Enthesitis in psoriatic arthritis – is the clinical evaluation enough?

Daniela-Raluca Decianu¹, Claudiu C. Popescu^{2,4}, Violeta-Claudia Bojinca^{1,4}, Mihai Bojinca^{3,4},
Andra-Rodica Balanescu^{1,4}, Ruxandra Ionescu^{1,4}

¹“Sf. Maria” Clinical Hospital, Bucharest, Romania

²“Dr. I. Stoia” Rheumatic Disease Center, Bucharest, Romania

³“Dr. I. Cantacuzino” Clinical Hospital, Bucharest, Romania

⁴“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Objective. In this study, we aim to evaluate the frequency of enthesitis in psoriatic arthritis (PsA), using musculoskeletal ultrasonography (MSUS) and to determine to what extent it is correlated to clinical spontaneous or provoked pain, disease activity and biologic inflammatory markers.

Methods. 320 entheses, belonging to 20 PsA patients, were evaluated clinically and MSUS. For each patient, the medical history form included questions regarding spontaneous pain, targeted to 16 enthesal sites. Then, a thorough entheses clinical exam was performed, evaluating pain upon pressure (digital pressure on the entheses overlying skin). Two Esaote My Lab machines were used, with 6-12/8-18 MHz linear probes. All evaluations were performed by the same clinician/ultrasonographer.

Results. The Achilles, followed by the quadriceps tendons were the most affected by MSUS-detected enthesitis, both in gray scale (GS) (100%, 75% respectively) and power Doppler (PD) (40%, 35% respectively), while the proximal patellar tendon (35% GS, 25% PD), the plantar fascia (40% GS, 25% PD) and the flexor tendons (45% GS, 25% PD) were the least affected.

Ultrasound abnormalities were found in up to 68.4% of the asymptomatic entheses, with high variation between the enthesal sites. The number of ultrasound-detected enthesitis for each patient was significantly correlated with the patient's global assessment for DAPSA and also with the CRP levels, in this lot of patients with high disease activity.

Conclusions. In PsA, the entheses involvement is a central feature, underscored in this study by the high percentages of both GS and PD abnormalities, even in the least affected enthesal sites.

There is a low correlation between clinical symptoms and imaging signs of enthesitis in PsA, which proves the need for an imagistic enthesitis score in the diagnostic process, in order to establish the full extent of the disease and a more personalised therapeutic plan.

Keywords: psoriatic arthritis, enthesitis, musculoskeletal ultrasonography

INTRODUCTION

Spondyloarthritis (SpA) forms a heterogeneous group of diseases with different phenotypes, but with several common features, such as the axial and peripheral joint clinical inflammation, genetic predispositions and trigger factors. The common ground in the pathogenesis of SpA seems to be enthesitis, which further leads to osteitis, periostitis and osteoproliferation, present in variate proportions in all SpA [1,2].

The high level of interest on the entheses in rheumatology is proven by the amount of knowledge

achieved on the subject in the last two decades, with the terminology evolving from entheses to enthesal organ and synovio-enthesal complex [3].

The entheses are fibrocartilaginous structures arising at the insertion sites of tendons, ligaments, joint capsules or nails. The insertional fibrocartilages is generally prone to microdamage, but avascular and lacking immune cells [3, 4]. Psoriatic arthritis (PsA) patients, with a particularly lower threshold to mechanical stress and a general pro-inflammatory state, easily develop a disproportional degree of inflammation after physiological mechanical stress, with a vessel tissue repair

Corresponding author:

Claudiu C. Popescu

E-mail: claudiu.popescu@reumatologiedrstoia.ro

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responses and vessel ingrowth activation of pro-inflammatory cytokines tumor necrosis factor (TNF) α and interleukin (IL) 17, accompanied by an inflow of innate immune cells [3-5].

In terms of immune pathways, IL-23, with IL-17 and TNF-mediated immune responses have a leading role in triggering enthesitis, while the proliferation process is mainly mediated by IL-22. Exogenous or gut bacteria could also play the role of a trigger factor and unleash an immune reaction, with autoimmunity aiming for fibrocartilage peptides, such as the versican or the bone morphogenetic protein (BMP), in particular in patients with a genetic predisposition, given by the presence of the HLA-B27 antigen. Also, triggered by TNF- α and IL-1, BMP-7 mostly, accompanied by BMP-2 and BMP-6 are involved in the new bone formation that follows the enthesal inflammation, leading to peripheral and axial bony spurs, enthesophytes and syndesmophytes. Therefore, enthesitis seems to be more a diffuse, continuous process in SpA and in PsA in particular, as proven by advanced imaging techniques and biopsy results, although initially assumed to be a focal lesion [6-11].

