Adding ultrasound to clinical examination reduced frequency of enthesitis in primary care psoriasis patients with musculoskeletal complaints

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Abstract

Objective

Part of the psoriasis patients with musculoskeletal complaints will have inflammation of the entheses. Entheseal inflammation is difficult to assess by clinical examination only. Therefore, we aimed to determine the frequency of clinically relevant ultrasound inflammation at the most commonly assessed entheses (MASEI; Madrid Sonographic Enthesis Index) in primary care psoriasis patients with one or more tender entheses.

Methods

Adult primary care psoriasis patients with musculoskeletal complaints (tender enthesis or arthritis at physical examination) had an ultrasound examination of seven entheses according to the MASEI. Clinically relevant ultrasound inflammation was defined as active inflammation on ultrasound in combination with at least one clinical feature at the same enthesis. Active ultrasound inflammation contained positive power Doppler signal or in case of the plantar aponeurosis increased thickness. Structural changes entailed calcifications, enthesophytes, increased thickness, hypoechogeneicity indicating irregular fibre structure and erosions. Clinically, an enthesis was scored positive by a tender enthesis at clinical examination, reported pain in the history or self-reported pain in the questionnaires.

Results

Of 542 primary care psoriasis patient, 111 patients had tender entheses and/or arthritis. These patients were both clinically and ultrasonographically evaluated. Active ultrasound inflammation accompanied with pain or tenderness at the enthesis was found in 36% of the patients (n=40). Most common were inflammation at the knee (n=11) and at the plantar aponeurosis (n=10). Structural changes were observed in 95% of the psoriasis patients independent of their clinical manifestation.

Conclusion

We found concurrent presence of ultrasound inflammatory changes and clinical symptoms in 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites.

Key words

ultrasonography, psoriatic arthritis, primary care, enthesitis, psoriasis

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Introduction

Enthesitis is an important domain in psoriatic arthritis (PsA). Since the introduction of the CASPAR classification criteria for PsA in 2006, psoriasis patients can classify as PsA with only enthesitis as inflammatory articular involvement (1). Increasing attention is paid to its assessment (2, 3), but up to now no consensus has been achieved on its measurements in the diagnostic setting. In both the classification criteria for PsA and spondyloarthritis (SpA), enthesitis is included. The CASPAR criteria suggest that the doctor diagnoses enthesitis as he sees fit. The ASAS criteria for peripheral SpA include only the Achilles tendon and the plantar aponeurosis without being specific which clinical characteristics need to present (4).

Enthesitis is defined as inflammation at tendon, ligament, joint capsules or aponeurosis insertion sites to bone. Entheseal pain can be severe, disabling and continuous, and can last for several years (5, 6). The ethiopathogenesis is poorly understood and may relate to mechanical stress on top of the immune response (7). Clinical assessment of the entheses is difficult as inflammation is often not visible or palpable. In addition, it may be difficult to anatomically locate the enthesis if it lies deep within the surrounding tissue (8). The location of several entheseal sites overlaps with those of the tender points of fibromyalgia (9). Furthermore, the presence of a tender enthesis is not necessarily indicative for underlying inflammatory disease as it could be related to overuse, metabolic disease or ageing (10). These challenges could lead to clinically false-positive patients.

To resolve the difficulties regarding clinical assessment of the entheses, inflammatory characteristics at the enthesis can be visualised by ultrasound (US) (11). Especially the use of the power Doppler mode improves the assessment of inflammation at the entheses (12, 13). New data about US enthesitis emerged in patients with psoriasis, PsA and healthy controls (14-16). So far, studies evaluated enthesitis in patients with psoriasis who were referred from the dermatologist (16-20). A significant higher prevalence of both grayscale (GS) and power Doppler (PD) US enthesopathy was found in patients with psoriasis than in controls (patients with dermatological diseases other than psoriasis) (16-18). In patients with PsA the severity of US abnormalities was even higher than in patients with psoriasis (20). US abnormalities at the entheses were present in both symptomatic (true-positive) and asymptomatic (false-positive or subclinical disease) psoriasis patients which suggests single application of US is not sufficient to detect clinically relevant entheseal inflammation (19, 21).

Little data is available on the presence of PsA in primary care psoriasis patients (22, 23). In several countries psoriasis patients are treated by their general practitioner and this might mean that cases of PsA are missed. In addition, these studies did not include US to assess inflammation at the entheses. In a large primary care based study the frequency of PsA in psoriasis patients was estimated to be 3.1% for arthritis and axial disease, increasing to 4.6% when enthesitis would be included (24).

