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Imaging Insights into the Diverse Manifestations of Psoriatic Arthritis

Inzichten in de diverse manifestaties van artritis psoriatica middels beeldvormend onderzoek
(met een samenvatting in het Nederlands)

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Chapter 1

General introduction and thesis outline

In the introduction of this thesis, at first an overview is provided on clinical features of psoriasis and psoriatic arthritis and its comorbidities. Next, the cardiovascular risk of patients with psoriatic disease is described. Then current imaging techniques to monitor disease activity at the joints, entheses and cardiovascular system are discussed. Last, the knowledge gaps in the field of imaging in psoriatic disease studied in this thesis are addressed.

Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease. It occurs in approximately in 0.05-0.21% of the European population, and around 30% of patients with psoriasis develops PsA.(1,2) PsA is an heterogeneous disease with diverse clinical manifestations; patients may exhibit nail and/or skin psoriasis and the following musculoskeletal features: arthritis, dactylitis (swelling of an entire digit or toe), enthesitis (inflammation at the site where tendons/ligaments attach to the bony surface), and axial disease (Figure 1).

There are no diagnostic criteria available for psoriatic arthritis. The diagnosis is often established by identification of inflammation of the peripheral joints, the entheses and/or spine in patients with psoriasis, usually in the absence of rheumatoid factor and anti-cyclic citrullinated peptide.(3) For research purposes, disease classification criteria are available; the Classification criteria for Psoriatic Arthritis (CASPAR).(4)

Table 1. Classification criteria for Psoriatic Arthritis (CASPAR). Psoriatic arthritis is defined in presence of joint, spine, or entheseal inflammation, in combination with ≥ three points from five categories.

Category	Points
Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis:	
• Current psoriasis	2
• Personal history of psoriasis	1
• Family history of psoriasis (first- or second-degree relative)	1
Typical psoriatic nail dystrophy (onycholysis, pitting, hyperkeratosis)	1
Negative rheumatoid factor	1
Current dactylitis or history of dactylitis	1
Hand or foot radiography: evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margin (excluding osteophytes)	1

PsA is part of the group of interrelated rheumatic diseases referred to as "spondylarthritis" (SpA; Figure 1). Other spondylartropathies include axial spondylarthritis (AS), reactive arthritis, SpA associated with inflammatory bowel diseases, and undifferentiated peripheral SpA. These disorders have shared musculoskeletal and extra-musculoskeletal (uveitis, psoriasis, and inflammatory bowel disease) features.(5) To a certain extent there is also a common genetic background between spondyloarthropathies, as there is familial clustering of diseases and an association with human leukocyte antigen (HLA)-B27 positivity.(6)

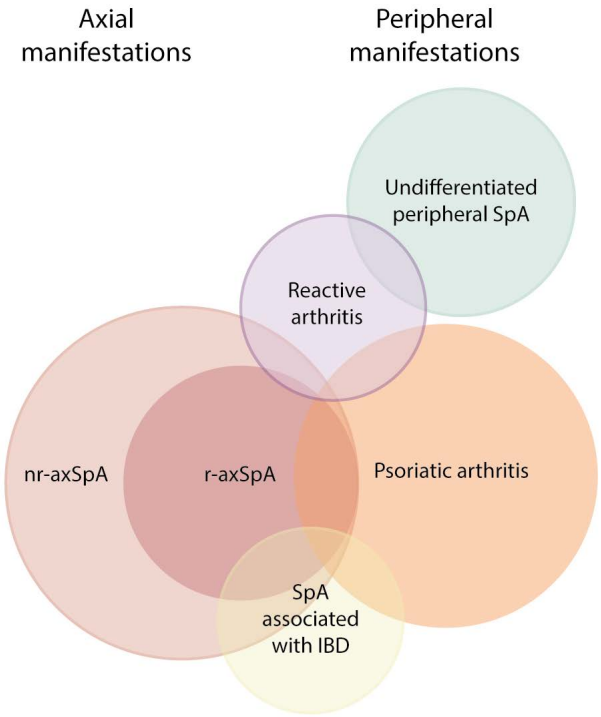

Figure 1. Overview of the spondyloarthropathies.
Figure adapted from Proft, F., Poddubnyy, D. Ther Adv Musculoskelet Dis 2018 Vol. 10, Issue 5–6, pages 129–139). Abbreviations: IBD= inflammatory bowel disease; nr-axSpA = non-radiographic axial spondyloarthritis; r-axSpA = radiographic axial spondyloarthritis; SpA = spondyloathritis.

Prolonged articular inflammation can lead to significant joint damage in PsA, by destruction of cartilage and bone (7,8). PsA has a large impact on quality of life, and patients report moderate to major impact on physical activity (78%) and work productivity (62%). Furthermore, patients report that the disease impacts their social lives: a high proportion of patients experience shame or disapproval and report that the disease affects their personal relationships.(9)

PsA is associated with an increased incidence of cardiovascular disease in comparison with the general population.(10) This elevated risk of cardiovascular disease can be partly attributed to increased traditional cardiovascular risk factors in PsA.(11) Another factor possibly contributing to the cardiovascular risk in PsA, is chronic low-grade systemic inflammation, leading to endothelial dysfunction, and accelerated atherosclerosis. To further explore this relation, vascular imaging studies in PsA could contribute.

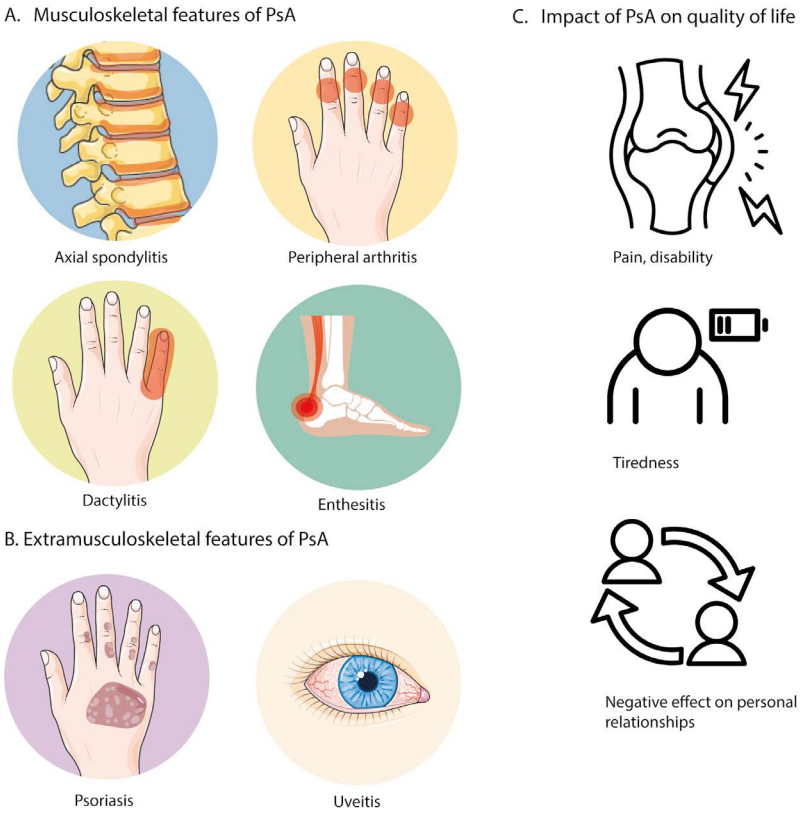

Figure 2. Musculoskeletal and extra-musculoskeletal features of PsA.
The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license. Abbreviation: PsA = psoriatic arthritis.

Over the past decades, pharmacological treatment options for PsA have expanded. Where PsA treatment was previously limited to nonsteroidal anti-inflammatory drugs (NSAID), steroids, and conventional synthetic disease modifying drugs (csDMARDs), we now have the possibility to treat patients with immunologically biological DMARDs (bDMARDs) and targeted synthetic drugs (tsDMARDs). This large range of pharmacological options can be challenging for the clinician. The European Alliance of Associations for Rheumatology (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have developed evidence-based treatment strategies for psoriatic arthritis.(12,13) However, treatment response rates vary between patients and efficacy may be lost over time. True disease remission is rare.(3) Currently, the optimal treatment strategy for the individual patient cannot be predicted, and unfortunately still is a trial and error approach.

Novel imaging techniques in psoriatic arthritis

Different imaging techniques, primarily conventional radiography, ultrasound, and magnetic resonance imaging (MRI), can be applied in clinical practice and research settings in patients with (suspected) PsA, for different purposes. First, imaging of tendons and joints focused on synovitis, sacroiliitis, enthesitis, and tendinitis supports the diagnostic process of PsA. This is important, since diagnostic delay can result in joint damage and unfavorable functional outcomes.(14,15) Next, imaging techniques can be applied to monitor treatment response in both routine care and clinical trials. Furthermore, imaging studies could advance our understanding of disease pathogenesis of PsA and its comorbidities. Finally, imaging measures can be used as a predictor of treatment response and/or functional disabilities.

Each imaging modality has different strengths and limitations. Conventional radiography is still the most commonly used modality in PsA. It is easy accessible, relatively cheap, and can monitor structural damage.(16) Structural changes in peripheral PsA follow the pattern of clinical joint involvement of an asymmetrical distribution with the joints of the hands (including distal interphalangeal joints), feet, ankles, knees, and shoulders most frequently affected. Radiographic features of PsA can be categorized into destructive and proliferative changes. Destructive changes are erosions and osteolysis, which may lead to the characteristic 'pencil-in-cup' phenomenon. Proliferative features are new bone formation and bony ankylosis. (17) However, conventional radiography lacks sensitivity for monitoring short term treatment response because structural changes are relatively slow phenomena, specifically in patients with early PsA, in whom little radiographic changes are

observed.(18) Furthermore, disease activity in soft tissue such as synovium, entheses, and tendons cannot be visualized with this technique.

MRI is a sensitive imaging technique, which can be used for diagnosis and monitoring of both structural and inflammatory changes in PsA. Inflammation within the bone can be primarily identified with MRI, as an abnormal fluid signal within the bone marrow ('bone marrow edema').(19) The Outcome Measures in Rheumatology (OMERACT) group has developed reliable scoring systems for assessment and monitoring of disease activity with MRI. The Heel Enthesitis Magnetic Resonance Imaging Scoring (HEMRIS) model was developed for evaluation of enthesitis in clinical care and trials.(20) However, HEMRIS has not yet been compared with clinical examination and other imaging modalities. Furthermore, there is limited data on the sensitivity to change of this scoring model. So far, in only one study evaluated, no changes were found in the HEMRIS after treatment with either secukinumab or placebo-secukinumab after 52 weeks.(21)

Positron emission tomography/computed tomography (PET/CT) with radiotracer 2deoxy218Ffluorodglucose (18FFDG) allows for *in vivo* visualization of cellular uptake of glucose. 18F-FDG is a glucose analogue, which, unlike glucose, cannot be further metabolized and therefore accumulates in metabolic active cells.(22) PET/CT is broadly used in oncology, but could also be of value in diagnosis and monitoring of inflammatory rheumatic diseases, such as PsA. Small pilot studies have demonstrated the ability of PET/CT to diagnose early synovitis in PsA.(23) But PET/CT also allows for imaging of extra-articular disease manifestations of PsA and comorbidities, such as atherosclerosis and vascular inflammation. In psoriasis patients, PET/CT studies have shown increased arterial inflammation as compared to controls.(24–27) Previously, it had not yet been established whether this was also the case for the PsA population.

Ultrasound is a valuable tool in clinical care and research in PsA. It can be applied at point of care, has low cost and artificial intelligence (AI) based interpretation is on the horizon. As ultrasound was not used in this thesis a detailed introduction is beyond the scope of this thesis, but future studies are clearly warranted.

Thesis objective and outline

The aims of this thesis are to investigate different imaging techniques to further improve monitoring of disease activity in early PsA, and to gain further insight in vascular inflammation in psoriatic disease.

Part one

This part appraises the role of the HEMRIS in diagnosis and monitoring of heel enthesitis in PsA. In **chapter 2**, baseline clinical assessment of enthesitis is compared with the advanced imaging modalities MRI and PET/CT, in patients with psoriasis, PsA, and AS included in the prospective EXTEND-UP study. In **chapter 3**, sensitivity to change of HEMRIS is evaluated in patients included in the EXTEND-UP study, and correlations between changes on MRI and clinical disease activity parameters are explored.

Part two

In part two, the study protocol of the TOFA-PREDICT trial is described (**chapter 4**). The goal of this clinical trial is to predict treatment response to tofacitinib in PsA patients, using a 'multi-omics' or 'systems medicine' approach. In this approach, data from various systems (clinical, transcriptomic, metabolomic, proteomic, flow cytometry, and imaging) to discover and validate profiles to predict treatment response are integrated. In this trial, MRI and PET/CT are used to predict and evaluate treatment response.

In **chapter 5**, baseline differences in MRI, PET/CT and conventional radiography outcomes in TOFA-PREDICT patients with active PsA, who are either DMARD-naïve or -resistant, are examined.

Part three

This part focuses on vascular inflammation in psoriatic disease. In **chapter 6**, the existing literature on vascular inflammation in psoriasis assessed with PET/CT, and the effects of biologic treatment on vascular inflammation is reviewed. In **chapter 7** vascular inflammation in patients with active PsA included in the TOFA-PREDICT study, in comparison with a control population is investigated.

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Chapter 2

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 Magnetic Resonance Imaging Scoring (HEMRIS) model 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 18F-FDG PET/CT were acquired. MRIs were assessed for enthesitis by two independent 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 (rs=0.26, p=0.03) and total HEMRIS (rs =0.25, 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 Magnetic Resonance Imaging Scoring (HEMRIS) model (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 to 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 edema, which is a specific inflammatory feature of enthesitis.(14,15)

Another imaging test that has the potential to diagnose enthesitis is 18F-fluorodeoxyglucose (18F-FDG) Positron Emission Tomography Computed Tomography (PET/CT), as 18F-FDG is a marker for inflammatory processes.(16) 18F-FDG PET/CT has been reported to detect inflammation at the enthesis in PsA 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 (HEMRIS) system and published an atlas with reference images.(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 18F-FDG PET/CT). Patients aged 18-65 years were included, in three different disease categories: psoriasis (diagnosed by a dermatologist with psoriatic arthritis excluded by a rheumatologist (in-training)), psoriatic arthritis (fulfilling Classification Criteria for Psoriatic Arthritis (CASPAR)(2)), and AS (fulfilling 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 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 standardized 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 18F-FDG whole-body PET/CT-scan. Laboratory parameters measured for the study were C-reactive protein (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 postcontrast 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-specialization 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 edema, 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 data. 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 summed HEMRIS scores of the left and right ankles.

PET/CT

Whole-body 18F-FDG PET/CT-scans were obtained for 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 70kg (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 one 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.

18F-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 FOVs. Within the VOIs, the maximum standardized uptake (SUVmax)-values were measured. Background activity was determined by measuring

the mean standardized uptake in a spherical VOI placed centrally in the right liver lobe. Target-to-background ratios were calculated by division of maximum standardized uptake at the enthesis, by mean standardized uptake at the liver. One independent reader, a senior rheumatology resident with a sub-specialization in imaging and five years of 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 dichotomized 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 males. 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.

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)**
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)
Current NSAID use, n (%):	1 (7.7)	6 (46.2)	8 (66.7)	15 (40.5)
Missing, n (%):	1 (7.7)	0	0	1 (2.6)

Table Legend. Data are presented as median (IQR), or n(%).
Abbreviations: BMI = body mass index, TJC = tender joint count, SJC = swollen joint count, CRP = C-reactive protein, PASI = Psoriasis Area and Severity Index, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, NSAID = Non Steroid Anti Inflammatory Drug, ESR = erythrocyte sedimentation rate

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% confidence interval (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 15.5–36.0%) 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 – 43.9%) (cut-off value: ≥1), or 10/70 (14.3%, CI 6.1 – 22.5%) (cut-off value: ≥2), of plantar fascias.

The HEMRIS subscore occurring most frequently in entheses with clinical enthesitis was 'peritendon hypersignal' (in 3/6 (50.0%) entheses). HEMRIS subscores stratified according to absence or presence of clinical enthesitis are provided in 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 (rs=0.26, p=0.03) and total HEMRIS (rs=0.25, 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.

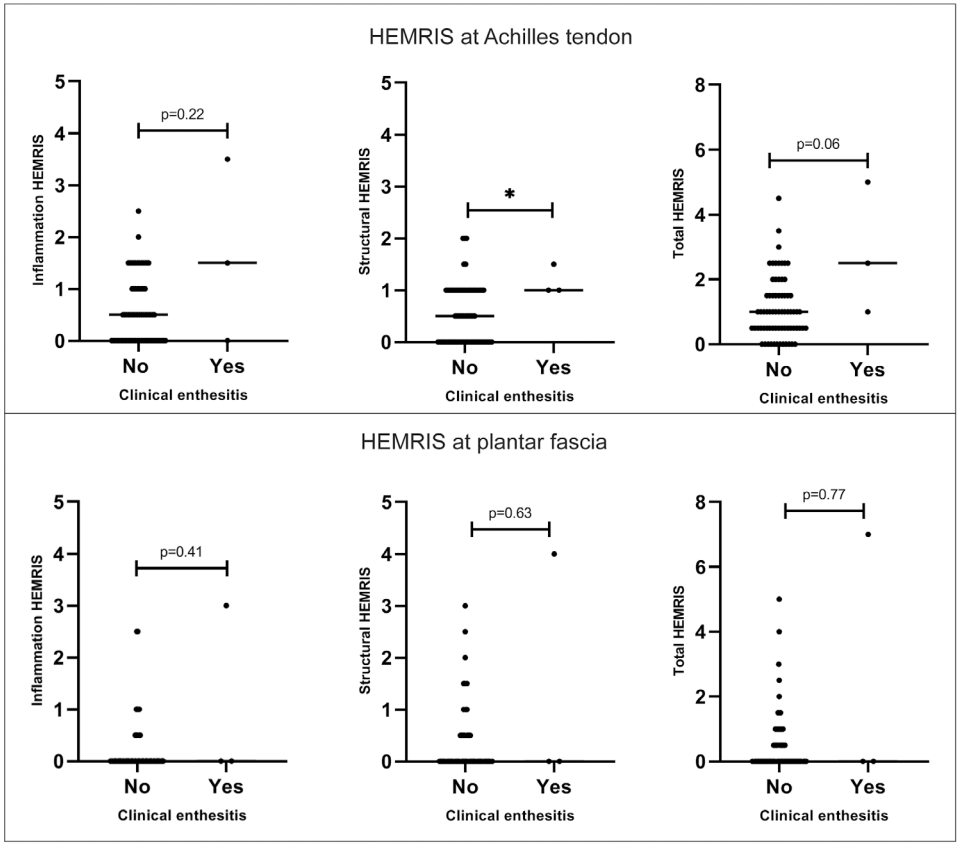

Figure 1. HEMRIS at Achilles tendon and plantar fascia entheses with and without clinical enthesitis.
Figures show individual HEMRIS values and the median.= p<0.05. Abbreviation: HEMRIS = Heel Enthesitis MRI Scoring System.*

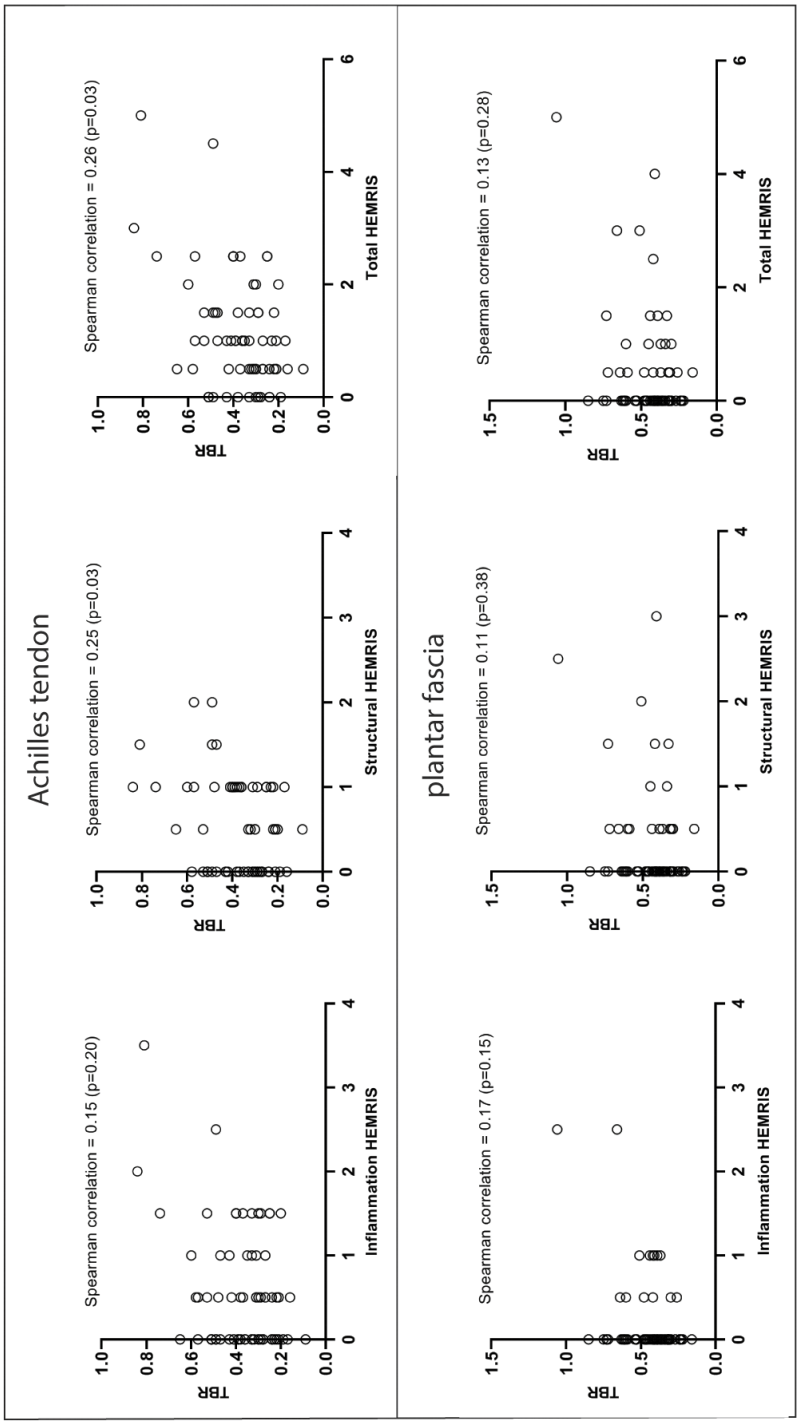

Figure 2. Correlation between inflammation, structural and total HEMRIS at the Achilles tendon and plantar fascia, and local uptake measured on PET/CT.

Abbreviations: HEMRIS = Heel Enthesitis MRI Scoring System, TBR = target-to-background ratio.

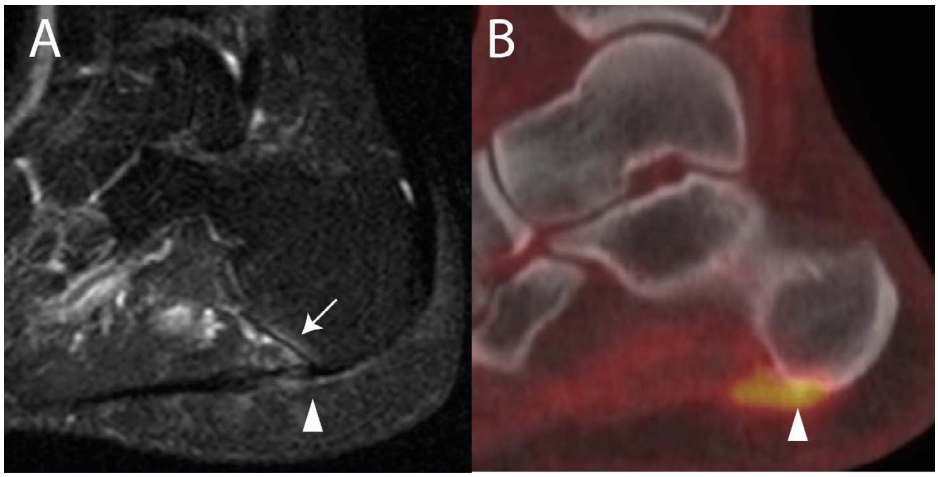

Figure 3. MRI and 18F-FDG PET/CT of a 54-year-old male with ankylosing spondylitis, showing abnormalities at the plantar fascia enthesis.
A. T2 SPAIR weighted image showing bone marrow edema (arrow), edema peritendon and intratendon hypersignal (arrowhead)
B. 18F-FDG PET/CT with increased uptake at the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

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

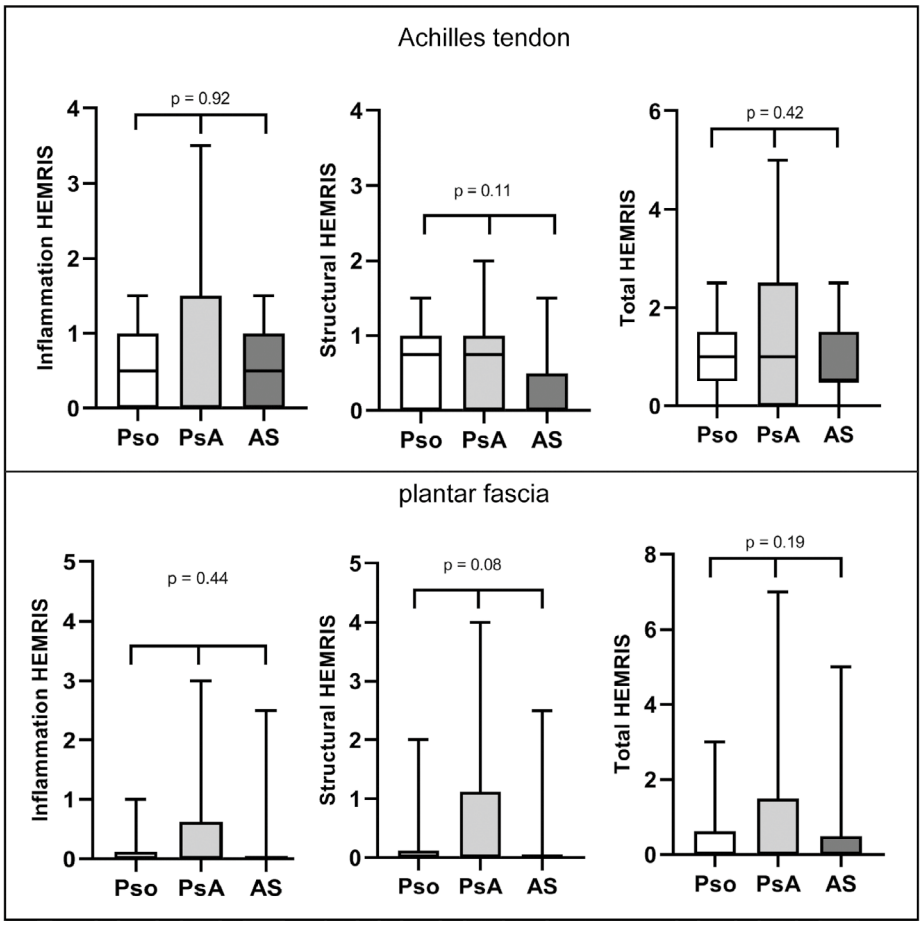

Figure 5. Inflammation, structural and total HEMRIS at the Achilles tendon and plantar fascia in patient categories Pso, PsA and AS.

