

Association of Physical Activity and Medication with Enthesitis on Ultrasound in Psoriatic Arthritis

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ABSTRACT. Objective. Enthesitis is a manifestation of psoriatic arthritis (PsA), but its symptoms are difficult to interpret clinically. We investigated the associations of ultrasonographic changes in entheses with clinical characteristics in patients with PsA, and compared enthesitis changes of patients aged 35 to 60 years with healthy volunteers of that age.

Methods. Consecutive patients with PsA participated in this cross-sectional study, irrespective of enthesitis complaints and age. We collected data about complaints, physical activity and activity avoidance, medication, and clinical enthesitis. Inflammatory and structural enthesitis changes were scored with the modified MADrid Sonographic Enthesitis Index (MASEI). Among all patients, associations between ultrasound (US) scores and clinical characteristics were investigated using linear regression. We compared US scores of healthy volunteers and patients with PsA aged 35–60 years using Wilcoxon rank-sum tests.

Results. Eighty-four patients with PsA and 25 healthy volunteers participated. In patients with PsA, we found a small association between higher inflammatory-modified MASEI score and older age (β 0.07, 95% CI 0–0.13) and current use of biologics (β 1.56, 95% CI 0.16–2.95). Patients who reported avoiding activities had significantly lower inflammatory-modified MASEI scores (β –1.71, 95% CI –3.1 to –0.32) than those who did not. The patients with PsA aged 35–60 years ($n = 50$) had similar inflammatory scores as healthy volunteers but higher structural scores (median 6 vs 2; $p = 0.01$).

Conclusion. Within patients with PsA, avoiding physical activity, younger age, and not using biologics were associated with less enthesitis inflammation. Patients with PsA and healthy volunteers aged 35 to 60 years displayed similar levels of inflammatory changes of the entheses, but patients had more structural damage. (J Rheumatol First Release May 1 2019; doi:10.3899/jrheum.180782)

Key Indexing Terms:

ENTHESITIS PSORIATIC ARTHRITIS HEALTHY VOLUNTEERS ULTRASOUND

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease that belongs to the group of spondyloarthropathies. It has a heterogeneous presentation of arthritis, psoriasis, spondylitis, dactylitis, and enthesitis^{1,2}. Enthesitis is one of the distinguishing features of spondyloarthropathies and is defined as inflammation of tendon, ligament, or joint capsule insertion. Enthesitis is found at

clinical examination in one-third of patients with PsA³, but tenderness of the enthesitis does not necessarily have an inflammatory origin. A better technique is needed to distinguish PsA-related inflammatory enthesitis from other enthesiopathies, such as metabolic, degenerative, and mechanical processes⁴.

With ultrasound (US), inflammatory and structural changes of the entheses can be assessed⁵ and quantified with a composite US score, such as the MADrid Sonographic Enthesitis Index (MASEI)⁶. In a previous study we evaluated the use of the MASEI in an extreme comparison; we compared patients newly diagnosed with PsA, patients with established disease, and young healthy volunteers⁷. We found that increased thickness of knee entheses and a subtle power Doppler (PD) signal were present in all groups, even in young healthy volunteers. We therefore modified the MASEI score: we excluded knee enthesitis thickness (i.e., quadriceps and both patellar tendon insertions) from the evaluation and graded PD severity. This modified MASEI score showed a good discrimination between entheses of patients and those of young healthy volunteers. Because the number of enthesitis abnormalities varied within all groups, we suspected that

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factors other than PsA-related inflammation could cause these US abnormalities. Previous studies, for example, showed that older age and higher body mass index (BMI) were associated with more enthesal abnormalities on US, both in patients with PsA and in healthy volunteers^{8,9}. Studies in healthy volunteers showed that physical activity is also associated with changes in entheses on US^{10,11}, although this is not confirmed in PsA, to our knowledge. We therefore aimed to investigate associations between modified MASEI scores and clinical characteristics in an average PsA population. In addition, we aimed to compare the modified MASEI scores of patients with PsA and healthy volunteers aged 35 to 60 years.