In this study we describe the frequency of US abnormalities at the entheses and its clinical information in primary care psoriasis patients who had at least one tender enthesis at clinical examination. We combined PD US and clinical information at the same enthesis to differentiate between active inflammation and other manifestations of enthesopathy.

Materials and methods

Patients

Adult patients with psoriasis (ICPC S91) were identified from 97 general practitioners (GPs) in the Rotterdam area. These patients were invited to participate in the SENSOR study. Details of this cross-sectional study can be found in Karreman *et al*. (24). In brief, patients who reported regular episodes of pain in joints, entheses or the lower back were eligible and invited for clinical evaluation by a trained nurse. Patients were not recruited consecutively. Data collection included a detailed clinical examination (amongst others, swollen joint count, tender joint count, entheses evaluation), demographic characteristics and symptom history.

Written informed consent was obtained from the participants. The study was approved by the medical ethic committee of Catharina Hospital, Eindhoven, the Netherlands.

Entheses evaluation

• *Clinical examination*

Physical examination included the 66/68 joint count for PsA and entheseal assessment following the Leeds Enthesitis Index (LEI) and the Maastricht Ankylosing Spondylitis Enthesis Score (MASES) (2, 3).

Other assessments included measurement of psoriasis severity by the PASI and body mass index.

If clinical examination indicated a painful enthesis on the LEI/MASES or indicated an arthritis, US examination of the entheses was performed.

• *Ultrasound examination*

An independent US examiner blinded for the clinical details performed the US using Esoate MyLab60 (probe LA 435). The six entheses of the Madrid Sonographic Enthesis Index (MASEI) (25) and the lateral epicondyle tendon insertion (elbow) were examined. Each tendon was examined in the longitudinal plane. Knee entheses were examined with the patient in supine position and the knee flexed at 20°. The Achilles tendon and the plantar aponeurosis were examined with the patient in prone position and the feet hanging over the edge of the examination table in neutral position. To examine the lateral aspect of the elbow, the patient was positioned with the elbow flexed, forearm extended and palm down. To examine the olecranon, the patient was asked to raise the elbow and to keep the elbow flexed (90°) with the hand palm resting on the table. According to the MASEI scoring system the following elemental lesions of enthesitis were evaluated at each site: calcifications, bursitis, erosions, PD signal in bursa or enthesis full tendon (cortical bone profile, intratendon and paratendon on the enthesis insertion) and thickness and structure (25). US abnormalities were divided into 'active inflammation' and 'structural change' parameters. Active inflammatory components on US included the presence of PD signal (<2 mm of the bony cortex) (15) or in case of the plantar aponeurosis an increased thickness (≥4.4 mm) (26). Structural changes included calcifications, erosions, structure, and increased thickness.

Table I. Baseline characteristics of primary care psoriasis patients (n=111).

	Suspected for enthesitis (n=88)	Suspected for arthritis (n=23)	*p*-value
Women (%)	57	39	0.130
Age, years (mean, SD)	54 (13)	54 (14)	0.936
LEI (median, IQR)	2 (1-4)	0 (0-1)	<0.001
MASES (median, IQR)	2 (0-4)	0 (0-1)	<0.001
MASEI (median, IQR)	7 (5-12)	10 (5-13)	0.302
Power Doppler positive, n (%)			0.626
1 enthesis	14 (16)	2 (9)	
2 entheses	12 (14)	3 (13)	
3 entheses	3 (3)	1 (4)	

LEI: Leeds Enthesitis Index (range: 0-6); MASES: Maastricht Ankylosing Spondylitis Enthesis Score (range: 0-13); MASEI: Madrid Sonographic Enthesis Index (range: 0-136); SD: standard deviation; IQR: interquartile range

• *Self-reported pain at the entheses*

Patients completed online self-reported questionnaires including the EARP (27) and PEST (28). From the EARP questionnaire we used the question regarding the Achilles tendon. From the PEST questionnaire we used those questions regarding pain of the heel, elbows, and knees. Patient history included questions about symptom history regarding previous episodes of entheseal inflammatory complaints, which were diagnosed by a GP.