Figures are median (range). Abbreviations: HEMRIS = Heel Enthesitis MRI Scoring System, Pso = psoriasis, PsA = psoriatic arthritis, AS = ankylosing spondylitis.

Discussion

Recently, the HEMRIS was introduced as a 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 33% 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 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 49-100% per anatomic location. Subclinical enthesitis was most frequently detected at the greater trochanter, Achilles tendons, and ischial tuberosity. It was hypothesized 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 (e.g. sports) remains to be performed in order 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 edema) were present. (26) Erdem et al evaluated foot involvement in 26 psoriasis patients without clinical arthritis or arthralgia.(27) The most common inflammatory and structural features on 1.5 T MRI-scans of the foot/ankle were Achilles tendonitis (57%), retrocalcaneal bursitis (50%), joint effusion/synovitis (46%), soft-tissue edema (46%), and para-articular 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 Arthritis Magnetic Resonance Imaging 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 18F-FDG PET/CT for assessment of enthesitis in spondyloarthritis is infrequently investigated. A previous study reported higher standardized 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 in order to compare 18F-FDG PET/CT with MRI assessment of enthesitis. As 18F-FDG is a marker for inflammatory processes, we hypothesized 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 vascularized anatomical structure, (30) and 18F-FDG PET/CT relies on intravenous supply of the glucose analogue 18F-FDG. Because of the unestablished clinical relevance of metabolic activity on 18F-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 18F-FDG PET/CT in the clinical evaluation of enthesitis yet. Our results on 18F-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 (i.e. bone-marrow edema 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 the selection of 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 postcontrast images. Using a head coil may have limited 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 edema, bone erosions, subchondral cysts, joint space narrowing, osteolysis, and/or soft-tissue edema) 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.

Competing Interests

None declared.

Contributorship

All authors listed have made substantial contributions to the study design, or the acquisition, analysis or interpretation of data, and approved the final version for publication.

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Ethical Approval Information

Ethical approval was provided by the medical ethics committee of the UMC Utrecht (registration number 15-429/M).

Data Sharing Statement

All data relevant to the study are included in the article or uploaded as supplementary information. Data are available upon reasonable request. Please contact corresponding author.

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Supplemental material

Supplemental Table 1. HEMRIS subscores stratified according to absence or presence of clinical enthesitis at the Achilles tendon and plantar fascia.

	Clinical Achilles tendon enthesitis (n= 3)	No clinical Achilles tendon enthesitis (n= 70)
Inflammatory HEMRIS Achilles tendon pathologies:		
Peritendon hypersignal, n (%)	2 (66.7)	13 (18.6)
Intra-tendon hypersignal (T2W), n (%)	1 (33.3)	9 (12.9)
Retrocalcaneal bursitis, n (%)	1 (33.3)	17 (24.3)
Bone marrow edema, n (%)	0	0
Structural HEMRIS Achilles tendon pathologies:		
Tendon thickness, n (%)	1 (33.3)	5 (7.1)
Bone erosion, n (%)	0 (0.0)	2 (2.9)
Bone spur, n (%)	1 (33.3)	25 (35.7)
Intra-tendon hypersignal (T1W), n (%)	1 (33.3)	5 (7.1)
	Clinical plantar fascia enthesitis (n= 3)	**No clinical plantar fascia enthesitis (n= 70)**
Inflammatory HEMRIS plantar fascia pathologies:		
Peri-aponeurosis hypersignal, n (%)	1 (33.3)	10 (14.3)
Intra-aponeurosis hypersignal (T2W), n (%)	1 (33.3)	3 (4.3)
Bone marrow edema n (%)	1 (33.3)	3 (4.3)
Structural HEMRIS plantar fascia pathologies:		
Tendon thickness, n (%)	1 (33.3)	10 (14.3)
Bone erosion, n (%)	0	0
Bone spur, n (%)	0	12 (17.1)
Intra-aponeurosis hypersignal (T1W), n (%)	1 (33.3)	1 (1.4)

Table Legend. Abbreviations: HEMRIS = Heel Enthesitis MRI Scoring System, T1W = T1 weighted, T2W = T2 weighted

Chapter 3

Longitudinal Follow-Up Using the Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) Shows Minimal Changes in Heel Enthesitis Assessed in Spondyloarthritis and Psoriasis Patients

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Abstract

Enthesitis is a common clinical feature of spondyloarthritis (SpA). For reliable assessment of enthesitis the Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) was developed. The aims of this study were to evaluate changes in HEMRIS over time and to evaluate whether these changes correlated with changes in clinical parameters. This single-center observational study followed patients with SpA and psoriasis, regardless of presence of clinical heel enthesitis, for two years. Clinical evaluation and ankle MRIs were performed annually. Changes in the HEMRIS were compared at one-year intervals using the Wilcoxon signed-rank test. The association between changes in the HEMRIS with changes in clinical parameters was evaluated using Spearman's correlation coefficient. In total, 38 patients were included. An increase in the inflammatory and structural HEMRIS was identified in, respectively, 12 (17.9%) and 4 (6.0%) patients in one-year intervals. We found non-significant changes in the HEMRIS during longitudinal follow-up. Changes in the HEMRIS did not correlate with changes in local or general disease activity. Our results show that MRI-findings of enthesitis assessed with HEMRIS changed in a small number of patients in a one-year interval in an observational setting. Changes in HEMRIS were not associated with changes in clinical disease activity.

Introduction

Enthesitis, defined as inflammation at the anatomical location where tendons, ligaments, and joint capsules insert to bone, is a key clinical feature of spondylarthropathies, including psoriatic arthritis (PsA) and ankylosing spondylitis (AS).(1,2) Recommended treatment strategies for enthesitis vary and may include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and, in PsA, advanced treatment with disease-modifying anti-rheumatic drugs (DMARDs).(3,4) However, a golden standard for evaluation of enthesitis is lacking. Clinical evaluation of enthesitis, which relies on the subjective assessment of pain after applying pressure at insertion sites, has limited sensitivity and specificity.(5–7)

To monitor enthesitis at an early stage and more accurately, imaging techniques, such as ultrasound and MRI could be employed.(8) An advantage of MRI over ultrasound is that it allows for visualization beyond the bone cortex and can detect peri-entheseal osteitis or 'bone marrow edema'. (1) For assessment of enthesitis with MRI in PsA and AS patients with a focus on the heel region, the Outcome Measures in Rheumatology (OMERACT) group developed and validated the Heel Enthesitis Scoring System (HEMRIS).(9,10) Using the HEMRIS, inflammatory and structural features of heel enthesitis can be assessed at the area of the Achilles tendon and plantar fascia. However, the sensitivity of HEMRIS for change over time needs to be further established in longitudinal studies, both for inflammatory and structural HEMRIS pathologies.(9) So far, one study was performed and did not show any significant changes after treatment with secukinumab or placebo-secukinumab after 52 weeks. (11)

Besides its potential for evaluation of treatment effects, HEMRIS could provide insights in the pathogenesis of PsA. It has been hypothesized that SpA originates at the enthesis.(5) Imaging of the enthesis could possibly identify individuals with subclinical enthesitis progressing from psoriasis to psoriatic arthritis at an early stage, or predict disease activity.

The aims of this study are to evaluate the sensitivity of HEMRIS for change during longitudinal follow-up and to assess whether changes in HEMRIS are associated with changes in clinical disease activity in psoriasis (Pso), PsA, and AS patients. As a secondary outcome, we compared HEMRIS in Pso patients with and without progression to PsA to assess if HEMRIS was predictive of later development of PsA.

Materials and Methods

Study Design and Patients

In this observational longitudinal study, carried out in an academic hospital, we included patients aged 18–65 years who were diagnosed with cutaneous Pso (diagnosed by a dermatologist, with PsA excluded by a rheumatologist), PsA (fulfilling Classification Criteria for Psoriatic Arthritis (CASPAR) (12)), and AS (fulfilling Assessment of SpondyloArthritis international Society (ASAS) (13) classification criteria). Patients were selected regardless of presence of clinical ankle enthesitis at the Achilles tendon or plantar fascia. Exclusionary criteria included current use of conventional or synthetic disease-modifying antirheumatic drugs (DMARDs) at time of inclusion. The current study focuses on longitudinal follow-up with HEMRIS, baseline MRI-results in comparison with clinical parameters and PET-CT were described in our previous paper.(14)

Ankle-MRI Protocol and Scoring

Both ankles were evaluated separately on a 3-Tesla MRI scanner (3T TX, Philips Healthcare, Best, The Netherlands) using a head coil. The MRI protocol included the following sagittal sequences: T2-weighted, T2-weighted Spectral Attenuated Inversion Recovery, T1-weighted SPIR (Spectral Presaturation with Inversion Recovery) before contrast, and T1-weighted SPIR after contrast. Baseline ankle MRIs were assessed by two independent musculoskeletal radiologists for inflammatory and structural features of heel enthesitis using the HEMRIS. The HEMRIS is a scoring system containing the following inflammatory and structural pathologies: intratendon hypersignal, peritendon hypersignal, bone marrow edema, bursitis (Achilles tendon only), tendon/aponeurosis thickening, enthesophyte, bone erosion and intra-tendon hypersignal on T1-Weighted images. All pathologies are scored on a scale of 0–3 (none/mild/moderate/severe). Examples of all grades of different HEMRIS pathologies are provided in an imaging reference atlas.(10)

The maximum HEMRIS of 2 ankles is 24 for entheseal inflammation at the Achilles tendon, structural damage at the Achilles tendon, and structural damage at the plantar fascia; 18 for entheseal inflammation at the plantar fascia; 42 for total entheseal inflammation; and 48 for total structural damage.

All HEMRIS subscores were averaged as suggested in the original HEMRIS publication.(9) Average HEMRIS subscores of 0.5, 1.5 or 2.5 were evaluated in a consensus meeting. Follow-up MRI-scans were evaluated for changes by a

musculoskeletal radiologist (IK). Ankle MRI-results were compared at one-year-intervals: MRIs obtained at year 1 were compared to baseline, and MRIs obtained at year 2 were compared to year 1. Change in HEMRIS was calculated by subtraction. For comparison of HEMRIS with disease activity, HEMRIS of both ankles were summated.

Clinical Assessments

Psoriasis activity was measured using the Psoriasis Area and Severity Index (PASI).(15) PASI > 10 was categorized as moderate to severe disease.(16) Disease activity in PsA was assessed with the validated composite outcome measure 'minimal disease activity' (MDA).(17) MDA is achieved when 5 out of 7 of the following criteria are met: tender joint count ≤ 1, swollen joint count ≤ 1, PASI ≤ 1, patient pain visual analogue score (VAS) ≤ 15, patient global disease activity VAS ≤ 20, health assessment questionnaire ≤ 0.5 and tender entheseal points (measured using the Leeds Enthesitis Index (18)) ≤ 1. Disease activity in AS was assessed with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).(19) The threshold value for active disease was set at ≥4. Enthesitis at the site of the ankle was assessed by palpation for tenderness of the insertions of the Achilles tendon and plantar fascia into the calcaneus. MDA-status, categorized PASI, categorized BASDAI and clinical assessment of enthesitis were compared at one-year intervals on three levels (stable, increase of disease activity and decrease of disease activity).

Data Analysis

Non-normally distributed continuous data were reported using medians and inter-quartile ranges (IQRs). Categorical variables were reported in frequencies and percentages. The initial HEMRIS of Pso patients with and without clinical progression to PsA were compared with the Mann–Whitney U Test.

Patients were followed for two years. We performed pairwise comparisons of the HEMRIS and clinical outcomes in one-year intervals. Overall change in HEMRIS in one-year intervals was assessed using the Wilcoxon signed-rank test. The potential association of changes in HEMRIS with changes clinical disease activity was assessed using Spearman's correlation coefficient. Differences in HEMRIS at baseline in Pso patients with and without progression to PsA were compared using the Mann-Whitney U Test. Due to the small sample size, we did not perform corrections for multiple measurements.

Patients that were lost to follow-up before the first follow-up visit were excluded from all analyses. Patients that were lost to follow-up after year 1 were only excluded

from pairwise analyses comparing year 1 and year 2. The predetermined significance level was set at $p < 0.05$. Statistical analysis was performed using SPSS version 26 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA).

Results

Patients' Characteristics

At baseline, 38 patients (76 ankles) were included. Baseline patient characteristics and MRI-results have been described previously.(14) For the current study, disease activity and MRI-results at inclusion and at year one are used as baseline values. Briefly, Pso patients had low disease activity and moderate-severe PASI scores were observed in only 5 (20.8%) patients at the baseline. PsA patients had 'minimal disease activity' at baseline in 45.8% (n = 11) (Table 1). At baseline, 22 (87.5%) AS patients had a BASDAI ≥ 4 (Table 1). Achilles tendon and plantar fascia enthesitis were observed in, respectively, eight (5.9.%) and six (4.5%) ankles assessed at baseline and at 52 weeks (pooled data; Table 1). At baseline, five patients (6.6%) were treated with a DMARD (Table 1).

Serial MRI observations were available for 36 participants at 2 time points (baseline and 52 weeks) and for 34 patients at 3 time points (baseline, 52 weeks, and 104 weeks). At baseline, one ankle-MRI was excluded from analysis because of insufficient image quality due to failure of fat suppression. At 104 weeks, the Achilles tendon could not be examined on one MRI-scan due to an artifact. In total, 137 serial MRI observations of heel enthesitis were available for change in HEMRIS; 137 at the location of the Achilles tendon and 138 at the location of the plantar fascia. At patient level (summated left and right HEMRIS) the total number of serial MRI observations for change in HEMRIS is 68 at the location of the Achilles tendon and 67 at the location of the plantar fascia.

Table 1. Patients' characteristics at baseline and 52 weeks (pooled data). Patients that were lost to follow-up were excluded from the analysis.

	Disease Category			
	Pso	**PsA**	**AS**	**All**
Total one year intervals, n	24	24	24	72
Demographics				
Male gender, n(%):	12 (50.0)	18 (75.0)	18 (75.0)	48 (66.7)
Age, median (IQR):	42.2 (34.7–53.4)	50.9 (40.6–52.9)	49.1 (38.8–52.2)	49.2 (36.8–52.8)
Disease duration in years, median (IQR)	22.5 (14.4–42.2)	7.8 (0.9–12.6)	8.7 (3.4–17.2)	NA
General disease activity:				
Pso: moderate-severe psoriasis, n (%)	5 (20.8)	NA	NA	NA
PsA: MDA, n (%)	NA	11 (45.8)	NA	NA
Missing, n (%)	NA	3 (12.5)	NA	NA
AS: BASDAI score ≥ 4, n (%)	NA	NA	22 (91.7)	NA
Medication:				
Current DMARD use, n (%):	0	4 (16.7)	1 (4.2)	5 (6.6)
Current NSAID use, n (%):	2 (8.3)	7(29.2)	16 (66.7)	25 (34.7)
Missing, n (%)	1 (4.2)	0	0	1 (1.4)
Inflammatory markers:				
ESR, median (IQR):	4.0 (2.0–10.0)	4.0 (2.0–6.0)	5.0 (3.0–6.0)	4.0 (2.0–6.5)
Missing, n (%)	2 (8.0)	0	1	2 (2.8)
CRP, median (IQR):	2.5 (0.9–5.7)	3.0 (1.6–4.6)	1.6 (0.9–4.4)	2.8 (1.2–4.5)
Missing, n (%)	2 (8.0)	0	1	3 (4.2)

Table 1. Patients' characteristics at baseline and 52 weeks (pooled data). Patients that were lost to follow-up were excluded from the analysis. (continued)

	Disease Category			
	Pso	**PsA**	**AS**	**All**
Local disease activity at the enthesis:				
Achilles tendon, n enthesis	48	48	48	144
Clinical enthesitis, n (%)	2 (4.2)	1 (2.1)	3 (6.3)	6 (4.2)
Missing, n (%)	0	4 (8.3)	6 (12.5)	10 (6.9)
Plantar fascia, n enthesis	48	48	48	144
Clinical enthesitis, n (%)	1 (2.1)	4 (8.3)	2 (4.2)	7 (4.9)
Missing, n (%)	0	4 (8.3)	6 (12.5)	10 (6.9)

Table Legend. Abbreviations: AS = ankylosing spondylitis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drugs, ESR = erythrocyte sedimentation rate, IQR = interquartile range, Pso = psoriasis, PsA = psoriatic arthritis, MDA = minimal disease activity, NA = not applicable, NSAID = non-steroidal anti-inflammatory drugs.

Change in Disease Activity during Follow-Up

In most patients, the overall mild psoriasis severity remained stable throughout the study. When compared at one-year intervals, a decrease in the PASI (disease activity no longer classified as 'moderate-severe') occurred in three patients (13.0%). No increases in PASI from mild to moderate-high disease activity were observed. Two (18.2%) patients with Pso developed psoriatic arthritis during the two years follow-up. Two Pso patients were lost to follow-up (Supplemental Figure S1). Activity of PsA increased in n = 3 (13.0%), decreased in n = 6 (26.0%) and remained stable in n = 9 (39.1%) patients in one-year observation intervals. One PsA patient was lost to follow-up, another was excluded from the analysis at the last time point since no MRI-scan was obtained (Supplemental Figure S1). Activity of ankylosing spondylitis, increased in 2 (8.3%) patients, decreased in 2 patients (8.3%) and remained stable in 19 patients (79.2%) during one-year observation intervals.

During follow-up, newly diagnosed clinical enthesitis was observed in four (3.2%) Achilles tendon entheses and six (3.2%) plantar fascia. Treatment with a DMARD was initiated in 6 (8.6%) patients during longitudinal follow-up (Supplemental Table S2).

Change in the HEMRIS during Follow-Up

Total HEMRIS for both ankles were low at the start of one-year intervals and after follow-up (median score ≤ 1, range 0–24 or 0–18; Supplementary Table S1). Increase in the inflammatory and structural HEMRIS (cut-off value: ≥1) were identified in, respectively, 12 (17.9%) and 4 (6.0%) patients during one-year follow-up intervals. No significant changes were observed in continuous HEMRIS during longitudinal follow-up (Figure 1). The HEMRIS subitems that changed most frequently during longitudinal follow-up were 'peritendon hypersignal' (in 13 plantar fascia and 16 Achilles tendons: Figure 2; Supple-mental Table S3) and 'retrocalcaneal bursitis' (in 20 Achilles tendons: Figure 3; Supplemental Table S3). No new bone erosions were observed during longitudinal follow-up (Supplemental Table S3).

Changes in clinical disease activity, assessed with measures of general disease activity (Figure 4) and with measures for local disease activity at the enthesis (Figure 5) were not associated with changes in HEMRIS. Changes in clinical disease activity, in sub-groups based on clinical diagnosis of Pso, PsA or AS, were not associated with changes in HEMRIS (Figure 6). No difference was observed in HEMRIS results at time of inclusion of the 2 Pso patients who developed PsA during longitudinal follow-up, in comparison to the 9 Pso patients that did not (Supplemental Figure S2).

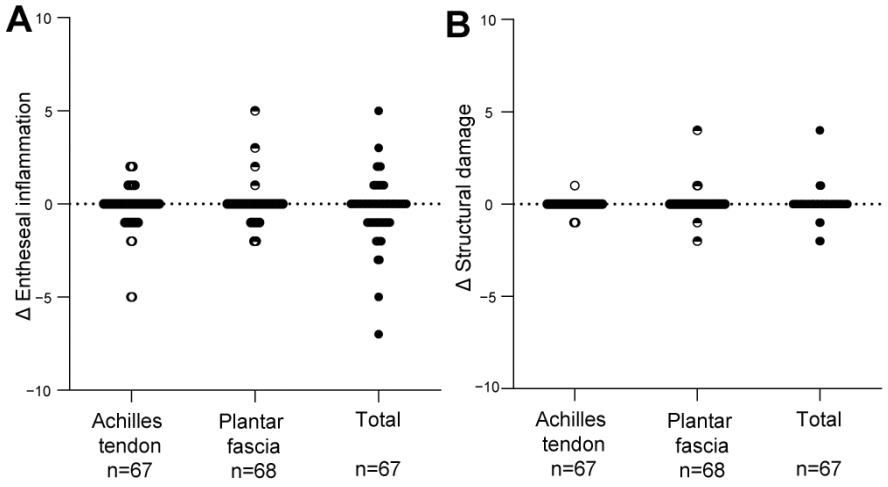

Figure 1. Change in HEMRIS Entheseal inflammation and HEMRIS Structural damage after longitudinal follow-up.

*After one-year follow up intervals, no significant changes were observed in (**A**) HEMRIS Entheseal inflammation, and (**B**) HEMRIS structural damage. Data are presented as the median change and individual values of change in HEMRIS (Delta HEMRIS). HEMRIS scores of both ankles were summated Abbreviations: Δ = delta, HEMRIS = Heel Enthesitis Scoring System.*

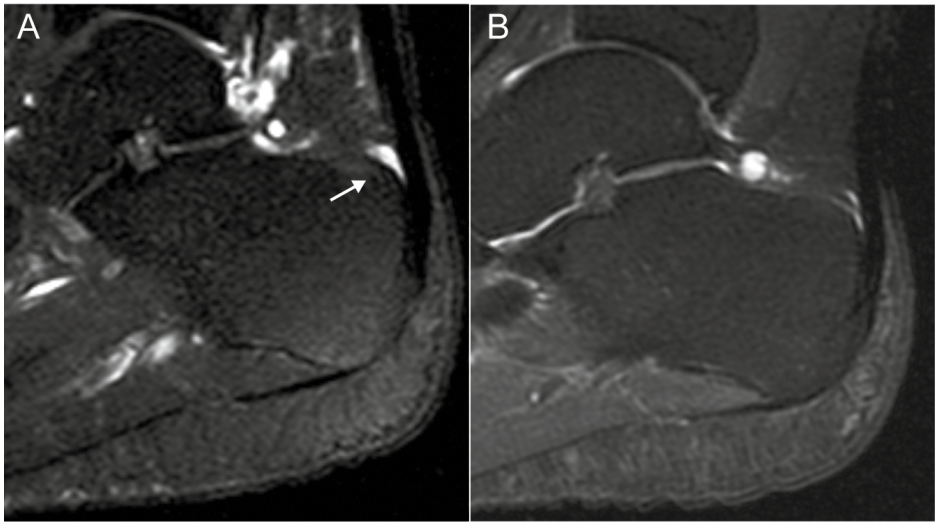

Figure 2.
MRI images of a 33-year old male with psoriasis, showing a decrease in retrocalcaneal bursitis after one-year longitudinal follow-up. (A) T2 SPAIR weighted image showing hypersignal at the retrocalcaneal bursa consistent with mild inflammation at the bursa (arrow: grade 1; mild), (B) T2 SPAIR weighted image showing no hypersignal at the retrocalcaneal bursa. SPAIR = Spectral Selection Attenuated Inversion Recovery.

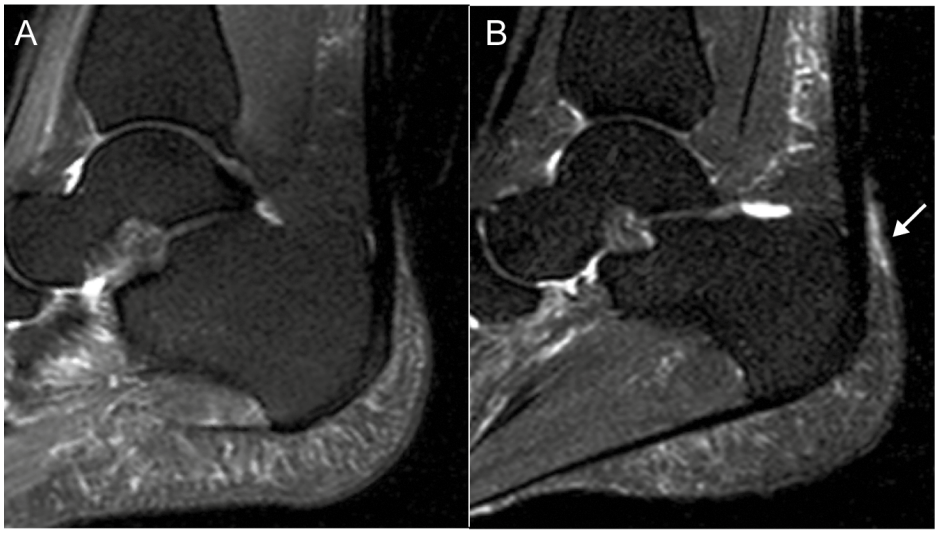

Figure 3.
MRI images of a 48-year old female with ankylosing spondylitis, showing an increase in peri-Achilles tendon hypersignal after one-year longitudinal follow-up. (A) T2 SPAIR weighted image showing no hypersignal surrounding the Achilles tendon, (B) T2 SPAIR weighted image showing hypersignal (arrow: moderate; grade 2) surrounding the Achilles tendon, close to its insertion. SPAIR = Spectral Selection Attenuated Inversion Recovery.

