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Comparison of the Heel Enthesitis MRI Scoring System (HEMRIS) with clinical enthesitis and local metabolic activity on PET-CT

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ABSTRACT

Objective To compare the Heel Enthesitis MRI Scoring model (HEMRIS) with clinical and PET/CT outcomes in patients with cutaneous psoriasis (Pso), psoriatic arthritis (PsA) or ankylosing spondylitis (AS).

Methods This prospective, observational study included 38 patients with Pso, PsA and AS. Patients were included regardless of presence or absence of clinical heel enthesitis. MRI-scans of both ankles and a whole-body ^{18}F-FDG PET/CT were acquired. MRIs were assessed for enthesitis by two independent and blinded observers according to the HEMRIS. A physician, blinded for imaging results, performed clinical evaluations of enthesitis at the Achilles tendon and plantar fascia.

Results In total, 146 entheses were scored according to the HEMRIS and clinically assessed for enthesitis (6 entheses were clinically affected). In Achilles tendons with clinical enthesitis, the HEMRIS structural damage score was significantly higher, compared to Achilles tendons without clinical enthesitis (respective median scores 1.0 and 0.5; p=0.04). In clinically unaffected entheses, HEMRIS abnormalities occurred in 44/70 (63%) of Achilles tendons and in 23/70 (33%) of plantar fascia. At the Achilles tendon, local metabolic activity measured on PET/CT was weakly associated with the structural (r_s=0.25, p=0.03) and total HEMRIS (r_s=0.26, p=0.03).

Conclusion This study revealed a high prevalence of subclinical HEMRIS abnormalities and discrepancy between HEMRIS and clinical and PET/CT findings. This may suggest that the HEMRIS is a sensitive method for detection of inflammatory and structural disease of enthesitis at the Achilles tendon and plantar fascia, although the clinical significance of these MRI findings remains to be determined in longitudinal studies.

Key messages

What is already known about this subject?

- Recently, the Heel Enthesitis MRI Scoring model (HEMRIS)[1] was developed for use in clinical trials and clinical practice in spondyloarthritis.

What does this study add?

- The first study to compare the novel HEMRIS to clinical examination and PET/CT in a cross-sectional cohort of patients with psoriasis, psoriatic arthritis and ankylosing spondylitis.
- HEMRIS abnormalities were highly prevalent in clinically unaffected entheses: in 63% of Achilles tendons and 33% of plantar fascia.
- Clinical enthesitis and local FDG-PET/CT uptake were related to HEMRIS abnormalities occurring at the Achilles enthesis.

How might this impact on clinical practice or future developments?

- Since subclinical HEMRIS abnormalities were frequently observed in the current study, the prospective value of HEMRIS should be evaluated in future longitudinal studies prior to implementation into clinical practice.

INTRODUCTION

Inflammation at the enthesis (enthesitis) is a key clinical feature of spondyloarthritis. Psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are both spondyloartropathies in which enthesitis is part of disease classification criteria.[2 3] Enthesitis is also considered in treatment recommendations for PsA.[4 5] Detection of enthesitis in patients with cutaneous psoriasis (Pso), can allow for early diagnosis of PsA and timely treatment initiation. Delay in diagnosis of PsA is associated with development of peripheral joint erosions and reduced functional outcome.[6] Beyond daily clinical practice, enthesitis is an important outcome measure in clinical trials in PsA and AS.[7 8]

Currently, there is no gold standard for the evaluation of enthesitis. In clinical examination, enthesitis is evaluated by local tenderness

when pressure is applied, but this method is considered to have low sensitivity.[9] Another challenge is the low specificity of clinical examination, for example to discriminate between tenderness at the enthesis caused by inflammation or another cause, such as fibromyalgia.[10 11] Hence, there is much interest in the use of imaging techniques for detection of enthesitis.

Imaging techniques used for assessment of enthesitis include magnetic resonance imaging (MRI) and ultrasound. Previous work has shown that MRI and ultrasound can detect subclinical disease activity at the enthesis.[12 13] MRI is currently the only imaging modality available to assess peri-entheseal bone marrow oedema, which is a specific inflammatory feature of enthesitis.[14 15]

Another imaging test that has the potential to diagnose enthesitis is ^{18}F-fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography CT (PET/CT), as ^{18}F-FDG is a marker for inflammatory processes.[16] ^{18}F-FDG PET/CT has been reported to detect inflammation at the enthesis in psoriatic arthritis patients,[17] while such features are not typically seen in healthy individuals.[18]

The heel, where the Achilles tendon and plantar fascia attach to the calcaneus, is a frequently affected anatomical site for enthesitis in spondyloarthritis since it is subjected to high mechanical stress.[8 19] Recently, the Outcome Measures in Rheumatology (OMERACT)-group developed and validated the Heel Enthesitis MRI Scoring system (HEMRIS).[1] This novel MRI scoring system takes both inflammatory and structural features of enthesitis into account. The HEMRIS was not previously compared with other diagnostic methods for enthesitis. We aimed to compare HEMRIS with clinical, laboratory and PET/CT outcomes in Pso, PsA and AS patients.