MATERIALS AND METHODS

Patients and setting. Consecutive patients of all ages with established PsA for at least 2 years attending the rheumatology clinic were eligible to participate, irrespective of disease activity or complaints. Patients were recruited from 3 outpatient clinics in the Netherlands (the academic hospital, Erasmus MC, and the general hospitals Vlietland Hospital and Albert Schweitzer Hospital) between May and August 2016. Healthy volunteers were invited if they were aged 35–60 years, without a history of any of the following: any rheumatic disease, Crohn disease, uveitis, familial hypercholesterolemia, or diabetes. Written informed consent was obtained from all participants according to the Declaration of Helsinki. The study was approved by the local medical research ethics committee of Erasmus MC, University Medical Centre Rotterdam (MEC-2012-549).

Data collection. In a structured interview, patients answered questions about their disease duration, physical activity, and avoidance of activity. Regarding physical activity, patients were asked whether they exercised regularly. Regarding avoidance, patients were specifically asked whether they avoided activities because of complaints or fear of complaints in daily life during exercise, work, household activities, and chores. We scored avoidance when patients reported avoiding activities because of pain or fear of pain. Fulfillment of CIASSification for Psoriatic ARthritis (CASPAR) criteria¹² and medication use was obtained from chart review.

Data collected during physical examination were height, weight, 66 swollen joint count, 68 tender joint count, enthesitis at clinical examination [Leeds Enthesitis Index (LEI) and Maastricht Ankylosing Spondylitis Enthesitis Score], and Psoriasis Area and Severity Index.

US examination was performed directly after clinical examination by a sonographer trained in enthesitis sonography (IH), who was blinded for clinical information. Patients were instructed by the researchers who conducted the interview and physical examination (MM, KW) that they should not communicate any clinical information to the sonographer. The 6 MASEI entheses and the lateral epicondyle were bilaterally examined using an Esaote MyLab60 with linear probes LA435 (6–18 MHz; Doppler frequency of 8.3 MHz, pulse repetition frequency of 750 Hz, and a wall filter of 3) and LA532 (4–13 MHz; 6.3 MHz, 750 Hz, and a wall filter of 4). The former was used for entheses of the upper limbs and the latter for the entheses of lower limbs. In each site, we scored calcifications, erosions, structural changes, thickness, PD signal, and bursitis. Only presence of PD signal within 2 mm of the cortex was scored. Patients were positioned according to the MASEI, but with the knee flexed at about 30° (rather than 70°) and resting on a pillow to ensure relaxing of the quadriceps muscle. The lateral epicondyle was examined in 90° flexion and a cutoff of 4.2 mm was used in this enthesitis¹³. If a PD signal was present, images of the severest PD signal were saved and scored by KW and IH, who had an interrater agreement of 93% (intraclass correlation coefficient). In addition to the original MASEI score, we calculated the modified MASEI by excluding the knee entheses thickness (i.e., quadriceps, and proximal and distal patellar tendon insertion) and grading of PD signal. All abnormalities were recorded

during US evaluation, and PD signal was graded by a second scorer (KW) on the static images. PD signal intensity was scored as follows: 0 = absent, 1 = 1 spot, 1.5 = 2 spots, 2 = confluent signal, 3 = confluent severe signal (Supplementary Figure 1, available with the online version of this article). Absolute agreement was 93% and weighted Cohen's κ using linear weights was 0.92. We distinguished an inflammatory component (sum of points for increased thickness, bursitis, and PD signal) and structural component (sum of points for structure, calcifications/enthesophytes, and erosions).

Statistical analysis. Within the total PsA population, the associations between clinical characteristics and (1) inflammatory modified MASEI, and (2) structural modified MASEI were investigated using multiple linear regression analyses. Using a forward selection ($p < 0.30$), the following independent variables were tested: age, BMI, disease duration (square-transformed), current use of disease-modifying antirheumatic drugs (DMARD), current use of nonsteroidal antiinflammatory drugs (NSAID), current use of biologics, avoidance of activities, exercise, and enthesitis at clinical examination. This was done for both inflammatory modified MASEI and structural modified MASEI as dependent variables. The latter was transformed $[(y + 1)^2]$ because of its skewed distribution. Modified MASEI scores of a subgroup of patients between the age of 35 and 60 years and of the healthy volunteers of the same age range were compared using the Wilcoxon rank-sum test.

