



## Enthesitis and its relationship with disease activity, functional status, and quality of life in psoriatic arthritis: a multi-center study

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Received: 22 August 2019 / Accepted: 19 November 2019 / Published online: 26 November 2019  
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### Abstract

Psoriatic arthritis (PsA) is an inflammatory arthritis with distinct phenotypic subtypes. Enthesitis is assigned as a hallmark of the disease, given its significant relations to disease activity and quality of life. Our objective is to evaluate the prevalence of enthesitis and its association with some clinical parameters, particularly quality of life, using data from a national registry. Patients with PsA meeting CLASSification criteria for Psoriatic Arthritis (CASPAR) were enrolled by means of a multi-centre Turkish League Against Rheumatism (TLAR) Network Project. The following information was recorded in web-based case report forms: demographic, clinical and radiographic data; physical examination findings, including tender and swollen joint counts (TJC and SJC); nail and skin involvement; Disease Activity Score-28 for Rheumatoid Arthritis with Erythrocyte Sedimentation Rate (DAS 28-ESR); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI); Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); Psoriasis Area Severity Index (PASI); Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s); Health Assessment Questionnaire (HAQ); Bath Ankylosing Spondylitis Functional Index (BASFI); Health Assessment Questionnaire for the spondyloarthropathies (HAQ-s); Psoriatic arthritis quality of Life scale (PsAQoL); Short Form 36 (SF-36); Hospital Anxiety Depression Scale (HADS); Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); and Fibromyalgia Rapid Screening Tool (FiRST) scores. The patients were divided into two groups, namely with and without enthesitis, based on the triple Likert-type physician-reported statement of ‘active enthesitis’, ‘history of enthesitis’ or ‘none’ in the case report forms. Patients with active enthesitis were compared to others in terms of these clinical parameters. A total of 1130 patients were enrolled in this observational study. Of these patients, 251 (22.2%) had active enthesitis according to the clinical assessment. TJC, HAQ-s, BASDAI, FiRST and PsAQoL were significantly higher whereas the SF-36 scores were lower in patients with enthesitis ( $p < 0.05$ ). Chronic back pain, dactylitis, and tenosynovitis were more frequent in the enthesopathy group (59.4%/39%, 13.1%/6.5% and 24.7%/3.4%, respectively). Significant positive correlations between the MASES score and the TJC, HAQ, DAS 28-ESR, BASDAI, FiRST and PsAQoL scores,

The preliminary results of the article were presented as poster presentation at the GRAPPA 2019 Annual meeting Meeting on July 11–13. The abstracts presented in that event were published in the October issue of the Journal of Psoriasis and Psoriatic Arthritis (JPPA). The full bibliographic information is <https://journals.sagepub.com/doi/full/10.1177/2475530319873502>. However, that work is almost different from this submitted version. Because we had divided patients into two categories as ones with active enthesitis and history of enthesitis, and ones without active enthesitis and any history of enthesitis. According to precious advice of senior authors given in that meeting, we have performed another classification in the current manuscript. We assigned patients with active enthesitis as enthesitis group, and ones without active enthesitis and with/without history of enthesitis were the ‘no enthesitis’ group. Therefore, all analysis results have changed completely.

This paper exhibits the data of a wide group of Turkish patients with PsA from almost all regions of the country. A total of 1130 patients were divided into two groups as ones with and without enthesitis and compared in terms of some clinical characteristics. This cross-sectional study suggests that enthesitis has relations to disease activity, functional status, and quality of life.

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and a negative correlation with the SF-36 score were found. When linear regression analysis was performed, the SF-36 MCS and PCS scores decreased by  $-9.740$  and  $-11.795$  units, and the FiRST scores increased by  $1.223$  units in patients with enthesitis. Enthesitis is an important involvement of PsA with significant relations to quality of life determined with PsAQoL and SF-36 scores. Our study found higher frequency of dactylitis and chronic back pain, and worse quality of life determined with SF-36 and PsAQoL scores in patients with enthesitis.

