Entheseal involvement in a group of psoriatic arthritis patients: An ultrasonographic study

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Abstract. Psoriatic arthritis (PsA) is an inflammatory potentially destructive disease that requires early diagnosis and therapeutic approach. Its main pathogenic event and the condition's hallmark is considered to be enthesitis. Clinical examination of the enthesis can be a challenge in the clinical practice; thus, ultrasonography (US) has emerged as an indispensable imaging tool for evaluating both structural and inflammatory changes of this structure. In the present study, we aimed to analyze the type and frequency of entheseal involvement in PsA patients by US examination, performing a retrospective study on 41 patients diagnosed with PsA. Ultrasonographically confirmed enthesitis, identified according to Outcome Measures in Rheumatology group (OMERACT, initially Outcome Measures in Rheumatoid Arthritis Clinical Trials) definitions, was present in 26 of the included patients, Achilles enthesis being the most common site involved. The prevalence of tendon structure abnormalities and the presence of entesophytes underlines the importance of chronic inflammation on entheseal sites. US examination has proven to be a reliable imaging method, with significant and continuous improvement, which is clearly a requisite part for current understanding and diagnosis of enthesitis and more than this, for the patient follow-up algorithm.

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory rheumatic disease that occurs in ~30% of patients with psoriasis. Although the diagnosis of arthritis is usually established years after skin involvement, the joint involvement sometimes can precede it, with peripheral arthritis, as well as spine inflammatory changes (1-4). Enthesitis, inflammation of the origin and insertion of ligaments, tendons, aponeuroses, annulus fibrosis and joint capsules, has been suggested to be the underlying feature of PsA and it is reported to be present in 30-50% of the cases (5,6). In PsA, as stated by the Classification Criteria for Psoriatic Arthritis (CASPAR) as well as by the Group for Research and Assessment of Psoriasis and Psoriatic arthritis (GRAPPA) recommendations, enthesitis identification is useful for diagnosis and treatment (7,8).

Clinical examination of enthesis can be a challenge in clinical practice, as its presentation can vary from asymptomatic to inflammatory, mechanical or traumatic type of involvement. Thus, it is highly necessary to use imaging techniques, such as magnetic resonance imaging (MRI) or ultrasonography (US), in order to properly detect the type and nature of the changes. US has emerged as an indispensable tool for evaluating all types of rheumatic conditions, offering the advantage of being non-invasive, reproducible and easily to be used by an experienced examiner (9-12). In PsA patients, US seems to have a higher importance compared to MRI, as it is more accurate in describing the structure, new bone formation or vascularization and at a higher detail (13-15). Several scores have been proposed in order to evaluate the extent of entheseal

Table I. Madrid Sonographic Enthesis Index (MASEI).

Data	Value
Inferior pole of the calcaneus: Plantar aponeurosis enthesis	
Plantar aponeurosis structure	(0 or 1)
Plantar aponeurosis thickness >4.4 mm	(0 or 1)
Inferior pole of calcaneus erosion	(0 or 3)
Inferior pole of calcaneus enthesis calcification	(0, 1, 2 or 3)
Plantar aponeurosis enthesis power Doppler	(0 or 3)
Superior pole of the calcaneus: Achilles tendon enthesis	
Achilles tendon structure	(0 or 1)
Achilles tendon thickness >5.29 mm	(0 or 1)
Retrocalcaneal bursitis	(0 or 1)
Posterior pole of calcaneus erosion	(0 or 3)
Posterior pole of calcaneus enthesis calcification	(0, 1, 2 or 3)
Posterior pole of calcaneus power Doppler	(0 or 3)
Tibial tuberosity: Distal patellar ligament enthesis	
Patellar ligament structure	(0 or 1)
Patellar ligament thickness >4 mm	(0 or 1)
Infrapatellar bursitis	(0 or 1)
Tibial tuberosity erosion	(0 or 3)
Tibial tuberosity enthesis calcification	(0, 1, 2 or 3)
Tibial tuberosity enthesis power Doppler	(0 or 3)
Inferior pole of the patella: Proximal patellar ligament enthesis	
Patellar ligament structure	(0 or 1)
Patellar ligament thickness >4 mm	(0 or 1)
Inferior pole of patella erosion	(0 or 3)
Inferior pole of patella enthesis calcification	(0, 1, 2 or 3)
Inferior pole of patella enthesis power Doppler	(0 or 3)
Superior pole of the patella: Quadriceps tendon enthesis	
Quadriceps tendon structure	(0 or 1)
Quadriceps tendon thickness >6.1 mm	(0 or 1)
Superior pole of patella erosion	(0 or 3)
Superior pole of patella enthesis calcification	(0, 1, 2 or 3)
Superior pole of patella enthesis power Doppler	(0 or 3)
Oleocranon tuberosity: Triceps tendon enthesis	
Triceps tendon structure	(0 or 1)
Triceps tendon thickness >6.1 mm	(0 or 1)
Oleocranon erosion	(0 or 3)
Oleocranon enthesis calcification	(0, 1, 2 or 3)
Oleocranon enthesis power Doppler	(0 or 3)

