Ultrasound assessment, unlike clinical assessment, reflects enthesitis in patients with psoriatic arthritis

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Abstract

Objective

Enthesitis is a major musculoskeletal manifestation of psoriatic arthritis (PsA). It is conventionally assessed clinically, by the presence of tenderness, despite its low reliability. However, ultrasound (US) provides a sensitive and feasible method for evaluating enthesitis. We investigated enthesitis as assessed clinically and by US in patients with PsA.

Methods

Forty-seven patients with PsA underwent US examination of the bilateral humeral medial epicondyles and insertions of the triceps, distal quadriceps, proximal/distal patellae, Achilles tendons, and plantar fascia. These 14 entheses were also clinically evaluated by tenderness. The correspondence between US and clinical enthesitis was evaluated, as well as their associations with inflammatory markers (C-reactive protein [CRP], matrix metalloproteinase-3 [MMP-3]), disease activity indices (Disease Activity in Psoriatic Arthritis [DAPSA], Disease Activity Score 28 joints [DAS28-CRP], Psoriatic Arthritis Screening and Evaluation [PASE], Psoriasis Area Severity Index [PASI]), radiographic damage (modified Total Sharp Score [mTSS]), and functional status (health assessment questionnaire [HAQ]), and axial involvement.

Results

Among 47 patients with PsA, 37 and 23 had US and clinical enthesitis, respectively. US and clinical enthesitis had very low concordance (kappa coefficient 0.04), with no correlation between enthesitis counts ($r=0.15$, $p=0.30$). The US enthesitis count correlated only with the MMP-3 level ($r=0.41$, $p=0.007$), whereas the clinical enthesitis count correlated with the DAPSA, DAS28-CRP, HAQ, and PASE ($r=0.50$, $p<0.001$; $r=0.44$, $p=0.002$; $r=0.41$, $p=0.008$; $r=0.54$, $p<0.001$, respectively).

Conclusion

US and clinical enthesitis are completely different entities. US enthesitis, but not clinical enthesitis, reflects inflammatory conditions.

Key words

Achilles tendon, enthesopathy, patellar ligament, psoriatic arthritis, ultrasonography, inflammation

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Introduction

About 30–50% of patients with psoriasis have clinical musculoskeletal manifestations characterised by inflammation in the peripheral joints, spine, entheses, and fingers usually known as dactylitis, which encounts for joint inflammation, flexor tenosynovitis and edema in the subcutaneous tissue, and is diagnosed as psoriatic arthritis (PsA) (1, 2). The Classification Criteria for PsA (CASPAR), which includes arthritis, spondylitis, and enthesitis, are frequently used to diagnose PsA (3). Although the sensitivity and specificity of the CASPAR are relatively high, it does not comprise diagnostic criteria.

Enthesitis, characterised by inflammation of the insertion of a tendon or ligament into the bone, is the most common manifestation of PsA. Assessment of enthesitis is important, as it is associated with disease activity and treatment response in PsA (4). Enthesitis is conventionally assessed during physician's clinical examination by evaluating the presence of tenderness, using the Leeds Enthesitis Index (LEI) (5), Maastrich Ankylosing Spondylitis Enthesitis Score (MASES) (6), or Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index (7). However, the presence of tenderness is not commensurate with the inflammatory condition. This suggests limitations to the reliability, validity, and sensitivity of the clinical assessment (8, 9).

PsA is usually treated according to the recommendations of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) (10) or the European League Against Rheumatism (EULAR) (11). Enthesitis is treated primarily by non-steroidal anti-inflammatory drugs (NSAIDs). If NSAIDs are not effective, then uses of biological disease-modifying antirheumatic drugs (bDMARDs), which suppress inflammation, are recommended. Thus, inflammation should be assessed precisely.

Fortunately, ultrasound (US) provides a relatively feasible and sensitive method for evaluating enthesitis (12-14). It is known that tenderness in the entheses and joints, which is assessed clinically by a physician, does not correlate with US assessment results (15-20). US examinations may be more sensitive and useful than are clinical evaluations in detecting subclinical enthesitis, which can induce bone destruction and disability (21). Additionally, the Outcome Measures in Rheumatology (OMERACT) US Specialist Interest Group evaluated eight entheses by US, including the bilateral humeral lateral epicondyles, superior/inferior poles of the patella, and Achilles tendon insertions, and reached an agreement regarding US assessment definitions (22).