**Keywords** Enthesitis · Psoriatic arthritis · Enthesopathy · Registry · Disease activity · Quality of life

## Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis that develops in up to 30% of patients with psoriasis [1]. It is characterized by a broad spectrum of clinical conditions, including axial skeletal involvement, enthesitis, dactylitis, uveitis and arthritis. Among those, enthesitis is assigned to be the hallmark of PsA [2, 3]. Recently, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) advised that six clinical domains of PsA should be taken into consideration in the management of the disease. These domains are enthesitis, peripheral arthritis, dactylitis, axial disease, skin disease and nail disease [4]. Moreover, Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) revised the PsA core set to include musculoskeletal disease activity (peripheral arthritis, dactylitis, enthesitis and axial symptoms), skin disease activity (skin psoriasis and nail dystrophy), fatigue, patient global evaluation, physical function, pain, health-related quality of life (HRQoL) and systemic inflammation. The non-mandatory items were economic costs, emotional well-being, participation and structural damage [5]. Enthesitis, which is defined as the inflammation of the junction where the tendon, ligament or joint capsule inserts into the bone, may be the primary pathological process underlying spondyloarthritis (SpA)-associated skeletal inflammation [6]. Enthesopathy can be a consequence of several clinical conditions including metabolic syndrome, mechanical injuries and degeneration, and rheumatologic conditions including SpA, in which enthesitis most commonly occurs at fibrocartilaginous attachments [7]. Although enthesitis affects 35–50% of patients with PsA, it can be challenging for the clinician to identify enthesitis in patients with PsA [2, 8, 9]. Enthesopathy may either be asymptomatic, interpreted as a mechanical injury or mistaken as central hypersensitization [9]. In most cases, enthesitis needs to be distinguished from fibromyalgia. Patients' genetic and socio-environmental factors may influence the pattern and severity of the disease. Therefore, correct analysis of data from different epidemiologies may contribute to improving comprehension of the disease, identification of its course and prognosis, as well as facilitating phenotype definition [10, 11]. Real-life data are of great importance to enhance the clinical understanding of physicians.

In the current study, we determine the prevalence of enthesitis and related clinical factors, particularly quality of life, in a observational multi-centre cohort of Turkish patients with PsA. According to an analysis of the PSUMMIT 1 and PSUMMIT 2 trials on patients with PsA, improvement in enthesitis was reported to be related to improvements in physical function and HRQoL [12]. Therefore, the primary endpoint of this study was to determine the clinical differences between patients with and without enthesitis in terms of disease activity and HRQoL. The secondary end points involved assessing whether these groups differed as regards to skin and nail changes and dactylitis.

## Methods

### Patients

Patients with PsA meeting the CASPAR (Classification criteria for Psoriatic ARthritis) [13] were enrolled by means of the multicenter Turkish League Against Rheumatism (TLAR)-Network in 2018. This multi-center, independent project involved 1130 patients from 25 university or public hospitals across Turkey. TLAR-Network is a collaboration platform to conduct scientific studies in rheumatology by supporting researchers from the proposal of a scientific project to all processes from data collection to control of data, analysis, and creation of publication. The study was conducted in accordance with the Helsinki Declaration. Ethics committee approval was obtained from the Sakarya University Ethics Committee on 25.01.2018 and with the number of 42 and all centers obtained written consents from patients. The inclusion criteria were being over 18 years old, meeting the CASPAR and accepting to participate in the study [13, 14]. The exclusion criteria were pregnancy, lactation and coexistent malignancy or other connective tissue diseases [15].

### Main outcome variable

Demographic, clinical and radiographic data including age, gender, body mass index (BMI), smoking status, physical examination findings such as presence of enthesitis and sites, dactylitis, chronic back pain, tender and swollen joint counts