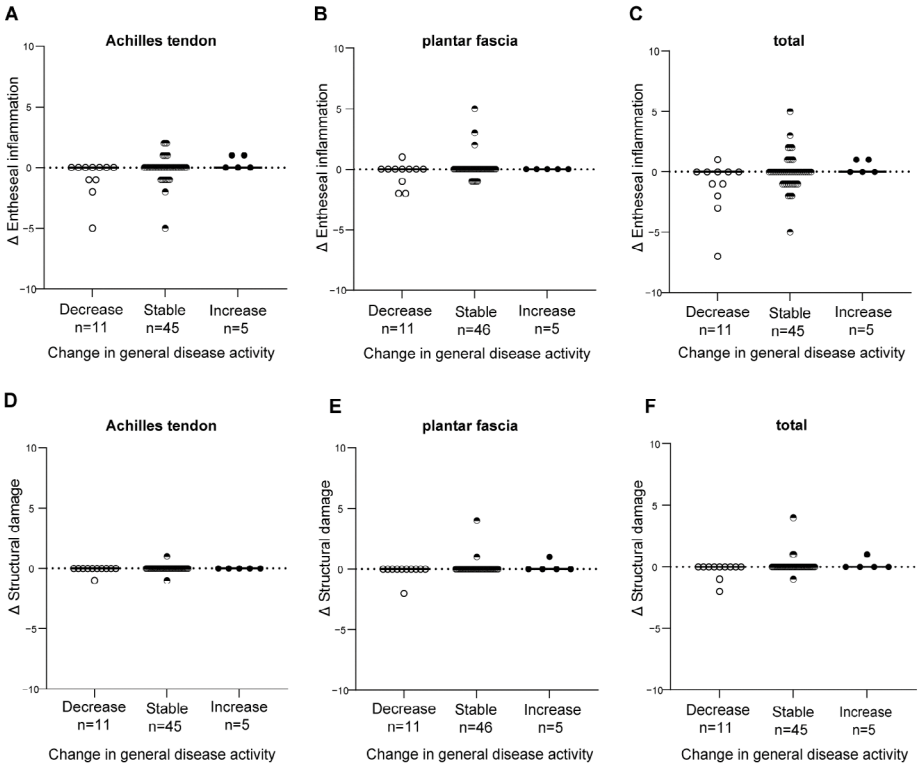

Figure 4. Changes in the HEMRIS in patients with different levels of change in general disease activity.

Changes in general measures of clinical disease activity were not associated with changes in the HEMRIS Entheseal inflammation and structural damage at the area of the Achilles tendon (A,D), plantar fascia (B,E), and Achilles tendon and plantar fascia combined (C,F). Clinical disease activity results were pooled but were assessed differently in each patient category, using the PASI for psoriasis, MDA for psoriatic arthritis and the BASDAI for ankylosing spondylitis. Data are presented as the median change and individual values of change in HEMRIS (Delta HEMRIS). Abbreviations: Δ = delta, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, HEMRIS = Heel Enthesitis Scoring System, MDA = minimal disease activity, PASI = Psoriasis Area and Severity Index.

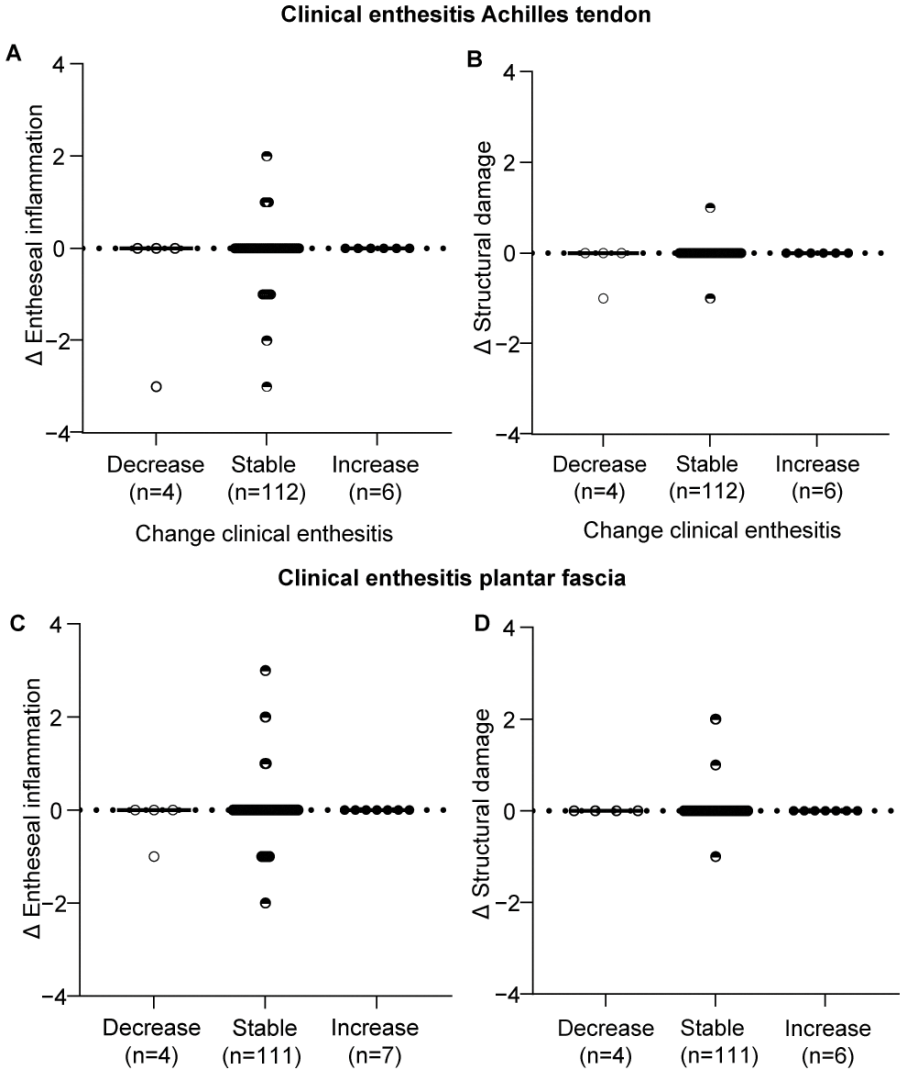

Figure 5. Change in the HEMRIS in patients with different levels of change in clinical enthesitis.

Changes in clinical disease activity at the enthesis were not associated with changes in HEMRIS Entheseal inflammation at the Achilles tendon (A and B) and the plantar fascia (C and D). Data are presented as the median change and individual values of change in HEMRIS Entheseal inflammation and structural damage scores. Abbreviations: Δ = delta, HEMRIS = Heel Enthesitis Scoring System.

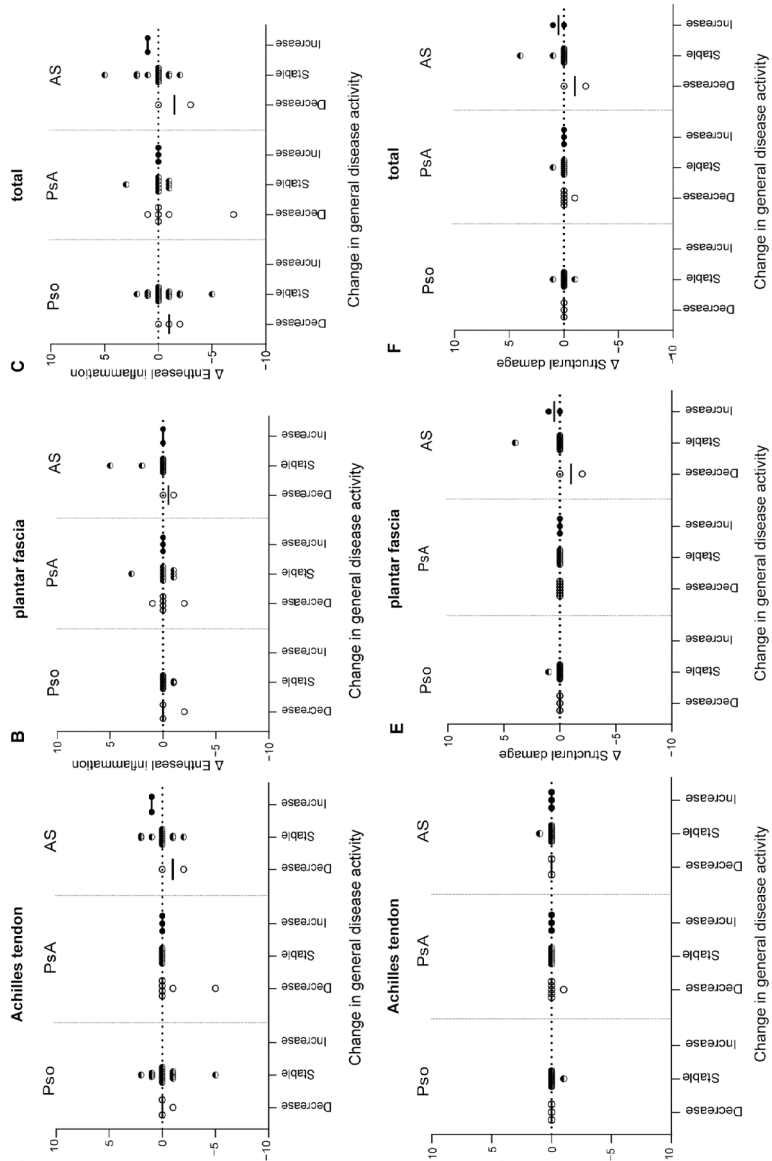

Figure 6. Changes in the HEMRIS in Pso, PsA and AS patients with different levels of change in general disease activity.
Change in general disease activity was not associated with change in HEMRIS at the area of the Achilles tendon (A,D), plantar fascia (B,E), and Achilles tendon and plantar fascia combined (total HEMRIS; (C,F)), in patients with Pso, PsA and AS. Data are presented as the median change and individual values of change in HEMRIS (Delta HEMRIS). Abbreviations: Δ = delta, HEMRIS = Heel Enthesitis Scoring System, Pso = psoriasis, PsA = psoriatic arthritis, AS = ankylosing spondylitis.

Discussion

In this prospective observational study in Pso and SpA (PsA and AS) patients with limited clinical disease activity at the enthesis, we evaluated whether ankle enthesitis on MRI, assessed using the HEMRIS, was sensitive to change during longitudinal follow-up. No significant differences were observed in the HEMRIS after a one-year follow-up intervals (Figure 1). The secondary objective was to evaluate whether changes in clinical disease activity, assessed with general measures of disease activity, or with clinical examination of enthesitis, were associated with changes in the HEMRIS. HEMRIS results were not associated with changes in general or local measures of disease activity (Figures 2, 4–6). Overall, results of this study indicate that the HEMRIS remains stable during longitudinal follow-up in an observational setting.

In the original publication of HEMRIS by the OMERACT group, change in inflammatory pathologies before and after anti-TNF therapy was evaluated in a group of SpA patients.(9) The standardized response mean of HEMRIS was 0.7, which is considered moderate. Since a clinical diagnosis of enthesitis was not mandatory for inclusion, the authors suggested that the responsiveness of HEMRIS would be 'good in trials with baseline enthesitis as an inclusion criterion'. Subsequently, clinical heel enthesitis was an inclusion criterion for patients included in the ACHILLES trial. However, a post-hoc analysis of the ACHILLES trial showed little changes in HEMRIS in both patients treated with secukinumab or placebo, while a higher but non-significant proportion of patients treated with secukinumab had resolution of clinical enthesitis.(11) Our results with minimal changes in HEMRIS are in line with findings of the ACHILLES trial.

A possible explanation for the minimal changes in the HEMRIS in our study, is the low initial HEMRIS (Supplemental Table S1), allowing for only a little window for improvement during longitudinal follow-up in an observational setting. The low HEMRIS results could possibly be caused by the selection of study patients: we included both Pso (skin disease only) and SpA patients, and clinical enthesitis was not an inclusion criterion. Clinical enthesitis was present in only 6% of ankles at the Achilles tendon and 5% of plantar fascia at baseline. At follow-up, clinical assessment of enthesitis remained stable in the vast majority of patients (Figure 5). A benefit of inclusion of patients without a clinical diagnosis of enthesitis is that it allows for evaluation of the clinical importance of subclinical MRI-findings. As reported in our previous paper on baseline data of the current cohort, subclinical MRI-abnormalities occurred in 62.9% of Achilles tendons and in 32.9% of plantar fascias.(14) Our results

indicate that subclinical HEMRIS findings are of limited clinical relevance since the large number of subclinical MRI findings did not predict the development of clinical enthesitis or structural changes on MRI after one and two years.

The finding that minimal changes in HEMRIS are not associated with changes in general disease activity, could be considered unexpected, since enthesitis has been attributed a major role in SpA disease pathogenesis in the proposed 'enthesitis model'.(2) With the subdivision of general and local disease activity in the categories 'stable disease', 'increase' and 'decrease' in clinical disease activity, we potentially bypass the effects of continuous high disease activity in SpA on structural HEMRIS pathologies. However, the formation of new structural HEMRIS pathologies occurred in only 6.0% of patients in one-year intervals and did not include bone erosions (Supplemental Table S3). Another possible explanation for the lacking association of HEMRIS with general disease activity is that with HEMRIS, only the ankle is assessed for enthesitis. Imaging multiple entheses at once with MRI can be done by using whole body MRI, but this technique has its challenges, such as limited image resolution and highly varying interrater agreement for enthesitis lesions.(20)

This analysis included patients with cutaneous Pso to assess if subclinical MRI changes at the enthesis could predict future progression to PsA. We did not find differences between HEMRIS at inclusion in Pso subjects with and without later development of PsA (Supplemental Figure S2). The results of this explorative analysis must be interpreted with caution though, due to the low number of Pso patients included (n = 13) and progressing to PsA (n = 2). Further work is required to evaluate the potential of HEMRIS as an imaging biomarker for future onset of inflammatory joint disease in Pso.

Strengths of the current study include its longitudinal design, assessment of MRI-scans by experienced radiologists and the comparison of MRI-results with clinical assessments of both general disease activity and local disease activity at the enthesis. The relatively small sample size remains a limitation. Since this is an exploratory study, no sample size calculations were made, which increases the chance of a type II error. To increase power, we analyzed the data over one-year intervals. With a total follow-up duration of two years, each subject occurred in the dataset twice (regarding comparisons of the HEMRIS with general measures of disease activity), or four times (regarding comparisons of the HEMRIS with clinical examination of enthesitis at both ankles). Analyses were not adjusted for multiple measurements in patients because of limited power, however no significant changes in HEMRIS were observed in the unadjusted analyses. Another limitation is the observational study design. Further

research in larger populations is required to further establish the responsiveness of HEMRIS to change and its association with change in clinical disease activity. In the ongoing TOFA-PREDICT study (EudraCT Number 2017-003900-28), we aim to investigate the effect of three different DMARDs (tofacitinib, methotrexate, and etanercept) on HEMRIS results in a PsA population with more active disease.

Conclusions

MRI findings of heel enthesitis assessed with HEMRIS changed in a small number of patients in an observational setting. Although changes of enthesitis evaluated on MRI were minimal in this study, quantitative MRI assessment of enthesitis could potentially visualize change in these structures in more detail.

Author Contributions

Methodology, E.F.A.L., N.J.K. and W.F.; formal analysis, N.J.K.; investigation, N.J.K. and I.t.K.; data curation, N.J.K.; writing—original draft preparation, N.J.K.; writing—review and editing, W.F., I.t.K., E.F.A.L., J.S. and P.A.d.J.; visualization, N.J.K.; supervision, W.F., J.S. and P.A.d.J.; project administration, N.J.K. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University Medical Center Utrecht (protocol code 15-429, 17-11-2015).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplemental information. Data are available upon reasonable request. Please contact the corresponding author.

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Conflicts of Interest

Wouter Foppen received research grants from Novo Nordisk and Pfizer, which were paid to the institution. Pim de Jong has a research collaboration with Vifor Pharma and Philips. Julia Spierings received a research grant from Boehringer Ingelheim

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Supplemental material

Supplemental Table S1. Total HEMRIS scores and change in total HEMRIS scores at Achilles tendon, plantar fascia and Achilles tendon and plantar fascia combined.

	Start of one-year interval	**End of one-year interval**	**Change scores**	**p-value***
Achilles tendon (summated scores left + right ankle)				
Total MRI-scores, n=	72	67	67	
Total HEMRIS entheseal inflammation score (0-24), median (IQR)	1.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.28
Total HEMRIS structural damage score (0-24), median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.0 (0.0-0.0)	0.32
Total missing MRIs, reasons:				
Missing, patient lost to follow-up (n=)	2	6	6	
Missing, MRI quality (n=)	2	3	3	
Plantar fascia (summated scores left + right ankle)				
Total MRI-scores, n=	72	68	68	
Total HEMRIS entheseal inflammation score (0-18), median (IQR)	0.0 (0.0-0.8)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.31
Total HEMRIS structural damage score (0-24), median (IQR)	0.0 (0.0-1.8)	0.0 (0.0-2.0)	0.0 (0.0-0.0)	0.68
Total missing MRIs, reasons:				
Missing, lost to follow-up (n=)	2	6	6	
Missing, MRI quality (n=)	2	2	2	
Total (Achilles tendon + plantar fascia, summated scores left + right ankle)				
Total MRI-scores, n=	72	68	67	
Total HEMRIS entheseal inflammation score (0-42), median (IQR)	1.0 (0.0-3.0)	1.0 (0.0-2.0)	0 (-1.0 - 0.0)	0.14
Total HEMRIS structural damage score (0-48), median (IQR)	1.0 (0.0-3.8)	1.0 (0.0-4.0)	0.0 (0.0-0.0)	0.89

Supplemental Table S1. Total HEMRIS scores and change in total HEMRIS scores at Achilles tendon, plantar fascia and Achilles tendon and plantar fascia combined. (continued)

	Start of one-year interval	End of one-year interval	Change scores	p-value*
Total missing MRIs, reasons:				
Missing, patient lost to follow-up (n=)	2	6	6	
Missing, MRI quality (n=)	2	3	3	

*Table Legend. *= Wilcoxon Signed Rank Test, n=total number of MRI-scans, HEMRIS = Heel Enthesitis MRI Scoring System, IQR = interquartile range, MRI = magnetic resonance imaging*

Supplemental Table S2: Patients' characteristics at follow-up.

	Disease category (at time of inclusion)			
	Psoriasis	**Psoriatic arthritis**	**Ankylosing spondylitis**	**All**
Total one year intervals, N =	23	23	24	70
General disease activity:				
Pso: moderate-severe psoriasis, n (%)	2 (8.7)	NA	NA	NA
PsA: MDA, n (%)	NA	14 (60.9)	NA	NA
Missing, n (%)	NA	3 (13.0)	NA	NA
AS: BASDAI score ≥ 4, n (%)	NA	NA	21 (87.5)	NA
Missing, n (%)	NA	NA	1 (4.2)	NA
Medication:				
Current DMARD use, n (%):	1 (4.3)	8 (34.8)	2 (8.3)	11 (16.2)
Missing, n (%)	0	1 (4.3)	1 (4.2)	2 (2.9)
Current NSAID use, n (%):	2 (8.7)	5 (21.7)	15 (62.5)	22 (32.4)

Supplemental Table S2: Patients' characteristics at follow-up. (continued)

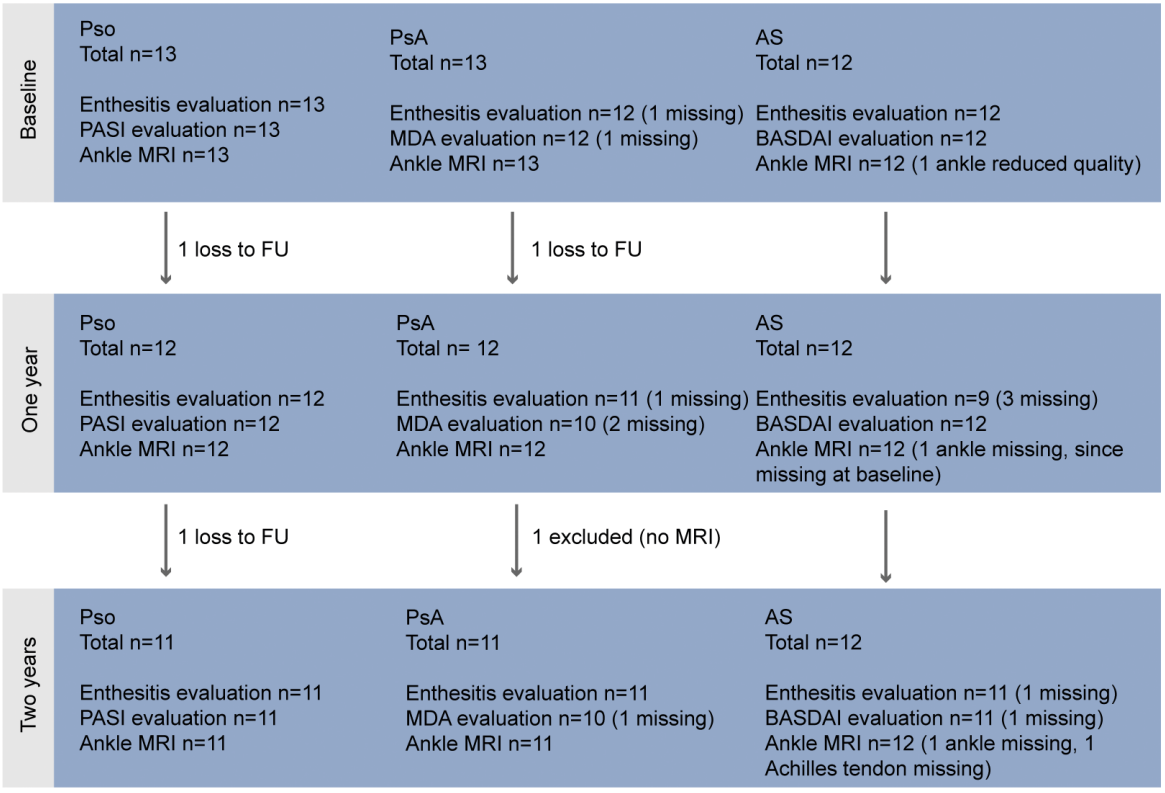
	Disease category (at time of inclusion)			
	Psoriasis	**Psoriatic arthritis**	**Ankylosing spondylitis**	**All**
Missing, n (%)	0	1 (4.3)	1 (4.2)	2 (2.9)
Inflammatory markers:				
ESR, median (IQR):	5.0 (2.0 - 13.0)	3.0 (2.0 - 6.0)	5.0 (2.0 - 9.3)	4.5 (2.0 -7.0)
Missing, n (%)	2 (2.9)	0	0	2 (2.9)
CRP, median (IQR):	1.6 (0.5 - 9.2)	3.5 (2.2-6.2)	1.3 (0.7 - 3.9)	2.2 (0.9-4.9)
Missing, n (%)	1	0	1	2 (2.9)
Total				
Local disease activity at the enthesis:				
Achilles tendon, N enthesis =	46	46	48	140
Clinical enthesitis, n (%)	4 (8.7)	0	4 (8.3)	8 (5.7)
Missing, n (%)	0	2 (4.3)	8(16.7)	10 (7.1)
Plantar fascia, N enthesis =	46	46	48	140
Clinical enthesitis, n (%)	6 (13.0)	5 (10.9)	0	11 (7.9)
Missing, n (%)	0	2 (4.3)	0	10 (7.1)

Table legend. Abbreviations: AS = ankylosing spondylitis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, CRP = C- reactive protein, DMARD = disease-modifying anti-rheumatic drugs, ESR = erythrocyte sedimentation rate, IQR = interquartile range,
Pso = psoriasis, PsA = psoriatic arthritis, MDA = minimal disease activity, NA = not applicable, NSAID = non-steroidal anti-inflammatory drugs.
Patients' characteristics at 52 and 104 weeks (pooled data). Patients that were lost to follow-up were excluded from the analysis.