RESULTS

In total, 84 consecutive patients with established PsA participated; mean age was 55 years (SD 11, age range: 26–76 yrs), 45 (54%) were male and mean BMI was 27 (SD 5). Median disease duration was 8 years. Disease activity was mild in our usual-care consecutive cohort: median swollen joint count was 0 (interquartile range; IQR 0–2) and median tender joint count 3 (IQR 0–7). Median LEI score was 0.5 (IQR 0–2). Forty patients (48%) reported that they exercise regularly, and avoiding activities was reported by 17 (43%) of those patients with regular exercise. Among patients not exercising regularly, avoidance of any physical activity was reported by 28 (64%, Table 1).

Association between US scores and clinical characteristics. Within patients, a small association was found between a higher inflammatory-modified MASEI score and older age (β 0.07, 95% CI 0–0.13) and current use of biologics (β 1.56, 95% CI 0.16–2.95). Patients who reported avoiding activities had significantly lower inflammatory-modified MASEI scores (β -1.71, 95% CI -3.1 to -0.32; Table 2). Older age was also associated with a higher score on structural modified MASEI (β 0.03, 95% CI 0.01–0.05, $p = 0.001$; Table 3). Current use of NSAID or DMARD, regular exercise, sex, and enthesitis at clinical examination were not associated with any of the modified MASEI scores.

Enthesis US scores. Total US scores of patients aged 35–60 years were compared with those of 25 healthy volunteers in the same age range. Healthy volunteers had a mean age of 47 (SD 6) years, 12 were male (48%), and the average BMI was 25 (SD 4; Supplementary Table 1, available with the online version of this article). The original median MASEI scores of 50 patients with PsA aged 35–60 years (14, IQR 9–21) were comparable to those of the 25 healthy volunteers (13, IQR 9–18; Table 4). Table 5 shows the prevalence of each

Table 1. Demographic and clinical characteristics of patients with PsA.

Characteristics	N = 84
Age, yrs	55 ± 11
Male	45 (54)
BMI	27 ± 5
Disease duration, yrs	8 (5–12)
Fulfilling CASPAR criteria	81 (96)
Swollen joint count (66)	0 (0–2)
Tender joint count (68)	3 (0–7)
LEI	0.5 (0–2)
MASES	1 (0–2)
PASI ^a	0.6 (0–2.8)
Regularly exercising	40 (48)
Avoidance of activity	45 (54)
Current medication use	
NSAID	31 (37)
DMARD	64 (76)
Prednisone	1 (1)
Biological DMARD	40 (48)

Data presented as mean ± SD, n (%), or median (interquartile range).
^aExcluding 1 patient without a history of psoriasis. PsA: psoriatic arthritis; BMI: body mass index; CASPAR: CLASSification for Psoriatic ARthritis; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; PASI: Psoriasis Area and Severity Index; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug.

Table 2. Association between ultrasound scores (inflammatory-modified MASEI) and clinical characteristics.

Variables	β	95% CI	p
Age	0.07	0–0.13	0.050
BMI	0.13	–0.01 to 0.27	0.063
Duration ²	0.04	–0.73 to 0.82	0.909
DMARD, no vs yes	1.23	–0.4 to 2.87	0.137
Biological DMARD, no vs yes	1.56	0.16–2.95	0.029
Avoidance of activity, no vs yes	–1.71	–3.1 to –0.32	0.017

Linear regression of 84 patients with PsA. MASEI: MADrid Sonographic Enthesis Index; BMI: body mass index; DMARD: disease-modifying antirheumatic drug; PsA: psoriatic arthritis.

Table 3. Association between ultrasound scores (structural modified MASEI) and clinical characteristics.