(TJC, SJC) over 53 joints including the distal and proximal interphalangeal joints of the hands, metacarpophalangeal and metatarsophalangeal joints, temporomandibular, manubriosternal, sternoclavicular, wrist, elbow, shoulder, knee, and ankle joints were analyzed. All assessments were performed by rheumatologists or physical medicine and rehabilitation specialists (17 rheumatologists and 20 physical medicine and rehabilitation specialists) taking care of rheumatic patients routinely in each center. Erythrocyte sedimentation rate (ESR), Disease Activity Score 28-ESR, (DAS 28-ESR) [16], the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [17], the Bath Ankylosing Spondylitis Functional Index (BASFI) [18], the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [19], Health assessment Questionnaire (HAQ) [20] and the Health Assessment Questionnaire for the spondyloarthropathies (HAQ-s) scores [21], nail and skin findings and Psoriasis Area Severity Index (PASI) [22], the Bath Ankylosing Spondylitis Radiology Index-spine (BASRI-s) [23], Psoriatic arthritis Quality of Life scale (PsAQoL) [24], Short form 36 (SF-36) [25], Hospital Anxiety Depression Scale (HADS) [26], Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [27], and Fibromyalgia Rapid Screening Tool (FiRST) [28] scores of patients were recorded in electronic case report forms (CRFs). The MASES was evaluated on 13 sites (1st costochondral joint left/right, 7th costochondral joint left/right, posterior superior iliac spine left/right, anterior superior iliac spine left/right, 5th Lumbar spinous process, and proximal insertion of Achilles tendon left/right) dichotomously as “no pain, 0 point” or “painful, 1 point” and summed up to a maximum score of 13 [19]. For the statistical analysis, the patients were divided into two groups as ones with and without active enthesitis. For this purpose, clinicians’ triple Likert-type assessment in CRFs marked as ‘active enthesitis’ or ‘enthesitis history’ or ‘no enthesitis’ was used. The main outcome variables were determined as quality of life determined by PsAQoL and SF-36.

## Statistical analysis

Statistical analyses were performed on SPSS v11.5 package program. Categorical variables were summarized using percentages, and continuous variables were given by mean, median, interquartile range and standard deviation.  $\chi^2$  test was used for comparison of the categorical data. Whether data distributed normally were analyzed with Kolmogorov–Smirnov test and histograms. Statistical comparisons between subgroups were evaluated using  $t$  tests for continuous variables with normal distribution. When the distribution of continuous data was not normal, Mann–Whitney  $U$  test was used. Correlations between variables were

investigated using Spearman’s coefficient. We performed linear regression analysis to investigate whether enthesitis is an independent predictor of disease activity and quality of life. Confidence intervals were calculated for 95%.  $p < 0.05$  was considered significant.

## Results

This multicenter observational study included 1130 patients with PsA (724 female, 406 male). The mean age of patients was  $46.9 \pm 12.2$  years. Enthesitis, tenosynovitis, dactylitis, chronic back pain, fingernail and toenail involvement, and current skin lesions were positive in 251 (22.2%), 92 (8.1%), 90 (8.0%), 492 (43.5%), 610 (54.0%), 556 (49.2%), and 840 (74.3%) patients at enrolment, respectively. Of the 1130 patients, 577 patients (51.1%) did not have active enthesitis or history of enthesitis. Of the remaining 553 patients with active or past enthesitis, 251 (45.4%) had active enthesitis at the time of enrolment and 302 (54.6%) had enthesitis in the past.

When 251 (22.2%) patients with enthesopathy and 879 patients (77.8%) without enthesopathy were compared, patients with enthesitis had more frequent tenosynovitis, dactylitis, and chronic back pain (24.7%/3.4%, 13.1%/6.5%, 59.4%/39.0%, respectively). TJC, HAQ-s, BASDAI, FiRST, and PsAQoL were significantly higher whereas SF-36 scores were lower in patients with enthesitis ( $p < 0.05$  for all). The comparison of clinical parameters of patients with and without enthesitis is given in Table 1.

Moreover, significant but weak positive correlations between the MASES score and TJC, HAQ, DAS 28-ESR, BASDAI, FiRST, and PsAQoL scores, and negative correlations with SF-36 scores were found ( $p < 0.005$  for all). The correlations between MASES and other indices are presented in Table 2.

The most common enthesitis site was Achilles insertion (39.6%) followed by lumbar 5th spinous process (36.5%) and 1st costochondral sites (27.6%). The distribution of enthesitis sites according to the MASES is given in Table 3.