METHODS

Study design and patients

This prospective observational study was performed in a single university hospital. As part of the study design, multiple imaging modalities were performed (MRI of the feet and whole-body ^{18}F-FDG PET/CT). We included patients aged 18–65 years, in three different disease categories: psoriasis (diagnosed by a dermatologist with psoriatic arthritis excluded by a rheumatologist (in-training)), psoriatic arthritis (fulfiling Classification Criteria for Psoriatic Arthritis (CASPAR)[2]) and AS (fulfiling Assessment of SpondyloArthritis international Society (ASAS) classification criteria.[3]) Exclusion criteria were current use of conventional or synthetic disease-modifying antirheumatic drugs (DMARDs), history of skin conditions other than psoriasis and contra-indications for MRI or PET/CT. Due to a separate analysis of the microbiome (unpublished data), patients with a history of inflammatory bowel disease or gastrointestinal surgery, or a strict diet were excluded from the study. Study participants were included regardless of the presence/absence of clinically suspected enthesitis. Incorporation of clinical examination, laboratory testing, as well as anatomical (MRI) and metabolic imaging (PET/CT) in this study enables assessment of mutual associations between different tests. All patients gave written informed consent for participation in the study. The study-protocol was approved by the local medical ethics committee (registration number 15–429/M).

Study assessments

Clinical assessments included height, weight, blood pressure, 66/68 joint counts, Psoriasis Area and Severity Index (PASI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Clinical assessment also included an overall assessment of enthesitis by means of the Leeds Enthesitis Index,[20] which evaluates enthesitis at the lateral humeral epicondyle, medial femur condyle, and Achilles tendon insertion. In addition, enthesitis was assessed at the plantar fascia. In accordance with the protocol for the Leeds Enthesitis Index, a standardised method of determining enthesitis was employed, defined as: pain or tenderness at the enthesis upon pressure of the thumb (pressure applied until examiner nail blanching occurred). Physicians that performed clinical assessments were blinded to imaging results that included MRI-scans of both feet and a ^{18}F-FDG whole-body PET/CT-scan. Laboratory parameters measured for the study were (CRP) and erythrocyte sedimentation rate (ESR).

MRI scanning protocol and HEMRIS scoring

Both feet and ankles were evaluated separately on a 3 Tesla MRI-scanner (Philips, type Achieve 3T TX, Koninklijke Philips Electronics NV, the Netherlands), using a head coil. By positioning both ankles in a head coil, both ankles were evaluated in the same position on the pre- and post-contrast images. The MRI-protocol included the following sagittal sequences: T2-weighted, T2-weighted Spectral Attenuated Inversion Recovery (SPAIR), T1-weighted SPIR (Spectral Presaturation with Inversion Recovery) before contrast, and T1-weighted SPIR after contrast.

MRI-scans were assessed for different enthesitis subscores using the semiquantitative HEMRIS[1] by two independent observers. The observers were a fellowship-trained musculoskeletal radiologist (IK) and a senior radiology resident with a sub-specialisation in musculoskeletal radiology (PHV). Both readers were blinded for clinical diagnosis and outcomes. The following pathologies were assessed at the calcaneal insertional site of the Achilles tendon and plantar fascia:

- Inflammatory pathologies: intratendon hypersignal, peritendon hypersignal, bone marrow oedema, and retrocalcaneal bursitis (Achilles tendon only).
- Structural pathologies: tendon thickening, enthesophyte, entheseal bone erosion, and intratendon hypersignal on T1W sequence.

Scores of both observers were averaged as suggested in the original HEMRIS publication. In case one observer scored a HEMRIS subitem as '0′ (absent) and the other observer as '1–3' (mild/moderate/severe), this HEMRIS subitem was discussed and agreed upon in a consensus meeting.

The OMERACT group suggested the use of 'total inflammation' and 'total structural' damage scores for the Achilles tendon and plantar fascia combined. In the present study, separate scores were calculated for the Achilles tendon and plantar fascia, because this allowed for comparison with clinical examination and PET/CT. Inflammation scores were calculated by summation of inflammatory variables, structural scores by summation of structural variables. A total HEMRIS score for each enthesis was created by summation of the inflammation and structural scores. For comparison of HEMRIS outcomes with clinical patient characteristics, such as age, BMI and laboratory parameters (ESR, CRP), we summated HEMRIS scores of the left and right ankles.

PET/CT

Whole-body ^{18}F-FDG PET/CT-scans were obtained for the evaluation of systemic inflammation, arthritis and ankle enthesitis. ^{18}F-FDG (dose 2,0 MBq/kg; radiation exposure is 2.7mSv for a patient of 70 kg[21]) was administered intravenously after an overnight fast. Glucose was measured before the scan. Two patients had glucose levels >8.3 (respectively 10.6 and 11.7), which was accepted for the purpose of this study.[22] The PET/CT-scans were acquired 1 hour after administration of ^{18}F-FDG. A non-contrast-enhanced low-dose CT was performed for attenuation correction (radiation exposure dose: 4.0 mSv). The PET/CT-reconstruction was compliant with European Association of Nuclear Medicine Research Ltd. (EARL) guidelines.