Despite being a central feature in SpA and despite the number of scores elaborated in order to standardize it, enthesitis remains underdiagnosed in the clinical everyday practice.

Convenient and comfortable, little time and cost consuming, with on spot results, ultrasound becomes a very handy bedside tool for detecting and monitoring enthesitis, while a physical evaluation alone has lower sensibility and specificity for SpA. It provides high fidelity image of the enthesal structure and also detailed information regarding the vascularity, transposing into the degree of local inflammation and therefore, disease activity [11-15].

In this context, the objective of this study is to evaluate the frequency of clinical and ultrasound enthesitis in Romanian PsA patients, with highly active disease. Also, we aim to determine to what extent the presence of MSUS GS and PD enthesal abnormalities is correlated to the disease activity, biologic inflammatory markers and to clinical pain, declared during a detailed, targeted medical history or detected in a thorough clinical exam.

METHODS

Design and patients

The study included 20 patients fulfilling the CASPAR criteria [16], in the random order of pre-

sentation to the Out-patient Clinic or the Department of Internal Medicine and Rheumatology of the “Sfânta Maria” Clinical Hospital or “Dr. I. Cantacuzino” Clinical Hospital, in Bucharest. Patients were recruited between October 2017 and June 2020. All patients suffered from highly active disease (DAPSA > 28) [14] and were naive to biological disease-modifying antirheumatic drugs (bDMARD). The study targeted the clinical and ultrasound involvement in PsA of 16 enthesal sites: Achilles tendon, plantar fascia, quadriceps tendon, proximal and distal patellar tendon, triceps tendon, extensor and flexor tendons of the hand, all evaluated on both sides. The exclusion criteria consisted of age below 18 years, overlap or other chronic inflammatory rheumatic disease, bDMARD therapy, history of knee/ankle/elbow surgery.

Medications which could influence the ultrasound findings were allowed as follows: oral glucocorticoids, if less than 10 mg prednisone equivalent per day and stable in the prior month; non-steroidal anti-inflammatory drugs (NSAIDs), if stable in the prior week, conventional synthetic DMARDs (csDMARDs: sulfasalazine, methotrexate, leflunomide), if stable in the prior month.

The study was approved by the local ethics committee and all patients gave written informed consent.

Patient-reported outcomes

The patient's global assessment and pain assessment were evaluated on a 10 cm visual analogue scale (VAS).

The reported pain upon pressure was provoked by applying digital pressure (policis, until nail whitening) on every enthesal site's overlying skin. Careful examination of adjacent joint excluded referred pain.

Clinical examination

Regarding spontaneous pain, the medical history form contained the question „Do you or did you ever feel pain in this particular spot?” (finger-pointed by the examiner, without touching the overlying skin) for each of the 16 enthesal sites. Pain described after a local traumatic event was disregarded, therefore not noted as a symptom of enthesitis. The responses were noted as 0 „absence of pain, ever” or 1 „presence of pain, in the present or in the past”.

A thorough clinical examination was performed, including a swollen joint count, a tender joint count,

as included in the DAPSA score [17] and also evaluating the digital pressure-provoked enthesal pain. The responses were noted as 0 „absence of pain during enthesal pressure” or 1 „presence of pain during enthesal pressure”.

All clinical examinations were done by the same rheumatologist, in parallel with the ultrasound examination.

Ultrasound

All ultrasound examinations were performed and interpreted by a single rheumatologist, EULAR Level I certified (June 2018, Amsterdam).

Two Esaote My Lab machines were used, with 6-12 MHz and 8-18 MHz linear probes.

Grey scale (GS) abnormalities consisted of: modified tendon structure, increased tendon width, insertional tendon calcification and insertional bone erosion. The presence of any one of the above was noted as a GS-modified enthesis. Considering the superficial location of the studied entheses, the ultrasound evaluation was performed using a high frequency (12-15 MHz).

Power Doppler (PD) was evaluated with a low wall filter (1), a pulse repetition frequency (PRF) of 500 to 1000 Hz, while lowering the gain from a high, artefact value, until the disappearance of the last spot below the cortical line. The identification of any grade of pathological PD signal was noted as present PD signal. Special attention was paid to always maintaining a thick enough layer of gel, to avoid small vessel compression and therefore to avoid a false negative PD signal.