According to the linear regression analysis, BASDAI and FiRST scores of patients with enthesitis increased by 0.857 and 1.223 units compared to the patients without enthesitis ( $R^2 = 0.033$ ,  $F = 31.438$ ,  $R^2 = 0.054$ ,  $F = 64.214$ , respectively,  $p < 0.001$ ). Also, PsAQoL score of patients with enthesitis increased by 2.461 units and SF-36 MCS and SF-36 PCS scores decreased by  $-9.740$  and  $-11.795$  units compared to the patients without enthesitis ( $R^2 = 0.026$ ,  $F = 30.589$ ,  $R^2 = 0.035$ ,  $F = 40.346$ ,  $R^2 = 0.044$ ,  $F = 51.500$ , respectively,  $p < 0.001$  for all) (Table 4).

**Table 1** Comparison of two groups with and without enthesitis regarding physical examination and clinical evaluation

Clinical parameter	Enthesitis positive <i>n</i> :251 (22.2%)	Enthesitis negative <i>n</i> :879 (77.8%)	<i>p</i>
BMI (mean ± SD)	29.12 ± 4.72	28.70 ± 5.10	0.226
Duration of PsA (years) (median IQR)	3 (6)	4 (8.5)	<b>0.001</b>
Diagnostic delay (years) (median IQR)	1.2 (4)	1 (4)	<b>0.036</b>
TJC (median IQR)	6 (10)	4 (7)	<b>0.001</b>
SJC (median IQR)	2 (3)	2 (3)	0.585
Active smoker, <i>n</i> (%)	77 (30.7)	214 (24.3)	0.126
Dactylitis, <i>n</i> (%)	33 (13.1)	57 (6.5)	<b>0.001</b>
Tenosynovitis, <i>n</i> (%)	62 (24.7)	30 (3.4)	<b>&lt; 0.001</b>
Fingernail involvement, <i>n</i> (%)	141 (56.2)	469 (53.4)	0.429
Fingernail onycholysis	24 (9.6)	100 (11.4)	0.417
Fingernail transverse lines	100 (39.8)	386 (43.9)	0.250
Fingernail hemorrhage	2 (0.8)	9 (1.0)	1.000
Fingernail hyperkeratosis	20 (8.0)	74 (8.4)	0.820
Fingernail oil-drop discoloration	14 (5.6)	27 (3.1)	0.061
Fingernail pitting	72 (28.7)	187 (21.3)	<b>0.014</b>
Toenail involvement, <i>n</i> (%)	127 (50.6)	429 (48.8)	0.616
Toenail transverse lines	84 (33.5)	278 (31.6)	0.582
Toenail pitting	22 (8.8)	66 (7.5)	0.512
Toenail hyperkeratosis	27 (10.8)	143 (16.3)	<b>0.031</b>
Toenail hemorrhage	2 (0.8)	5 (0.6)	0.655
Overall skin involvement, <i>n</i> (%)	206 (82.1)	634 (72.1)	<b>0.006</b>
Auricula	63 (25.1)	157 (17.9)	<b>0.011</b>
Scalp	131 (52.2)	403 (45.8)	0.076
Umbilical	55 (21.9)	163 (18.5)	0.233
Gluteal cleft	25 (10)	55 (6.3)	<b>0.044</b>
Extensor area	176 (70.1)	603 (68.6)	0.647
Chronic back pain, <i>n</i> (%)	149 (59.4)	343 (39.0)	<b>&lt; 0.001</b>
MASES score (median IQR)	4 (4)	0 (3)	<b>&lt; 0.001</b>
FiRST score (median IQR)	4 (3)	2 (4)	<b>&lt; 0.001</b>
BASRI-s (median IQR)	2 (4)	2 (4)	0.451
PASI score (median IQR)	2.1 (3.9)	1.5 (3)	<b>&lt; 0.001</b>
HAQ score (median IQR)	0.4 (0.65)	0.25 (0.65)	<b>&lt; 0.001</b>
HAQ-s score (median IQR)	0.67 (0.83)	0.33 (1)	<b>&lt; 0.001</b>
DAS 28-ESR score (mean ± SD)	3.63 ± 1.16	3.33 ± 1.23	<b>0.001</b>
ESR (mm/h) (mean ± SD)	21.23 ± 14.86	20.97 ± 15.57	0.809
PsAQoL score (median IQR)	8 (10)	4 (10)	<b>&lt; 0.001</b>
BASFI score (median IQR)	3.4 (3.2)	3.1 (3.0)	0.108
BASDAI score (median IQR)	4.95 (2.9)	3.9 (2.9)	<b>&lt; 0.001</b>
FACIT-F (median IQR)	22 (17)	18 (15)	<b>&lt; 0.001</b>
SF-36 MCS (median IQR)	46.25 (31.75)	62.63 (37.81)	<b>&lt; 0.001</b>
SF-36 PCS (median IQR)	45 (35.75)	61.25 (38.75)	<b>&lt; 0.001</b>
HADS depression (median IQR)	7 (6)	6 (6)	<b>0.004</b>
HADS anxiety (median IQR)	7 (6)	6 (6)	0.076