abnormalities, among which is the MAdrid Sonographic Enthesitis Index (MASEI), which has proven to be a reliable tool in detecting signs of both subclinical and constituted disease (13,16).

The present study aimed to analyze the type and frequency of entheseal involvement in PsA patients, by US examination, using MASEI and OMERACT definitions, as well as a search for correlations between the presence of enthesitis and a series of disease variables. The aim of our study was to provide a possible pattern of involvement for enthesis in PsA patients, in order to optimize the management of these patients.

Patients and methods

We performed a retrospective study on 41 patients diagnosed with PsA based on CASPAR criteria (7), in a one-year interval between 2018 and 2019, admitted into the Rheumatology Department of the Emergency County Hospital Craiova, Romania. We collected data that included demographic, clinical, laboratory parameters and imagistic methods, in accordance to the study protocol.

The study was performed in accordance with the ethics and deontology principles of the Helsinki Human Right's

Declaration and was approved by the Emergency County Hospital Craiova Ethics Committee (under the number of 28690/2019). Written informed consent was obtained from each patient.

US. The examination was performed by an expert sonographer (FAV), blinded to the history, clinical findings, and biology of each patient, using an Esaote MyLab 25 machine, equipped with a high frequency linear probe (10-18 MHz). Enthesitis was evaluated and defined according to OMERACT (Outcome Measures in Rheumatology) definitions (17). The MASEI items were evaluated according to the description (16) (Table I).

Statistical analysis. Statistical analysis was performed using GraphPad Prism 5.5 (GraphPad Software, Inc.). Results are presented as mean ± SD and data were analyzed using t-test and one-way ANOVA for comparing groups, and Pearson/Spearman's coefficient for evaluating correlations. We considered a level of $P<0.05$ statistically significant.

Results

We included 41 consecutive patients, 27 women and 14 men, with a mean age of 53.44±0.91 years and a mean disease duration of 6.63±4.26 years, ranging from 0.5 to 12 years. We registered a mean body mass index (BMI) of 27.44±6.35 [11 (26.82%) patients were overweight and 13 (31.70%) obese]. The general characteristics of the study group are presented in Table II.

In regard to inflammatory markers, we found a mean value of 11.66±26.6 mg/dl for C reactive protein (CRP) and 33.27±25.59 for erythrocyte sedimentation rate (ESR).

Synthetic disease-modifying anti-rheumatic drugs (DMARDs) were a therapeutic option for all the patients and biologic DMARD for 39.02% (16 patients).

In regards to scoring the disease activity, we found a mean disease activity in the Disease Activity Index for Psoriatic Arthritis (DAPSA) score of 11.80±4.91, with limits between 2 and 25.8. For the Psoriasis Area Severity Index (PASI), we registered values between 0 and 28, with a mean of 15.32±7.12.

Enthesitis, according to OMERACT definitions, was present in 26 of the included patients (63.41%). We identified Achilles enthesis (AT) as the most common site [19 (46.34%)], followed by distal patellar tendon (DP) [11 (26.82%)], quadriceps tendon (QT) [11 (26.82%)], proximal patellar tendon (PP) [9 (21.94%)] and plantar aponeurosis (PA) [9 (21.94%)] (Table III, Figs. 1-3). Given the fact that all patients received DMARD therapy, synthetic with/without biologic, the US evaluation of our study group did not show a high percentage of active Power Doppler (PD) enthesitis in the evaluated sites, except AT (24.32%) (Table III, Fig. 2).

