number of erosions in psoriatic arthritis group but not in the only skin psoriasis patients and with the calcification score in psoriatic arthritis, only skin psoriasis and healthy controls [Erosions: Psoriatic arthritis Spearman $r = 0.44$, $P = 0.0006$; only skin psoriasis Spearman $r = 0.28$, $P = 0.07$ (n.s.); Calcification score: Psoriatic arthritis Spearman $r = 0.6$, $P < 0.0001$; only skin psoriasis Spearman $r = 0.36$, $P = 0.02$; healthy controls Spearman $r = 0.38$, $P = 0.01$].

Interestingly, the thickness total score correlates with the BMI of the only skin psoriasis patients and controls [only skin psoriasis Spearman $r = 0.42$, $P = 0.006$; healthy controls Spearman $r = 0.33$, $P = 0.02$] but not with the BMI of the psoriatic arthritis group [Spearman $r = 0.17$, $P = 0.18$ (n.s.)]

A slight correlation was found between the thickness total score and the age of patients with only skin psoriasis and psoriatic arthritis [psoriatic arthritis Spearman $r = 0.29$, $P = 0.03$; only skin psoriasis Spearman $r = 0.33$, $P = 0.03$]. No correlation was found between the thickness total score and the age of onset of only skin psoriasis and psoriatic arthritis.

Finally, the thickness total score strictly correlates with the MASEI index in the three groups [psoriatic arthritis Spearman $r = 0.63$, $P < 0.0001$; only skin psoriasis Spearman $r = 0.52$, $P = 0.0005$; healthy controls Spearman $r = 0.57$, $P < 0.0001$].

Enthesis chronic abnormalities

The comparative analysis of the calcification score across the three groups and the bone erosion count is summarized in Table 3.

A sub-analysis conducted on psoriatic arthritis patients with erosive changes of entheses revealed that of the 8



Figure 1a: Normal ultrasound aspect of the insertion of the triceps tendon on the olecranon tuberosity

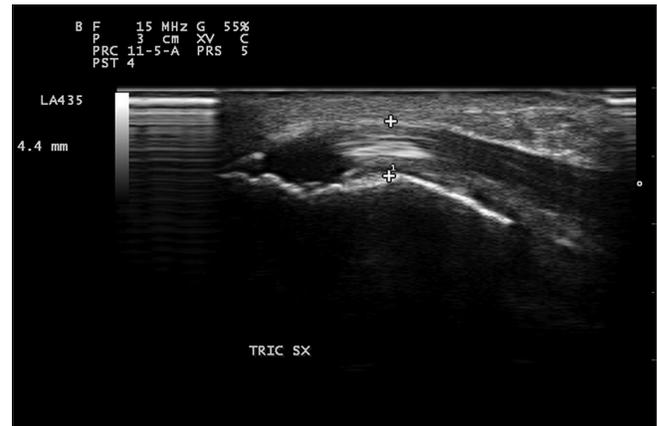


Figure 1b: Erosions, calcifications and thickening of the same site in an arthritis patient

Table 4: Thickness of entheses affected by bone erosion

Enthesis site	PsA (n=57)		
	Number of patients	Thickness of tendon at the insertion	Abnormal thickness cut-off values ^{4,6,12,14}
Lateral epicondyle right (elbow)	7	5.9±0.86	>4.6
Lateral epicondyle left (elbow)	7	5.3±0.7	
Olecranon tuberosity right	6	4.8±0.33	>4.3
Olecranon tuberosity left	6	4.8±0.96	
Superior pole of the calcaneus right	18	5.5±0.7	>5.2
Superior pole of the calcaneus left	17	5.4±1.1	
Superior pole of the patella right	18	7.9±1.23	>6.1
Superior pole of the patella left	19	8±1.1	
Inferior pole of the patella right	11	4.5±0.75	>4
Inferior pole of the patella left	9	5±0.9	
Tibial tuberosity right	15	5.4±1.1	>4
Tibial tuberosity left	9	5.6±1	
Medial epicondyle of femur (medial collateral ligament) right	25	4.6±0.92	>4.3
Medial epicondyle of femur (medial collateral ligament) left	21	4.5±0.7	

Data are expressed in mm as mean±SD. The thickness cut-off values are expressed in mm. PsA: Psoriatic arthritis, SD: Standard deviation



Figure 2a: Normal ultrasound aspect of medial collateral ligament at the insertion on medial epicondyle of femur