Statistically significant *p* values are given in bold (*p* < 0.05)

*TJC* tender joint count, *SJC* swollen joint count, *FiRST* Fibromyalgia Rapid Screening Tool, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *HAQ-s* Health Assessment Questionnaire for the spondyloarthropathies, *PASI* Psoriasis Area Severity Index, *BASRI-s* The Bath Ankylosing Spondylitis Radiology Index, *PsAQoL* Psoriatic Arthritis Quality of Life, *ESR* erythrocyte sedimentation rate, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *SF-36* Short form 36, *HADS* Hospital Anxiety Depression Scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue

**Table 2** Correlations between MASES and other clinical indices

	MASES		95% CI	
	$r_s$	$p$	Lower	Upper
BMI	0.082	0.013	0.018	0.146
TJC	0.341	<0.001	0.272	0.406
SJC	0.123	0.018	0.022	0.221
FiRST score	0.334	<0.001	0.275	0.390
BASRI-s score	−0.039	0.241	−0.104	0.026
PASI score	0.192	<0.001	0.129	0.254
HAQ score	0.201	<0.001	0.138	0.262
HAQ-s score	0.194	<0.001	0.131	0.255
DAS28-ESR score	0.275	<0.001	0.212	0.335
PsAQoL score	0.276	<0.001	0.215	0.335
BASDAI score	0.290	<0.001	0.224	0.354
BASFI score	0.160	<0.001	0.081	0.237
ESR (mm/h)	0.030	0.371	−0.035	0.094
FACIT-F	0.233	<0.001	0.171	0.293
SF-36 MCS	−0.290	<0.001	−0.348	−0.230
SF-36 PCS	−0.269	<0.001	−0.328	−0.208
HADS anxiety	0.173	<0.001	0.110	0.235
HADS Depression	0.175	<0.001	0.112	0.237

*BMI* Body mass index, *TJC* tender joint count, *SJC* swollen joint count, *HAQ-s* Health Assessment Questionnaire for the spondyloarthropathies, *FiRST* Fibromyalgia Rapid Screening Tool, *MASES* Maastrich Ankylosing Spondylitis Enthesitis Score, *PASI* Psoriasis Area Severity Index *BASRI-s* The Bath Ankylosing Spondylitis Radiology Index, *PsAQoL* Psoriatic Arthritis Quality of Life, *DAS 28-ESR* Disease Activity Score28, *ESR* erythrocyte sedimentation rate, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *SF 36* Short form 36, *HADS* Hospital Anxiety Depression Scale, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue

$p < 0.05$  statistical significance;  $r_s$  Spearman's correlation coefficient

## Discussion

We analyzed the prevalence of enthesitis and its association with clinical factors, particularly HRQoL in patients with PsA, all of which seem rather compatible with the literature. We found that approximately half of the patients with PsA experienced enthesitis either at enrolment or in the past, and that patients with active enthesitis had higher rates of tenosynovitis, dactylitis and chronic back pain as well as higher TJC, FiRST and PsAQoL scores and lower SF-36 scores. Enthesitis may be considered as a sign of increased disease burden due to its association with several clinical aspects, and a major determinant of disease activity.