Variables	β	95% CI	p
Age	0.03	0.01–0.05	0.001
BMI	0.04	0–0.08	0.054
Duration ²	0.11	–0.1 to 0.32	0.302

Linear regression of 84 patients with PsA. Transformation of structurally modified MASEI: $(y + 1)^2$. MASEI: MADrid Sonographic Enthesis Index; BMI: body mass index; PsA: psoriatic arthritis.

abnormality in the total PsA group, in the subgroup aged 35 to 60 years, and in the healthy volunteer group. After excluding knee enthesitis thickness and grading PD score, the

resulting modified MASEI scores were 11 (IQR 6.5–15) in patients and 7.5 (IQR 5–9; $p = 0.01$) in healthy volunteers. The inflammatory contribution (i.e., thickness, bursitis, and PD signal) to this modified MASEI was similar in patients (5, IQR 2–7) and healthy volunteers (3.5, IQR 2–5.5). The structural contribution (i.e., calcification, erosion, and structural changes) was significantly higher in patients (6, IQR 3–10) than in healthy volunteers (2, IQR 1–6; $p = 0.01$). Presence of PD signal was similar in patients and healthy volunteers.

DISCUSSION

We found that in a PsA population not selected based on complaints of the entheses, older age and the current use of biologics were associated with higher inflammatory scores, while patients reporting avoidance of activity had lower inflammatory scores. Having more structural changes in PsA was associated only with older age. No effects were seen on US of BMI, current NSAID use, regular exercise, sex, and clinical symptoms of enthesitis, possibly because we did not have the power to detect a small effect. Inflammatory changes of the entheses occurred as often in healthy volunteers of the same age. The patients with PsA did, however, have twice as many structural changes of the entheses.

The finding that regular exercise was not related to US changes but avoidance of activity was related seems contradictory. This may relate to the way we recorded avoidance, that is, in more domains than only sports activities, and patients could report both avoiding activity and exercising regularly. In the statistical analysis, US changes were associated more with avoidance than with physical activity. Physical activity probably both influences and is influenced by the pathology of tendons and entheses, making the interpretation of sonographic abnormalities difficult. Some patients avoiding physical activity might have had enthesitis and consequently altered their behavior. The relationship between physical activity and sonographic enthesitis changes has not been shown in PsA before, although some work has been done in athletes. Changes of tendons and entheses have been observed through US in the patellar tendons of athletes immediately after they played high-level badminton matches¹⁰ or ran a marathon¹¹. The respective strain on the tendons might be different, but in both cases, some reaction after physical exercise was seen on US. This could be a physiological response or an early sign of a pathological reaction: other studies have shown that abnormalities on US could precede clinical manifestations of overuse injuries in healthy athletes^{14,15}. In contrast, a study assessing the MASEI scores of 30 athletes (who were running or playing soccer for at least 6 h per week) and 29 non-athletes (who were playing a sport < 1 h per week) could not show a difference¹⁶. These data suggest that in a healthy situation, tendons and entheses have adapted to the regular level of physical activity but do respond to a change in physical

Table 4. Comparison of enthesitis ultrasound scores between patients with PsA and healthy volunteers (HV).

Variables	Total PsA Patients, n = 84	PsA Patients Aged 35–60 Yrs, n = 50	HV Aged 35–60 Yrs, n = 25	p, PsA vs HV Aged 35–60 Yrs
MASEI	15.5 (11–22)	14 (9–21)	13 (9–18)	0.39
Modified MASEI	12 (7.3–17)	11 (6.5–15)	7.5 (5–9)	0.005
Inflammatory-modified MASEI	5 (2.8–7.5)	5 (2–7)	3.5 (2–5.5)	0.16
Structural modified MASEI	7 (3–10)	6 (3–10)	3 (1–6)	0.005
PD				
PD in any entheses	74 (88)	44 (88)	22 (88)	1.00
PD in ≥ 2 entheses	47 (56)	27 (54)	17 (68)	0.25
Confluent PD in any entheses	35 (42)	20 (40)	9 (36)	0.74
Severe PD in any entheses	7 (8)	4 (8)	0 (0)	0.29
Average PD score ^a	1.5 (1.3–1.8)	1.5 (1.3–1.7)	1.5 (1.3–1.5)	0.44

Data presented as median (interquartile range) or n (%) unless otherwise specified. ^a In 74 and 44 patients and 22 HV where PD was present. PsA: psoriatic arthritis; MASEI: MADrid Sonographic Enthesis Index; modified MASEI: MASEI with lateral epicondyle, excluding knee entheses thickness, and grading of PD; PD: power Doppler.