• *Definition of enthesitis*

In this study we combined data from US and clinical examination, and patient-reported questionnaires to define active inflammation at the enthesis. We defined enthesitis as active inflammation on US (presence of PD signal and/or increased thickness of the plantar aponeurosis) in combination with at least one clinical feature at the same enthesis: i) tender point LEI/MASES, ii) self-reported pain at the elbow, knee, Achilles tendon and heel from the EARP or PEST questionnaire, iii) self-reported entheseal complaints (defined as previous episodes of entheseal inflammatory complaints, diagnosed by a GP).

Statistical analysis

To determine differences in baseline characteristics and US findings between patients suspected for enthesitis and patients suspected for arthritis we used descriptive statistics. Depending on the distribution of the data we used the independent *t*-test or Wilcoxon-Mann-Whitney test. Frequencies were compared using a Chi-square test. Analyses were made using STATA 12.0.

Results

In total, 111 patients of the total study population with psoriasis (n=524) who reported regularly musculoskeletal complaints were evaluated by US. Of these patients, 88 patients were referred for US because they had at least one tender enthesis on the LEI/MASES. The other 23 patients were referred for suspected arthritis and also underwent an evaluation of the entheses by US. Nine (8%) patients had a confirmed diagnosis of PsA by a rheumatologist. Patient characteristics are presented in Table I.

Entheses evaluation

• *Clinical examination*

The median number of tender entheses on the LEI was 2 (IQR: 0-3). The median number of tender entheses on the MASES was 1 (IQR: 0-3). Patients suspected for enthesitis had more tender entheses on both the LEI and the MASES (median (IQR): 4 [1-7]) than patients suspected for arthritis (median (IQR): 2 [0-4]; $p<0.0001$). The most common tender entheses were found at the lateral epicondyle of the humerus (52%) and at the medial epicondyle of the femur (50%) (Table III).

• *Ultrasound examination*

In 106 (95%) patients (n=111) we detected one or more US abnormalities at the enthesis [Table II]. There was no difference in US findings between patients suspected for enthesitis and patients suspected for arthritis.

In 50 (45%) patients we found US abnormalities indicating inflammatory disease at the enthesis [Table III]. Thirty-five (32%) patients were PD positive on US of whom 5 (5%) also had a thickened plantar aponeurosis. Fifteen (14%) patients only had a thickened plantar aponeurosis. Positive PD signal was found most often at the lateral epicondyle of the humerus (21 patients, 19%) and at the insertion of the quadriceps tendon at the superior pole of the patella (13 patients, 12%). In 19 (17%) patients we found positive PD signal at more than one enthesis. Of note, we did not find any indication of inflammatory disease at the triceps enthesis at the olecranon.

Structural changes of the enthesis on US [Table III] were very common. Increased thickness of the distal patella tendon at the tuberositas tibiae (69%), and calcifications at the enthesis of the quadriceps tendon (superior pole patella: 59%) and at the enthesis of the Achilles tendon (63%) were found most often. Structural changes without indication of inflammatory disease were found in 56 (50%) patients.

Table II. Ultrasound abnormalities at the enthesis using the MASEI score (n=111).

Insertion	PD signal	Structure	Thickness	Bursitis	Erosion	Calcification
Lateral epicondyle tendon (elbow)*	21 (19)	19 (17)	51 (46)		35 (32)	47 (42)
Triceps tendon*	0	25 (23)	18 (16)		9 (8)	26 (23)
Quadriceps tendon*	13 (12)	12 (11)	53 (48)		3 (3)	66 (59)
Proximal patella tendon*	2 (2)	4 (4)	29 (26)		2 (1)	15 (14)
Distal patella tendon*	9 (8)	3 (3)	77 (69)	1 (1)	3 (3)	23 (21)
Achilles tendon*	4 (4)	1 (1)	12 (11)	0	1 (1)	70 (63)
Plantar aponeurosis*	†	1 (1)	20 (18)		0	20 (18)

*n (%); MASEI: Madrid Sonographic Enthesis Index (range: 0-136); PD: power Doppler; † not detectable.

Table III. Ultrasound and clinical findings per entheseal site (n=111).

Insertion	US inflammatory (n,%)	US structural (n,%)	Tender point (n,%)	Self-reported (n,%)
Lateral epicondyle tendon (elbow)	21 (19)	62 (56)	58 (52)	54 (49)
Triceps tendon	0	49 (44)	†	54 (49)
Quadriceps tendon	13 (12)	68 (61)	55 (50)*	79 (71)
Proximal patella tendon	2 (2)	37 (33)		
Distal patella tendon	9 (8)	74 (67)		
Achilles tendon	4 (4)	68 (61)	32 (29)	19 (17)
Plantar aponeurosis	20 (18)	16 (14)	†	61 (55)

US: inflammatory; †: not included in LEI/MASES; *: medial epicondyle femur.