Enthesitis is often not considered as the primary outcome measure in studies of peripheral SpA and PsA although it is assumed to be a key pathology for these disorders [6]. The main limitations for reporting enthesitis in daily practice are absence of overt clinical inflammatory signs such as objective swelling or increase in acute phase reactants. Enthesitis

**Table 3** Distribution of affected enthesitis sites in MASES

Enthesitis site	$n$	%
1st costo-condral right ( $n = 692$ )	188	27.4
1st costo-condral left ( $n = 685$ )	191	27.6
7th costo-condral right ( $n = 651$ )	132	20.3
7th costo-condral left ( $n = 654$ )	136	20.8
Anterior superior iliac spine, right ( $n = 657$ )	147	22.4
Anterior superior iliac spine, left ( $n = 668$ )	157	23.5
Posterior superior iliac spine, right ( $n = 636$ )	138	21.7
Posterior superior iliac spine, left ( $n = 642$ )	150	23.4
Right iliac crest ( $n = 666$ )	154	23.1
Left iliac crest ( $n = 659$ )	159	24.1
Lumbar 5th spinous process ( $n = 718$ )	262	36.5
Achilles tendon, right ( $n = 740$ )	276	37.3
Achilles tendon, left ( $n = 758$ )	300	39.6

is frequently assessed via clinical examination and rarely radiography as it may be inconclusive [29]. Several enthesitis assessment tools including the Leeds Enthesitis Index (LEI), Mander Enthesitis Index (MEI) [30], Spondyloarthritis Research Consortium of Canada (SPARCC), and the MASES with some variations in reliability, validity, and sensitivity are commonly used in practice [30]. In the present study, we used the MASES, and an imaging modality was not employed due to multi-center design.

There are several PsA cohorts worldwide. In Corrona Psoriatic Arthritis/Spondyloarthritis Registry from the United States, both cross-sectional and prospective analyses were conducted on enthesitis [14, 31]. In a similar way, our patients with enthesitis had significantly higher rates of chronic back pain than patients without enthesitis. In a prospective longitudinal cohort study, conducted between 2008 and 2014, the prevalence of enthesitis was reported to be 35%. Similar to our data, the Achilles tendon was the most common site of involvement. They reported that enthesitis was associated with more active disease as determined based on joint count and the presence of tenosynovitis and dactylitis, which is similar to our results [8]. In the multi-centre cohort of the GRACE Project, 49% of the PsA patients had enthesitis with a median MASES score of 1.1. [32]. Table 5 presents information on the prevalences of enthesitis in these two studies as well as other studies including the Toronto PsA cohort study [10], Dutch southwest Early Psoriatic Arthritis cohort study (DEPAR) [33], Recent-Onset PsA Registry of the Spanish Society of Rheumatology (REAPSER) [34], Reykjavik cohort of the Iceland [35], the PsART study from our country [11], and juvenile PsA cohort CARRA [36] study. The different rates may potentially be attributed to the patients' disease onset profile, the differences in the enthesitis indices used, ethnic differences, and variations in number of patients included in the studies.



**Table 4** Linear regression analysis of enthesitis and clinical parameters

	<i>df</i>	Estimate ( <i>B</i> )	95% CI		<i>p</i> value
			Lower	Upper	
<b>BASDAI</b>					
Constant		4.144	3.993	4.295	<0.0001
Presence of enthesitis	1	0.857	0.557	1.156	<0.0001
<b>PsAQoL</b>					
Constant		6.292	5.881	6.704	<0.0001
Presence of enthesitis	1	2.461	1.588	3.334	<0.0001
<b>HAQ score</b>					
Constant		0.400	0.370	0.431	<0.0001
Presence of enthesitis	1	0.115	0.050	0.180	<0.0001
<b>HAQ-s</b>					
Constant		0.614	0.570	0.658	<0.0001
Presence of enthesitis	1	0.192	0.098	0.285	<0.0001
<b>SF-36 MCS</b>					
Constant		57.714	56.306	59.143	<0.0001
Presence of enthesitis	1	− 9.740	− 12.749	− 6.732	<0.0001
<b>SF-36 PCS</b>					
Constant		59.045	57.524	60.565	<0.0001
Presence of enthesitis	1	− 11.795	− 15.019	− 8.570	<0.0001
<b>FiRST score</b>					
Constant		2.189	2.048	2.330	<0.0001
Presence of enthesitis	1	1.223	0.923	1.522	<0.0001