Supplemental Table S3. Change in HEMRIS subscores after longitudinal follow-up

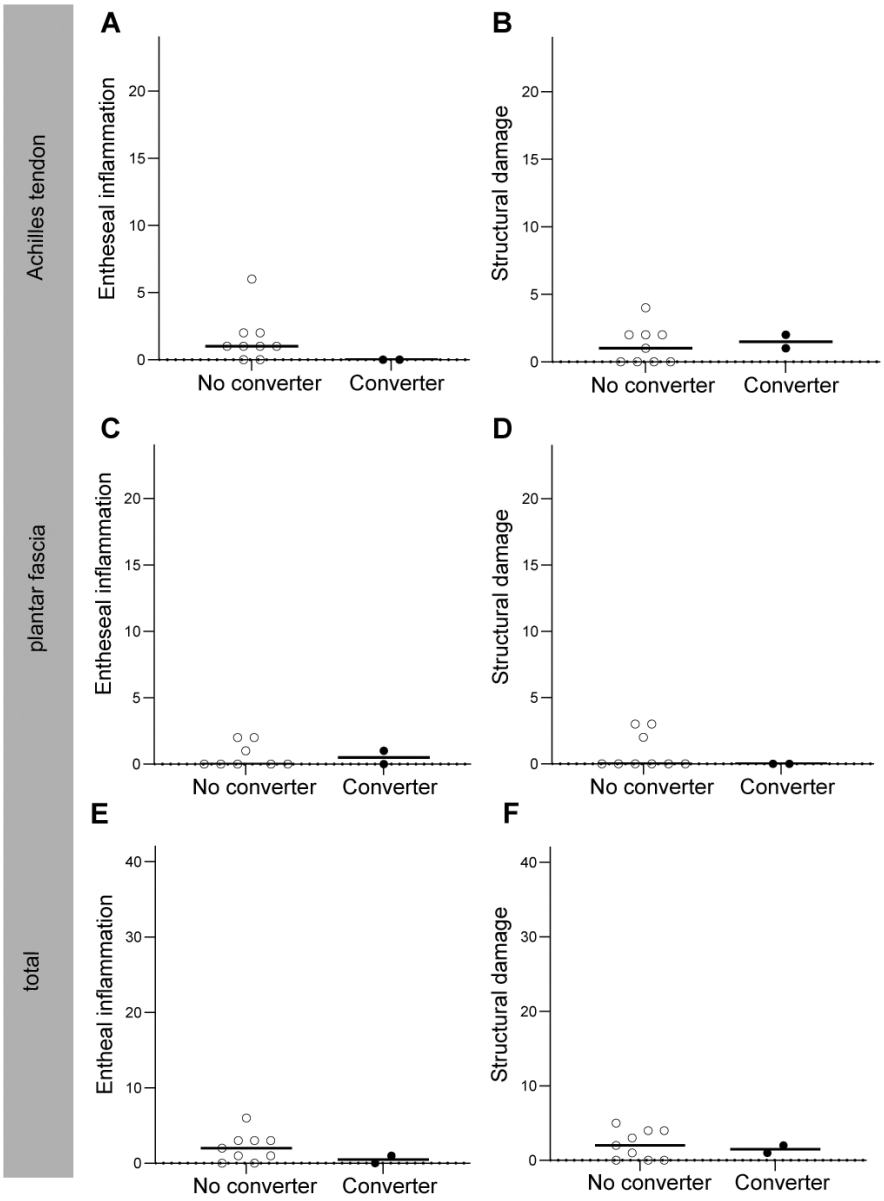
	Achilles tendon	Plantar fascia
Total observations, n=	137	138
Tendon thickening		
• Increase, n(%)	1 (0.7)	1 (0.7)
• Decrease, n(%)	0 (0)	3 (2.2)
Tendon hypersignal T1W:		
• Increase, n(%)	1 (0.7)	1 (0.7)
• Decrease, n(%)	5 (3.6)	3 (2.2)
Bone spur:		
• Increase, n(%)	1 (0.7)	0 (0)
• Decrease, n(%)	0	1 (0.7)
Tendon erosion:		
• Increase, n(%)	0 (0)	0 (0)
• Decrease, n(%)	0 (0)	0 (0)
Bone marrow edema:		
• Increase, n(%)	0 (0)	2 (1.4)
• Decrease, n(%)	0 (0)	1 (0.7)
Tendon hypersignal T2W:		
• Increase, n(%)	0 (0)	2 (1.4)
• Decrease, n(%)	6 (4.4)	3 (2.2)
Peritendon hypersignal:		
• Increase, n(%)	3 (1.8)	5 (3.6)
• Decrease, n(%)	10 (7.3)	11 (28.9)
Retrocalcaneal bursitis:		
• Increase, n(%)	10 (7.3)	NA
• Decrease, n(%)	10 (7.3)	NA

Table legend. Abbreviations: NA = not applicable, T1W = T1-weighted images, T2W = T2-weighted images



Supplemental Figure S1. Flowchart.

Clinical evaluations at each time point (baseline, one year follow up and two years follow-up). Abbreviations: AS = ankylosing spondylitis, FU = follow-up, Pso= psoriasis, PsA = psoriatic arthritis, MRI= magnetic resonance imaging



Supplemental Figure S2. Change in the HEMRIS in Pso patients with and without progression to PsA.

No differences were observed in respective HEMRIS inflammation and structural damage results at the Achilles tendon (A and B), plantar fascia (C en D) and plantar fascia and Achilles tendon and plantar fascia combined (E and F) at inclusion in Pso patients that later developed PsA ('converter', n=2), in comparison with Pso patients that did not developed PsA. ('no converter', n=11). Abbreviations: Pso = psoriasis, PsA = psoriatic arthritis.

Chapter 4

The TOFA-PREDICT study protocol: A Stratification trial to determine key immunological factors predicting Tofacitinib efficacy and drug free remission in Psoriatic Arthritis (PsA).

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Abstract

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory, musculoskeletal disease that affects up to 30% of psoriasis patients. Current challenges in clinical care and research include personalised treatment, understanding the divergence of therapy response and unravelling the multi-factorial pathophysiology of this complex disease. Moreover, there is an urgent clinical need to predict, assess and understand the cellular and molecular pathways underlying the response to disease modifying anti-rheumatic drugs (DMARDs). The TOFA-PREDICT clinical trial addresses this need. Our primary objective is to determine key immunological factors predicting Tofacitinib efficacy and drug-free remission in PsA.

Methods and analysis

In this investigator-initiated, phase III, multi-centre, open-label, four-armed, randomized controlled trial, we plan to integrate clinical, molecular, and imaging parameters of 160 PsA patients. DMARD-naive patients are randomized to methotrexate or tofacitinib. Additionally, patients that are non-responsive to csDMARDs continue their current csDMARD and are randomized to etanercept or tofacitinib. This results in four arms with each 40 patients. Patients are followed for one year. Treatment response is defined as minimal disease activity (MDA) at week 16. Clinical data, biosamples, and images are collected at baseline, 4 weeks, and 16 weeks; at treatment failure (treatment switch) and 52 weeks. For the first 80 patients, we will use a systems medicine approach to assess multi-omics biomarkers and develop a prediction model for treatment response. Subsequently, data from the second 80 patients will be used for validation.

Ethics and dissemination

The study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands, is registered in the European Clinical Trials Database and is carried out in accordance with the declaration of Helsinki. The study's progress is monitored by Julius Clinical, a science-driven contract research organization.

Registration details

MREC reference number: NL63439.041.17; EudraCT reference number: 2017-003900-28.

Strength and limitations of this study

Strengths

1. Our multi-omics systems medicine approach integrates molecular, imaging, and clinical data, which facilitates identification of pre-treatment profiles that are associated with DMARD response in PsA.
2. We use a two-step data analysis approach to both discover and validate predictive profiles.
3. Sensitive imaging techniques are used to evaluate treatment response at multiple time points, enabling comparison with conventional response measures.

Limitations

4. Although the TOFA-PREDICT study includes therapies with three different mechanisms of action (MTX, a TNF inhibitor and a Janus Kinase Inhibitor), this does not cover the full therapeutic armamentarium available for PsA.
5. The two-step approach with discovery and validation bisects the cohort, leading to reduced sample size per treatment group.

Introduction

Background

Psoriatic arthritis (PsA) is a chronic, auto-inflammatory and auto–immune, musculoskeletal disease that affects up to 30% of patients with psoriasis.(1) It is considered a heterogeneous disease, as patients have a variable disease course and clinical phenotype.(1–4) The hallmarks of PsA include cutaneous psoriasis, nail dystrophy, peripheral arthritis, axial spondyloarthritis, dactylitis, and enthesitis.(1–3) PsA may also feature extra-musculoskeletal manifestations and comorbidities that impact overall morbidity and mortality, including anxiety, depression, uveitis, inflammatory bowel disease, metabolic syndrome, and cardiovascular events.(5–11)

PsA can cause severe joint damage early in the disease course, contribute to functional disability and chronic pain, and as such negatively impact quality of life.(2,4,12–14) Delayed treatment initiation is associated with progression of joint erosions, decreased long-term physical function and reduced risk of medication-free remission.(13–16) A delayed diagnosis of six months may already negatively impact physical function and joint erosions.(14) These data highlight the necessity of

timely initiation of effective treatment with disease-modifying anti-rheumatic drugs (DMARDs).(17,18)

Challenges in treatment and assessing response to therapy

The care for patients with PsA faces several challenges.(19) The first challenge arises in unravelling the mechanisms that underlie pathogenesis. Although over the past 15 years many researchers have studied its complex etiology, the exact molecular mechanisms underpinning PsA pathogenesis remain unknown.(3,20) It is important to improve our understanding of the genetic, environmental, and immune-mediated factors that initiate and maintain the disease, as discoveries about dysregulated immunological pathways can facilitate the development of new therapies. For example, identification of the implications of the tumor necrosis factor alpha (TNF) and interleukin (IL)-23/IL17 pathways have led to rapid development of effective therapeutic agents.(1,3) Moreover, stratification of patients with inflammatory arthritis by immunological phenotype for selection of therapy has shown promise. For example, favourable treatment response in PsA patients that were stratified based upon circulating T helper cell profiles has been reported.(21) In rheumatoid arthritis, a machine learning model based upon divergent transcriptional signatures in peripheral blood mononuclear cells (PBMCs), monocytes, and CD4+ T cells, was reported to predict treatment response in adalimumab or etanercept (ETN) treated patients.(22) These examples underline how unravelling disease pathogenesis may improve clinical practice.

The second challenge comprises a lack of methods to select the optimal treatment for each patient.(4,12,23) Evidence-based treatment strategies for PsA were developed by the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). However, treatment response rates are disappointing.(24,25) Up to 40% of patients respond insufficiently to a first DMARD, and strongly divergent drug responses are observed.(3,4,12) Although conventional synthetic (cs)DMARDs are frequently used as first-line therapy, there is limited evidence available on their effectiveness in PsA.(26–28) Moreover, the number of csDMARDs, biologic (b)DMARDs, and targeted synthetic (ts) DMARDs is rapidly increasing and head-to-head trials are scarce.(23,29–31) Hence, clinicians have no tools at their disposal to predict which DMARD will be effective for an individual patient.(23) This lack of precision medicine is a clinically relevant problem for a potentially aggressive disease, that may impact quality of life, affect

multiple organ systems, has an economic burden on the healthcare system, and demands costly treatment that potentially causes adverse events.(12–19,21)

The third challenge comprises the wide array of novel imaging modalities and the growing number of analytical methods that have become available for the evaluation of therapy response in PsA. Conventional radiography lacks sensitivity, especially in early disease patients in whom little radiographic abnormalities are observed.(32) Furthermore, the visual interpretation of medical images is time-consuming, bound with interobserver variation and limited to semi-quantitative outcomes that may be insensitive to detect small changes over time. On the contrary, computer-based medical image analysis can generate uniform, quantitative results in a (semi)-automatic manner. Adding these techniques in trials and in clinical practice may add to unravelling mechanisms as well as improvement of treatment.

Rationale

Overall, there is an urgent clinical need to assess and understand the cellular and molecular pathways underlying DMARD treatment response in PsA. To this end the TOFA-PREDICT trial was designed. In this investor-initiated, phase III, multi-centre, four-armed, randomized trial, a multi-omics systems medicine approach is used to integrate pre-treatment clinical, transcriptomic, metabolomic, proteomic, flow cytometry, and imaging data to discover PsA patients profiles that predict response to tofacitinib (TOF), as compared to methotrexate (MTX) and etanercept (ETN). By expanding our knowledge of the underlying mechanisms, course and treatment response, the TOFA-PREDICT study also aims to identify novel biomarkers for diagnosis and disease monitoring.(3,19)

In the TOFA-PREDICT trial sensitive imaging techniques, including magnetic resonance imaging (MRI) and Fluorine-18-fluorodeoxyglucose positron emission tomography/computerized tomography (18F-FDG PET/CT), are applied to monitor disease activity. The current trial can deliver important data on the value of these more advanced imaging methods. With the use of ankle MRI-scans early, possibly reversible, and inflammatory features of PsA can be visualized at the heel, which is the most frequently affected site for enthesitis in PsA.(33,34) Moreover, 18F-FDG PET/CT might aid in the measurement of local and systemic inflammation in PsA, including (peri)-articular and vascular inflammation.

Objectives

Primary

Identify pre-treatment profiles with integrated clinical, transcriptomic, metabolomic, proteomic, flow cytometric, and imaging data that predict response to treatment with tofacitinib, in DMARD-naïve and DMARD non-responsive PsA patients

Secondary

Compare clinical efficacy of treatment with tofacitinib, methotrexate and etanercept in DMARD-naïve and DMARD-non responsive patients with active PsA

Compare structural response to treatment of active PsA with tofacitinib, methotrexate, and etanercept using (semi)quantitative ankle-MRI outcomes, radiographic outcomes, and 18F-FDG PET/CT outcomes

Determine (medication specific) molecular mechanisms predicting and underlying clinical response to tofacitinib, in comparison to methotrexate, and etanercept in active PsA

Methods And Analysis

Study setting

TOFA-PREDICT is a multicentre (seven) investigator-initiated, phase III, open-label, four-arm, randomized controlled study conducted in the Netherlands. A total of 160 PsA patients that fulfil the ClASsification criteria for Psoriatic ARthritis (CASPAR) will be included in two groups, each with two treatment arms.(35) The first group consists of DMARD-naïve patients, who are randomized to MTX (arm 1) or TOF (arm 2). The second group consists of DMARD non-responsive patients, who continue csDMARD background therapy and are randomized to addition of ETN (arm 3) or TOF (arm 4).

Eligibility criteria are displayed in Table 1. The TOFA-PREDICT trial started on April 4, 2018 and the scheduled end date is July 1,2025. By the end of 2022, inclusion of the first cohort of 80 patients is completed. The evaluation of the first cohort will be initiated early 2023.

Table 1. TOFA-PREDICT eligibility.

INCLUSION CRITERIA	
General	
1	Patients aged 18-75 years.
2	Fulfilment of CASPAR criteria for psoriatic arthritis (PsA).
3	Psoriatic arthritis disease duration of ≥8 weeks.
4	Active arthritis based on ≥2 swollen joints AND ≥2 tender joints.
Concomitant therapies	
5	In case of oral corticosteroid use, a stable dose of ≤10 mg/day of prednisone (or equivalent) for ≥4 weeks prior to baseline visit is allowed.
6	In case of NSAID use, a stable dose one week prior to baseline visit is allowed.
7	In case of current topical treatment of psoriasis, the following regimens are allowed: Non-medicated emollients Topical corticosteroids ≤1% for only palms, soles, face and intertriginous areas Tar or salicylic acid preparations and shampoos for only the scalp
Specific for DMARD non-responsive patients (arm 3 and 4)	
8	Current use of csDMARD (MTX, LEF, SSZ) On the highest tolerable dosage (max dose 25 mg/week) A stable dose ≥4 weeks prior to baseline Without previous serious toxicity In case of MTX: concomitant folate supplementation ≥5 mg/week
9	History of 1 bDMARD prior to inclusion is allowed, except: Prior use of etanercept. Primary failure of other TNFi than etanercept (adalimumab, golimumab, infliximab, certolizumab).
EXCLUSION CRITERIA	
General	
10	Pustular psoriasis only.
11	Diagnosis of fibromyalgia or history of any rheumatic autoimmune or inflammatory disease other than PsA.
12	Any condition possibly affecting oral drug absorption, such as gastrectomy, diabetic gastro enteropathy or bariatric surgery (e.g. gastric bypass).
13	A skin condition at the time of baseline that could interfere with evaluation of psoriasis severity.
14	Previous participation in any study with tofacitinib as IP.
15	Participation in other studies involving investigational drug(s) ≤4 weeks prior to baseline visit.
Specific for DMARD-naïve patients (arm 1 and 2)	

16	History of csDMARD, bDMARD or tsDMARD use.
Specific for DMARD non-responsive patients (arm 3 and 4)	
17	History of ≥2 bDMARDs or ≥1 tsDMARD.
Therapies	
18	Prior treatment with non-B cell-specific lymphocyte depleting therapies, alkylating agents or total lymphoid irradiation. Rituximab or other selective B-lymphocyte depleting agents are allowed, if discontinued ≥1 year prior to first dose of the IP and normal CD19/20+ counts by flow cytometry analysis.
19	Specific concomitant therapies, being: Injected corticosteroids ≤4 weeks prior to baseline visit UVB phototherapy ≤2 weeks prior to baseline visit PUVA (psoralens and UVA) phototherapy ≤4 weeks prior to baseline visit Topical treatments that could affect psoriasis severity (corticosteroids, tars, keratolytics, anthralin, vitamin D analogs, retinoids) ≤2 weeks prior to baseline visit
Safety	
20	Pregnant females, females planning pregnancy, breastfeeding females and females of childbearing potential not using highly effective contraception. Women of childbearing age must test negative for pregnancy prior to enrolment.
21	Blood dyscrasias within three months prior to baseline visit, including: Haemoglobin <10 g/dL White blood cell count <3.0 x 10^9/L (<3000/mm^3) Absolute neutrophil count ≤1.5 x 10^9/L (<1500/mm^3) Absolute lymphocyte count <1.0 x 10^9/L (<1000/mm^3) Platelet count <100 x 10^9/L (<100,000/mm^3)
22	Estimated Creatinine Clearance <40 ml/min based on Cockcroft formula.
23	Total bilirubin, AST or ALT more than two times the upper limit of normal at screening visit.
24	History of an infected joint prosthesis at any time, with the prosthesis still in situ.
25	Oral antimicrobial therapy ≤2 weeks prior to baseline visit.
26	Vaccination with live or attenuated vaccines: ≤6 weeks prior to baseline visit Planned during the study period ≤6 weeks following discontinuation of the IP
27	History of alcohol or drug abuse (unless in full remission for ≥6 months prior to baseline visit).
28	Significant trauma or surgical procedure ≤1 month prior to baseline visit, or any planned elective surgery during the study period.
29	Active, latent or inadequately treated infection with *Mycobacterium tuberculosis* as defined by: Positive QuantiFERON-TB Gold In-Tube test within 3 months prior to the screening visit Suspected radiographic features on chest radiograph within 3 months prior to the screening visit Medical history of inadequately or untreated latent or active *Mycobacterium tuberculosis* infection

30	Positive serologic screening for infection with human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, or history of any other chronic infection.
31	Increased risk for gastrointestinal perforation, such as diverticulitis.
32	History of any immunodeficiency or a first-degree relative with a hereditary immunodeficiency.
33	History of any lymphoproliferative disorder (such as Epstein Barr Virus related lymphoproliferative diseases), history of lymphoma, leukaemia, or signs and symptoms suggestive of current lymphatic disease.
34	History of a disseminated herpes zoster or simplex infection, or recurrent (≥1 episode) herpes zoster infections.
35	History of active infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, ≤6 months prior to baseline visit.
36	Current history of lymphoma and malignancy, except for Adequately treated or excised non-metastatic basal cell cancer of the skin, squamous cell cancer of the skin and cervical carcinoma in situ. Adequately treated solid malignant tumours without recurrence after a minimal follow-up period of 10 years.
37	Current or recent history of a severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurologic disease.
38	Other severe acute or chronic, medical or psychiatric conditions, or laboratory abnormalities, that may Increase the risk associated with study participation or IP administration Interfere with interpretation of study results

Table Legend. Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; bDMARD: biologic DMARD ('biological') e.g. inhibitors of tumour necrosis factor and interleukin-17A; CASPAR: ClASsification criteria for Psoriatic Arthritis; csDMARD: conventional synthetic DMARD e.g. methotrexate, leflunomide or sulfasalazine; DMARD: disease modifying anti-rheumatic drug; IP: investigational product; LEF: leflunomide; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PsA: psoriatic arthritis; SSZ: sulfasalazine; tsDMARD: targeted synthetic DMARD; TNFi: tumour necrosis factor alpha inhibitor; UVA: ultra-violet A; UVB: ultra-violet B.

Interventions

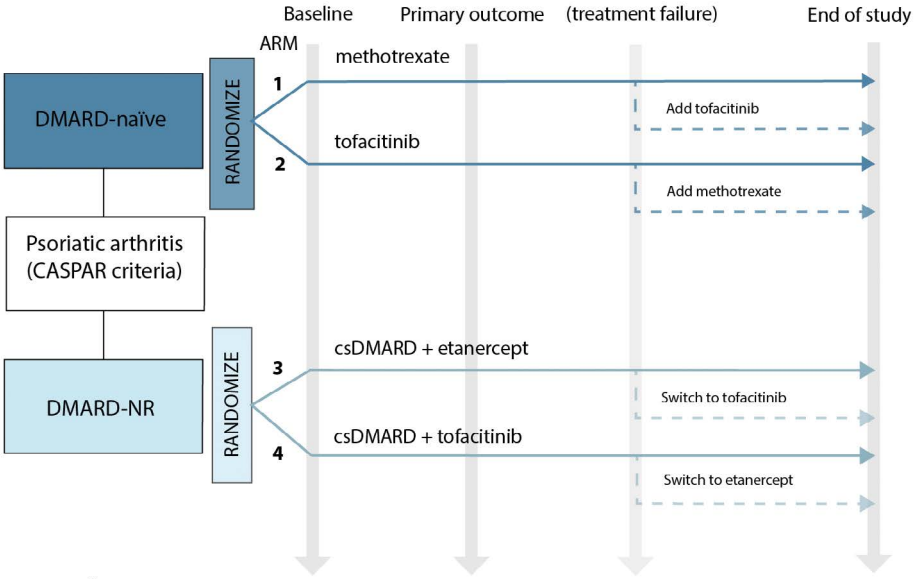
The first group of patients are DMARD-naïve and have active PsA. Typically, these patients are at an early stage of PsA. Patients are randomized to receive either MTX monotherapy 25mg once a week, subcutaneously (standard of care therapy, arm 1) or TOF monotherapy 5mg twice daily, orally (investigational therapy, arm 2). Randomization is performed per site in computer-generated random blocks. Patients will be assessed according to a predefined schedule of regular study visits (Table 2). In case of treatment failure (see heading "Treatment failure"), combination therapy

will be initiated: patients randomized to MTX will also start TOF, and vice versa. If drug intolerance warrants discontinuation of the drug, a switch will be made to the alternate drug as monotherapy (TOF to MTX and vice versa).

The second group of patients are non-responders to previous treatment with either MTX, leflunomide (LEF) or sulfasalazine (SSZ), or to previous treatment with combination therapy of a csDMARD and one previous bDMARD. A history of one bDMARD prior to inclusion is allowed, except for prior use of ETN. Prior use of a tsDMARD (Janus kinase inhibitor, abatacept) is also not allowed. Only patients who have had secondary treatment failure to a TNFi, defined as initial good response, but diminished clinical efficacy over time, are eligible to participate in the study.(36) These DMARD non-responders continue background therapy with csDMARD and are randomized to receive the addition of either ETN 50mg once a week, subcutaneously (arm 3) or TOF 5mg twice daily, orally (arm 4). ETN was chosen as it was reimbursed and no preference for a specific TNF-inhibitor is mentioned in current EULAR and GRAPPA international guidelines for the treatment of PsA.(24,25) In the event of treatment failure or drug intolerance (see heading 'Treatment failure'), a switch from ETN to TOF or vice versa will be made (Figure 1).

Study visits

Study visits are performed at baseline, week 4, week 16, week 26, week 39 and week 52. Each study visit comprises multiple study assessments (a schematic overview is depicted in Table 2). From week 16 onwards, the American College of Rheumatology (ACR)50 score is calculated every study visit, to determine treatment failure.(37) The ACR50 score is described in the outcomes section. Patients are evaluated additionally to the above-described visits according to regular clinical practice, including blood sampling for safety measurements according to regular practice. During all visits, adverse events and serious adverse events are documented with respect to safety



Week	0	4	16		26	39	52
Questionnaires & Physical examination	√	√	√	(√)	√	√	√
Blood sample	√	√	√	(√)			√
X-rays (hands, feet)	√						√
MRI (ankles)	√		√				√
18F-FDG PET/CT (whole-body)	√						√

Figure 1. Study design.
Treatment failure is defined as not attaining the ACR50 response on two consecutive study visits (interval four weeks), starting from week 16. Abbreviations: 18F-FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; CASPAR: ClASsification criteria for Psoriatic ARthritis; DMARD: disease modifying anti-rheumatic drug; NR: non-responder to conventional synthetic and a maximum of one biologic DMARD therapy; MRI: magnetic resonance imaging.

Table 2. Schematic overview of study assessments.