^{18}F-FDG uptake at the insertion sites of the Achilles tendon and plantar fascia into the calcaneus was evaluated by placing spherical volumes of interest (VOIs) with a diameter of 3.0 cm. VOIs were placed in the middle of the Achilles tendon and plantar facia at site of the enthesis on fused PET/CT images using the Nuclear Medicine fusion tool in IDS7 version 22.1 (Sectra AB, Linköping, Sweden) allowing a clear anatomical landmark for placing the VOIs. Within the VOIs, the maximum standardised uptake (SUVmax)-values were measured. Background activity was determined by measuring the mean standardised uptake in a spherical VOI placed centrally in the right liver lobe. Target-to-background ratios were calculated by division of maximum standardised uptake at the enthesis, by mean standardised uptake at the liver. One independent reader, a senior rheumatology resident with a sub-specialisation in imaging and five years' experience (BK), performed all measurements.

Statistical analysis

Baseline patient characteristics were described with medians and interquartile ranges (IQRs), or frequencies and percentages. For analysis of continuous HEMRIS outcomes, the average of the two observers was used. For analysis of dichotomised HEMRIS outcomes, the consensus scores were used.

Continuous HEMRIS outcomes and PET/CT target-to-background ratios of entheses with and without clinical evidence of enthesitis, were compared using the Mann–Whitney test. Continuous HEMRIS outcomes of Pso, PsA and AS entheses were compared using the Kruskal–Wallis test. Association between continuous HEMRIS scores and clinical, laboratory (ESR, CRP) and PET/CT outcome measures was assessed using the Spearman rank correlation coefficient. Missing values (see Results section) were excluded from the analysis. The predetermined significance level was set at $p<0.05$. All analyses were conducted using SPSS version 25 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

RESULTS

Patients' characteristics

38 patients were included in this study: 13 Pso patients, 13 PsA patients, and 12 AS patients. The median age was 48.4 (IQR 35.4–52.5) years and 66% were male. The median PASI was 4.4 (IQR 3.2–9.9) in Pso and 4.6 (IQR 2.2–9.3) in PsA. The PsA group had a median of one swollen and one tender joint. In AS the median BASDAI score was 3.8 (IQR 2.0–4.3). Table 1 provides descriptive statistics of patient characteristics in more detail.

HEMRIS outcomes in patients with and without clinical enthesitis

75 ankle MRI-scans were evaluated, the MRI-scan of one ankle was not assessable for enthesitis because of inadequate fat suppression. In one patient, clinical assessment of enthesitis was not performed. This resulted in a total 146 entheses that were evaluated for enthesitis with both clinical examination and MRI (HEMRIS). Clinical enthesitis was observed in 3/74 (4.1%) Achilles tendons and 3/74 (4.1%) of plantar fascia.

Figure 1 presents HEMRIS scores (inflammation score, structural damage score, total score) of Achilles tendons and plantar fascia with and without clinical enthesitis. A higher structural damage score was observed in Achilles tendons with clinical enthesitis, compared to Achilles tendons without clinical enthesitis (respective median scores 1.0 and 0.5; p=0.04). In 44/70 (62.9%, 95% CI (CI) 51.5–74.2%) Achilles tendons without clinical enthesitis, subclinical inflammatory and/or structural HEMRIS lesions (score ≥1) were observed. When using a higher cut-off value (≥2), subclinical HEMRIS lesions were still identified in 18/70 (25.7%, CI 15.5 to 36.0%) Achilles tendons.

No differences in HEMRIS inflammation, structural damage or total scores were observed between plantar fascia with and without clinical enthesitis (figure 1). In clinically unaffected plantar fascia, subclinical inflammatory and/or structural HEMRIS lesions were observed in 23/70 (32.9%, CI 21.9 to 43.9%) (cut-off value: ≥1), or 10/70 (14.3%, CI 6.1 to 22.5%) (cut-off value: ≥2), of plantar fascias.

The HEMRIS subscore occurring most frequently in entheses with clinical enthesitis was 'peritendon

Table 1 Patient demographics by disease category (psoriasis, psoriatic arthritis or ankylosing spondylitis)

	Disease categories			
	Psoriasis (n=13)	Psoriatic arthritis (n=13)	Ankylosing spondylitis (n=12)	Total (n=38)
Clinical features:				
Male sex, n (%):	6 (46.2)	10 (76.9)	9 (75.0)	25 (65.8)
Age in years, median (IQR):	41.4 (30.0–52.3)	50.5 (42.4–52.8)	48.5 (37.9–51.9)	48.4 (35.4–52.5)
Disease duration in years, median (IQR):	20.8 (11.0–40.2)	6.3 (0.5–11.9)	8.2 (2.7–17.9)	NA
BMI, median (IQR):	25.1 (22.3–35.4)	25.1 (24.1–28.6)	25.4 (22.9–27.3)	25.1 (23.0–27.3)
TJC, median (IQR)	NA	1.0 (0.0–5.5)	0.0 (0.0–0.0)	NA
SJC, median (IQR)	NA	1.0 (0.5–5.5)	0.0 (0.0–0.0)	NA
Leeds enthesitis index (IQR)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	0.0 (0.0–1.75)	NA
PASI (IQR)	4.4 (3.2–9.9)	4.6 (2.2–9.3)	NA	NA
BASDAI (IQR)	NA	NA	3.8 (2.0–4.3)	NA
CRP (IQR)	3.0 (1.0–5.1)	2.0 (1.5–4.8)	3.2 (1.3–7.5)	3.0 (1.4–5.3)
ESR (IQR)	5.0 (2.0–11.0)	4.0 (2.0–6.0)	5.0 (3.0–13.0)	5.0 (2.0–8.5)
Medication				
Current NSAID use, n (%):	1 (7.7)	6 (46.2)	8 (66.7)	15 (40.5)
Missing (NSAID use), n (%):	1 (7.7)	0	0	1 (2.6)