• *Self-reported pain at the entheses*

In total, 105 patients (95%) reported pain at a location relevant to the enthesis: the elbow, knee, Achilles tendon, or heel. Pain in the knee was most frequently reported (71%), followed by the heel (55%) and elbow (49%). Nineteen (17%) patients reported pain at the Achilles tendon insertion.

• *Patients fulfilling enthesitis definition*

Patients who had clinical symptoms and PD at one of their enthesis or a thickened plantar aponeurosis were classified as having US confirmed inflammatory enthesitis. Of the 50 patients with US abnormalities indicating inflammatory disease, the US findings were confirmed by clinical information in 40 patients (36%). These patients were classified as having active (US confirmed inflammatory) enthesitis. Twenty-eight patients had active enthesitis at one enthesis. These were found at the knee (n=11), at the insertion of the plantar aponeurosis (n=10), at the lateral epicondyle of the humerus (n=6) and at the Achilles tendon (n=1). Ten patients had active enthesitis at two entheses, and two patients had active enthesitis at three entheses. Thirty-two cases were referred because they had at least one tender enthesis on the LEI/MASES. The other eight cases were referred for suspected arthritis.

Ten patients had inflammatory US abnormalities while they did not report clinical problems. We found a positive PD signal in five patients. The PD signal was found at the enthesis of the lateral epicondyle of the humerus (n=3), at the entheses of the knee (n=1), and in 1 patient both at the lateral epicondyle (humerus) and the Achilles enthesis. The plantar aponeurosis was thickened in five patients without clinical symptoms.

Figure 1 shows the distribution of the US findings, both structural changes and active inflammation combined with the clinical findings at each entheseal site.

Five patients had a painful enthesis clinically without having any US abnormalities. These patients all had a painful knee, combined with a painful enthesis at the lateral epicondyle of the humerus (n=4), with a painful heel (n=2), or a tender Achilles enthesis (n=1).

The other 56 patients had a painful enthesis with structural changes on US.

Discussion

In 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites (n=111) enthesitis was present, defined as concurrent presence of US inflammatory changes and clinical symptoms. US assessment included five elemental lesions: the presence of calcifications, erosions, increased thickness, changes in fibre structure, and positive PD signal. We indicated the first 4 lesions as 'structural changes' of the enthesis which were present in 95% of the patients, while we named positive PD signal the 'inflammatory component', present in 32% of the patients. One exception was made for the plantar aponeurosis as US was not able to elicit any PD signal in this area. Therefore, increased thick-

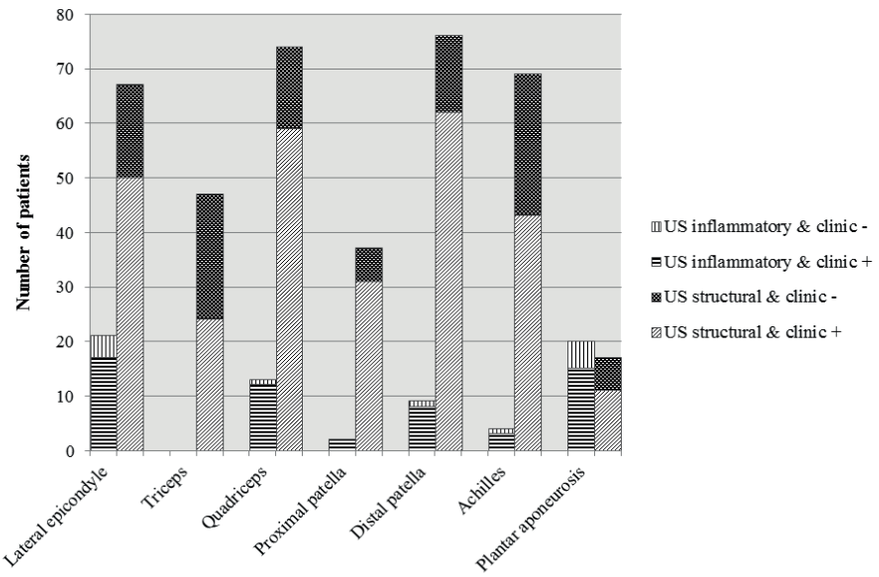

Fig. 1. Distribution of the ultrasound findings, both structural changes (US structural) and active inflammation (US inflammatory), in combination with the clinical findings.
-: negative; +: positive at each entheseal site.