Category	Assessment	Screening	Baseline	FU	Primary endpoint	FU	FU	End of study	Treatment failure [5]
	Week number	n.a.	0	4	16	26	39	52	t.b.d.
Eligibility	Sign informed consent	√							
	Medical History	√							
	In- & exclusion criteria	√	√						
	Randomization		√						
Anamnestic	Online questionnaires [1]		√	√	√	√	√	√ [6]	√
	Patients wellbeing	√	√	√	√	√	√	√ [6]	√
	Adverse event evaluation		√	√	√	√	√	√ [6]	√
	Medication annotation	√	√	√	√	√	√	√ [6]	√
Physical examination	Length		√						
	Weight		√	√	√	√	√	√	√
	Vital signs [2]		√	√	√	√	√	√	√
	Basic physical exam		√	√	√	√	√	√	√
	TJC (76) and SJC (78)		√	√	√	√	√	√ [6]	√
	Dactylitis evaluation		√	√	√	√	√	√ [6]	√
	Leeds enthesitis Index and enthesis plantar fascia		√	√	√	√	√	√ [6]	√
	PASI and BSA		√	√	√	√	√	√ [6]	√

Table 2. Schematic overview of study assessments. (continued)

Category	Assessment	Screening	Baseline	FU	Primary endpoint	FU	FU	End of study	Treatment failure [5]
	VAS physician		√	√	√	√	√	√ [6]	√
Blood sample	Clinical chemistry & haematology [3]	√		√	√	√	√	√ [6]	
	Systems medicine approach [4]		√	√	√			√	√
Imaging	X-rays (hands, feet)		√					√ [6]	
	MRI (ankles)		√		√			√	
	^{18}F-FDG PET/CT (whole body)		√					√	
Evaluation	Response				√	√	√	√ [6]	√

Table Legend. 1 Questionnaires: Assessment of SpondyloArthritis (ASAS) health index, Dermatology Life Quality Index (DLQI), EuroQol five dimension scale (EQ-5D), Health Assessment Questionnaire (HAQ), self-administered psoriasis area and severity index (SAPASI) and the Work Productivity and Activity Impairment (WPAI) questionnaire, supplemented by the Visual Analogue Scale (VAS) for general wellbeing and pain. 2 Vital signs: blood pressure, pulse and temperature (auricular measurement). 3 At screening visit: Hepatitis B surface antigen (HbsAg), Hepatitis B core IgG, Human Immunodeficiency Virus (HIV)-1 and 2 antibodies, p24 antigen, interferon-γ release assay (IGRA), Rheumatoid Factor (RF), Anti-citrullinated peptide/protein antibodies (ACPAs), haemoglobin (Hb), haematocrit (Ht), thrombocytes, erythrocytes, leucocytes and differentiation, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (eGFR), sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, glycosylated haemoglobin (HbA1c), triglycerides and cholesterol (total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)). At follow-up visits: Hb, Ht, thrombocytes, erythrocytes, leucocytes, ESR, CRP, ALT, eGFR, triglycerides and cholesterol. 4 Systems medicine approach to collect '-omics' data: proteomics, transcriptomics and metabolomics. At baseline, week 4, week 16, week 52 a total of 85 mL blood is drawn for isolation of serum, plasma, peripheral blood mononuclear cells (PBMCs), , B cells, myeloid dendritic cells (mDCs), monocytes and peripheral blood leukocytes (PBLs). In case of treatment failure only 35 mL blood is drawn for isolation of serum, plasma and PBMCs. 5 A 'treatment failure visit' is planned when the ACR50 response is not attained at a regular study visit; starting from week 16. Treatment failure is defined as again not attaining the ACR50 at this extra study visit four weeks later. 6 Selection of data obtained after resuming treatment in regular care for patients that discontinue trial medication due to (serious) adverse events, treatment failure after cross-over or other reasons. Abbreviations: 18F-FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; BSA: body surface area; FU: follow-up; MRI: magnetic resonance imaging; PASI: psoriasis area and severity index; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale; X-ray: conventional radiographic photograph.

Treatment failure

Treatment failure is defined as failing to achieve an ACR50 response on two consecutive visits from week 16 onwards. If a patient does not attain the ACR50 response at a regular study visit, an additional study visit is scheduled 4 weeks later. At this 'treatment failure' visit the ACR50 response is re-assessed. In the event that the ACR50 response is again not attained, 'treatment failure' is confirmed and a cross-over to the alternate treatment protocol within that study group takes place (Figure 1). A minimum washout of 1 week will be applied to patients switching from TOF to ETN (or vice versa). If the ACR50 response is attained at the 'treatment failure'-visit, regular 12-week visit intervals will continue and the patient will not switch therapy. In addition, drug intolerability that warrants discontinuation (e.g., side-effects, laboratory abnormalities) is defined as treatment failure at any time point. In the case of MTX, dosage lowering is the first step in case of drug intolerability. For ETN and TOF, dosage changes are not possible and drug intolerability indicates treatment failure. Cross-over will not take place in the last 3 months of follow-up.

MTX dosage adjustments

MTX is initiated in the DMARD-naïve arm at a dosage of 15mg/week subcutaneously. The dosage is increased to 25 mg/week after 4 weeks, unless the ACR50 response is attained or side effects prevent safe dosage escalation. By increasing the dosage to 25mg/week at week 4, the primary end point of the study can be compared between MTX and TOF at week 16 (i.e., 12 weeks of administering the maximal dosage of MTX). MTX dosage may be reduced during follow-up if ACR50 has been attained and/or if side-effects occur, in accordance with standard clinical care.

Escape medication

In accordance with standard clinical care, the following escape therapies are allowed: non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, and from week 24 onwards, topical corticosteroids.

End of study

After 52 weeks of follow-up, all patients will resume regular clinical care while continuing the DMARD therapy that was initiated during the study. Treatment in regular care will also be resumed by patients that discontinue trial medication due to (serious) adverse events, treatment failure after cross-over or other reasons. From

these patients, we will only collect a selection of data after 52 weeks of follow-up (Table 2: footnote 6).

Data collection and samples

All collected clinical data are entered in an online database (Research online; Julius Centre UMC Utrecht) designed for the TOFA-PREDICT trial. Blood samples for the multi-omics analyses are collected at several time points throughout the study (Figure 1). In addition, blood samples are taken to monitor drug safety after the start of MTX, TOF or ETN. Blood samples for the multi-omics analyses are collected at seven different study sites After protocolized transport, all blood samples are processed in a standardized way in the University Medical Center (UMC) Utrecht. The samples are pseudo-anonymized and after magnetic-activated cell sorting, peripheral blood mononuclear cell subsets are stored. Additionally, serum, plasma and peripheral blood mononuclear cell subset lysates are stored. All blood samples for multi-omics analyses are registered with Quaero Systems. The multi-omics analyses of the stored samples are performed in batches at a later stage, taking confounders such as treatment arm, visit number and demographics into account. All data are integrated at the Data Research Environment (anDREa). The omics data will be made available in public databases after primary analyses and publication.

Patient and public involvement statement

Patients were not involved in the development of the research question, the design and conduct of the study, choice of outcome measures nor recruitment.

Outcomes

Systems medicine approach

The primary objective is to discover and validate pre-treatment clinical, transcriptomic, metabolomic, proteomic, flow cytometric, and imaging profiles that predict treatment response. Response and nonresponse are defined as attaining or not attaining MDA, respectively, after 16 weeks of treatment. To define these profiles, a multi-omics systems medicine approach will be used for which transcriptomic, metabolomic, proteomic, and flow cytometry data are collected. Transcriptomic and flow cytometry analysis will be performed on peripheral blood mononuclear cell(subset)s. Proteomic and metabolomic analyses will be performed on serum and/or plasma samples. These molecular and cellular data will be added to the

clinical, structural, and imaging data (ankle-MRIs, whole body 18F-FDG PET/CT, and radiographs of the hands and feet). Systems medicine data analyses will be used to combine the different omics-layers in our attempt to identify profiles that predict treatment response.

Clinical efficacy measures

We use MDA at week 16 as the primary outcome for the identification of molecular and cellular profiles that predict treatment response. MDA is a validated, PsA-specific composite measure that includes evaluation of arthritis (tender and swollen joint count), skin disease (Psoriasis Area and Severity Index (PASI) and Body Surface Area (BSA)), enthesitis, and patient reported outcomes (Health assessment Questionnaire (HAQ), visual analogue scale (VAS) for pain and VAS for patient global assessment).(38,39) The clinical relevance of composite measures that include multiple disease domains has become increasingly evident over recent years.(38–40) To define treatment failure, we use the ACR50 response, because treatment effect during follow-up is most commonly detected as a change from baseline. ACR50 is a composite measure defined as 50% improvement in the number of both swollen and tender joints, next to 50% improvement in at least three of the following outcomes: HAQ, acute phase reactant (we use CRP), VAS for patient global assessment, VAS for physician global assessment and VAS for pain.(37,41,42) We calculate the ACR50 every 12 weeks starting from week 16. Moreover, we assess dactylitis, blood pressure, body mass index (BMI), laboratory parameters, additional patient-reported outcomes and calculate additional PsA-specific composite indices.(43)

Patient-reported measures

At baseline, week 4, 16, 26, 39, 52 and at treatment failure visits, patients fill out online questionnaires to monitor disease activity and their mental and physical health. TOFA-PREDICT employs the following questionnaires: Assessment of SpondyloArthritis (ASAS) health index, Dermatology Life Quality Index (DLQI), EuroQol five-dimension scale (EQ-5D), HAQ, self-administered psoriasis area and severity index (SAPASI), the Work Productivity and Activity Impairment (WPAI) questionnaire and two VAS scores to assess pain and the patients' global assessment.(44–49)

Imaging measures

Three imaging techniques are applied in the TOFA-PREDICT study: MRI-scans of both ankles, whole body 18F-FDG PET/CT and conventional radiography of the hands and

feet. At baseline, week 16 and 52 MRI-scans of both ankles are obtained. MRI-scans are performed using MR-equipment with a field strength of 1.5 or 3 Tesla. The ankles are scanned separately using an extremity coil. The MRI-protocol was developed in accordance with the European Society of Musculoskeletal Radiology (ESSR) recommendations and contains the following sequences: 3D proton density (PD) with fat suppression (FS), transversal T1 Turbo Spin Echo (TSE) and 3D T1 FS before and after intravenous gadolinium injection.(50) The estimated total time in the MRI room is <60 min per patient per visit. Ankle-MRIs are visually evaluated using PsAMRIS, adapted for the heel, and HEMRIS measures.(33,51) Using deep learning, quantitative outcome measures for ankle-MRIs will be developed aiming to quantify (peri)articular inflammatory joint changes such as synovitis, bone marrow oedema, and enthesitis.

At baseline and week 52, whole-body 18F-FDG PET/CT-scans are obtained. ^{18}F-FDG is administered intravenously after an overnight fast. Dosing of ^{18}F-FDG depends on local guidelines. After administration of ^{18}F-FDG, the 18F-FDG PET/CT is performed one hour later. A non-contrast-enhanced low-dose CT is performed for attenuation correction. In this multicentre trial, all PET/CT-reconstructions are compliant to European Association of Nuclear Medicine Research Ltd. (EARL) guidelines in order to achieve comparable quantitative outcome parameters, such as standardized uptake values (SUVs).(52) The main 18F-FDG PET/CT outcome measures are vascular and (peri)articular inflammation.

At baseline and at week 52 radiographs of hands and feet are acquired. Radiographs of hands and feet are evaluated using the PsA-modified Sharp-van der Heijde score.(53) MRI, 18F-FDG PET/CT and radiography observers are blinded to diagnosis and treatment.

Sample size calculation

The primary objective of TOFA-PREDICT is to predict the treatment response (attaining or not attaining MDA after 16 weeks of treatment in active PsA), using the multi-omics analysis of pre-treatment omics data. To evaluate the sample size needed to detect differentially expressed genes/proteins (DEGPs) between responders and non-responders we simulated several scenarios. These scenarios used a range of number of prognostic genes (50-500), dispersion (0.1 – 0.5), and False Discovery Rates (FDR; 0.01 – 0.1) with in each scenario assuming a minimum fold-change in DEGPs of 2, 80% power, and testing of a total of 20,000 genes with a mean expression (read count) of 50. Separate analyses were performed for an equal distribution between responders

and non-responders (50:50) and for unequal distributions of responders and non-responders (40:60 and 25:75). Results in the scenario assuming 400 differentially expressed genes, an FDR of 0.05 and an unequal distribution between responders and non-responders (40:60) assuming dispersion values as found in previous RNA-seq data from our group (e.g. CD14+ monocytes, dispersion value 0.11) resulted in a sample size of 20 patients per arm. Therefore, we assumed a sample size of 80 (20 patients per arm) to be sufficient to detect relevant expression signatures. Sample size was calculated using the R package 'RnaSeqSampleSize' (version 3.6.1).(54) For other omics platforms, required sample sizes are considered smaller based on the smaller number of markers (e.g. proteins up to 180 and metabolites up to 800). To enable external validation, a similar cohort will follow the first 80 patients up to a total of 160 included patients.

Data analyses

Systems medicine approach

Different layers of baseline omics data will be analysed separately and will be integrated with clinical (e.g. gender, disease duration, etc.), patient-reported parameters, and imaging data for the discovery and validation of molecular and cellular signatures that serve as biomarkers to predict treatment response after 16 weeks of treatment (primary endpoint). Furthermore, molecular signatures will be computed using omics data collected at week 4 and 52 (or treatment failure) in addition to baseline data. We will explore the molecular signatures using bioinformatic approaches. The observations made during the exploration of the data will guide the choice of tools and algorithms for the next step of the data analysis.(55) For each analysis step, we will perform permutation analysis and k-fold cross validation to test the reliability of the molecular signature. Moreover, we will integrate multi-omics data to discover molecular signatures that are supported by different layers of data, strengthening the reliability of the discovered signature. For prediction at baseline, the expression (i.e., fold change) of the separate omics layers will be analysed. Thereafter, using resulting relevant expression signatures in addition to established clinical and imaging predictors as features, we will build integrated and internally validated machine learning (ML) models to predict response to TOF and separately response to MTX and ETN. A final statistical analysis plan (SAP) will be defined prior to database lock using the optimal techniques for analysing expression profiles and optimal ML models to use. Genes or gene modules from these signatures and models will bring forth new hypotheses that can be verified experimentally, contributing

towards a better understanding of the disease mechanisms and a predictive model for disease outcome and therapy response.

Two-step analysis

After inclusion of the first 80 patients (~20 patients per group), the first step of the predictive multi-omics analysis will be performed. Of all the available multi-omics data, predictive biomarkers are identified as either relevant (statistically significant), irrelevant (statistically insignificant) or promising (based on clinical and scientific reasons without formal statistical significance). For each –omics platform, an optimal predictive assay for treatment response will be developed. Also, all relevant biomarkers will be integrated in multi-omics approaches and added to clinical data and structural imaging data to develop an exploratory prediction model for treatment response. To externally validate the identified biomarkers, we implement a second step in the analysis. Both the relevant and promising biomarkers will be analysed in the subsequent cohort of 80 patients, to replicate the results from the first phase. The proposed –omics assays from the first cohort will be validated in the second cohort. Finally, the combined relevant and promising biomarkers of all 160 patients will be integrated in multi-omics approaches and added to structural imaging data and clinical data to develop a final and clinically applicable prediction model using pre-treatment markers. In this phase, the added predictive value of omics markers over known, easily available (clinical) baseline predictors will also be assessed.

Clinical efficacy and structural response

Efficacy of treatment and imaging outcomes will be compared between different treatment arms using logistic or linear regression analyses taking into account established prognostic indicators (such as structural damage, elevated acute phase reactants and polyarthritis, to be finalised in the SAP) and centre (as the stratification factor used in randomisation). The significance level (α) will be set at 0.05, with p-values less than or equal to α considered statistically significant.

Missing data and SAEs

Cases that are lost to follow-up and other missing data will be presented descriptively. If the percentage of missing data exceeds 5%, multiple imputation will be performed, based on data type and quantity of the missing data. For binary secondary drug efficacy outcomes missing data will be defined as non-response, to prevent overestimation of the effect. Serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be reported descriptively.

Statements

Ethics And Dissemination

Ethics approval and informed consent
The study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands (reference number NL63439.041.17), and is carried out in accordance with the declaration of Helsinki. The trial is registered in the European Clinical Trials (EudraCT) Database (reference number 2017-003900-28). All participants provided written informed consent. The study progress is monitored by a science-driven contract research organization (Julius Clinical).

Dissemination plan
The results of the primary and secondary objectives of the study will be published in international peer-reviewed journals and on national and international scientific conferences.

Author Contributions

All authors substantially contributed to discussion, reviewing, revising and improvement of the protocol and writing of the manuscript before submission. FP, NK, JP and NV are the lead investigators. FL and MH are the principal instigators. JT and JS provided clinical input and supervision of research clinicians. EL contributed to study design. PW is responsible for methodology and statistics in the design and analysis of the study. MH, PW, FL and SH contributed to the analysis plan and processing of blood samples. WF, MJ, SA, FL and PJ are responsible for imaging in design and completion of the study. In each participating site a lead investigator (rheumatologist) is responsible for identification, recruitment, data collection and

completion of CRFs, follow up of study patients, adherence to study protocol and investigators' brochure and participation in feedback sessions during the conduct of this study. Lead investigators and other contributing colleagues in the participating sites are listed in the TOFA-PREDICT author group.

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Competing Interest Statement

The authors state they have no conflicts of interest and have no disclosures.

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Chapter 5

Structural and Inflammatory Imaging Parameters in Psoriatic Arthritis: A comparison of DMARD-Naive and DMARD-Failure Patients

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Abstract

Objectives:

To compare inflammatory and structural differences in active Psoriatic Arthritis (PsA) between DMARD-naive and DMARD-failure patients using diverse imaging approaches for future analyses. Additionally, to explore the influence of patient demographics on imaging findings.

Methods

Of the 80 patients (mean age 51.3 years, and 58.8% female) included from the discovery cohort of the ongoing multicentre TOFA-PREDICT trial, 40 were DMARD-naive and 40 were DMARD-failure, all meeting classification criteria for PsA with a minimum disease duration of eight weeks. Baseline conventional radiographs of hands and feet, magnetic resonance imaging (MRI)-scans of both ankles, and whole-body F-18-fluorodeoxyglucose positron emission tomography with computed tomography (^{18}F-FDG PET/CT)-scans were evaluated for inflammatory and structural imaging parameters, including Sharp-van der Heijde (SHS), Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) and Deauville synovitis scoring. Differences between groups and the influence of patient demographics were examined with multiple linear regression.

Results

At baseline, patient demographics were similar between groups. Imaging parameters showed limited inflammation and structural damage. Inflammatory imaging parameters were not significantly different ($p>0.200$). Among structural parameters, only HEMRIS Achilles tendon structural damage was significantly different ($p=0.024$, $R^2=0.071$) and, SHS Joint Space Narrowing was near significant ($p=0.050$, $R^2=0.048$) with higher values for both in DMARD-failures. After correction of patient demographics, these differences in imaging disappeared (both $p>0.600$).

Conclusion

At baseline, PsA patient groups were comparable concerning structural and inflammatory imaging parameters, especially after correcting for patient demographics. Thus, combining DMARD-naive and DMARD-failure patient groups (and correcting for patient demographics) may offer a more comprehensive understanding of PsA progression for future analyses.

Key messages

- DMARD-naive and DMARD-failure PsA patients displayed comparable inflammation, and structural damage on imaging.
- In our study, failing a DMARD was not associated with worsened imaging findings.
- After correction of patient demographics, DMARD-naive and DMARD-failure patients can be combined for future analyses.

Introduction

Psoriatic arthritis (PsA) is a complex, chronic inflammatory and heterogeneous musculoskeletal disease which may arise in up to 30 % of Psoriasis (PsO) patients. (1,2) The heterogeneity of PsA leads to challenges in identifying an effective disease-modifying antirheumatic drug (DMARD) for an individual patient.(3) Comparing different patient profiles would improve the understanding of underlying differences that might be contributing to varying outcomes and optimizing the treatment response. However, to this date, limited research is available comparing patients who never used a DMARD versus patients who previously used DMARDs, using diverse radiographic manifestation of PsA. Thus, more insight into the structural and inflammatory manifestation of PsA using various imaging approaches in these different patient profiles is needed.

Different medical imaging techniques can help us investigate the heterogeneous manifestation of PsA by examining a range of inflammatory and structural outcomes. Three imaging techniques that can be used for this examination are conventional radiography, Magnetic Resonance Imaging (MRI) and (^{18}F -FDG) Positron Emission Tomography/Computed Tomography (PET/CT). Conventional radiographs are valuable for assessing structural damages, particularly in the frequently involved joints of the hand and feet.(4) The Sharp-van der Heijde (SHS) score adapted for PsA is a well-established method for conventional radiographs to score the erosion and joint space narrowing in the hands and feet.(5)

MRI is a frequently used technique to assess both inflammatory and structural damage (6). Applying the recently developed scores Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) and Psoriatic Arthritis Magnetic Resonance Imaging Scoring System (PsAMRIS) by Outcome Measures in Rheumatology (OMERACT) group (7,8) on MRI scans provide ways to capture the different aspects

of the disease such as bone erosion and inflammation. ^{18}F-FDG PET/CT is another valuable technique to detect inflammatory manifestation of PsA.(9) It can be used to evaluate synovitis using the most commonly affected large synovial joints such as the shoulder, knee, and ankle.(4,10) In addition, this technique allows for the assessment of systemic inflammation, by evaluation of aortic vascular inflammation.(11,12)

In the literature on PsA, various imaging techniques were used to analyze the disease characteristics of PsA. However, no research combined the described imaging techniques and scores to comprehensively capture the heterogenic manifestation of PsA. Additionally, to the best of our knowledge, no previous studies compared two distinctive patient groups: DMARD-naive (those who have never used conventional synthetic DMARD [csDMARD) and DMARD-failure (non-responders to previous csDMARD treatment) using both structural and inflammatory imaging assessment methods. Therefore, this study aimed to characterize the impact of PsA in two different patient groups with active PsA, namely DMARD-naive and DMARD-failure patients as an explanatory research to identify potential underlying differences for future analyses. Thus, the objective of these analyses were to detect potential differences in inflammatory and structural imaging parameters between DMARD-naive and DMARD-failure patients at baseline and, to evaluate the influence of patient demographics on the observed differences in inflammatory and structural imaging parameters for future PsA studies.

Methods

Study Design and Patients

Patients with PsA and active disease were included in the TOFA-PREDICT study, a multicentre trial that studies prediction of therapy response in PsA (EudraCT 2017-003900-28). This ongoing trial is conducted in The Netherlands and coordinated by the University Medical Center Utrecht. Participants in this study fulfilled the following criteria: meeting the classification criteria for Psoriatic Arthritis (CASPAR) (13), aged 18-75 years, a disease duration of a minimum of eight weeks, and evidence of active peripheral arthritis (≥2 swollen joints and ≥2 tender joints). Details about the inclusion and exclusion criteria, and study design can be found in the previously published study design paper.(14)

While in the TOFA-PREDICT trial patients receive treatment and are followed over time, the current study is a cross-sectional evaluation of patients with active PsA at baseline. In total, the TOFA-PREDICT trial will include two cohorts of 80 PsA patients

with active disease. For this study, the first cohort of 80 patients were used, since the inclusion for this cohort was completed whereas in the second cohort, inclusion is still ongoing. Among these 80 patients, 40 were DMARD-naive patients who had previously not used any DMARDs (conventional or targeted synthetic, or biologic) and 40 were DMARD-failure patients who did not respond sufficiently to previous csDMARD treatment and still had active peripheral arthritis. Baseline patient demographics and the following baseline imaging studies were analysed from these patients: conventional radiographs of the hands and feet, MRI scans of both ankles, and whole-body 18F-FDG PET/CT. All the patients included in this study provided written consent and the study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands (MREC reference number: NL63439.041.17).

Clinical Assessments

Baseline clinical parameters for PsA patients included the following: age, gender, body mass index (BMI), smoking status, time since diagnosis of Psoriatic Arthritis (years), time since diagnosis of Psoriasis (years), tender joint count (78), swollen joint count (76), psoriasis area and severity index (PASI), health assessment questionnaire (HAQ) (15). Laboratory evaluation included C-reactive protein (CRP). Additionally, outcome measures like the presence of dactylitis and enthesitis were included.

Conventional Radiography

Radiographs of both hands and feet were evaluated using the PsA-modified SHS score to quantify erosion and joint space narrowing (JSN) (5). Erosion was scored on a scale of 0-3 (none/ discrete erosion/ large erosion not passing midline/ large erosion passing midline) and JSN on a scale of 0-4 (normal/ asymmetrical or minimal narrowing up to 25%/ definite narrowing with loss of up to 50% of the normal space /definite narrowing with loss of 50-99% of the normal space or subluxation/ absence of a joint space, presumptive evidence of ankyloses, or complete subluxation). Scoring was done by one observer (musculoskeletal radiologist) blinded for clinical information. Scores of hands and feet were summed to achieve total erosion and JSN scores. Thus, the maximum scores were 208 (160 hands, 48 feet) and 80 (44 hands, 36 feet) for JSN and erosion, respectively.

MRI: HEMRIS and PsAMRIS Scores

MRI-scans of both ankles were performed with a field strength 1.5 or 3 T MR-equipment and an extremity coil. The MRI-protocol adhered to the European Society of Musculoskeletal Radiology recommendations and included the following sequences: 3D proton density with fat suppression (FS), transversal T1 turbo spin echo and 3D T1 FS before and after intravenous gadolinium injection.(16) Ankle MRIs were visually assessed with the HEMRIS evaluation using inflammatory and structural pathologies at the site of the entheses of the Achilles tendon and plantar fascia (7,8):
HEMRIS inflammatory pathologies (0-21):

- Achilles tendon (scale: 0-3 for each pathology): Achilles tendon intra-tendon hypersignal, Achilles tendon peritendon hypersignal, Achilles tendon bone marrow oedema and Achilles tendon retrocalcaneal bursitis.
- Plantar fascia (scale: 0-3 for each pathology): Plantar fascia bone marrow oedema, plantar fascia peri-aponeurosis hypersignal, and plantar fascia intra-aponeurosis hypersignal.

HEMRIS structural pathologies (scale: 0-18):

- Achilles tendon (scale: 0-3 for each pathology): Achilles tendon thickness, Achilles tendon bone spur and Achilles tendon bone erosion.
- Plantar fascia (scale: 0-3 for each pathology): Plantar fascia bone spur, plantar fascia bone erosion and plantar fascia tendon thickness.