All abnormalities have been confirmed in two perpendicular planes.

Acute phase reactants and disease activity

Laboratory tests included C-reactive protein (CRP; normal < 5 mg/dl; latex-immunoturbidimetry method using commercially-available kits) and ESR (normal < 20 mm/h; Westergren method).

The disease activity was measured using DAPSA, a composite score being preferred, for better reliability [17].

Statistics

Distribution normality was assessed using descriptive statistics, normality and stem-and-leaf plots, and Kolmogorov-Smirnov tests. Differences of continuous variables (e.g. age) among categorical

variables (e.g. Achilles enthesitis) were tested with non-parametric tests for independent variables (Mann-Whitney tests). Associations of two dichotomous variables (e.g. ultrasound involvement and RF positivity) were studied with χ^2 or Fisher's exact tests. Correlations of continuous variables (e.g. number of enthesitis and DAPSA) were evaluated with Spearman rho indices. The performance of ultrasound compared to clinical examination (for example GS involvement of Achilles tendon insertion and spontaneous pain reported by the patient) was examined using sensitivity, specificity and Cohen's kappa indices (strength of agreement: <0.2 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and >0.80 very good) [18]. The statistical tests were considered significant if $p < 0.05$ and were computed with IBM SPSS Statistics version 22.0 for Windows (Armonk, NY, IBM Corp.).

RESULTS

General and PsA characteristics

The study included 20 PsA patients, mostly men (75%), with a mean age of approximately 45 years, predominantly with oligoarticular phenotype and high disease activity (Table 1).

TABLE 1. General and PsA characteristics (n = 20)

men (n; %)	15 (75%)
age (y; mean (SD))	44.7 (10.5)
smoking (n; %)	2 (10%)
urban dwelling (n; %)	15 (75%)
oligoarticular PsA (n; %)	12 (60%)
polyarticular PsA (n; %)	8 (40%)
PsA duration (y; median (IQR))	2.0 (4.8)
dactylitis (n; %)	6 (30%)
nail dystrophy (n; %)	14 (70%)
PtGA (VAS; mean (SD))	7.9 (1.0)
PtPA (VAS; mean (SD))	8.2 (1.0)
DAPSA (mean (SD))	38.6 (9.6)
CRP (mg/l; mean (SD))	51.5 (21.5)
ESR (mm/h; mean (SD))	73 (25)
csDMARDs (n; %)	16 (80%)
glucocorticoids (n; %)	6 (30%)

CRP - C-reactive protein (normal < 5 mg/l); csDMARDs - conventional synthetic disease-modifying anti-rheumatic drugs; DAPSA - Disease Activity in Psoriatic Arthritis; ESR - erythrocyte sedimentation rate (normal < 20 mm/h); IQR - interquartile range; PsA - psoriatic arthritis; PtGA - patient's global assessment; PtPA - patient's pain assessment; SD - standard deviation; VAS - visual analogue scale (0-10); y - years.

Enthesitis prevalence

Clinically, the most affected site on clinical examination was Achilles tendon enthesitis (80%), fol-

lowed by quadriceps tendon enthesitis (60%; Table 2), a pattern which was followed by ultrasound findings (the most frequent GS and PD involved structures were Achilles and quadriceps tendons).

TABLE 2. Clinical and ultrasound enthesitis prevalence by site (n = 20)

a) clinical involvement	symptomatic (spontaneous)		symptomatic (examination)	
	unilateral	bilateral	unilateral	bilateral
Achilles' tendon	8 (40%)	1 (5%)	16 (80%)	5 (25%)
plantar fascia	4 (20%)	0 (0%)	7 (35%)	2 (10%)
quadriceps tendon	10 (50%)	5 (25%)	12 (60%)	7 (35%)
proximal patellar tendon	5 (25%)	1 (5%)	6 (30%)	2 (10%)
distal patellar tendon	3 (15%)	2 (10%)	7 (35%)	3 (15%)
triceps tendon	3 (15%)	0 (0%)	7 (35%)	2 (10%)
flexor tendons	3 (15%)	0 (0%)	6 (30%)	0 (0%)
extensor tendons	5 (5%)	0 (0%)	7 (35%)	2 (10%)
b) ultrasound involvement	GS involvement		PD involvement	
	unilateral	bilateral	unilateral	bilateral
Achilles' tendon	20 (100%)	13 (65%)	8 (40%)	3 (15%)
plantar fascia	8 (40%)	3 (15%)	5 (25%)	0 (0%)
quadriceps tendon	15 (75%)	11 (55%)	7 (35%)	2 (10%)
proximal patellar tendon	7 (35%)	3 (15%)	5 (25%)	1 (5%)
distal patellar tendon	14 (70%)	7 (35%)	4 (20%)	2 (10%)
triceps tendon	10 (50%)	7 (35%)	4 (20%)	0 (0%)
flexor tendons	9 (45%)	0 (0%)	5 (25%)	0 (0%)
extensor tendons	10 (50%)	3 (15%)	6 (30%)	2 (10%)