**Table 5** Comparison of the PsA cohorts/studies evaluating enthesitis

Cohort	CORRONA	CORRONA	CARRA	TORONTO	PsART	Reykjavik	ULISSE	REAPSER	DEPAR
Region	United States	United States	United States and Canada	Canada	Turkey	Iceland	Italy	Spain	Dutchland
Year	2017	2017	2017	2011	2016	2007	2019	2017	2018
Design	Retrospective/cross-sectional	Prospective	Cross-sectional	Prospective	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Number of patients	1567	803	361	1066	1081	220	140	250	405
Methods to detect enthesitis	Physical examination	Physical examination	Physical examination	Physical examination	Physical examination	Physical examination	Physical examination + ultrasound	Physical examination	Physical examination
Index	SPARCC	SPARCC	–	–	LEI	–	LEI/MASES	–	LEI/MASES
Prevalence	27%	35%	32.7%	35.8%	11.4%	49%	66.4% (clinical examination) 53.7% (ultrasound)	25%	46%

Higher FiRST scores among patients with enthesitis, the positive correlation between the FiRST and MASES index scores and the linear regression analysis results, indicating that enthesitis is an independent predictor for an increase in the FiRST scores, are other striking results of our study. Although FiRST is considered as a screening tool rather than as a diagnostic tool, it may provide with substantial data regarding widespread pain [28]. It is well known that central

sensitisation syndromes are more frequent in patients with several types of rheumatic diseases, including SpA, PsA, and RA and it is detected in 10–40% of all cases [37]. Therefore, the importance of distinguishing between fibromyalgia, which is the prototype of central sensitisation syndromes [38], and polyenthesitis in SpA patients has been addressed in prior studies [9]. In a study to identify the clinical features used in the differential diagnosis of PsA and fibromyalgia,

the presence of  $\geq 6$  fibromyalgia-associated symptoms and  $\geq 8$  tender points were reported to be the best predictors of fibromyalgia [39]. However, many of the enthesal points used in the enthesitis assessment tools are near the joints and tender points for fibromyalgia, contributing to the possibility of misclassification. Ultrasound (US) is alleged to be more sensitive than clinical examination in enthesitis [40]. However, it is challenging for clinicians to incorporate US into their daily practice in PsA due to the time needed to examine multiple enthesopathy sites [41]. Fibromyalgia should be considered when dealing with PsA patients with higher enthesopathy scores upon evaluation. Unfortunately, our study did not involve questioning the patients about somatic symptoms or examining their tender points to differentiate fibromyalgia based on the available classification criteria [42, 43].

Another hallmark of PsA, dactylitis with specificity approaching 95% in SpA [44] was present in 8.0% of our patients. In an international multi-center psoriasis and PsA trial, the frequency of active dactylitis was found to be 3.4–12.8% [45]. In our study, dactylitis was also found to be more frequent in the enthesopathy subgroup. Although accepted evidence suggests that dactylitis is primarily related to flexor tenosynovitis [46], a recent study using high-resolution MRI to explore dactylitis in PsA demonstrated that enthesitis was common in PsA dactylitis. Furthermore, the authors concluded that 'digital polyenthesitis', related to the flexor tendon pulleys and fibrous sheaths, provides a possible explanation for its association with flexor tenosynovitis [47]. Our results regarding significantly higher rates of dactylitis and tenosynovitis in patients with enthesitis are in accordance with that study's findings. An association between extensor tendon enthesopathy, distal interphalangeal (DIP) joint involvement, and nail pathology has been widely acknowledged [48]. Some authors proposed the term 'nail-enthesitis theory' to refer to the increased prevalence of extensor tendon enthesitis in digits with involved nails [49]. In line with these data, our patients with enthesitis had more frequent fingernail pitting.