We carried out further statistical analysis on the possible correlations between the presence of enthesitis and certain variables. We found a moderately positive correlation between the presence of enthesitis and inflammatory markers (r=0.42, P=0.005 for CRP and r=0.36, P=0.020 for ESR). Another significant correlation was established between US enthesitis, patient age (r=0.37, P=0.05) and PASI score (r=0.43, P=0.004).

Table II. General characteristics of the study group (N=41).

Patients (N)	Data values
Female, n (%)	27 (65.86)
Male, n (%)	14 (34.14)
Mean age (years)	54.34±0.91
Disease duration (years)	6.63±4.26
Type of psoriasis, n (%)	
Nail	24 (58.53)
Skin	35 (85.36)
Nail and skin	24 (58.53)
Sine psoriasis	5 (12.19)
Type of psoriatic arthritis, n (%)	
Peripheral	32 (78.04)
Axial and peripheral	9 (21.95)
CRP (mg/dl)	11.66±26.60
ESR (mm/h)	32.27±25.59
DAPSA	11.80±4.91
PASI	15.32±7.12
BMI (kg/m^2)	27.44±6.35
Uric acid (mg/dl)	4.77±1.48
Current medication, n (%)	
DMARD non-biologic	41 (100)
DMARD biologic	16 (39.02%)
MASEI score (mean ± SD)	13.2±5.8

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAPSAl, Disease Activity Index for Psoriatic Arthritis; PASI, Psoriasis Area Severity Index; BMI, body mass index; DMARD, disease-modifying anti-rheumatic drug; MASEI, Madrid Sonography Enthesitis Index.

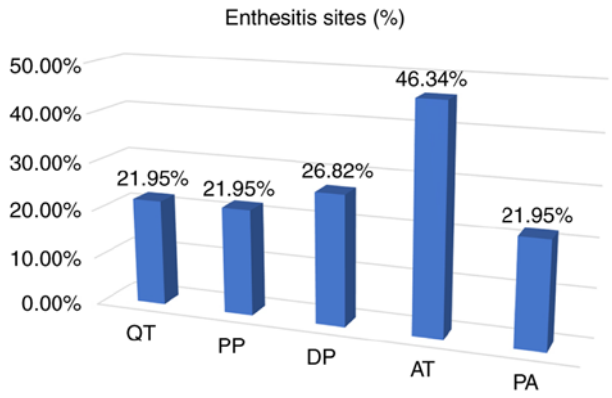

Figure 1. Enthesitis site distribution in the PsA study group. PsA, psoriatic arthritis; QT, quadriceps tendon; PP, proximal patellar tendon; DP, distal patellar tendon; AT, Achilles tendon; PA, plantar aponeurosis.

Of the 18 patients with a moderate/severe PASI score, 13 had entheseal involvement at US evaluation.

When we analyzed our data for the effect of body mass index (BMI) on entheseal damage, although the value of Pearson correlation coefficient was 0.35, we noted that US examination found a high percentage of enthesitis in overweight and obese

Table III. Ultrasonography (US) changes according to MASEI.

	Abnormal tendon structure n (%)	Thickened tendon n (%)	Erosion n (%)	Enthesis calcification/ enthesophyte n (%)	Enthesis PD n (%)	Bursitis n (%)
TT	2 (4.87)	1 2.43	0	4 (9.75)	0	0
QT	8 (19.51)	3 (7.31)	1 (2.43)	7 (17.07)	3 (7.31)	0
PP	5 (12.19)	4 (9.75)	1 (2.43)	3 (7.31)	1 (2.43)	0
DP	6 (14.63)	5 (12.19)	0	2 (4.87)	2 (4.87)	0
AT	12 (29.26)	7 (17.07)	6 (14.63)	7 (17.07)	10 (24.39)	2 (4.87)
PA	6 (14.63)	3 (7.31)	2.43	9.75	0	0

MASEI, Madrid Sonography Enthesitis Index; TT, tibial tuberosity; QT, quadriceps tendon; PP, proximal patellar tendon; DP, distal patellar tendon; AT, Achilles tendon; PA, plantar aponeurosis. Enthesitis PD was defined as the presence of Power Doppler signal, within the enthesis, at less than 2 mm from the bone cortical. Bursitis was defined as the presence of a hypoechoic/anechoic area at the level of a specific bursa.