The aim of the present study was to compare US and clinical assessments of the entheses for the presence of enthesitis, and investigate the relationships between enthesitis counts, as determined by each assessment method, and clinical features, including disease activity and structural damage, in patients with PsA.

Materials and methods

Setting

Among outpatients with psoriasis at the Department of Dermatology in our institution, those with any suspicious musculoskeletal manifestations were referred to the Department of Orthopaedics and evaluated for PsA. A total of 107 patients with psoriasis underwent screening for PsA from January 2015 to March 2017. Among these, 63 patients fulfilled the CASPAR. After excluding patients who were under 20 years old, refused to provide consents, or had missing data, 47 patients were finally eligible for inclusion in the present study. This study was registered as the ISLAND study (Identification of riSk factors for spondyLoArthropathy in patieNts Diagnosed with psoriasis) in the University hospital Medical Information Network (UMIN) Clinical Trials Registry (registration number: UMIN000024292). Osaka City University Hospital Certified Review Board approved the study protocol, which was conducted in accordance with the Declaration of Helsinki (approval no.: 3146). Informed consent for participation in this study was provided by all patients.

Study measures

Data regarding age, disease durations of psoriasis and musculoskeletal manifes-

tations, and medication status (*i.e.* the use of NSAIDs and bDMARDs) were recorded. Patients underwent blood examinations for the levels of C-reactive protein (CRP) and matrix metalloproteinase-3 (MMP-3), as well as conventional radiographic examinations of the bilateral hands, feet, and sacroiliac joints, and the entire spine. These two inflammatory markers are reported to reflect the activity of arthritis in PsA (23). The modified Total Sharp Score (mTSS) was calculated as a measure of bone structural damage (24).

Patients also completed surveys, including the health assessment questionnaire (HAQ), as a measure of functional status, and the Psoriatic Arthritis Screening and Evaluation (PASE) (25), as a measure of musculoskeletal involvement. Furthermore, the Psoriasis Area Severity Index (PASI) was calculated as a measure of skin disease severity, and the Disease Activity in Psoriatic Arthritis (DAPSA) (26) and Disease Activity Score 28 joints (DAS28-CRP) scores were calculated as measures of disease severity in the peripheral joints or entheses. The presence of inflammatory back pain (IBP) (27), as a measure of axial involvement, was also assessed (28).

US and clinical assessments of enthesitis

Fourteen entheses, including the bilateral humeral lateral epicondyles, and the insertions of the triceps, distal quadriceps tendons, proximal/distal patella tendons, Achilles tendons, and plantar fascia were examined by 3 expert sonographers certified by Japan College of Rheumatology, using a HI-VISION Ascendus US system (Hitachi-Aloka Medical, Tokyo, JAPAN) with a 18-MHz linear transducer. They are blinded to the clinical assessment. US greyscale imaging parameters were set to obtain maximal contrast between all the structures under examination. PD settings were standardised to the following values: pulse repetition frequency, 800 Hz; and Doppler frequency, 7.5 or 10 MHz. The colour gain was set just below the level at which colour noise appeared at the underlying bone (no flow should be visualised at the bony surface). To confirm that the PD signal represented real blood flow and not an artifact, the spectral Doppler was used. The 14 evaluated entheses are included in the OMERACT US definition (29) and MAdrid Sonographic Enthesis Index (MASEI) (30). We evaluated inflammatory components of OMERACT definition to assess the presence of present inflammation at 14 entheses (29). Entheses with positive PD signals with hypoechoic and/or thickened insertion of the tendon within 2 mm from the bone surface (or thickening of more than 4.5 mm at the plantar fascia by the grey scale) were considered as reflecting "US active enthesitis. As the PD signal is usually difficult to find at the plantar fascia, owing to its depth and the thick skin of the plantar, we evaluated the presence of thickening at this site, rather than the PD signal. The bilateral humeral lateral epicondyles and triceps insertions to the olecranon were examined in the seated position, with the elbow at 90 degrees flexion and the forearm in the neutral position. The distal quadriceps and proximal/distal patella tendons were examined in the supine position, with the knee at 30 degrees flexion. The Achilles tendon and plantar fascia were examined in the prone position. We did not assess the presence of enthesophytes, as it is common in post-traumatic conditions and in those with degenerative changes (31).