Total inflammation and structure scores were achieved by adding plantar fascia and Achilles tendon scores and used for analysis. Also, the separate scores for the Achilles tendon and plantar fascia were analysed for a detailed assessment.
PsAMRIS (7,8), adapted for the heel, was used to evaluate synovial enhancement, tenosynovitis, periarticular bone oedema and erosions:

- PsAMRIS synovial enhancement (scale: 0-3 for each pathology): Synovial enhancement of anterior ankle, posterior ankle, tarsal sinus and midfoot.
- PsAMRIS tenosynovitis (scale: 0-3 for each pathology): Tenosynovitis of tibialis posterior, flexor digitorium longus, flexor halluxis longus tibialis and peroneal tendons.
- PsAMRIS bone erosion (scale: 0-10 for each pathology): Periarticular bone erosion of tibia, fibula, talus and calcaneus.
- PsAMRIS bone oedema (scale: 0-10 for each pathology): Periarticular bone oedema of tibia, fibula, talus and calcaneus.

All the measures were scored by two independent musculoskeletal radiologists blinded for clinical information. Subsequent consensus readings were performed in

cases of disagreement. The indicated pathologies were summated per ankle to be averaged between the left and right ankle. Thus, final scores reflect both ankles, with a maximum of 21 for HEMRIS inflammation (12 for Achilles tendon and 9 for plantar fascia), 18 for HEMRIS structure (9 for Achilles tendon and 9 for plantar fascia), 12 for PsAMRIS synovial enhancement and tenosynovitis, 40 for PsAMRIS bone erosion and oedema.

PET/CT

Whole body ^{18}F-FDG PET/CT was performed after overnight fasting and one hour after intravenous administration of Fluorodeoxyglucose (^{18}F-FDG). For co-registration and attenuation correction, a non-contrast-enhanced low-dose CT was obtained. To ensure repeatability and reproducibility of quantitative PET/CT outcome measures, PET/CT reconstructions were executed following the guideline of European Association of Nuclear Medicine Research Ltd. (EARL).(17) Afterwards, the quality of PET/CT scans was assessed, and synovitis was scored (based on the Deauville scale (18)) at the shoulder, elbow, carpus, hip, knee and ankle. All the pathologies were scored on a scale of 0-4 (no enhanced uptake / slight uptake, but < blood pool / uptake > mediastinal, but < liver / uptake moderately > liver / uptake > 3 times liver uptake). Scoring was completed by one observer (nuclear radiologist) blinded for clinical information. At the end, all joint scores were summated to obtain one synovitis score with a maximum of 48.

Vascular inflammation of the aortic wall was calculated to evaluate systemic inflammation. Target-to-background ratios (TBR) were used to assess aortic vascular inflammation in a reliable and reproducible manner.(11,12,19) Two-dimensional region of interests (ROIs) were manually drawn on PET/CT scans around the external aortic contour in axial setting using IntelliSpace software. ROIs were placed along the aorta on every slice that it was visible to acquire maximum standardized uptake value (SUV). The SUVmax values per slice along the aorta were averaged to obtain SUVmax for the entire aorta and per aortic segment (ascending aorta, aortic arch, descending aorta, suprarenal abdominal aorta and infrarenal abdominal aorta (12)). Background activity SUVmean was derived from averaging at least six ROIs in the superior vena cava (SVC), or, in one case, at the inferior vena cava due to visual spill of activity at the myocardium. Subsequently, the maximum TBR of the aorta was calculated by dividing SUVmax of the aorta by SUVmean of the SVC.(17,20) The same approach was used for the calculation of maximum TBR per aortic segments.

Classification of Imaging Parameters

All the parameters that were derived from medical images were classified as inflammatory or structural imaging parameters as shown below:

Inflammatory imaging parameters: Aortic vascular inflammation (TBR), PET/CT Synovitis, HEMRIS inflammation, HEMRIS inflammation Achilles tendon, HEMRIS inflammation plantar fascia, PsAMRIS synovial enhancement, PsAMRIS tenosynovitis and PsAMRIS bone oedema.

Structural imaging parameters: HEMRIS structure, HEMRIS structure Achilles tendon, HEMRIS structure plantar fascia, PsAMRIS bone erosion, SHS erosion and SHS joint space narrowing.

Statistical Analysis

Descriptive statistics (median with interquartile range [IQR] for continuous and non-normally distributed variables, mean with standard deviation [SD] for continuous and normally distributed variables, frequencies with percentages for categorical variables) were used to summarize baseline patient characteristics. Since most imaging parameters were scored on an ordinal scale, they were assumed to be non-normally distributed and logarithmically (log) transformed before statistical evaluation to normalize the distribution. Furthermore, in cases where scans were performed but part of the subscores were missing, these missing scores were imputed using linear regression.

Patient demographics were compared between groups using the independent t-test for normally distributed variables, Mann Whitney U for non-normally distributed variables, and a chi-square test for categorical variables. Each imaging parameter was compared between groups with a univariable analysis using linear regression with the (log transformed) imaging parameters as dependent variable and grouping as independent variable. For imaging parameters shown to be different between groups ($p<0.1$), sub-scores were evaluated separately. Based on the p-value, imaging parameters with a significant difference between groups were evaluated with a multivariable analysis using multiple linear regression to inspect the influence of patient characteristics on this difference. Grouping and clinical parameters were included as independent variables and the imaging parameter (log transformed) as the dependent variable.

Among all the clinical parameters, only six were chosen for the multivariable analysis mentioned above: gender, age, BMI, smoking status, time since diagnosis of PsA, and time since diagnosis of psoriasis. These were chosen based on significant

differences between the groups (Table 1), clinician input and the literature.(21–24) Among these clinical parameters, smoking status was combined as ever smokers (current and ex-smokers grouped) and never-smokers (patients who have never smoked) for the analyses. Furthermore, clinical parameters were considered confounding and left in the optimized multiple linear regression model if they changed the effect estimate (unstandardized B) of the grouping variable by 10% or more. Statistical analyses were performed using SPSS version 27 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and the significance level was set at $p<0.05$.

Results

Patient Characteristics

All participants had at least one type of available imaging data and parameters. Among all the imaging data, three MRI and one PET/CT datasets were missing for DMARD-naive patients whereas five MRI and three PET/CT datasets were missing for DMARD-failure patients. All conventional radiograph data were present for every patient. The majority of the patient demographics were comparable between the groups (Table 1). However, DMARD-naive patients were on average younger and had a shorter disease duration (time since diagnosis of PsA and time since diagnosis of psoriasis $p<0.008$).

Univariable Analysis: Differences in Imaging Parameters

Generally, observed values for inflammation (Figure 1) and structural damage (Figure 2) were low, considering the maximum of each imaging score. Most of the results did not differ significantly between the patient groups (Table 2). Inflammatory parameters seemed to be slightly higher in DMARD-naive patients, whereas for structural damage, DMARD-failure patients showed somewhat higher values (Figure 1 and 2). The majority of the patients had some sort of inflammation or structural damage (Supplementary Table S1). Among all the imaging parameters, only HEMRIS structure Achilles tendon was significantly different between groups ($p=0.024$, $R^2=0.071$), while SHS JSN showed near significance ($p=0.050$, $R2=0.048$), with higher values in DMARD-failure for both parameters. These observed differences were not clearly explained by one specific sub-score (Supplementary Figure S1 and S2).

Table 1. Baseline patient characteristics given in mean(SD), median(IQR) or frequencies(%) and their p-values.

	DMARD-naive	DMARD-failure	
Characteristics	**(n = 40)**	**(n = 40)**	**P-Values**
Patient Demographics			
Age, years (median (IQR))	48.8 (45.1 - 58.0)	55.4 (49.5 - 60.8)	0.013
Female, n (%)	18.0 (45.0)	15.0 (37.5)	0.496
BMI (kg/m^2), mean (SD)	28.3 (5.4)	28.2 (4.3)	0.963
Smoking status, n (%)	-	-	0.181
Smoker	7.0 (17.5)	2.0 (5.0)	-
Ex-Smoker	16.0 (40.0)	16.0 (40.0)	-
Never Smoked	17.0 (42.5)	22.0 (55.0)	-
Time since diagnosis of Psoriatic Arthritis (years), median (IQR)	0.1 (0.1 - 0.8)	7.4 (2.4 - 17.1)	<0.001
Time since diagnosis of Psoriasis (years), median (IQR)	2.9 (0.3 - 18.6)	11.5 (5.6 - 25.0)	0.007
Disease Related Variables			
PASI (Psoriasis area severity index), median (IQR)	1.5 (0.6 - 4.8)	1.1 (0.0 - 2.4)	0.168
CRP (mg/L), median (IQR)	3.5 (1.0 - 11.5)	3.2 (1.0 - 9.5)	0.835
HAQ (median (IQR))	0.6 (0.3 - 1.3)	0.7 (0.4 - 0.9)	0.820
Presence of dactylitis currently, n (%)[a]	10.0 (25.0)	10.0 (25.0)	1.000
Presence of enthesitis currently (LEI), median (IQR) [a]	0.0 (0.0 - 0.0)	0.0 (0.0 - 1.0)	0.513
Medication use			
History use of DMARD n (%):	-	-	-
None	40.0 (100.0)	0.0 (0.0)	<0.001
csDMARD[b]	0.0 (0.0)	36.0 (90.0)	<0.001
bDMARD[c]	0.0 (0.0)	4.0 (10.0)	0.040
History use of Prednisone, n (%)	7.0 (17.5)[d]	12.0 (30.0)	0.189
Current use of medication	-	-	-

Table 1. Baseline patient characteristics given in mean(SD), median(IQR) or frequencies(%) and their p-values. (continued)

	DMARD-naive	DMARD-failure	
Characteristics	**(n = 40)**	**(n = 40)**	**P-Values**
Methotrexate n (%)	0.0 (0.0)	32.0 (80.0)	<0.001
Methotrexate median (IQR) dosage (mg/week)	0.0 (0.0 - 0.0)	20.0 (15.0 - 25.0)	
Leflunomide n (%)	0.0 (0.0)	5.0 (12.5)	0.021
Leflunomide median (IQR) dosage (mg/day)	0.0 (0.0 - 0.0)	20.0 (20.0 - 20.0)	
Sulfasalazine n (%)	0.0 (0.0)	4.0 (10.0)	0.040
Sulfasalazine median (IQR) dosage (mg/day)	0.0 (0.0 - 0.0)	2500.0 (2000.0 - 3000.0)	
Daily use of NSAID n (%)	21.0 (52.5)	18.0 (45.0)	0.502

Table Legend. BMI, Body Mass Index; CRP, C-reactive protein; HAQ, health assessment questionnaire; LEI, Leeds enthesitis index; DMARD, Disease-Modifying Antirheumatic Drug; csDMARD, conventional synthetic Disease-Modifying Antirheumatic Drug; bDMARD, biological Disease-Modifying Antirheumatic Drug; NSAID, Non-Steroid Anti-Inflammatory Drug.
a Presence of dactylitis and enthesitis were determined by the physician
b csDMARD group consists of: sulfasalazine, leflunomide, hydroxychloroquine and methotrexate
c bDMARD groups consists of: golimumab, adalimumab, infliximab, certolizumab, secukinumab, ixekizumab and ustekinumab
d In terms of the oral use of corticosteroid for DMARD-naive patients, a stable dose of ≤10 mg/day of prednisone (or equivalent) for ≥4 weeks prior to baseline visit was allowed

Table 2. The difference between the groups in terms of imaging parameters and their p-values.

	DMARD-naive (n=40)	DMARD-failure (n=40)	
Imaging Parameters	Median(IQR)[a]	Median(IQR)[a]	P-Values[b]
Inflammatory Imaging Parameters	-	-	-
TBR Aorta	1.7 (1.6-1.7)	1.6 (1.5-1.7)	0.534
PET/CT Synovitis Total (0-60)	4.0 (1.0-10.0)	4.0 (2.0-6.5)	0.984
HEMRIS Inflammation (0-21)	3.5 (2.5-4.5)	3.5 (2.0-5.0)	0.854
HEMRIS Inflammation Achilles Tendon (0-12)	2.0 (1.5-2.5)	2.0 (1.5-3.5)	0.125
HEMRIS Inflammation Plantar Fascia (0-9)	1.5 (0.5-3.0)	1.0 (0.5-1.5)	0.438
PsAMRIS Synovial Enhancement (0-12)	0.0 (0.0-1.0)	0.0 (0.0-0.9)	0.770
PsAMRIS Tenosynovitis (0-12)	3.0 (1.0-5.5)	2.0 (1.0-5.0)	0.223
PsAMRIS Bone Oedema (0-40)	0.0 (0.0-0.5)	0.0 (0.0-0.0)	0.899
Structural Imaging Parameters	-	-	
HEMRIS Structure (0-18)	1.5 (0.8-3.3)	2.5 (1.0-3.5)	0.090
HEMRIS Structure Achilles Tendon (0-9)	0.5 (0.0-1.0)	1.0 (0.5-1.5)	0.024
HEMRIS Structure Plantar Fascia (0-9)	1.0 (0.3-2.0)	1.5 (0.5-3.0)	0.311
PsAMRIS Bone Erosion (0-40)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.630
SHS Erosion (0-80)	3.5 (0.3-10.8)	6.5 (1.0-18.5)	0.128
SHS Joint Space Narrowing (0-208)	2.0 (0.0-9.3)	5.0 (0.3-14.0)	0.050

Table Legend. HEMRIS, Heel Enthesitis Magnetic Resonance Imaging Scoring System; SHS, Sharp-van der Heijde; DMARD, disease-modifying antirheumatic drug; PsA, Psoriatic Arthritis.

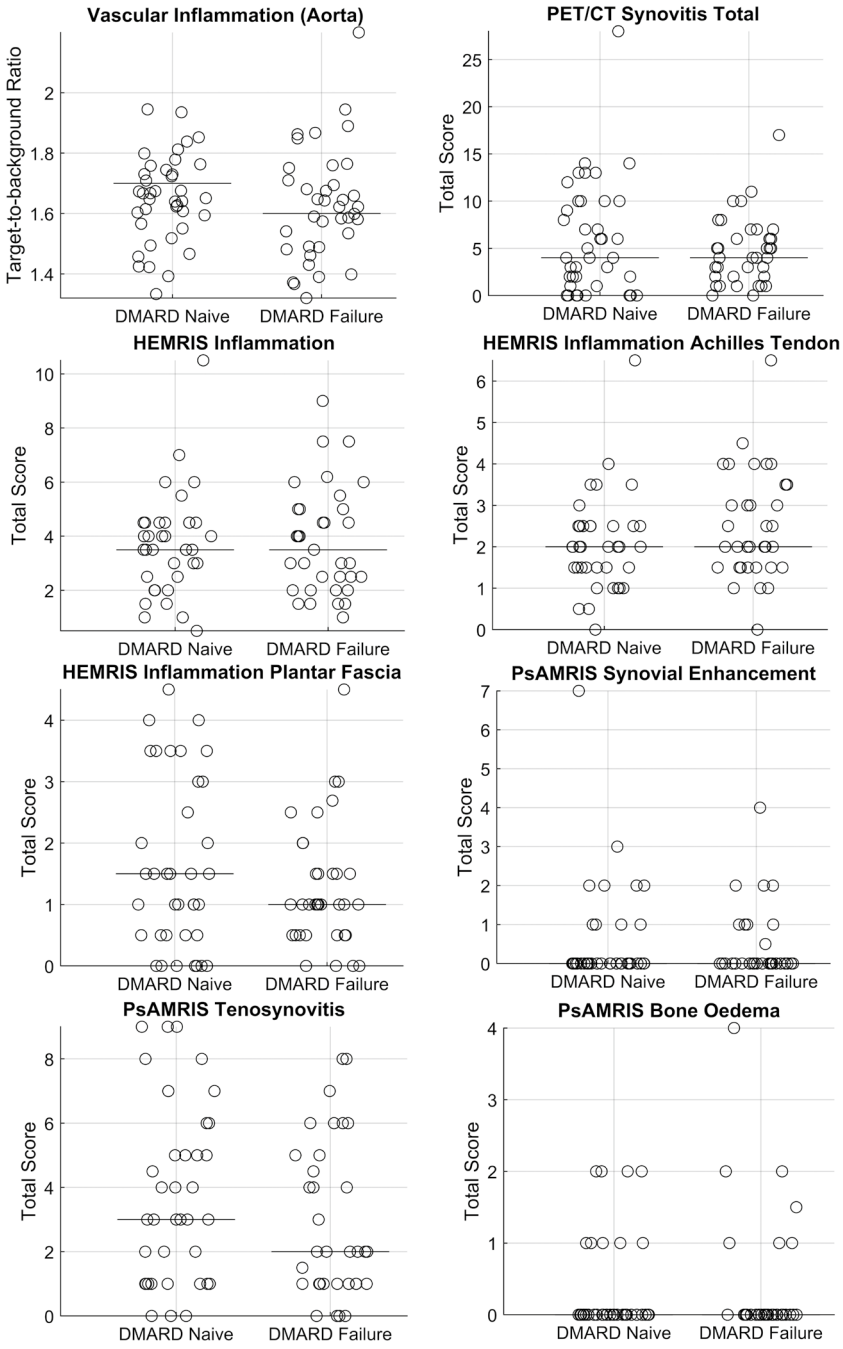

Figure 1.
Illustration of between group differences for inflammatory imaging parameters. Each circle represents an individual, and the line represents the median value of the group.

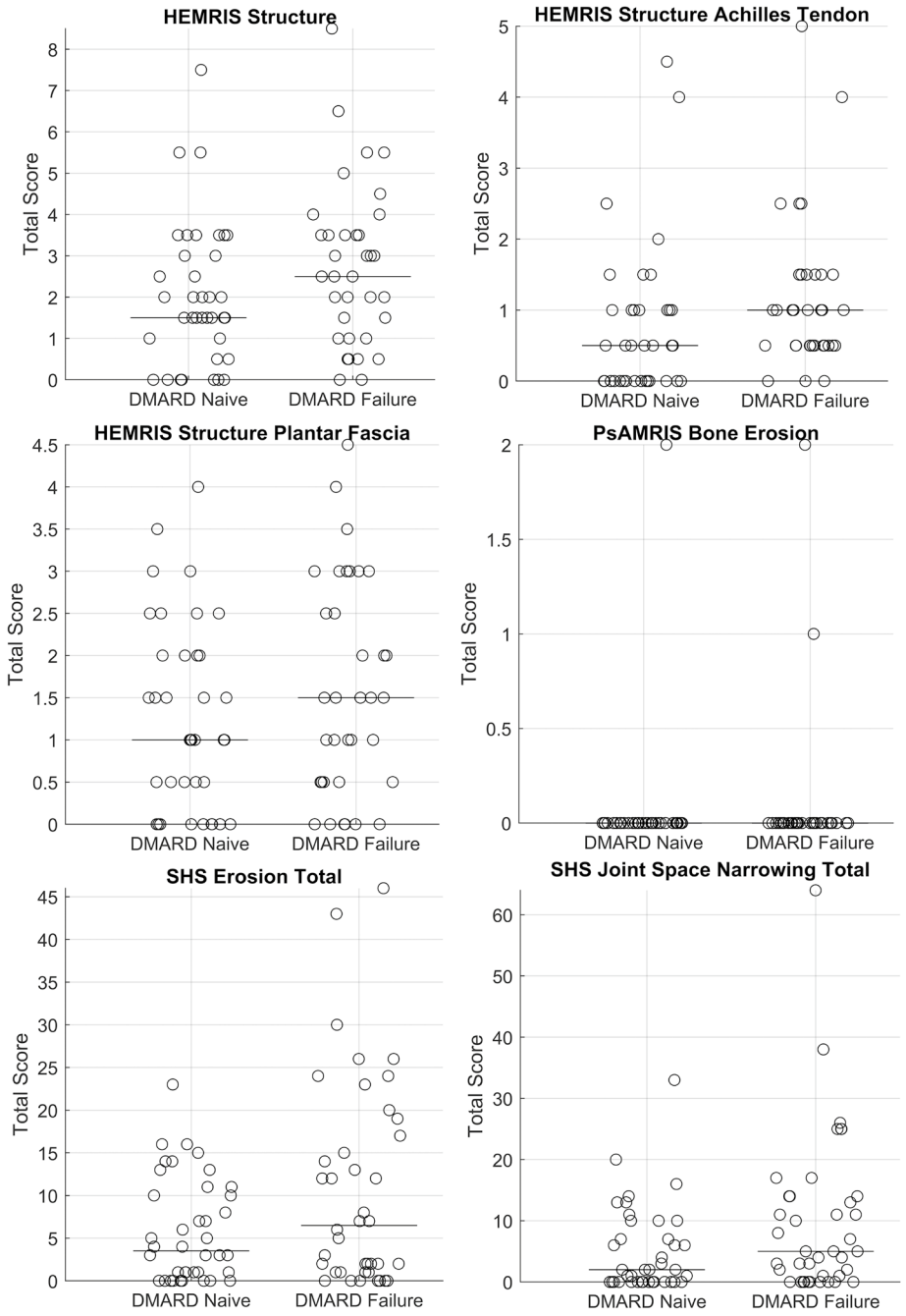

Figure 2.
Illustration of between group differences for structural imaging parameters. Each circle represents an individual, and the line represents the median value of the group. HEMRIS structure Achilles tendon (p=0.024) is statistically significant whereas SHS JSN (p=0.050) has near significance.

Multivariable Analysis: Influence of Clinical Parameters

Multiple linear regression analyses showed several clinical parameters were confounders and the differences between groups in HEMRIS structure Achilles tendon and SHS JSN were influenced by these confounders (Table 3). For HEMRIS structure Achilles tendon, confounders were time since diagnosis of PsA, and ever smoking, while for SHS JSN these were time since diagnosis of PsA, ever smoking, age, BMI and gender in the optimized models. After correcting for these confounders, the imaging parameters were no longer significantly different between groups (both p>0.600). Older patients had significantly more JSN (p<0.001), and ever smoking patients had significantly more structural damage at Achilles tendon (p=0.037). Remaining confounders did not influence the imaging parameters significantly (Table 3).

Table 3. Multiple linear regression analysis results of the (near) significant imaging parameters.

	Before Clinical Parameter Correction	**After Clinical Parameter Correction**	
	P-Value	**P-Value**	**Standardized Coefficients Beta**
HEMRIS Structure Achilles Tendon	-	-	-
Grouping (DMARD-naive or DMARD-failure)	0.024	0.711	0.050
Time since diagnosis of PsA	-	0.177	0.183
Ever smoking	-	0.037	0.247
SHS Joint Space Narrowing	-	-	-
Grouping (DMARD-naive or DMARD-failure)	0.050	0.982	0.002
Time since diagnosis of PsA	-	0.071	0.223
Ever smoking	-	0.560	-0.057
Age	-	<0.001	0.414
BMI	-	0.134	0.147
Gender	-	0.174	-0.132

Table Legend. HEMRIS, Heel Enthesitis Magnetic Resonance Imaging Scoring System; SHS, Sharp-van der Heijde; DMARD, disease-modifying antirheumatic drug; PsA, Psoriatic Arthritis.

Discussion

This study, to our knowledge, is the first study that combines various imaging approaches to analyze the heterogeneous manifestations of PsA by comparing two patient groups, namely DMARD-naive and DMARD-failure. These groups were compared to evaluate whether they differ in inflammatory and structural imaging parameters. The results showed that structural damage and inflammation scores were similar between the groups, especially after adjusting for patient demographics. This result implies that DMARD-failure was not associated with worsened inflammatory and structural imaging findings in our study.

Only HEMRIS structure Achilles tendon was significantly different between groups, while SHS JSN showed near significance, with higher values in DMARD-failure for both parameters which indicates more structural damage. The clinical relevance of these differences is doubtful, since between-group differences were very low (approximately 0.5 on a scale 0-9 for HEMRIS structure Achilles tendon and 3.0 on a scale 0-208 for SHS JSN). Furthermore, after correcting for confounding clinical parameters, the differences between the groups disappeared. To ensure that the lack of differences between groups was not the result of our averaging approach between joints, sensitivity analyses for HEMRIS and PsAMRIS were performed, where maximum scores of right and left were examined instead of averaging for these imaging parameters. However, this did not change the results. Moreover, the regression analysis revealed that older patients exhibit significantly more JSN and patients who ever smoked had more structural damage at the Achilles tendon. However, the case related to JSN may be due to other factors such as overuse of joints or ageing rather than reflecting the severity of PsA.

We considered whether our lack of differences between DMARD-failure and naive patients was due to our cohort having low disease activity compared to literature in terms of inflammation and structural damage. Understanding the disease activity profile of our cohort is crucial for the interpretation of our results and statistical findings. We systematically searched the literature and found that our patient demographics were similar compared to existing PsA cohorts. Also, inflammation markers such as CRP were shown to be in a similar range (Supplementary Table S2). Finally, although there were only a few publications, values for TBR (25) and HEMRIS (26) were found to be very well-matched. Therefore, our cohort seems to be a representative cohort for PsA and our re-assuring findings likely generalize to PsA patients.

One of the primary strengths of this study is the involvement of multimodal imaging modalities and scores, allowing us to capture the various inflammatory and structural aspects of PsA. This provides a broader perspective on the heterogenic manifestation of the disease. Most of the studies on PsA focuses on using one imaging approach such as MRI or conventional radiograph for their analysis, whereas ours uses several (conventional radiograph, MRI and PET/CT) to capture the different characteristics. Moreover, the comparison of PsA patient groups based on their prior DMARD use has not been investigated. Our study utilizes the categorization of the two patient groups and provides information about PsA patients who never used a DMARD compared to patients who failed on DMARD and still had active peripheral arthritis. These findings can be useful in clinical practice by providing insights into disease progression and disease characteristics for treatment decisions. The comparison of these groups revealed that failing a DMARD may not lead to increased inflammation or structural damage.