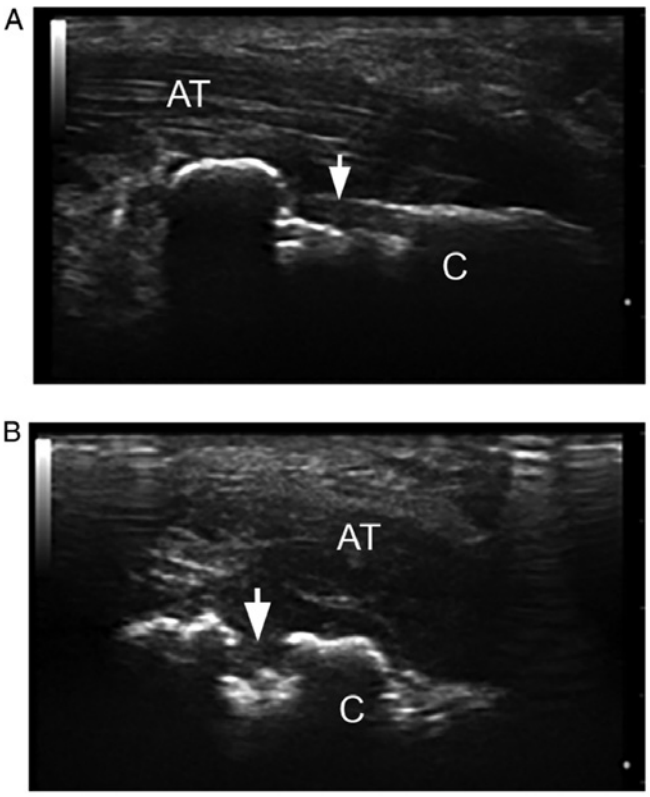

Figure 2. Grey scale US of Achilles tendon. (A) Longitudinal and (B) transverse scan: Hypoechoic Achilles tendon (AT), with loss of the fibrillar pattern, mostly near to the cortical calcaneus (C in the images) bone (<2 mm), findings suggestive for enthesitis. Moreover, we observed erosion (arrow), like step-down changes, identified in two perpendicular views. US, ultrasonography; AT, Achilles tendon; C, calcaneus (Esaote, MyLab25 18 MHz).

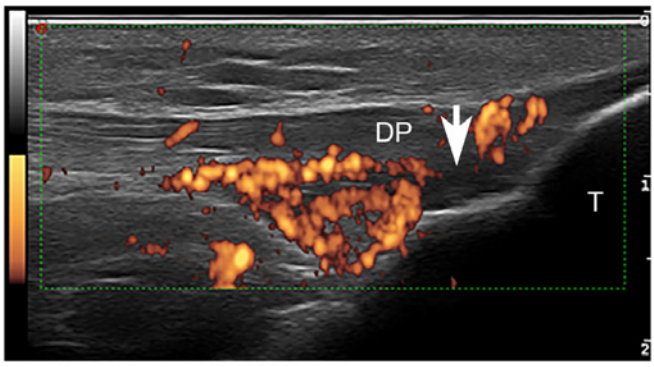

Figure 3. Power Doppler US image of the patellar tendon's distal enthesis, revealing a hypoechoic tendon, with lack of a homogenous fibrillar pattern (arrow), mostly near to the cortical bone (<2 mm), with intense power Doppler signal. US, ultrasonography; T, tibial tuberosity; DP, distal patellar tendon (Esaote, MyLab25 18 MHz).

patients (16 of 22, compared to 10 of the 19 patients with a normal BMI).