Additionally, we examined the same entheses for tenderness. Painful entheses were considered as reflecting "clinical enthesitis."

Evaluation of the concordance between US and clinical assessments

The prevalence and concordance of US active and clinical enthesitis were investigated overall and for each of the 14 evaluated entheses. Furthermore, we determined the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of clinical enthesitis for US active enthesitis.

Evaluation of the relationships between enthesitis counts and clinical features

The relationships between the enthesitis count, as determined by each assessment method, and clinical features, including inflammatory markers, and measures of disease activity, bone damage, and axial involvement, were investigated.

Statistical analysis

Patient characteristics are displayed as means ± standard deviations (SD). The concordance between assessments was evaluated by the kappa value. Associations between the enthesitis count, as determined by each assessment method, and clinical features were evaluated by the Spearman's correlation coefficient. All statistical analyses were performed using EZR v.1.37 (32). All p-values were two-sided, and $p<0.05$ was considered statistically significant.

Results

Patients' characteristics

The characteristics of the 47 patients with PsA are shown in Table I. The mean age was 56.4 years and mean disease duration of psoriasis was 126 months. The mean HAQ score was 0.47. Skin symptoms were relatively well-controlled (mean PASI, 7.2). The mean disease duration of musculoskeletal manifestations was 90.8 months and the mean PASE was 45.9. The mean mTSS was 12.6 points. The disease activity in peripheral joints was moderate, with a mean DAPSA score of 20.4 and DAS28-CRP score of 3.23. The prevalence of IBP was 36.2%. Some patients were treated with NSAIDs (14.9%) for musculoskeletal symptoms and/or bDMARDs (14.9%; infliximab, n=3; adalimumab, n=3; ustekinumab, n=1) for skin lesion.

Prevalence and concordance of enthesitis as determined by US and clinical assessments

Among the 47 patients, 37 and 23 had at least one count of US active and clinical enthesitis, respectively, with a mean enthesitis count of 3.82 and 3.52 (out of 14 entheses), respectively (Table I). The prevalences of US active and clinical enthesitis were 22% and 13%, respectively (Table II). The sensitivity, specificity, PPV, and NPV of clinical enthesitis for US active enthesitis were 0.16, 0.88, 0.27, and 0.78, respectively. The kappa coefficient of

Table I. Characteristics of all patients with PsA.

Patients with PsA (n=47)	
Age, years	56.4 ± 15.2
Female, %	53.2
BMI, kg/m^2	23.6 ± 4.1
Disease duration for psoriasis, months	169.9 ± 164.1
Disease duration for PsA, months	90.8 ± 123.6
NSAID use rate, %	14.9
bDMARD use rate, %	14.9
PASE	45.9 ± 15.2
PASI	7.2 ± 10.1
DAPSA	20.4 ± 18.2
DAS28-CRP	3.23 ± 1.37
HAQ	0.47 ± 0.48
mTSS	12.6 ± 18.6
CRP, mg/dl	0.90 ± 2.46
MMP-3, ng/mL	84.35 ± 53.91
Prevalence of clinical enthesitis among all patients†, %	49.0
Clinical enthesitis count among patients with clinical enthesitis	3.52 ± 2.78
Prevalence of US active enthesitis among all patients†, %	78.7
US active enthesitis count among patients with US active enthesitis	3.82 ± 2.29
Prevalence of IBP, %	36.2

Data are shown as means ± standard deviation.
PsA: psoriatic arthritis, BMI: body mass index, PASE: Psoriatic Arthritis Screening and Evaluation, PASI: Psoriasis Area Severity Index, DAS28: Disease Activity Score 28 joints, CRP: C-reactive protein, HAQ: Health Assessment Questionnaire, mTSS: modified Total Sharp Score, US: ultrasound, IBP: inflammatory back pain, MMP-3: matrix metalloproteinase-3, NSAID: non-steroidal anti-inflammatory drug, bDMARD: biologic disease-modifying anti-rheumatic drug, DAPSA: Disease Activity in Psoriatic Arthritis.
†Clinical and US enthesitis were assessed at 14 entheses (bilateral humeral lateral epicondyles, and the insertions of the triceps, distal quadriceps tendons, proximal/distal patella tendons, Achilles tendons, and plantar fascia).