Nonetheless, our study has certain weaknesses that should be taken into consideration. Firstly, the sample size of 80 patients might not be enough to capture the diversity of PsA, although these results can be validated using the TOFA-PREDICT validation cohort (another group of 80 patients). Another limitation could be raised due to primarily focusing on hands and feet for assessment. Since the commonly affected joints are the hands and feet, followed by knees, wrists, ankles, and shoulders (4), we analyzed these joints using various imaging techniques. Other locations like the spine and sacroiliac joints are not included in our analysis. Selectively analyzing images from these commonly affected joints may not be enough to capture the full spectrum of disease manifestation. To overcome this limitation to some extent, TBR was used in our study as a more general measure of inflammation. In addition, PsAMRIS, adapted for ankles, is an approach that was not validated. This lack of validation constitutes a potential limitation, as the reliability and accuracy of this modified method have not been established yet.

In conclusion, DMARD-naive and DMARD-failure PsA patients with active disease showed similar inflammation and structural damage on imaging, especially after the correction of patient demographics. Thus, combining DMARD-naive and DMARD-failure patient groups (after correction of patient demographics) may offer a more comprehensive understanding of PsA progression and treatment decisions for future analyses.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplemental material

Supplemental Table S1. Median (interquartile range) values of different imaging subscores.

	DMARD-Naive (n=40)	DMARD-Failure (n=40)
Median (IQR)	-	-
TBR Vascular Inflammation	-	-
Ascending Aorta	1.7 (1.6-1.8)	1.7 (1.5-1.8)
Aortic Arch	1.7 (1.5-1.8)	1.6 (1.5-1.8)
Descending Aorta	1.7 (1.5-1.8)	1.6 (1.5-1.8)
Suprarenal Abdominal Aorta	1.7 (1.6-1.8)	1.6 (1.4-1.7)
Infrarenal Abdominal Aorta	1.6 (1.4-1.6)	1.6 (1.5-1.7)
PET/CT Synovitis	-	-
Shoulder	2.0 (0.0-3.0)	2.0 (1.0-2.0)
Elbow	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Carpus	0.0 (0.0-2.0)	0.0 (0.0-1.0)
Hip	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Knee	2.0 (0.0-4.0)	1.0 (0.0-3.0)
Ankle	0.0 (0.0-0.0)	0.0 (0.0-0.0)
SHS	-	-
Hand Erosion	3.5 (0.0-8.0)	3.5 (0.0-12.0)
Feet Erosion	0.0 (0.0-1.0)	1.0 (0.0-5.0)
Hand JSN	1.0 (0.0-7.0)	3.0 (0.0-9.8)
Feet JSN	0.0 (0.0-2.0)	2.0 (0.0-5.0)
HEMRIS Structure	-	-
Achilles Tendon Thickness	0.0 (0.0-0.5)	0.0 (0.0-0.5)
Achilles Tendon Bone Spur	0.0 (0.0-0.5)	0.5 (0.0-1.0)
Achilles Tendon Bone Erosion	0.0 (0.0-0.0)	0.0 (0.0-1.0)
Plantar Fascia Tendon Thickness	0.5 (0.5-1.3)	0.5 (0.0-1.0)
Plantar Fascia Bone Spur	0.5 (0.0-1.0)	1.0 (0.0-1.5)
Plantar Fascia Bone Erosion	0.0 (0.0-0.0)	0.0 (0.0-0.0)
HEMRIS Inflammation	-	-
Achilles Tendon Retrocalcaneal Bursitis	0.5 (0.0-0.8)	0.5 (0.0-1.0)

Supplemental Table S1. Median (interquartile range) values of different imaging subscores. (continued)

	DMARD-Naive (n=40)	DMARD-Failure (n=40)
Achilles Tendon Peritendon Hypersignal	0.5 (0.0-1.0)	0.5 (0.0-1.0)
Achilles Tendon Intratendon Hypersignal	1.0 (0.8-1.0)	1.0 (1.0-1.5)
Achilles Tendon Bone Marrow Edema	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Plantar Fascia Bone Marrow Edema	0.0 (0.0-0.5)	0.0 (0.0-1.0)
Plantar Fascia Periaponeurosis Hypersignal	0.5 (0.0-1.0)	0.0 (0.0-0.5)
Plantar Fascia Intraaponeurosis Hypersignal	0.5 (0.0-1.0)	0.0 (0.0-1.0)
PsAMRIS Synovial Enhancement	-	-
Anterior Ankle	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Posterior Ankle	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Tarsalsinus	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Midfoot	0.0 (0.0-0.0)	0.0 (0.0-0.0)
PsAMRIS Tenosynovitis	-	-
Tibialis Posterior	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Peroneal Tendons	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Flexor Digitorium Longus	0.0 (0.0-1.0)	0.0 (0.0-1.0)
Flexor Halluxis Longus Tibialis	1.0 (0.0-3.0)	0.0 (0.0-2.0)
PsAMRIS Bone Erosion	-	-
Tibia	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Fibula	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Talus	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Calcaneus	0.0 (0.0-0.0)	0.0 (0.0-0.0)
PsAMRIS Bone Edema	-	-
Tibia	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Fibula	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Talus	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Calcaneus	0.0 (0.0-0.0)	0.0 (0.0-0.0)

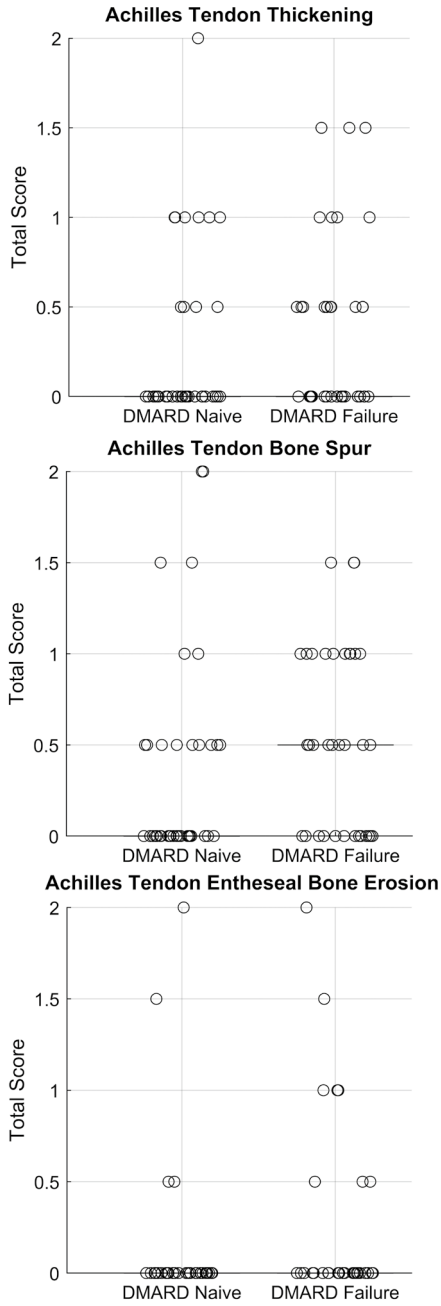
Table Legend. TBR, Target-to-background ratio; SHS, Sharp-van der Heijde; HEMRIS, Heel Enthesitis Magnetic Resonance Imaging Scoring System; PsAMRIS, Psoriatic Arthritis Magnetic Resonance Imaging Scoring System [adapted for the ankle].

Supplemental Table S2.

	Present study			**Araujo [27]**	**Wells [28]**
Patient profile	Total 80 active PsA patients	40 DMARD-naive patients	40 DMARD-failure patients	PsA patients who used DMARDs	csDMARD naive and biologic naive PsA patients
Number of patients	80	40	40	26	527
Age (years) (mean)	51.3	48.5	54.1	55.2	49.4
Female (%)	58.7	55.0	62.5	23.1	52.6
BMI (kg/m^2) (mean)	28.3	28.3	28.2	26.5	29.1
Time since first diagnosis of PsA (years) (mean)	6.2	1.7	10.8	6.5	3.4
Time since first diagnosis of Psoriasis (years) (mean)	13.8	11.5	16.5	-	15.8
PASI (mean)	3.2	3.5	2.9	0.2	7.2 (Scale[0-72])
CRP (mg/L) (mean)	8.6	10.3	6.8	1.8	9.0
HAQ (mean)	0.8	0.8	0.7	0.2	1.1
Presence of dactylitis (percentages)	23.7	25.0	22.5	-	65.1
Presence of enthesitis (percentages)	20.0	15.0	25.0	-	490.9
ESR (mean)	15.5	19.4	11.6	8.6	-

Table Legend. PsA, Psoriatic Arthritis; DMARD, disease-modifying antirheumatic drug; BMI, Body Mass Index; PASI, Psoriasis Area Severity Index; CRP, C-Reactive Protein; HAQ, Habitual Activity Questionnaire; ESR, Erythrocyte Sedimentation Rate.

	Kane [29]	Mease [30]	Gladman [31]		Shin [32]	Zisman [33]	Szentrpetery [34]
	Early PsA patients	PsA patients at baseline receiving biologics and/or targeted synthetic DMARDs	2 groups early PsA patients: Group 1 < 2 disease duration, group 2 >2 years disease duration		PsA patients in Korea	PsA patients in Israel	Recent-onset (<12 months), treatment naive PsA
	129	148	436	641	22	149	32
	41.2	54.7	-	-	42.2	58.2	40.0
	47.3	54.0	42.4	44.8	54.5	57.0	46.9
	-	33.1	-	-	≥ 25 (n=11)	-	-
	<1 years (9.9 months)	11.8	0.9	11.0	5.9	-	-
	-	-	-	-	10.8	15.5	-
	-	-	6.2	5.5	-	-	3.3 (0.0-27.7) median
	27.6 (n=112)	4.3	-	-	-	above 5 (n=86)	6.6
	0.7 (n=74)	-	-	-	-	-	0.6
	28.7	13.5	-	-	22.7	-	31.2
	-	31.7	-	-	-	-	-
	24.0 (n=124)	17.1	-	-	-	-	12.0



Supplemental figure S1.
Subscores of HEMRIS Structure Achilles Tendon for both patient groups. In tendon thickening (p=0.391), bone spur (p=0.128), and bone erosion (p=0.230) plots, each circle represents an individual value and the line represents the median value

Chapter 6

Increased vascular inflammation on PET/CT in psoriasis and the effects of biologic treatment: systematic review and meta-analyses

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Abstract

Purpose

This systematic review and meta-analyses evaluate if aortic vascular inflammation is increased in moderate-severe psoriasis compared to a healthy control group and if biologic treatment, compared to placebo, reduces aortic vascular inflammation in moderate-severe psoriasis.

Methods

The systematic review and meta-analyses were reported following PRISMA guidelines. PubMed and Embase databases were searched on June 16, 2021, for the terms 'psoriasis', 'psoriatic arthritis', and 'PET/CT' or 'vascular inflammation'. Pooled effect sizes were estimated for vascular inflammation outcome measures using a random-effects model with inverse variance weighting.

Results

Four studies, with a total of 224 subjects, were included in the quantitative analysis that studied vascular inflammation in psoriasis compared to healthy controls. Pooled results showed significantly increased vascular inflammation in patients with moderate-severe psoriasis at the entire aorta (composite score) and all aortic segments, except for the infrarenal aorta ($p = 0.06$). Results of studies assessing treatment effects of different biological agents on vascular inflammation were inconsistent.

Conclusion

Overall, the evidence reviewed indicates that there is an association between psoriasis and aortic vascular inflammation, but there is insufficient evidence for a beneficial effect of biologic treatment.

Introduction

Psoriasis is a chronic immune-mediated skin disease, with an estimated prevalence of 2–4% in Western countries.(1, 2) Psoriasis is frequently accompanied by comorbidities, of which psoriatic arthritis is the most common.(3) Patients with psoriasis have an increased risk of developing cardio-vascular events, independent of traditional risk factors for cardiovascular disease (CVD).(4–6) A potential explanation for the increased risk of CVD is that inflammation in psoriasis is not strictly limited to the skin. It has been suggested that cutaneous inflammation in psoriasis could exert systemic effects by releasing inflammatory products and altered leukocytes into the circulation.(7, 8) This chronic systemic inflammatory state could accelerate atherosclerosis and eventually lead to cardiovascular events. Given the proposed association of cutaneous psoriasis with atherosclerosis, it has been hypothesized that the processes leading to cardiovascular diseases in psoriasis could be halted by systemic anti-psoriatic therapy, such as biologic agents.(9) Biologics can be highly effective in treating psoriatic skin disease, yet their effect on reducing atherosclerosis is uncertain.

F-18-fluorodeoxyglucose positron emission tomography with computed tomography (FDG PET/CT) can be used to quantify the inflammatory activity at the arterial wall. FDG-uptake at the arterial wall is a non-invasive biomarker for atherosclerosis and is strongly predictive of future cardiovascular events.(10, 11) In psoriasis patients, FDG-uptake of the aortic wall is associated with aortic atherosclerosis measured with MRI (quantified as aortic wall thickness).(12) Currently, a comprehensive review that evaluates vascular inflammation detected by PET/CT in psoriasis patients in comparison with healthy controls is lacking.

The primary objective of this systematic literature review and meta-analysis is to determine if vascular inflammation is increased in moderate-severe psoriasis patients compared to healthy controls. The secondary objective is to study if biologic psoriasis treatment reduces aortic vascular inflammation in moderate to severe psoriasis. We focused on moderate to severe psoriasis, since biological treatment is mainly reserved for this category.(1) Furthermore, the increased cardiovascular risk observed in psoriasis may be restricted to severe psoriasis.(13)

Methods

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, (14) and registered in the PROSPERO-database (registration number: CRD42021232715).

Search strategy

PubMed and Embase databases were searched on June 16, 2021, for combinations of synonyms, MeSH and Emtree terms for (i) 'psoriasis', 'psoriatic arthritis' and 'PET/CT' and (ii) 'psoriasis', 'psoriatic arthritis' and 'vascular inflammation' (Supplementary Table S1 and S2). After removing duplicates, two independent researchers (JNP and NJK) screened all articles on title and abstract and subsequently selected articles on full text, using predefined eligibility criteria (Fig. 1). Similar citations in PubMed and reference citations of the selected articles were screened for relevant articles not identified in the original search.

Study selection primary outcome measure: vascular inflammation in psoriasis compared to healthy controls

All original studies that compared vascular inflammation in psoriasis patients with healthy controls were included in the qualitative analysis. Studies/patients with mild psoriasis and studies with missing data that were relevant to the analysis were excluded from the quantitative analysis.

Study selection secondary outcome measure: therapeutic effect of biologic treatment on vascular inflammation in psoriatic disease

All original studies assessing the therapeutic effect of systemic psoriasis treatment on vascular inflammation in psoriatic disease were included in the qualitative analysis addressing the second research question. Observational studies, studies in patients with mild psoriasis and studies with missing data that was relevant to the analysis were excluded from the quantitative analysis.

Data extraction

Data were extracted from individual studies by one researcher (JNP or NJK) and verified by the other. Data items that were sought were (if applicable): number of participants, characteristics of study population, type of treatment received, a description of subjects included as healthy controls, use of placebo group, vascular inflammation out-comes, and PET/CT-protocol. The authors were contacted when data relevant to the quantitative analysis were not available. All studies were assessed for relevance, validity, and risk of bias using predefined criteria (Tables 1 and 2).

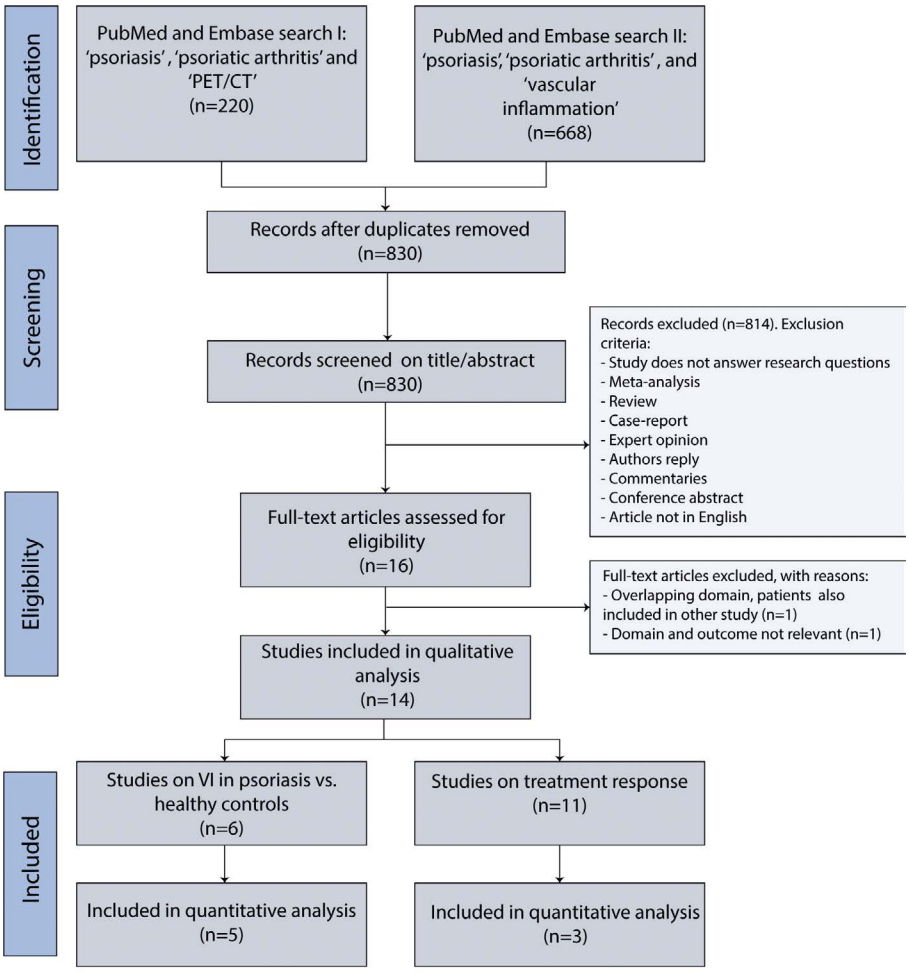

Figure 1. Flowchart.
Abbreviations: PET/CT = positron emission tomography/computed tomography, Pso = psoriasis, VI =vascular inflammation

Table 1. Relevancy and validity assessment of studies evaluating primary outcome measure: vascular inflammation in psoriasis compared to healthy controls.

Study	Relevance		Validity					
	Domain	Determinant	Outcome	Results	Number of patients	Selection bias	Detection bias	Reporting bias
Goyal (2020)	+/-	+/-	+	-	+	-	?	+
Hjuler (2017)	+	+	+	+ / -	-	+ / -	?	+
Kim (2018)	+/-	+/-	+ / -	+ / -	+ / -	+ / -	?	+
Rose (2013)	+	+	-	+	-	+ / -	?	+
Kaur (2018)	+	+	+ / -	-	+ / -	+ / -	+	+
Youn (2015)	-	+	+	+	-	+ / -	?	-

Legend table 1

	+	+ / -	-
Domain	only moderate-severe psoriasis	all psoriasis (no restrictions in PASI/BSA)	only mild psoriasis;
Determinant (anatomical location vascular inflammation measurements)	aortic segments	whole aorta	other arteries than aorta measured
Outcome (vascular inflammation outcome measure)	TBR_{max}	SUV_{max}	SUV_{mean}
Results	same conclusion after adjusting for age, sex, BMI, hypertension and LDL-cholesterol	same conclusion after adjusting for age, sex and/or BMI	no additional analysis to adjust for age, sex or other cardiovascular risk factors
Number of psoriasis patients	>30	15-30	<15
Selection bias (patient-matched healthy controls)	age-, sex-, and cardiovascular risk factor-matched healthy controls	age- and sex-matched healthy controls	healthy controls not matched
Detection bias (standardized measurement and interpretation outcome)	blinded SUV measurements by independent assessor	n.a.	assessor not blinded
Reporting bias	reporting of all vascular inflammation outcomes	n.a.	selective reporting of significant vascular inflammation outcomes

Table 2. Relevancy and validity assessment of studies evaluating secondary outcome measure: therapeutic effect of biologic treatment on vascular inflammation in psoriatic disease.

Study	Relevance			Validity					
	Domain	Determinant	Outcome: location	Outcome: VI measurement	Results	Number of patients	Selection bias	Information bias	Detection bias
Bissonnette (2013)	+[a]	+	+/-	+	+ / -	+	+	+	+
Bissonnette (2017)	+[b]	+	+/-	+	-	+	+/-	+	+
Mehta (2018)	+	+	+	+	?	+	+/-	+	+
Gelfand VIP-U (2020)	+	+	+	+	+	+	+	+	+
Gelfand VIP-S (2020)	+	+	+	+	+	+	+	+	+
Dey (2017)	+/-[c]	-	+	+	+	+	+	+/-	+
Eder (2018)	+/-[d]	+/-	+	+	+	+	?	+/-	?
Goyal (2020)[e]	+	-	+	+	-	+/-	+	+/-	?
Kaur (2018)	+	+	+/-	+/-	-	+/-	+	+	+
Kim (2018)[e]	+	+ / -	+/-	+/-	-	-	+	+/-	?
Rivers (2018)	+	-	+	+	-	-	-	+/-	?

Legend Table 2.

	+	+ / -	-
Domain	only moderate-severe psoriasis	all psoriasis (no restrictions in PASI/BSA)	only mild psoriasis;
Determinant	DMARD-treatment compared to placebo/control	DMARD-treatment, no placebo/control group	other
Outcome (anatomical location vascular inflammation measurements)	Entire aorta (composite score)	Aortic segment(s)	other arteries than aorta measured
Outcome (vascular inflammation outcome measure)	TBR_{max}	SUV_{max}	SUV_{mean}
Results	same conclusion after adjusting for age, sex, BMI, hypertension and LDL-cholesterol	same conclusion after adjusting for age, sex and/ or BMI	no additional analysis to adjust for age, sex or other cardiovascular risk factors
Number of psoriasis patients	>30	15-30	<15
Selection bias (loss to follow-up)	≤ 10% loss to follow-up	> 10% loss to follow-up	unknown percentage
Information bias (study design)	randomized clinical trial	prospective case -or cohort study	retrospective study
Detection bias (standardized measurement and interpretation outcome)	SUV measurements by blinded assessor	n.a.	assessor not blinded
Reporting bias	reporting of all vascular inflammation outcomes	n.a.	selective reporting of significant vascular inflammation outcomes

[a]*Patients were required to have a history of coronary atherosclerosis or a minimum of 3 risk factors for cardiovascular disease.*
[b]*TBR was required to be 1.6 or higher*
[c]*Patients with known cardiovascular disease and hypertension excluded*
[d]*Psoriatic arthritis patients only*
[e]*Subgroup of patients from the original trial.*

PET/CT outcome measures for vascular inflammation

The measures of interest of the meta-analyses were defined as:

- primary outcome measure: the difference in vascular inflammation between patients with moderate to severe psoriatic disease and healthy controls.
- secondary outcome measure: the difference in change in vascular inflammation between patients with moderate-severe psoriatic disease after treatment with a biologic or placebo.

Vascular inflammation can be quantified on PET/CT with different parameters: maximal standardized uptake value (SUV_{max}), mean SUV (SUV_{mean}), and target-to-background ratio (TBR). SUV_{max} and SUV_{mean} are calculated in a 'region of interest' (ROI) that comprises the arterial wall and lumen. The SUV_{max} represents the most intense voxel activity within the ROI and SUV_{mean} represents the mean voxel activity. The TBR corrects for venous blood-pool uptake and is calculated by taking the ratio of SUV_{max} in the arterial wall and SUV_{mean} of the venous blood pool.(15) Vascular inflammation was measured with different outcome measures (SUV_{max}, SUV_{mean}, TBR) in studies comparing patients with psoriasis and healthy controls (research question I). To compare the results of these studies, we standardized these outcome measures to a uniform scale using the standardized mean difference (SMD = difference in mean outcome between patient groups/ standard deviation of outcome among subjects), which allows for comparison of the different measures for vascular inflammation used in the included studies.(16) Vascular inflammation was measured with 'TBR' by all studies assessing treatment response (research question II). The difference in change in TBR between different treatment groups (biologic treatment or placebo) was assessed using the mean difference. Vascular inflammation is typically measured over standardized regions of the aorta: the ascending, descending, suprarenal and infrarenal aorta. To evaluate the effects of systemic treatment, we preferred the use of a 'composite score' for the entire aorta (Table 2).

Statistical analysis

We performed two quantitative meta-analyses for the two separate research questions. Missing standard deviations were obtained from reported confidence intervals or p-values related to the difference between means of two groups (16). Pooled effect sizes were estimated using a random-effects model with inverse variance weighting. For quantitative analyses, heterogeneity was evaluated using the I^2 statistic. Statistical analyses were conducted with Review Manager version 5.4.1. P values < 0.05 were considered statistically significant.

Results

Search

After the removal of duplicates, 830 articles remained for screening on title and abstract. No relevant articles were identified by assessing reference citations of the selected articles and similar citations in PubMed. 16 Full-text articles were screened for eligibility (Fig. 1. Flowchart).