Among patients with PsA, arthritis is known to impair HRQoL. However, the association between HRQoL and enthesitis was not thoroughly evaluated. In a recent study on DEPAR PsA cohort, SF-36 was used to assess HRQoL, and enthesitis was evaluated using LEI and/or MASES scores. Given that higher SF-36 scores represent a better state of HRQoL, based on clinical examination, patients with enthesitis were reported to have significantly lower scores on all the SF-36 domains than patients without enthesitis [33]. Furthermore, in our study, the patients with enthesitis had higher PsAQoL and lower SF-36 scores. Although the association between enthesitis and HRQoL has been poorly investigated in PsA, some studies were performed in SpA. In a study on 1505 Brazilian patients with SpA, of whom

18.4% had PsA, it was reported that 53.8% of the patients with PsA had enthesitis, and the SpA patients with enthesitis at clinical examination had a lower HRQoL [50]. The higher PsAQoL and lower SF-36 scores we observed in patients with enthesopathy are in correspondence with previous studies [12].

One of the strengths of our study is that it reports on data of a wide group of patients with PsA from almost all regions of Turkey. The population is highly representative and selection bias is unlikely since the patients were enrolled consecutively. However, our study has some limitations as well. It did not use other disease activity indices involving laboratory data such as ASDAS (Ankylosing Spondylitis Disease Activity Index) [51] instead of the BASDAI to determine the severity of axial disease. DAPSA (Disease Activity Index for Psoriatic Arthritis) [52] would be more appropriate than DAS 28 for peripheral arthritis because it counts more joints prone to psoriatic involvement. One of the major limitations of the study is that it used the MASES to assess enthesitis. The MASES does not score some of the main enthesitis sites in PsA, such as plantar fascia insertions into the calcaneum, medial femoral condyles, and lateral epicondyles of the humerus. The LEI has been used in several PsA trials and it was developed and validated specifically for PsA. Therefore, if LEI, MEI or SPARCC had been used in our study, more reliable results could have been obtained. Another limitation is that our description of enthesitis solely depends on clinical symptoms and signs; it is not based on objective evidence exhibited by imaging because enthesitis lacks apparent inflammatory characteristics, such as swelling and erythema. It was already emphasized that it is not good to be too reliant on clinical examination of enthesitis as a marker of underlying disease, except for the Achilles tendon insertion [53]. The relatively low prevalence of enthesitis determined in our study may have been due to this limitation. Another limitation is the missing data, which is not a challenge for HAQ, HAQ-s, FiRST, PASI, PsAQoL, BASRIS, and ESR. However, missing data may be a concern for the BASDAI, MASES, and BASFI scores around 20%, probably due to not having been performed on patients that only have peripheral involvement. Finally, this study presents an observational analysis of the relationship between enthesitis and disease activity, function, and HRQoL. It did not analyze the changes in these parameters over time or after treatments. In the light of our findings, as announced by the GRAPPA and the OMERACT, we consider that enthesitis should be incorporated to daily practice as well as evaluation for arthritis, spondylitis, and skin. For this purpose, composite indices such as Composite Psoriatic Disease Activity Index (CPDAI) or modified CPDAI (mCPDAI) [54], and The Psoriatic Arthritis Disease Activity Score (PASDAS) [55] which involve assessment for enthesitis should be used in determination of overall psoriatic disease activity.

Furthermore, patients with PsA and polyenthesitis should also be overviewed to exclude coexisting fibromyalgia and chronic widespread pain conditions.

## Conclusion

Enthesitis is among the most important clinical PsA phenotypes displaying significant associations with HRQoL, shown by lower PsAQoL and SF-36 scores in this study. All patients with PsA, particularly those with dactylitis, chronic back pain, and tenosynovitis should be examined for enthesitis. Fibromyalgia should be distinguished from polyenthesitis in patients with PsA.

**Acknowledgements** We acknowledge dr Nazmiye Kurşun for statistical consulting and Scribendi Editing Services for external editing.

**Author contributions** All authors have substantial contributions to the conception or design of the work, drafting or revising it critically for important intellectual content, have approved the final version to be published, and in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All co-authors are fully responsible for all aspects of the study and the final manuscript in line with the IJME 4 criteria.

## Compliance with ethical standards

**Conflict of interest** Authors declare no conflicts of interest or financial support.

**Ethical approval** Ethics committee approval was obtained from the Sakarya University Ethics Committee on 25.01.2018 and with the number of 42 and conducted in accordance with the Helsinki Declaration.

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