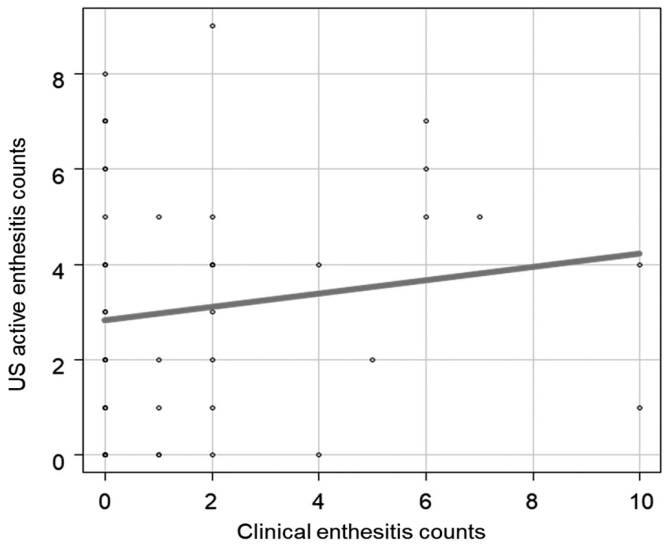

Fig. 1. Relationship between US active and clinical enthesitis counts.
Clinical and US active enthesitis counts were not correlated (r=0.15, p=0.30).
US: ultrasound.

the concordance between assessment methods was 0.04 (95% Confidential Interval (CI) -0.07 to 0.16) (Table II). The prevalences of US active and clinical enthesitis and the concordance between assessment methods are shown according to each enthesis in Table II. The concordance between assessment methods was very low for all entheses.

Relationships between the enthesitis count, as determined by each assessment method, and clinical features

Enthesitis counts by US and clinical assessments were not correlated (r=0.15, p=0.30) (Fig. 1). The US active enthesitis count was significantly correlated with the MMP-3 level (r=0.41, p=0.007), but was not correlated with the DAPSA (r=-0.08, p=0.59), DAS28-CRP (r=-0.06, p=0.67), CRP level (r=0.06, p=0.69), PASE (r=0.03, p=0.84), PASI (r=-0.23, p=0.21), mTSS (r=0.12, p=0.41), HAQ scores (r=0.04, 0.82), and IBP presence (r=-0.24, p=0.13) (Table III). In contrast, the clinical enthesitis count was significantly correlated with the DAPSA (r=0.50, p<0.001), DAS28-CRP (r=0.45, p=0.001), PASE (r=0.54, p<0.001), and HAQ scores (r=0.41, p=0.008), but was not correlated with the CRP level (r=-0.02, p=0.92), MMP-3 level (r=-0.08, p=0.61), PASI (r=-0.06, p=0.75), mTSS (r=-0.01, p=0.97), and IBP presence (r=0.02, p=0.90) (Table III).

Discussion

We assessed 14 entheses for enthesitis using US and conventional clinical tenderness assessments in 47 patients with PsA. We found that the US assessment detected enthesitis more frequently than did the clinical assessment. Furthermore, there was no concordance between US active and clinical enthesitis, no correlation between US active and clinical enthesitis counts, and the sensitivity, specificity, PPV, and NPV of clinical enthesitis for US active enthesitis were very low. Additionally, the US active and clinical enthesitis counts correlated with different measures; the US active enthesitis count only correlated with the MMP-3 level, whereas the clinical enthesitis count correlated with indices of disease activity and functional status, including the DAPSA, DAS28-CRP, PASE, and HAQ scores.

Although it is important to evaluate the presence of enthesitis to predict structural damage and disability (33), consensus regarding which entheses should be assessed and how they should be assessed has not been reached. Thus, there is uncertainty about clinical assessment (8, 9). In fact, the entheses were assessed differently in recent randomised controlled trials (RCTs). For example, a MASES score >1 was considered to indicate the presence of enthesitis in the PSUMMIT1 (ustekinumab) trial (34), whereas a LEI >1 was considered to indicate the presence of enthesitis in the FUTURE-2 (secukinumab) (35) and SPIRIT-P1

Table II. The validity of clinical assessments for US assessments of enthesitis.