Table 5. MASEI score per component per entheses location.

Variables	Structure			Thickness			Erosion			Calcification*			PD Signal			Bursitis		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Lateral epicondyle tendon	1	1		53	50	30	4	3		49	41	16	26	30	18			
Triceps tendon	1	2		13	11		2	3		24	23	2	1	2	2			
Quadriceps tendon				70	64	60				65	66	48	34	32	42			
Proximal patella tendon	1	1		74	72	68	1	1		8	7	2	11	10	12			
Distal patella tendon				96	98		1	1		10	8	14	53	30	36			
Achilles tendon	1	1		10	12	2	2	3		52	55	42	5	4	4			
Plantar fascia				33	23	12				1								

Data shown as no. abnormalities (%) per group. * Calcification is expressed as no. tendons with a score > 0. A: total PsA group; B: patients with PsA aged 35–60 yrs; C: healthy volunteers aged 35–60 yrs. MASEI: MADrid Sonographic Enthesis Index; PD: power Doppler; PsA: psoriatic arthritis.

activity. We found a similar relationship in patients with PsA, though we did not directly study the modifying effect of PsA by comparing the relationship with that in healthy volunteers. Longitudinal studies are needed to investigate whether the response of entheses to physical activity is altered in PsA.

Comparable inflammatory scores of healthy volunteers and patients with PsA suggest that US evaluation of the entheses is of limited value in screening for inflammation. This was also concluded by Groves, *et al*, who compared magnetic resonance imaging (MRI) and US evaluation of the elbow in patients with PsA and rheumatoid arthritis who reported elbow pain¹⁷. In one-third of cases, inflammation could be seen on MRI but not on US. The larger extent in which structural changes were present in patients with PsA in our study suggests that patients have been subject to more chronic inflammation of the entheses than healthy volunteers of similar age.

The higher occurrence of inflammatory changes of the entheses in patients using biological DMARD (bDMARD) was an interesting but unexpected finding because bDMARD are recommended in the treatment of enthesitis in PsA. One explanation is that patients taking bDMARD are a selected population with more severe inflammation. Michelsen, *et al*

investigated Achilles enthesitis in patients with PsA and found that use of biologicals was associated with more structural damage, but not with inflammatory activity¹⁸. This contradicts our study; we found an association with inflammatory activity and not with structural damage. A second possible explanation is that tendons and entheses recover at a slow rate and not all patients may have used bDMARD for a long enough period. A study in ankylosing spondylitis showed that inflammatory US lesions did not change after 6 months of tumor necrosis factor (TNF)-blocking therapy¹⁹. But in a similar study, Aydin, *et al* did find a decrease in US lesions after 2 months of therapy, as did Naredo, *et al* after 6 months of followup^{20,21}. Similarly, a study using MRI in axial spondyloarthritis found a decrease in enthesitis after 2 years of treatment with etanercept²². A third explanation is that the effect of bDMARD on enthesitis is heterogeneous and depends on the type of treatment [i.e., TNF inhibitors, anti-interleukin (IL)-17, or anti-IL-12/IL-23].

A limitation of our study is its cross-sectional design, which makes it difficult to interpret the association between clinical symptoms and US scores. The relationship between physical activity and enthesitis might be subject to information bias, and the exact effect of physical activity on

entheses is better investigated in an experimental setting. For example, the reporting of physical activity and avoidance of physical activity might be influenced by a history of enthesitis and different adaptive behavior and coping strategies. Second, physical activity, and in particular longterm effects of physical activity, are difficult to measure and the measurement of self-reported physical activity could be biased. Third, this study has an exploratory characteristic, in which multiple factors of influence were tested. The models were fitted to this established usual-care population with relatively low disease activity and use of NSAID and biologics by the majority. For these reasons, future studies — preferably longitudinal studies — are needed to confirm these results.

In this cross-sectional study, avoidance of physical activity, younger age, and not using bDMARD were associated with less inflammation of the entheses. Patients with PsA and healthy volunteers aged 35 to 60 years displayed similar levels of inflammatory changes of the entheses, but patients with PsA had more structural damage. The only way to understand these associations is to investigate changes of entheses on US in prospective longitudinal studies.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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