Discussion

PsA is a disease that requires early diagnosis and therapeutic approach in order to prevent future tendon and articular damage and its consequent functional impairment. Entheseal involvement is a hallmark of the disease, more commonly found in PsA patients compared to other inflammatory or non-inflammatory conditions, directly related to both peripheral and axial structural damage (1). Clinical examination can be challenging in identifying enthesitis, both for asymptomatic patients as for those presenting signs and symptoms similar to other conditions and often requires additional imaging techniques (18).

US is a well-established validated method for detecting enthesitis (19), both subclinical and clinical manifestations, in patients with PsA and psoriasis, providing an accurate information on both structural and inflammatory changes. Moreover, it has been reported to be a real-time, reproducible, and cost-effective technique. Several previous studies, which have focused on enthesis evaluation in PsA patients, have proven that this condition is particularly known to be an entheseal disease, with significant impact on disease activity and quality of life. In order to obtain a proper indicator of disease activity and treatment response, patient evaluation should mandatorily include US entheseal assessment (7,15-18).

The involvement of US entheseal in PsA patients, as aimed by our research, revealed it to be present in a high percentage of patients. The data found in our study (63.41%) is similar to data reported by Gutierrez *et al*, in a study conducted on

45 patients (20). Other publications have also demonstrated similar data (1,21-24).

The prevalence of tendon structure abnormalities and enthesophytes as reported by significant scientific reports is similar to our results, underlying the importance of chronic inflammation on entheseal sites (1,21).

The most common site of inflammation found in our patients was represented by Achilles enthesis. Michelsen *et al* assessed 141 patients and revealed percentages of over 50 for structural damage and 16.3 for inflammatory activity, when examining AT, similar to our results (25). The observation made by the aforementioned study, that AT insertion is the site of major entheseal abnormalities, was also confirmed by Perrotta *et al* (26). A recent multi-center study, that enrolled a total number of 1,130 PsA patients, reported that 22.2% presented with active enthesitis (27).

The observation that the PASI score was correlated with enthesitis is in full agreement with the report of Moshrif *et al* (21), as well as with other studies (28,29).

Analyzing the associations between different variables and the presence of enthesitis, we observed a moderately positive correlation with body mass index (BMI). Although the calculated Pearson correlation coefficient was 0.35, overweight and obese patients presented a higher prevalence of entheseal abnormalities. BMI, a variable with significant role in entheseal findings, is generally higher in PsA patients, compared to healthy subjects. The mean BMI calculated for our group was 27.44±6.35. US scores, such as MASEI, and more specifically AT abnormalities and entesophytes presence, were demonstrated to be positively correlated to an increased BMI (1,30-33). In our study group, we also obtained a moderately positive inter-relationship between the two variables. Nevertheless, BMI is also a factor of biomechanical stress, which can input certain abnormalities of this structure.

The lack of Doppler activity in our patients may have been related as already mentioned to the fact that most patients were already receiving disease-modifying anti-rheumatic drug (DMARD) treatment, but, at the same time, we realized the fact that the machine's sensitivity on vascularization might have influenced the results. Other limitations of the study include the small number of patients and the fact that we had only one US examiner and no other imaging technique was used to confirm the findings.

In conclusion, enthesitis, the defining feature of PsA and an important part of the disease pathogenesis, predicts patient outcome, future structural changes and noticeably impacts the quality of life of these patients. US examination has proven to be a reliable imaging method, with significant and continuous improvement, which is clearly a requisite part of the current understanding and diagnosis of enthesitis and patient follow-up algorithm.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

BAC, ALB, RMD and FAV conceived and designed the current study. BAC, ALB, CDP, SCF and SCD provided administrative support. BAC, ALB, CDP, SCF, RMD, SBC, MVB, SCD, HVP, RAI, ATS, AMV and FAV searched the literature for pertinent data and findings. BAC, CDP, SCF, RMD, SBC, SCD, AMV and FAV collected and collated the data. BAC, CDP, SCF, RMD, SBC, PLC, SCD, MVB, HVP, RAI, ATS and FAV analyzed and interpreted the data. All authors wrote the manuscript and all authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Emergency County Hospital Craiova Ethics Committee (under the number of 28690/2019). Written informed consent was obtained from each patient.

Patient consent for publication

The patients consented to the publication of their data and images in the present study.

Competing interests

The authors declare that they have no competing interests.

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