	Prevalence of clinical enthesitis	Prevalence of US active enthesitis	Sensitivity	Specificity	PPV	NPV	kappa coefficient
All 14 entheses	0.13 [0.10-0.16]	0.22 [0.19-0.26]	0.16 [0.10-0.23]	0.88 [0.85-0.91]	0.27 [0.18-0.38]	0.78 [0.75-0.82]	0.04 [-0.07 to 0.16]
Humeral lateral epicondyles	0.22 [0.14-0.32]	0.29 [0.20-0.39]	0.30 [0.14-0.50]	0.81 [0.69-0.89]	0.38 [0.18-0.62]	0.74 [0.62-0.84]	0.11 [-0.14 to 0.36]
Insertion of the triceps	0.02 [0.00-0.08]	0.19 [0.12-0.29]	0.00 [0.00-0.26]	0.97 [0.91-1.00]	0.00 [0.00-0.91]	0.80 [0.71-0.88]	-0.04 [-0.44 to 0.36]
Distal insertion of the quadriceps tendon	0.18 [0.11-0.27]	0.31 [0.22-0.41]	0.24 [0.10-0.44]	0.85 [0.74-0.92]	0.41 [0.18-0.67]	0.71 [0.60-0.81]	0.10 [-0.15 to 0.35]
Proximal insertion of the patella tendon	0.12 [0.06-0.20]	0.13 [0.07-0.21]	0.08 [0.00-0.39]	0.88 [0.79-0.94]	0.09 [0.00-0.41]	0.87 [0.78-0.93]	-0.04 [-0.43 to 0.35]
Distal insertion of the patella tendon	0.06 [0.02-0.13]	0.27 [0.18-0.37]	0.12 [0.03-0.31]	0.96 [0.88-0.99]	0.50 [0.12-0.88]	0.75 [0.65-0.84]	0.10 [-0.20 to 0.40]
Insertion of the Achilles tendon	0.13 [0.07-0.21]	0.20 [0.13-0.30]	0.00 [0.00-0.25]	0.84 [0.74-0.91]	0.00 [0.00-0.36]	0.77 [0.66-0.85]	-0.19 [-0.53 to 0.15]
Insertion of the plantar fascia	0.16 [0.09-0.25]	0.18 [0.11-0.27]	0.24 [0.07-0.50]	0.86 [0.76-0.93]	0.27 [0.08-0.51]	0.84 [0.74-0.91]	0.10 [-0.21 to 0.41]

The prevalence of clinical and US active enthesitis, their concordance, and the sensitivity, specificity, PPV, and NPV of clinical enthesitis for US active enthesitis (overall and at each enthesis) are shown with 95% confidential intervals.
US: ultrasound, PPV: positive predictive value, NPV: negative predictive value.

Table III. Relationships between the enthesitis count by each assessment method and clinical features.

	Clinical enthesitis counts		US active enthesitis counts	
	r	*p*-value	r	*p*-value
DAPSA	0.503	<0.001*	-0.080	0.592
DAS28-CRP	0.439	0.002*	-0.064	0.671
CRP	-0.015	0.920	0.060	0.688
MMP-3	-0.080	0.611	0.406	0.007*
PASE	0.541	<0.001*	0.032	0.840
PASI	-0.058	0.751	-0.225	0.208
mTSS	-0.006	0.969	0.123	0.412
HAQ	0.405	0.008*	0.036	0.820
IBP	0.019	0.904	-0.241	0.125

The clinical enthesitis count was correlated with disease activity and functional status measures, including the DAPSA, DAS28-CRP, PASE, and HAQ score, whereas the US active enthesitis count was correlated with the MMP-3 level.
DAPSA: Disease Activity in Psoriatic Arthritis, DAS: Disease Activity Score, CRP: C-reactive protein, MMP-3: matrix metalloproteinase 3, PASE: Psoriatic Arthritis Screening and Evaluation, PASI: Psoriasis Area Severity Index, mTSS: modified Total Sharp Score, HAQ: Health Assessment Questionnaire, IBP: inflammatory back pain. *$p<0.05$.