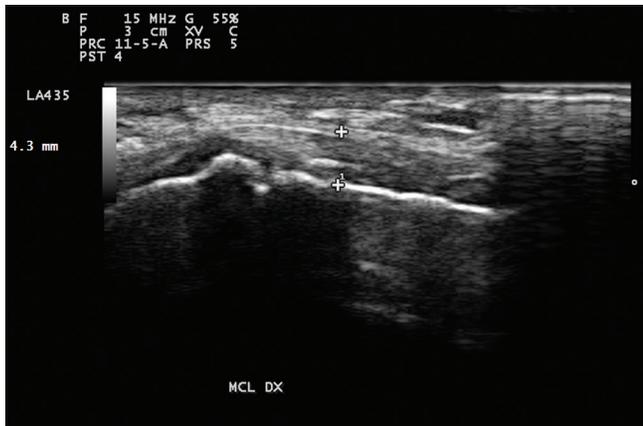


Figure 2b: Erosion, calcifications and thickening of the same site in an arthritis patient

entheses examined, erosive changes were observed mainly at the following sites: (i) medial epicondyle of femur, (ii) superior pole of the patella, and (iii) superior pole of the calcaneus.

It is important to note that the average thickness of the entheses affected by bone erosions increased compared to the normal values [Table 4].

Discussion

Ultrasound has a relevant role in the diagnosis and management of psoriatic arthritis mainly owing to its capacity to diagnose clinically undetectable arthritis and enthesitis. Moreover, previous reports have indicated the usefulness of ultrasound in detecting signs of enthesitis in only skin psoriasis patients without clinical signs of inflammatory arthritis.^{8-10,13}

The purpose of our study was to clarify whether ultrasound measurement of entheses thickness allows differentiation of patients with only skin psoriasis from psoriatic arthritis patients with asymptomatic enthesitis.

In our opinion, the thickness measurement represents the most reproducible method for assessing the inflammatory enthesitis. In fact, the power Doppler signal may not be detected even during the course of inflammation, especially in the very early stages of the disease. On the contrary,

findings such as calcifications or erosions are expression of chronic inflammation and irreversible damage.^{11,12,19}

Our analysis showed (for the first time), that the major differences in thickness between psoriasis cases with and without psoriatic arthritis were at the following entheses sites: (i) olecranon tuberosity and (ii) superior pole of the patella [Table 2]. Therefore, these two should be regarded as critical when scanning for enthesitis by ultrasound in psoriatic patients. Regarding the comparative analysis of the entheses thickness between only skin psoriasis and healthy controls, we found statistically significant differences at the lateral and medial entheses of the elbow at the level of the superior pole of the patella and at the tibial insertion of the patellar tendon.

Our data is consistent with the hypothesis suggested by recent studies that a subclinical involvement of tendons and entheses is present in these patients.^{10,14}

From a histopathological viewpoint, the tendon thickening detected by ultrasound may be explained by the disorganization of the normal fibrillar architecture, which is already present in the very early stages of the disease, as reported in recent studies.²

Another novel finding of the present study was the measurement of the thickness of the medial collateral ligament at the site of the femoral origin. Although the clinical relevance of the above-mentioned site is emphasized by the fact that it is included in the Leeds score, it has never been investigated by ultrasound in either only skin psoriasis or psoriatic arthritis. Our ultrasound data shows that the thickness of entheses at this site is increased in psoriatic arthritis, but not in only skin psoriasis and healthy controls [Table 2]. It may be noted that this site was the only one where there were no thickness differences between only skin psoriasis and healthy controls [Table 2]. The significance of this last finding is at present unknown.

The fact that the entheses thickness correlates with BMI and the age of the patients implies that there are many factors which could influence the entheses thickness; nevertheless, interestingly we found a strong correlation between the thickness total score and the number of erosions.

In particular, in psoriatic arthritis patients the highest entheses thickness was seen in areas where bone erosions were also present. These findings together with the data of a correlation between the entheses thickness and the degree of calcification may indicate that thickening is an alteration closely linked to damage of the entheses [Figure 1].

Once again, the medial epicondyle of femur was the commonest site of involvement in psoriatic arthritis because erosive changes were seen in 50% of the patients studied [Figure 2].

The most important limitation of our study was the small sample of patients studied. In addition, the results do not include a comparative analysis with data from patients with clinically evident signs of enthesitis. This reinforces the need of longitudinal studies aimed to validate our preliminary observations.

Our results clearly demonstrate the existence of significant differences in the entheses thickness between psoriatic arthritis and only skin psoriasis, even in sites never considered previously.

The present study confirms that the ultrasound measurement of entheses thickness is a reliable and accurate method to evaluate in clinical practice; the degree of entheses involvement in psoriasis patients especially in absence of clear signs of enthesitis detectable on clinical examination.

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Conflicts of interest
There are no conflicts of interest.

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