GS – grey scale; PD – power Doppler

Correlations with clinical PsA variables

Regarding the Achilles tendon, compared to patients who did not complain of spontaneous pain, those who reported pain in any Achilles tendon insertion also reported a significantly higher pain assessment for the DAPSA score (a median of 8 compared to a median of 7, $p = 0.047$). Also, compared to patients with normal bilateral clinical examination of Achilles tendons, those with pain elicited by pressure at both Achilles tendon insertions had significantly higher median CRP (78.8 mg/l compared to 47.6 mg/l; $p = 0.008$) and ESR (98 mm/h compared to 61 mm/h; $p = 0.042$). The prevalence of bilateral GS involvement of Achilles tendons was significantly higher among men (80%) compared to women (20%; $p = 0.031$). 19 (47.5%) of the 40 evaluated Achilles tendon insertions were normal on physical

examination. From the total of 19 clinically normal Achilles entheses, 13 (68.4%) had GS involvement and 1 (5.3%) had PD enthesitis.

All patients with positive PD in at least one plantar fascia had oligoarticular PsA, while only 53.3% of those without positive PD in at least one plantar fascia had oligoarticular PsA ($p = 0.035$). The prevalence of oligoarticular PsA among patients with positive clinical examination of any plantar fascia was significantly higher than the prevalence of this disease phenotype among patients with no objective pain of plantar fasciae (100% compared to 38.5%; $p = 0.015$). There were no smokers among patients without spontaneous plantar fascia pain, while 50% of those with spontaneous plantar fascia pain were active smokers ($p = 0.032$). From the 40 evaluated plantar fasciae, 31 (77.5%) were normal on physical examination, of which 3 (9.7%) had GS involvement of the entheses.

With regard to the quadriceps tendon, patients who reported spontaneous pain of any quadriceps tendon insertion had significantly higher median patient-reported pain for DAPSA (9 compared to 7; $p = 0.035$) and ESR (88 mm/h compared to 54 mm/h; $p = 0.007$), than those without spontaneous symptoms. Compared to patients with normal examinations of quadriceps tendons insertions, those with pain in any quadriceps tendon insertion on physical examination had significantly higher median ESR (88 mm/h compared to 58 mm/h; $p = 0.031$). 21 (52.5%) of the quadriceps tendon insertions were clinically normal, amongst which 8 (38.1%) had GS enthesal abnormalities.

Patients with GS involvement of any proximal patellar tendon insertion reported a significantly higher global assessment for DAPSA (9 compared to 7; $p = 0.046$), compared to those without GS involvement of proximal patellar insertions. Of the 40 evaluated proximal patellar tendon insertions, 32 (80%) were normal on physical examination, of which 5 (15.6%) had GS involvement, while regarding the distal patellar tendon insertions, 30 (75%) were clinically normal, of which 15 (50%) had GS signs of enthesitis.

On the subject of the triceps tendon, patients with bilateral GS involvement had a significantly higher median disease duration (5.0 years compared to 2.5 years; $p = 0.046$) and median CRP (67.2 mg/l compared to 44.7 mg/l; $p = 0.011$; Figure 1a). Also, patients who reported pain in at least one triceps insertion had a significantly lower median disease

duration (0.5 years compared to 4.5 years; $p = 0.040$). 31 (77.5%) of the triceps entheses were normal on physical examination, 9 (29%) of which had GS abnormalities.