(ixekizumab) trials (36, 37). In addition, clinical assessments have limited reliability. In contrast, US assessments of enthesitis are reported to have high reliability (14). The OMERACT US initiative reached an agreement regarding US assessment definitions, and concluded that a positive PD signal and the presence of enthesophytes are the most reliable and feasible US findings of enthesitis (29). Furthermore, positive PD signals are often found at entheses that present with no tenderness; such cases are recognised as subclinical enthesitis and are only detectable by an US assessment. Some patients with psoriasis have subclinical enthesitis (38, 39). Subclinical enthesitis can cause structural damage and disability (33). Thus, US is useful for assessing enthesitis and the early diagnosing of PsA (40).

In the present study, 14 entheses were assessed by US and clinical tenderness in 47 Japanese patients with PsA. Consistent with previous reports (15-20), we found that these two assessments showed no concordance and were completely different approaches. In the present study, clinical enthesitis had very low sensitivity, specificity, PPV, and NPV for US active enthesitis. Consistent with previous reports (38, 39), these results suggest that many patients without tenderness in the entheses had subclinical enthesitis as detected by an US examination. Pereira *et al*. reported that synovitis was similarly found in both painful and painless joints by an US examination in patients with rheumatoid arthritis (RA) (41). Similarly, Kristensen et al. reported that US active enthesitis, with the exception of tendon thickening and hypo-echogenicity, was not correlated with the LEI and SPARCC (18). These results are consistent with those of the present study, and suggest that tenderness is completely different from inflammation, which cannot be assessed only by tenderness in patients with PsA or RA. Thus, the inflammatory condition should be assessed by an US examination, not by tenderness. However,

many clinical trials, such as the RCTs previously described, only assessed enthesitis clinically, without an US examination.

The present study also investigated the relationships between clinical and US active enthesitis counts and clinical features. Consistent with previous studies, there was no relationship between clinical and US active enthesitis counts. While the US active enthesitis count was significantly correlated with the level of an inflammatory marker, MMP-3, the clinical enthesitis count was significantly correlated with measures of disease activity and functional status, including the DAPSA, DAS28-CRP, PASE, and HAQ score. Neither assessment method was significantly correlated with measures of structural damage and axial involvement. The relationship between PASE and clinical enthesitis count is likely because the PASE comprises patient-reported outcomes and the severity of joint symptoms. Furthermore, the DAPSA and DAS28-CRP contain the tender joint count, and patients with many painful entheses have a high HAQ score (*i.e.* lower function). However, the fact that the US active enthesitis count was correlated with the MMP-3 level is interesting. While the CRP level is minimally influenced by enthesitis (42) and the DAS28-CRP may underestimate the disease activity of PsA (43), the MMP-3 level has been reported as higher in patients with PsA than in healthy controls, and is useful in diagnosing PsA early (44). In addition, MMP-3 level could predict structural damage (45). However, the value of the MMP-3 level in PsA remains uncertain. The present study suggests that the MMP-3 level reflects the severity of enthesitis. However, the MMP-3 level cannot identify the site of enthesitis, as it is a systemic synovial inflammatory marker. In addition, among 26 patients with negative MMP-3 titer, 20 had US active enthesitis. This fact suggests that the enthesitis cannot be predicted only by MMP-3 level and supports the necessity of conducting US examinations.

The present study has several limitations. First, the US assessment may overestimate enthesitis because positive PD signals at the entheses were also observed in conditions of overuse. Second, as all participants were initially consulted to the Department of Dermatology at a single university hospital for skin lesions, there might be a selection bias regarding patient characteristics. Finally, the present study comprised a small number of patients.

In conclusion, the clinical assessment of enthesitis differed completely from the US assessment of enthesitis. The US active enthesitis count correlated with the MMP-3 level and reflected inflammation, whereas the clinical enthesitis count correlated with the DAPSA, DAS28-ESR, PASE, and HAQ score and reflected disease activity and disability. These results suggest that US examinations are essential for preventing the underestimation of enthesitis.

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