Data are presented as median (IQR), or n(%).
BMI, Body mass index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, ; DMARD, Disease-Modifying Antirheumatic Drug; ESR, Erythrocyte sedimentation rate; NSAID, Non-Steroid Anti Inflammatory Drug; PASI, Psoriasis Area and Severity Index; SJC, Swollen joint count; TJC, Tender joint count.

hypersignal' (in 3/6 (50.0%) entheses). HEMRIS subscores stratified according to absence or presence of clinical enthesitis are provided in online supplemental table 1.

HEMRIS in relation to metabolic activity measured on PET/CT

At the Achilles tendon, local metabolic activity measured on PET/CT was weakly associated with the structural (r_s=0.25, p=0.03) and total HEMRIS (r_s=0.26, p=0.03) (figure 2). There was no correlation between local ^{18}F-FDG uptake measured on PET/CT at the plantar fascia and HEMRIS scores (figure 2). There were no differences between entheses with and without clinical enthesitis in regard to local ^{18}F-FDG uptake. MRI- and PET/CT-images showing examples of enthesitis at the Achilles tendon and plantar fascia, are presented in figure 3 and figure 4.

HEMRIS in relation to clinical patient characteristics and laboratory parameters

HEMRIS structural damage scores at the plantar fascia and Achilles tendon were not significantly different in ankles from different patient categories Pso, PsA and AS (figure 5). In Pso patients, none of whom had clinical enthesitis, HEMRIS structural or inflammatory abnormalities (cut-off value: ≥1) were observed in 17/26 (65%) of Achilles tendons and 9/26 (35%) of plantar fascia.

Age was correlated with the sum of the left and right structural HEMRIS at both the Achilles tendon (r_s =0.44; p=0.01) and plantar fascia (r_s=0.36; p=0.03), and the sum of the left and right total HEMRIS at the Achilles tendon (r_s=0.36; p=0.03). BMI was correlated with the sum of left and right total HEMRIS (r_s=0.37; p=<0.05) at the plantar fascia. Clinical parameters SJC, ESR and CRP were not significantly correlated with the HEMRIS.

DISCUSSION

Recently, the HEMRIS was introduced as scoring system for use in clinical trials in spondyloarthritis and as a tool for assessment of enthesitis using MRI in clinical practice.[1 23] As data on the new system are limited we compared HEMRIS outcomes with clinical, laboratory and PET/CT findings in patients prone to develop enthesitis. Subclinical MRI lesions (HEMRIS cut-off value: ≥1) were frequently observed and even a higher cut-off value of ≥2 still yielded a high prevalence of subclinical HEMRIS lesions. In case of clinical enthesitis, higher structural damage scores were observed at the Achilles tendon. There was a weak, but significant correlation between the structural and total HEMRIS scores at the Achilles tendon and metabolic activity on PET/CT. In patients with Pso, all without clinical evidence of involvement of the entheses, subclinical MRI lesions occurred in 65% of Achilles tendons and 35% of plantar fascias.

An interesting observation in our study is that we frequently detected subclinical inflammatory and structural MRI lesions at the plantar fascia and Achilles tendon. The literature on this is limited, but our finding is consistent with that of Poggenborg *et al*, who acquired whole-body