Regarding the flexor tendons, patients with at least one GS involvement of flexor enthesitis had significantly higher median CRP (67.2 mg/l compared to 40.3 mg/l; $p = 0.020$; Figure 1b), while those with at least one site of flexor enthesitis with PD had a significantly higher median DAPSA score (39.3 compared to 29.5; $p = 0.015$). Of the 40 scanned flexor tendon insertions, 34 (85%) were normal on physical examination, 6 (17.6%) of which had ultrasound GS involvement and 1 (2.9%) PD signal.

Concerning the extensor insertions, patients with at least one extensor enthesitis with PD had significantly

cantly higher median CRP (72.8 mg/l compared to 46.1 mg/l; $p = 0.020$; Figure 1c), similar to those with at least one extensor enthesitis with pain on clinical examination, who also had significantly higher median CRP (66.8 mg/l compared to 44.7 mg/l; $p = 0.024$; Figure 1d). 31 (77.5%) of the evaluated extensor tendon insertions were clinically normal, of which in 7 (22.6%) ultrasound GS abnormalities were detected and in 2 (6.5%), PD signal.

The extent of enthesitis involvement was directly proportional with activity indices, as indicated by the significant correlation of the number of GS and PD enthesitis with CRP (Figure 2, left pane) and DAPSA (Figure 2 right pane).

The number of ultrasound-detected enthesites (calculated as the sum of GS involvement of investi-

FIGURE 1. Higher median CRP levels in patients with corresponding enthesitis on ultrasound or clinical examination

FIGURE 2. Correlations of the number of ultrasound-detected enthesites with disease activity indices (CRP and DAPSA)

gated sites) was significantly and positively correlated with patient's global assessment for DAPSA ($\rho = 0.481$; $p = 0.032$) and CRP levels ($\rho = 0.615$; $p = 0.004$).

GS and PD involvement of evaluated enthesitis sites did not exhibit significant correlations with age and disease duration.

Generally, the best performance of clinical and ultrasound examination was noticed with regard to the evaluation of quadriceps, proximal patellar and triceps tendons (Table 3), with good and very good agreement between the two methods. Conversely, the lowest performance of clinical and ultrasound examination was noticed for Achilles, distal patellar and flexor tendons, with non-significant agreement indices.

TABLE 3. Performance and agreement of clinical and ultrasound evaluation of enthesitis ($n = 20$)

	Se	Sp	kappa	p
AT GS-SSP	40.0%	-	-	-
AT GS-SPR	80.0%	-	-	-
AT PD-SSP	50.0%	66.7%	0.17	0.456
AT PD-SPR	50.0%	100%	0.29	0.068
PF GS-SSP	75.0%	68.8%	0.30	0.110
PF GS-SPR	85.7%	84.6%	0.68	0.002
PF PD-SSP	50.0%	81.3%	0.29	0.197
PF PD-SPR	71.4%	100.0%	0.77	< 0.001
QC GS-SSP	100.0%	50.0%	0.50	0.010
QC GS-SPR	100.0%	62.5%	0.67	0.002
QC PD-SSP	60.0%	90.0%	0.50	0.019
QC PD-SPR	58.3%	100.0%	0.53	0.007
PP GS-SSP	80.0%	80.0%	0.53	0.015
PP GS-SPR	83.3%	85.7%	0.66	0.003
PP PD-SSP	100.0%	100.0%	1.00	< 0.001
PP PD-SPR	83.3%	93.3%	0.88	< 0.001
DP GS-SSP	33.3%	23.5%	0.17	0.133
DP GS-SPR	71.4%	30.8%	0.02	0.919
DP PD-SSP	66.7%	88.2%	0.48	0.028
DP PD-SPR	42.9%	92.3%	0.39	0.061
TC GS-SSP	66.7%	52.9%	0.10	0.531
TC GS-SPR	85.7%	69.2%	0.50	0.019
TC PD-SSP	100.0%	94.1%	0.83	< 0.001
TC PD-SPR	57.1%	100.0%	0.63	0.002
FX GS-SSP	66.7%	58.8%	0.14	0.413
FX GS-SPR	50.0%	57.1%	0.06	0.769
FX PD-SSP	66.7%	82.4%	0.39	0.071
FX PD-SPR	66.7%	92.9%	0.63	0.005
EX GS-SSP	80.0%	60.0%	0.30	0.121
EX GS-SPR	71.4%	61.5%	0.30	0.160
EX PD-SSP	80.0%	86.7%	0.63	0.005
EX PD-SPR	71.4%	92.3%	0.66	0.003