ness was chosen to assess inflammatory changes at the enthesis of the plantar aponeurosis, which was present in 18% of the patients. In total, 45% of the patients (n=50) had US inflammatory changes. Combined with clinical information at the same enthesis this led to 36% of the patients (n=40) having enthesitis. In part of our study population (9%; n=10) we found US inflammatory components, but these were not confirmed by clinical information. This could be related to subclinical disease, which could be predictive for the development of PsA in patients with psoriasis (21, 29-31).

Considerable advances have been made in the use of US to evaluate entheses. Nevertheless, context of clinical information remains needed to differentiate between active inflammation and other manifestations of enthesopathy (10). By adding US to the clinical evaluation of entheses we were able to visualise the presence of active inflammatory involvement of the enthesis. This could help to differentiate patients with non-inflammatory entheseal pain from patients with entheseal involvement related to inflammation, helping physicians to make informed decisions about whom to treat with anti-inflammatory drugs. First-line treatment recommendations for enthesitis in PsA patients are NSAIDs. After insufficient response to NSAIDs, treatment can be switched to biological agents (32, 33). Since rheumatologists are quite reserved to prescribe biologic agents to treat enthesitis, US might give more certainty for detecting inflammatory disease at tender entheses. However, further research regarding the treatment of US confirmed enthesitis is needed.

One of the difficulties we came across was the absence of general accepted definitions for both the clinical presentation as well as the US presentation of enthesitis. The OMERACT US Task Force recently debated the latter, but they did not come to a definite conclusion what would be inflammatory (15). The main reason for this was the discussion on entheseal thickness. Part of the US examiners felt this to belong to inflammatory changes while other examiners attributed this to structural changes. Both could be true. In the acute phase, increased thickness might be present due to inflammation as shown by McGonagle *et al*. with soft tissue and bone edema at the plantar aponeurosis insertion on MRI appearances (34). However, thickening could also be the result of a disorganised repair process (scar tissue) in which no inflammation is present anymore.

There are several strengths and weaknesses to discuss when interpreting the results of our study. At first, for practical reasons we choose to apply US, rather than MRI. US was easy accessible, we could apply it to different locations at once and there were no safety issues. It has the disadvantage that it is reader dependable, which was solved by one examiner for all patients. However, US cannot depict bone edema which is also indicative for inflammatory changes like MRI does. MRI is capable of detecting soft tissue changes associated with surrounding soft tissue edema in the region adjacent to the enthesis (10). However, application of MRI would require long acquisition time to evaluate 7 entheses bilaterally. There have been recent advances in whole body MRI but issues need to be solved such as field of view, image resolution for small structures and body position (35). Secondly, patient position during the US examination of the knee entheses was not ideal. In our study maximum flexion of the knee was 20°, which could have influenced our PD signal at the entheseal level of the knee entheses. Previous studies found an severe decrease of PD signal when the knee was flexed at 30° (36). Flexion of the knee could increase intratendinous tension, which facilitates collapse of the microvessels. Thirdly, due to the aim of our initial study, which was to estimate the prevalence of PsA in primary care psoriasis patients, we did not include control patients. However, there is a substantial body of evidence that shows the usefulness of the MASEI score in differentiating patients with PsA/SpA from healthy controls (20, 37), especially if using inflammatory changes (PD signal) rather than structural changes (21). This stresses our choice to use a positive PD signal at the enthesis as an indication for active US enthesitis. A strength of our study is that we included primary care patients with psoriasis with musculoskeletal complaints. Most studies evaluating enthesitis with US have included psoriasis patients in secondary care referred by the dermatologist (16). Our study population is a different population in which it would be beneficial to screen for PsA and to improve early diagnosis of PsA.

In conclusion, enthesitis defined as concurrent presence of US inflamma-

tory changes and clinical symptoms was present in 36% of the primary care psoriasis patients who had tenderness at one or more entheseal sites. Combining clinical data and US at the same enthesis reduced the frequency of entheseal lesions that should be evaluated by the rheumatologist compared to clinical exam only. Consensus needs to be reached to find a generally accepted definition for enthesitis which would be feasible in daily clinical work.

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