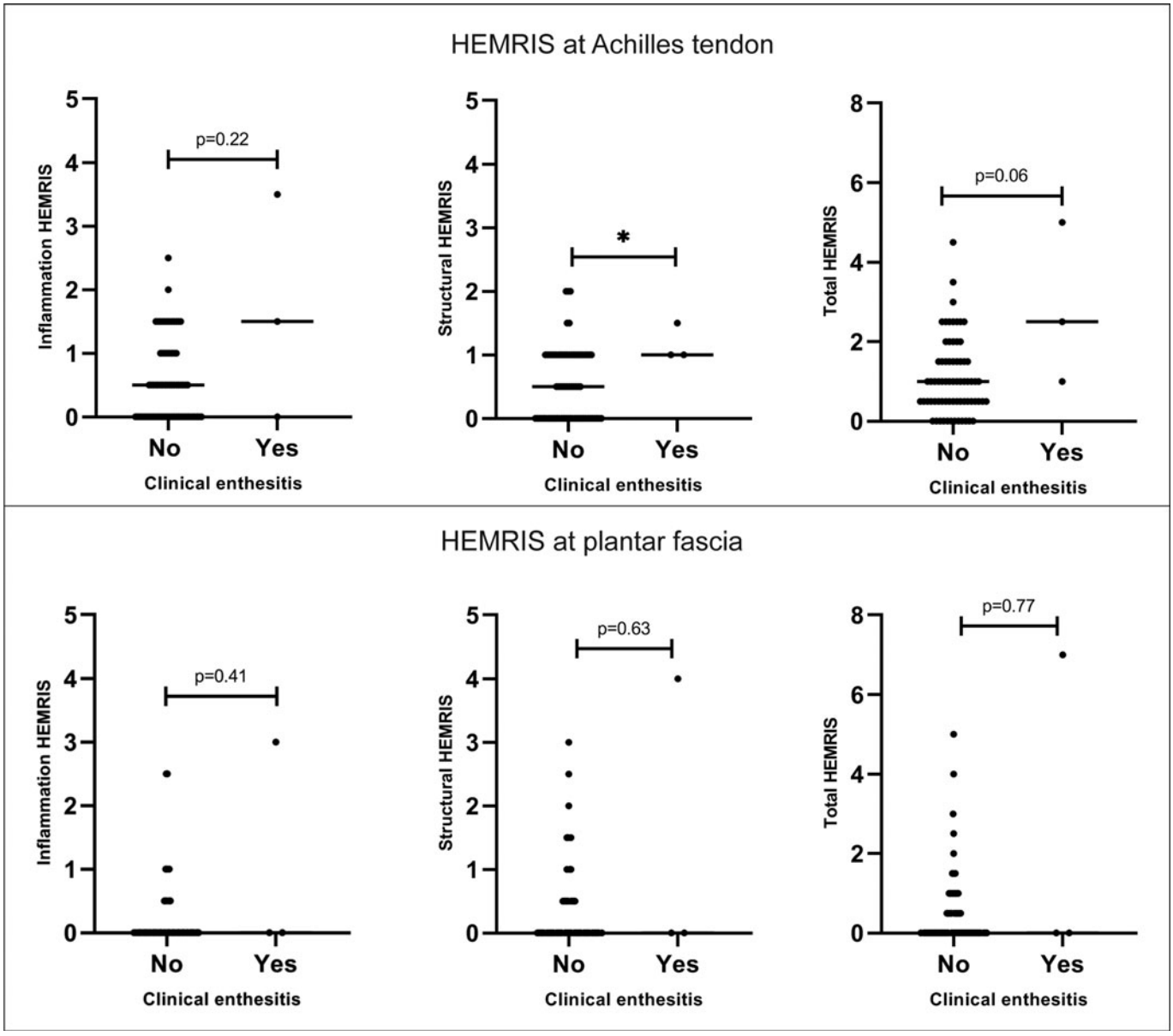

Figure 1 HEMRIS at Achilles tendon and plantar fascia entheses with and without clinical enthesitis. Figures show individual HEMRIS values and the median. *p<0.05. HEMRIS, Heel Enthesitis MRI Scoring System.

MRIs in 18 PsA patients, 18 AS patients and 12 healthy controls and compared MRI-findings with clinical examination.[24] The agreement of whole-body MRI and clinical assessment of enthesitis varied from 49 to 100% per anatomic location. Subclinical enthesitis was most frequently detected at the greater trochanter, Achilles tendons and ischial tuberosity. It was hypothesised that this could be due to high mechanical stress in these anatomical locations.[12 24] The clinical significance of subclinical MRI findings at the enthesis in PsA and AS patients remains to be determined. Enthesopathy may be observed in asymptomatic persons without rheumatological conditions as a result of mechanical overload, degeneration, endocrine disease, trauma or as an adverse-effect to certain medications.[19 25] Evaluation of a group of healthy volunteers with detailed information on BMI, endocrinological conditions, and exposure to mechanical stress (eg, sports) remains to be performed to define 'normal degeneration'. To evaluate whether HEMRIS can predict future development of synovitis or erosions, we aim to follow our study participants for a period of two years to better examine the clinical relevance of the results.

Another finding is that subclinical MRI lesions were frequently observed in psoriasis patients. The occurrence of subclinical MRI lesions in psoriasis patients is consistent with previous research. Mathew *et al* performed low field (0.2 Tesla) MRI-scans of the foot in 53 psoriasis patients without clinical arthritis. In 34% of MRI-scans of psoriasis patients, inflammatory features (synovitis, tenosynovitis and/or bone-marrow oedema) were present.[26] Erdem *et al* evaluated foot involvement in 26