AT – Achilles tendon; DP – distal patellar tendon; EX – extensor tendons; FX – flexor tendons; GS – gray scale; PD – power Doppler; PF – plantar fascia; PP – proximal patellar tendon; QC – quadriceps tendon; Se – sensitivity; Sp – specificity; SSP – spontaneous pain; SPR – pain on pressure (clinical examination); TC – triceps tendon

DISCUSSIONS

The rate of ultrasound-detected enthesitis was much higher than that observed clinically, a result that was predictable to some extent, considering the literature data [10,13,14,19-21]. Using ultrasound, signs of enthesitis were detected in up to 68.4% of the clinically normal entheses, asymptomatic after both medical history and physical examination. In variable percentages, in all of the evaluated tendon insertions, enthesitis had a higher rate of detection by ultrasound than by clinical evaluation alone. Lower rates of asymptomatic signs of enthesitis and therefore a better correlation between clinical and ultrasound results were found in points of high mechanical stress and pressure, like the plantar fascia, where it is more likely for an enthesal calcification do cause pain.

A much better correlation was found with the inflammation markers and the composite index specific to the disease. The number of ultrasound-detected enthesitis was significantly correlated with the patient's global assessment for DAPSA, while in different tendons, the presence of pain, GS or PD abnormalities were correlated with a higher DAPSA score. This finding is in agreement with existing data associating enthesitis with a more active disease, more pain, a greater overall disease burden of PsA and worse prognostic outcomes [1,22,23]. Pain, both spontaneous and elicited by pressure, was significantly correlated with higher median biologic inflammatory markers. Also, a bilateral involvement was correlated with higher CRP levels. Considering that a highly active disease was one of the inclusion criteria, a comparison with the ultrasound findings in a low disease activity patient is an obvious checkpoint further along this study, but at this point, unavailable.

Given the limited number of patients, no significant correlation was found between ultrasound-defined enthesitis and age or disease duration. Only triceps GS signs of enthesitis were found to be correlated to a higher disease duration, but the olecranon process is also known to be prone to high mechanical stress and repeated trauma [4,24].

Regarding the symptoms, in some entheses, like the triceps insertion, spontaneous pain correlated with a lower disease duration, suggesting better reliability on the patient's reported outcomes in the first years of the disease, rather than later, when possible degenerative or psychosocial factors could be added.

According to recent studies, the prevalence of fibromyalgia has been reported in 16-22% of PsA patients, leading to significantly higher patient-reported outcomes and DAPSA score in patients with concomitant fibromyalgia [25,26]. Objective pain at clinical examination correlated better with the oligo-articular form of PsA.

The limitations of the study are mostly with reference to the small number of PsA patients at this point in the study. For better correlations regarding more tendons and the entire lot, more patients are being enrolled in the study. Also, the patients are evaluated dynamically, after undergoing therapy and obtaining variable rates of lower disease activity than at baseline.

The possible pre-existence of degenerative enthesal abnormalities, mostly GS, could be falsely interpreted in the context of PsA. A further research direction on this subject is examining enthesitis patterns in healthy subjects.

This study will continue prospectively, evaluating the dynamics of the ultrasound and clinical abnormalities after 6 months and 12 months of bDMARD versus non-bDMARD therapy, compared to baseline.

CONCLUSIONS

Enthesitis is a relatively unique, hallmark feature of PsA, preceding synovitis and nail involvement in the pathogenesis of PsA. Clinical examination alone, even when it is positive, offers clinicians low amount of information regarding structural abnormalities and degree of activity, imaging techniques, such as ultrasound and magnetic resonance imaging (MRI),

having the capacity of completing a well conducted medical history and clinical examination. In this direction, ultrasound has better availability in the clinical, everyday practice.

The correlation between ultrasound GS and/or PD enthesitis and pain is low, especially in the Achilles tendon. The means of measuring the disease activity correlate better to the extent of enthesitis for each patient, in this lot of high disease activity PsA patients, but a comparison with the ultrasound enthesal patterns in patients with low disease activity is due.

The increased rates of ultrasound-detected enthesal involvement, both GS and PD, compared to the clinical findings, either spontaneous or elicited tenderness, even in the least affected enthesal sites, underscores the need for an imagistic enthesitis score in the diagnostic process.

This would be useful not only in order to establish the full extent of the disease, but also to design a more personalized therapeutic plan, even more so considering the need to distinguish between the disease-related patient-reported outcomes and the possible intricate degenerative or psychosomatic pathology.

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