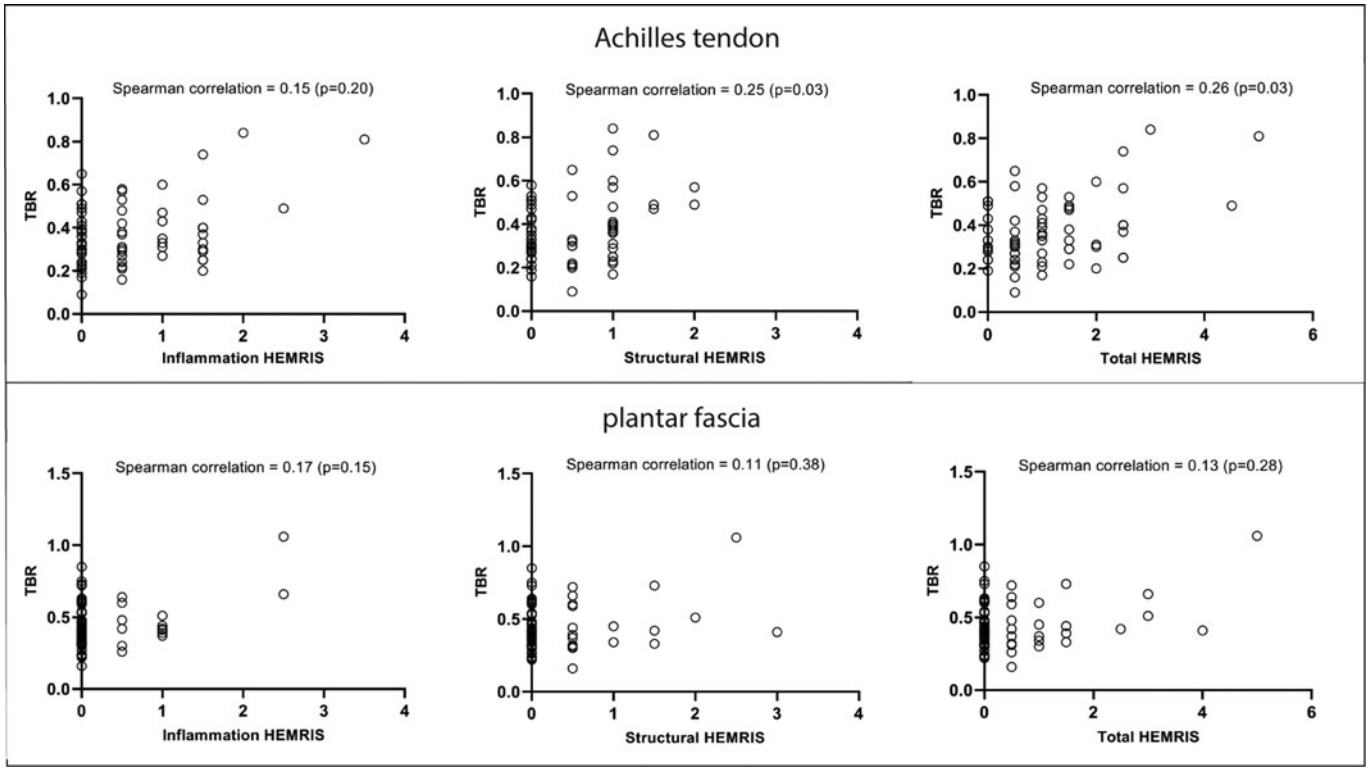

Figure 2 Correlation between inflammation, structural and total HEMRIS at the Achilles tendon and plantar fascia, and local uptake measured on PET/CT. HEMRIS, Heel Enthesitis MRI Scoring System.

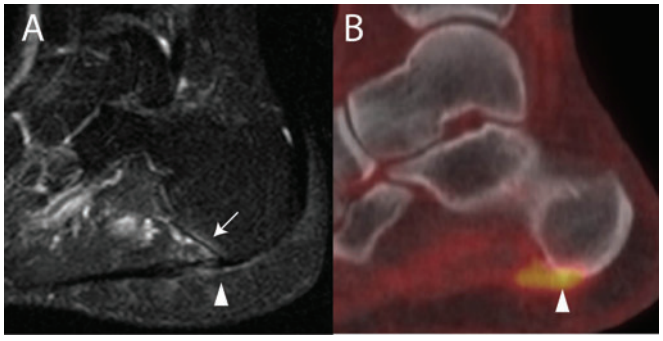

Figure 3 MRI and 18F-FDG PET/CT of a 54-year-old male with ankylosing spondylitis, showing abnormalities at the plantar fascia enthesis: (A) T2 SPAIR weighted image showing bone-marrow oedema (arrow), oedema peritendon and intratendon hypersignal (arrowhead). (B) ^{18}F-FDG PET/CT with increased uptake at the plantar fascia enthesis (arrowhead). 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography/CT; magnetic resonance imaging, MRI; SPAIR, Spectral Attenuated Inversion Recovery.

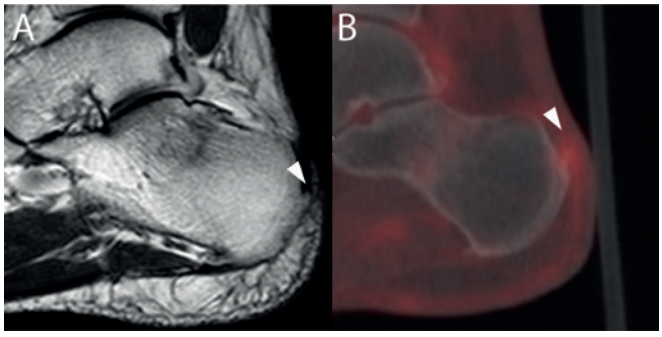

Figure 4 MRI and 18F-FDG PET/CT of a 50-year-old male with psoriasis, showing abnormalities at the Achilles tendon enthesis: (A) T2-weighted image showing a small calcaneal enthesophyte at the insertion of the Achilles tendon (arrowhead). (B) 18F-FDG PET/CT with increased uptake at the Achilles tendon enthesis (arrowhead). 18F-FDG PET/CT, 18F-fluorodeoxyglucose positron emission tomography/CT; MRI, MRI.

psoriasis patients without clinical arthritis or arthralgia.[27] The most common inflammatory and structural features on 1.5T MRI-scans of the foot/ankle were Achilles tendonitis (57%), retrocalcaneal bursitis (50%), joint effusion/synovitis (46%), soft-tissue oedema (46%), and paraarticular enthesophytes (38%).

However, the clinical significance of inflammatory or structural MRI lesions in asymptomatic psoriasis patients is currently unclear. To date, there is only one longitudinal study that evaluated the impact of subclinical MRI-findings in psoriasis patients. Faustini *et al* acquired 1.5 MRIs of the dominant hand of 55 psoriasis patients without signs of PsA: classification as PsA according to CASPAR criteria was an exclusion criterium. In 26/55 (47%) of patients subclinical MRI inflammation was detected.[28] The MRI features synovitis, tenosynovitis, osteitis and erosions (measured using The OMERACT Psoriatic

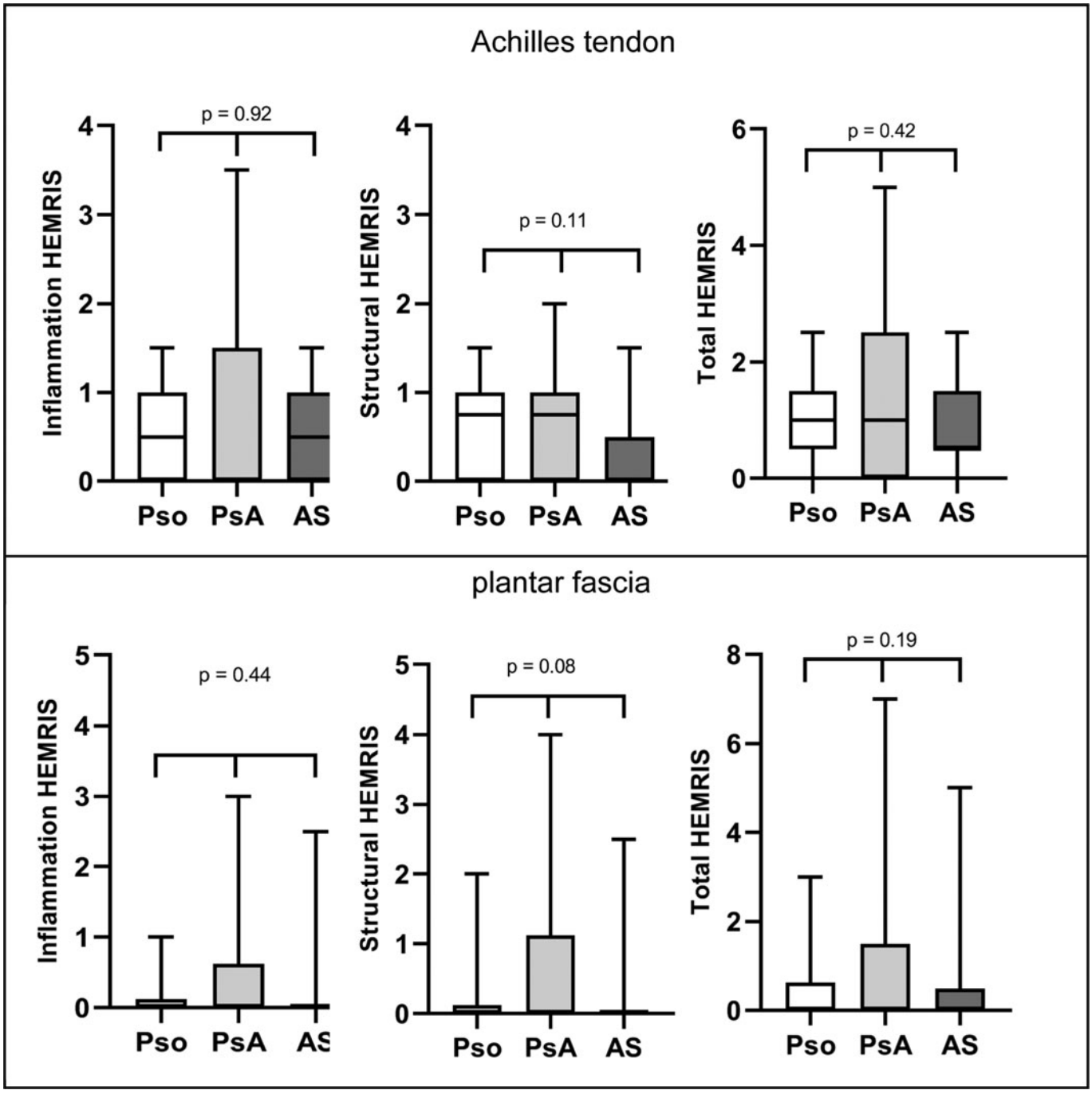

Figure 5 Inflammation, structural and total HEMRIS at the Achilles tendon and plantar fascia in patient categories Pso, PsA and AS. Figures are median (range). AS, Ankylosing spondylitis; HEMRIS, Heel Enthesitis MRI Scoring System; Pso, Psoriasis; PsA, Psoriatic arthritis.

Arthritis MRI Scoring System (PsAMRIS[29])) were not associated with progression from psoriasis to psoriatic arthritis, although this could be due to the small sample size and relatively short follow-up period of one year. To evaluate whether HEMRIS can predict future progression to PsA, we aim to follow patients for a period of two years.

The use of ^{18}F-FDG PET/CT for assessment of enthesitis in spondyloarthritis is infrequently investigated. A previous study reported higher standardised uptake values (SUVs) at the entheses (knees excluded) of spondyloarthritis patients, compared to patients diagnosed with rheumatoid arthritis, non-rheumatic diseases and healthy subjects.[17] The authors suggest that this indicates that PET/CT could be used as an alternative method to diagnose enthesitis.

In the current study, PET/CT was performed for study purposes only to compare ^{18}F-FDG PET/CT with MRI assessment of enthesitis. As ^{18}F-FDG is a marker for

inflammatory processes, we hypothesised that the inflammatory HEMRIS would be associated with metabolic uptake at the enthesis on PET/CT. However, inflammatory HEMRIS at the Achilles tendon and plantar fascia were not associated with local uptake on PET/CT (figure 2). Our results did identify a weak correlation between the structural and total HEMRIS at the Achilles tendon and metabolic activity on PET/CT (figure 2). A possible explanation for the limited association between MRI and PET/CT, is that the enthesis is a poorly vascularised anatomical structure,[30] and ^{18}F-FDG PET/CT relies on intravenous supply of the glucose analogue ^{18}F-FDG. Because of the unestablished clinical relevance of metabolic activity on ^{18}F-FDG PET/CT at the site of the Achilles tendon and plantar fascia enthesis, in combination with the associated radiation exposure, there is no role for ^{18}F-FDG PET/CT in the clinical evaluation of enthesitis yet. Our results on ^{18}F-FDG PET/CT provide fundamental insight into the pathogenesis of enthesitis, but in agreement with previous work the diagnostic value for AS/spondyloarthritis has not been proven.[31 32]

Ultrasound is an alternative imaging modality that can also evaluate entheses, with one major advantage being the fact that it is more readily available. A disadvantage of ultrasound is the operator-dependency. In addition, ultrasound cannot detect changes beyond the bone cortex, while enthesitis is considered to be an inflammatory process that also impacts the bone (ie, bone-marrow oedema as seen by MRI and immunopathology that includes the bone).[19] Nonetheless, ultrasound remains a potential modality for investigating enthesitis in clinical practice or trials.[33 34]

Strengths of the current study include the use of the HEMRIS score as described, PET/CT, blinded clinical examination and laboratory findings. By including a population of asymptomatic patients, we were able to assess the frequency of subclinical HEMRIS lesions. The study was designed principally to recruit patients free of immunomodulatory drugs and patients were not selected based on presence or absence of clinical enthesitis. A study limitation is therefore the low number of patients with clinical enthesitis and that we have selected patients with relative low disease activity. In the present study, both ankles were positioned in a head coil on the 3T MRI and imaged separately to allow evaluation in the same position on the pre- and post-contrast images. Using a head coil may limit the resolution. A dedicated ankle coil and smaller field of view would improve the image quality and more subtle changes may be observed resulting in an even higher prevalence of subclinical findings. Furthermore, this study did not include a control group of healthy subjects. One previous study found no MRI abnormalities (specifically: enthesophyte, bone marrow oedema, bone erosions, subchondral cysts, joint space narrowing, osteolysis and/or soft-tissue oedema) on foot/ankle MRIs in a group of 10 healthy volunteers.[27] However, this study was performed before publication of HEMRIS. The occurrence of HEMRIS lesions in findings in an asymptomatic, healthy control group remains to be determined.

In conclusion, our results indicate that HEMRIS is a sensitive tool for detection of inflammatory and structural MRI lesions at the enthesis. Longitudinal follow-up will be critical to determine the clinical significance of the HEMRIS lesions and the metabolic activity at the enthesis, measured on PET/CT. Currently, HEMRIS does not provide a threshold for clinical relevance. A threshold and/or the use of a healthy control group would be useful for future studies on clinical correlation. We collected detailed information on all study participants but did not take physical activity into account. Since high mechanical stress is a known risk factor for enthesitis[19], this would be recommended for future clinical studies.

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