Study selection and quality assessment primary outcome measure: vascular inflammation in psoriasis compared to healthy controls

The definition of healthy subjects varied greatly between studies and in five out of six studies, it remained unclear whether concomitant inflammatory conditions were sufficiently ruled out (Supplementary Table S3). Six studies were included in the qualitative analysis (17–22), of which four studies were included in quantitative analysis (Fig. 1. Flowchart).(17–20) Since the domain concerned patients with 'moderate-severe'-psoriasis, respectively 134 and 10 patients with mild psoriasis from the studies by Goyal et al. (20) and Kim et al. (19) were excluded from the quantitative analysis. The total number of subjects (psoriasis + healthy controls) included in the meta-analysis was 112 in studies assessing the whole aortic vessel and 112 in studies assessing aortic segments. Quality assessments are reported in Table 1. PET/CT protocols, including slice thickness, PET-scanner, reconstruction methods and normalization for body weight, differed between studies (Supplementary Table S5). Most researchers utilized TBR to quantify vascular inflammation. Three studies reported SUVs instead.(17, 19, 22) Three studies had small sample sizes with < 15 psoriasis patients included (17, 18, 22). In most studies, healthy controls were matched based on cardiovascular risk profile but not in the study by Goyal et al. (20), possibly introducing selection bias. In the study by Youn et al. (22), only significant vascular inflammation outcomes were reported in absolute numbers. Therefore, and since the domain was not relevant (mild psoriasis only), this study was not included in the quantitative analysis. Overall quality of the studies included in the quantitative analysis was considered moderate.

Study selection and quality assessment secondary outcome measure: therapeutic effects of systemic treatment on vascular inflammation in psoriatic disease

Eleven studies were included in the systematic review on treatment response of biologics on aortic vascular inflammation in psoriasis.(19–21, 23–30) Three randomized-controlled trials (RCTs), with a total of 106 patients, were included in the quantitative analysis assessing treatment effects of anti-TNF inhibitor adalimumab. (23, 24, 31) Quality assessments of studies assessing the therapeutic effects of systemic treatment on vascular inflammation in psoriasis are reported in Table 2. Of studies included in the quantitative analysis, available details regarding PET protocols varied between studies (Supplementary Table S5). Two RCTs assessing treatment effects of adalimumab on vascular inflammation only included patients with a baseline TBR ≥ 1.6 (Supplementary Table S4), thereby limiting the generalizability of results.(23, 24) It has been suggested that a TBR ≥ 1.6 should be considered as 'active' vascular inflammation.(32) One study required patients to have a history of coronary atherosclerosis or a minimum of 3 risk factors for cardiovascular disease.(23) Two studies reported a loss to follow-up higher than 10%.(24, 25) Overall quality of the RCTs included in the quantitative analysis was considered moderate.

Vascular inflammation in psoriasis in comparison with healthy controls

Summaries of studies included in the systematic review are described in Supplementary Table S3. All studies reported higher vascular inflammation in at least one aortic segment in psoriasis patients compared with healthy controls.(17–22) None of the studies reported higher aortic inflammation in healthy controls compared to moderate/severe psoriasis patients. Most studies performed additional analyses to correct for cardiovascular risk factors (Supplementary Table S3) and reported that aortic vascular inflammation remained significantly elevated in psoriasis.(17–19, 22) In one study, vascular inflammation remained elevated in all aortic regions, except the aortic arch, after adjusting for cardiovascular risk factors.(17) Pooled results show significantly increased vascular inflammation at all aortic segments, except for the infrarenal aorta ($p = 0.06$), in patients with moderate-severe psoriasis in comparison with healthy controls (Fig. 2).

We performed sensitivity analyses to evaluate the effect of inclusion of patients with mild psoriasis, instead of only moderate-severe psoriasis. After the inclusion of 134 patients with mild psoriasis from the study by Goyal et al. (20), pooled results measured at the aorta showed that vascular inflammation remains higher in the

psoriasis group (standardized mean difference = 0.62; 95% CI − 0.03 to 1.28), but this finding was no longer significant (p = 0.06). However, these results must be interpreted with caution since a high variation in vascular inflammation outcomes (I^2 = 64%) was observed after inclusion of the population with mild psoriasis. After inclusion of a small group of 15 patients with mild psoriasis, included in the study by Kim et al. (19), vascular inflammation remained significantly increased in psoriasis compared to healthy controls at the ascending aorta, aortic arch, descending aorta and infrarenal aorta.

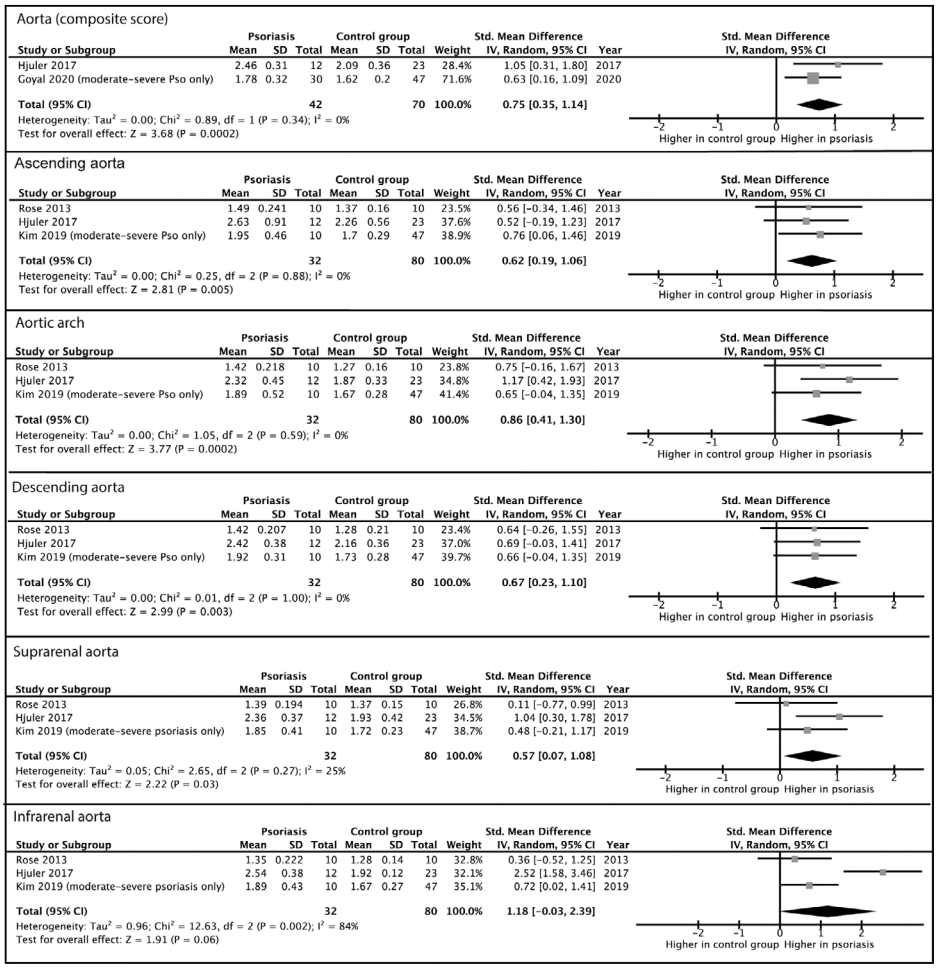

Figure 2. Increased aortic inflammation in moderate-severe psoriasis patients, in comparison to healthy controls.
Abbreviations: Pso=psoriasis, SD = standard deviation

The therapeutic effect of systemic treatment on vascular inflammation in psoriasis

Summaries of studies included in the systematic review are described in Supplementary Table S4. All cohort studies included in the systematic review reported a decrease in vascular inflammation at the entire aorta or several aortic segments in patients with psoriasis after treatment with different regimens, including biologics (Supplementary Table S4).(19–21, 28–30) Five RCTs have evaluated the treatment effects of different biological agents, adalimumab, secukinumab and ustekinumab, on vascular inflammation in psoriasis (Supplementary Table S4) (23–27). Treatment duration of the RCTs varied from 12 to 16 weeks. Three RCTs assessing treatment effects of adalimumab reported inconsistent results (Fig. 2).(23–25) In a small RCT with 30 psoriasis patients, a decrease in vascular inflammation was seen after treatment with TNF-inhibitor adalimumab, in comparison with a control group receiving topical treatment, therapeutic ultraviolet light or no treatment.(23) This positive treatment effect of adalimumab was not replicated in two larger RCTs comparing adalimumab with placebo.(24, 25) Due to high heterogeneity in vascular inflammation outcomes (I^2 = 95%), pooling of results of the individual studies assessing adalimumab treatment was unreliable (Fig. 3). One RCT reported improved vascular inflammation after 12 weeks of treatment with ustekinumab in comparison with placebo (Fig. 3), however no difference in vascular inflammation was observed after 52 weeks (open-label extension period) in comparison to baseline (Supplementary Table S4) (26). Another RCT performed by the same group, showed that treatment with secukinumab had no significant impact on aortic vascular inflammation.(27)

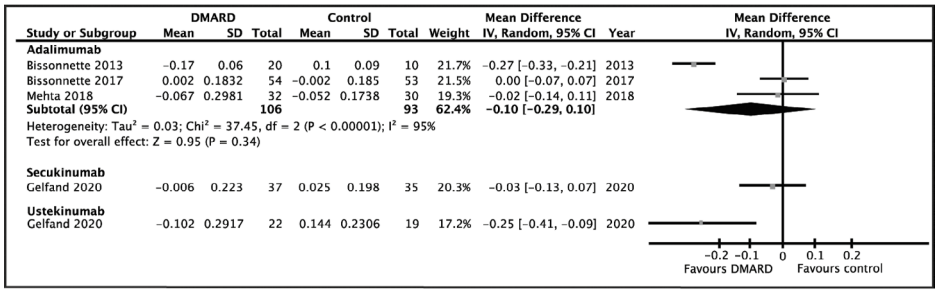

Figure 3. Treatment effect of biologic treatment on aortic inflammation in psoriasis.
Pooled results of adalimumab are unreliable due to high heterogeneity (I^2 = 95%). In the two studies performed by Bissonnette (2013 and 2017), aortic inflammation was measured at ascending aorta only. In all other studies, vascular inflammation was measured at the entire aorta (composite score). Abbreviation: SD = standard deviation.

Discussion

The current systematic review and meta-analysis show consistent evidence of increased aortic vascular inflammation in patients with moderate-severe psoriasis compared to healthy controls. This finding was significant for the entire aorta (composite score) and separate aortic segments (ascending aorta, aortic arch, descending aorta, suprarenal aorta), except for the infrarenal aorta. Most studies included in the meta-analysis comparing vascular inflammation in psoriasis with healthy controls performed additional analyses to correct for traditional cardiovascular risk factors (17–19, 22), and demonstrated that vascular inflammation remained significantly elevated, except for at the aortic arch region in one study.(17) This finding is important since traditional cardiovascular risk factors such as age (33), male gender (34), diabetes(35), and Framingham risk score(36) are associated with vascular inflammation assessed with PET/CT. Studies evaluating the effects of biologic treatment on vascular inflammation in moderate-severe psoriasis reported inconsistent results. Overall, the evidence reviewed here suggests that there is an association between psoriasis and vascular inflammation, but there is insufficient evidence to indicate a beneficial effect of biologic agents on the vascular inflammation measured on PET/CT.

The finding that vascular inflammation is increased in moderate to severe psoriasis is consistent with previous literature, as multiple studies have observed an association between psoriasis and cardiovascular disease, although it may only be an independent risk factor in patients with severe psoriasis.(4, 6, 37–39) The observed effect might even be an underestimation, as we were unable to conclude that concomitant inflammatory conditions were sufficiently ruled out in the healthy control groups. A large volume of published studies describes plausible mechanistic links between psoriasis and cardiovascular disease. Genome-wide association studies concluded that a shared genetic profile of psoriasis and coronary heart disease can only partially explain their association (39). One theory, described as the ‘psoriatic march’, suggests that psoriasis can attribute to cardiovascular disease in a cascade of events.(9) According to this hypothesis, the circulating pro-inflammatory cytokines and adipokines released by psoriatic skin will increase insulin resistance, which leads to endothelial dysfunction, atherosclerosis and eventually thromboembolic complications, such as myocardial infarction or stroke. Another viewpoint is that the link between psoriasis and cardiovascular disease should be considered as an ongoing, two-way process.(38) Psoriasis and atherosclerosis share several pathogenic

features, including Th1-cell-mediated inflammation, extravasation of T-cells and macrophages, and release of pro-inflammatory cytokines and endothelins.(1, 7, 38, 40–42) On one hand, inflammatory modulators and hormones produced in atherosclerotic lesions could promote a pro-inflammatory state that increases the risk of psoriasis development.(7) On the other hand, the inflammatory processes that characterize psoriasis could instigate the development of comorbidities, including hypertension, diabetes and ischemic heart disease.(38, 40)

With regard to the secondary research question of this review, if biologic therapy reduces vascular inflammation in psoriasis, an unexpected finding was that vascular inflammation did not always improve when psoriasis lesions and the inflammatory marker CRP did. Since systemic inflammation is considered to play a crucial role in the increased risk of cardiovascular disease in psoriasis, it was hypothesized that the anti-inflammatory effects of biologic therapies would improve atherosclerotic lesions as measured by PET/CT. However, two studies observed no reduction in aortic vascular inflammation, despite the substantial improvement in psoriasis severity after treatment with adalimumab and secukinumab.(25, 27) Moreover, one RCT observed a reduction in high-sensitivity C-reactive protein after adalimumab treatment, but no change in vascular inflammation from baseline.(24) A potential explanation could be the relatively short-term evaluation period of 12–16 weeks used in the different RCTs. A recent systematic review and meta-analysis by González-Cantero et al. (43) describes the effects of biologic agents on blood-based cardiometabolic risk biomarkers in psoriasis, in studies also assessing imaging biomarkers, in more detail.

Another unexpected finding is that the effects of biologic agents on vascular inflammation are not consistent. Our conclusion is in line with the previously mentioned meta-analysis by González-Cantero et al., who did not find a significant reduction in aortic vascular inflammation in patients treated with adalimumab. (43) One small RCT reported a positive effect of TNF-inhibitor adalimumab on vascular inflammation (23), this finding was not repeated in two larger RCTs.(24, 25) This inconsistency may be due to the difference in inclusion criteria between studies: patients included in the trial that reported a positive effect of adalimumab, were required to have an history of coronary atherosclerosis, or ≥ 3 risk factors for cardiovascular disease.(23) The difference in history of cardiovascular disease could influence vascular inflammation outcomes, since vascular inflammation is associated with cardiovascular events.(11)

The inconsistent effects of secukinumab and ustekinumab on vascular inflammation could potentially be explained by their modes of action. One RCT

reported a decrease in vascular inflammation after treatment with inhibitor anti-IL-12/IL-23 inhibitor ustekinumab (26), while anti-IL-17 inhibitor secukinumab did not reduce vascular inflammation (27). Gelfand and colleagues (27), who studied the effects of secukinumab on vascular inflammation, argue that reduction of bio-available IL-17A may have a limited effect on cells associated with early aortic inflammation measured by FDG-uptake on PET/CT. Another study assessing the early vascular effects of secukinumab in psoriasis, by measuring flow-mediated dilation—a parameter of vascular endothelial function—, showed consistent results: no difference in flow-mediated dilation was observed between patients treated with secukinumab or placebo.(44)

While the effects of biologics on vascular inflammation vary between studies, statins are known to reduce vascular inflammation in patients with a history of cardiovascular disease (45). A recent observational study in psoriasis patients showed that patients receiving statin treatment, have lower vascular inflammation (TBR_{max}) at the ascending aorta and aortic arch (after adjustment for sex and age).(46) Furthermore, 3-month statin therapy gave a reduction in carotid arterial inflammation in a study in subjects with ankylosing spondylitis.(47) Ankylosing spondylitis is a chronic inflammatory autoimmune disease related to psoriasis, with shared genetic and immunologic mechanisms.(48)

There are some limitations to the two meta-analyses. The first limitation is that the overall sample sizes were small. Another limitation is that results of both meta-analyses are only representative for the psoriasis population with moderate-severe disease, not for patients with mild disease. We considered the patient category with moderate-severe psoriasis to be the most relevant, since these patients are usually eligible for systemic treatment, and the increased risk of cardiovascular disease beyond traditional risk factors may apply to severe psoriasis only.(13) We performed sensitivity analyses to determine the effect of inclusion of patients with mild psoriasis in the quantitative analysis that compared vascular inflammation in psoriasis and healthy controls. Results indicated that vascular inflammation results of patients with mild and moderate-severe psoriasis could not be pooled. There was substantial heterogeneity ($I^2 = 64\%$) between vascular inflammation outcomes (measured at the entire aorta) of the studies by Hjuler et al. (18) (moderate-severe psoriasis only) and Goyal et al. (20) (all psoriasis). The high heterogeneity could be explained by the difference between study populations in the sensitivity analysis since previous research has shown that skin disease severity in psoriasis is associated with vascular inflammation.(28)

The quality and risk of bias of all studies included were assessed using predefined criteria. The studies included in the systematic review assessing the primary research question utilized different quantitative measures for FDG-uptake of the arterial wall (vascular inflammation): TBR and SUV. The benefit of using TBR (the ratio of average arterial SUV to blood-pool SUV) is that it allows for correction of the error from the blood glucose and insulin level that may influence the SUV.(49) When using SUVs to quantify vascular inflammation, lean body mass as a mass estimate in the calculation of SUV (SUV_{lbm}) is preferred over bodyweight (SUV_{bw}), to avoid overestimation of FDG-uptake in obese patients (50). For reproducibility of results and comparison of measurements, it is recommended that PET scans are reconstructed according to EARL recommendations.(51) For future studies on vascular inflammation in psoriasis, we recommend using TBR or SUV_{lbm} to quantify vascular inflammation and performing PET reconstructions according to EARL recommendations.

This review and meta-analysis demonstrate an association between moderate-severe psoriasis and aortic inflammation on PET/CT. This finding is in line with the theory that inflammation in psoriasis is not limited to the skin but also affects the cardiovascular system. Vascular inflammation can progress to atherosclerosis and ultimately to cardiovascular events. Physicians should be aware of the increased risk of cardiovascular disease in severe psoriasis and ensure adequate monitoring and treatment of modifiable cardiovascular risk factors.

Author contributions

NJK: Literature search and review, meta-analysis, writing, editing. JNP: literature review, meta-analysis, writing, editing. EFAL: editing. RAPT: editing. PMJW: meta-analysis, edit-ing. BdK: editing. PAdJ: editing. WF: literature review, Meta-analysis, writing, editing.

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Declarations

Conflicts of interest
The department of Radiology of the UMC Utrecht receives research support from Philips Healthcare. Prof de Jong provides consultancy to Sanifit and InoZyme. All other authors declare no conflict of interest.

Ethics approval
Not applicable. This article does not contain any studies with human or animal subjects performed by the any of the authors.

Consent to participate
Not applicable.

Consent for publication
Not applicable

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Supplemental material

Supplemental Table S1. Search I PubMed & Embase 16-06-2021: combination of psoriasis/ psoriatic arthritis and PET/CT.

Source	Search syntax	Results
(1) PubMed	(psoriasis[MeSH Terms] OR psoria*[Title/Abstract]) AND (positron emission tomography[MeSH Terms] OR positron emission tomograph* [Title/Abstract] OR PET[Title/ Abstract])	104
(2) Embase	('psoriasis'/exp OR psoria*:ab,ti,kw) AND ('positron emission tomography'/exp OR 'positron emission tomgraphy':ab,ti,kw OR pet:ab,ti,kw) Filters: Sources: Embase and MEDLINE Publication types: Article, Article in Press	172
(1) and (2) combined (duplicates removed)		220

Table Legend. Abbreviations: Emtree: Embase subject headings; MeSH: medical subject headings. PET: positron emission tomography.

Supplemental Table S2. Search II PubMed & Embase 16-06-2021: combination of psoriasis/ psoriatic arthritis and vascular inflammation.

Source	Search syntax	Results
(1) PubMed	(psoriasis[MeSH Terms] OR psoria*[Title/Abstract]) AND ((((((vasculitis[Title/Abstract])) OR (vascular inflammat*[Title/Abstract])) OR (arterial inflammat*[Title/ Abstract])) OR (aortitis[Title/Abstract])) OR (("Vasculitis"[Mesh:NoExp]) OR "Aortitis"[Mesh]))	498
(2) Embase	('psoriasis'/exp OR psoria*:ab,ti,kw) AND (vasculitis:ti,ab,kw OR 'vascular inflammat*':ti,ab,kw OR 'arterial inflammat*':ti,ab,kw OR aortitis:ti,ab,kw OR vasculitis/mj OR aortitis/exp) Filters: Sources: Embase and MEDLINE Publication types: Article, Article in Press	395
(1) and (2) combined (duplicates removed)		668

Table Legend. Abbreviations: Emtree: Embase subject headings; MeSH: medical subject headings. PET: positron emission tomography.

Supplemental Table S3. Higher aortic VI in patients with psoriasis compared to healthy controls.

Study	Subjects, no. [e)]	Psoriasis severity	FDG (activity)	Uptake time and protocol	VI outcome	TBR calculation	VI location
Rose (2013) Am J Cardiovasc Dis	Pso n=10; RA = 5, HC n=10	Moderate-severe Pso (BSA>10	5.18 MBq/kg	~60 minutes. Eight hour fast. 6 mm axial slices.	SUV_{mean} (formula SUV not reported)	NA	Aortic segments
Hjuler (2017) Br J Dermatol	Pso n=12; HC n=23	Moderate-severe (PASI≥10)	5 MBq/kg	60 minutes. Overnight fast. 3 mm axial slices.	TBR_{max} & $TBR_{max\ 10\ pixels}$ [b] & SUV_{max} & SUV_{mean} (formula SUV =SUVbw)	Arterial SUV_{max} divided by bloodpool (SVC) SUV_{mean}	Entire aortic vessel & aortic segments
Kim (2018) J Am Acad Dermatol	Pso n=25; HC n=47	All psoriasis, subgroup moderate-severe psoriasis (PASI>10 or BSA>10%)[c]	5.18 MBq/kg	60 minutes. 5 mm axial slices.	SUV_{max} (formula SUV not reported)	NA	Aortic segments

Result PsO vs HC	Adjustment results for cardiovascular risk factors	Summary of findings
- Ascending: 1.49 ± 0.241 vs 1.37 ± 0.160; p=0.0001* - Arch: 1.42 ± 0.218 vs 1.27 ± 0.160; p=0.0001 * - Descending: 1.42 ± 0.207 vs 1.28 ± 0.210; p<0.0001 *[a] - Suprarenal: 1.39 ± 0.194 vs 1.37 ± 0.150; p=0.1067 - Infrarenal (1.35 ± 0.222 vs 1.28 ± 0.140; p=0.0002	In multivariate analysis adjusting for cardiovascular risk factors (age, gender, hypertension, LDL, and BMI), Pso was associated with increased VI, except in the aortic arch region.	In moderate-severe Pso, significantly more VI in the aortic arch, ascending, descending and infrarenal aorta.
TBR_{max} - Entire: 2.46 ± 0.31 vs 2.09 ± 0.36; p=0.005 * - Ascending: 2.63 ± 0.91 vs 2.26 ± 0.56; p=0.13 - Aortic arch: 2.32 ± 0.45 vs 1.87 ± 0.33; p=0.002 * - Descending: 2.42 ± 0.38 vs 2.16 ± 0.36; p=0.05 * - Suprarenal: 2.36 ± 0.37 vs 1.93 ± 0.42; p=0.005 * - Infrarenal: 2.54 ± 0.38 vs 1.92 ± 0.12; p <0.001 * $TBR_{max\ 10\ pixels}$ - Entire: 2.13 ± 0.21 vs 1.92 ± 0.30; p=0.03* - Ascending: 2.24 ± 0.61 vs. 2.05 ± 0.44; p=0.29 - Aortic arch: 2.01 ± 0.24 vs 1.72 ± 0.25; p=0.003* - Descending: 2.14 ± 0.24 vs 2.00 ± 0.33; p=0.21* - Suprarenal: 2.04 ± 0.25 vs 1.73 ± 0.33; p=0.009* - Infrarenal: 2.13 ± 0.21 vs. 1.75 ± 0.34; p=0.001* SUV_{max} - Entire: 4.01 ± 0.83 vs 3.31 ± 0.56; p=0.005* - Ascending: 4.30 **± 1.64 vs 3.55 ± 0.71; p =0.07** - Aortic arch: 3.77 ± 0.95 vs 2.96 ± 0.48; p=0.002* - Descending: 3.93 ± 0.77 vs 3.44 ± 0.6; p= 0.05 - Suprarenal: 3.90 ± 1.16 vs 3.08 ± 0.80; p=0.02* - Infrarenal: 4.17 ± 1.12 vs 3.06 ± 0.76; p=0.002	Associations remain significant after adjusting (ANCOVA) for BMI and age.	In moderate-severe Pso, significantly more VI (measured with TBR_{max}) at the entire aorta, aortic arch, suprarenal and infrarenal aortic segments.
All psoriasis: - Ascending: 1.88 ± 0.37 vs 1.70 ± 0.29; p=0.028 * - Arch: 1.85 ± 0.38 vs 1.67 ± 0.28; p=0.025 * - Descending: 1.90 ± 0.31 vs 1.73 ± 0.28; p=0.028 * - Suprarenal: 1.83 ± 0.38 vs 1.72 ± 0.23; p=0.185 - Infrarenal: 1.87 ± 0.38 vs 1.67 ± 0.27; p=0.012 *[d] Moderate-severe psoriasis (n=10): - Ascending: 1.89 ± 0.52 vs 1.70 ± 0.29; p=NR - Arch: 1.95 ± 0.46 vs 1.67 ± 0.28; p=NR - Descending: 1.92 ± 0.31 vs 1.73 ± 0.28; p=0.NR - Suprarenal: 1.85 ± 0.41 vs 1.72 ± 0.23; p=0.185 - Infrarenal: 1.89 ± 0.43 vs 1.67 ± 0.27; p=0.012 *[d]	Same results after multivariate analysis adjusting for age, sex and BMI (p<0.05).	In psoriasis, significantly more VI in aortic arch, ascending, descending and infrarenal aorta.

Supplemental Table S3. Higher aortic VI in patients with psoriasis compared to healthy controls. (continued)

Study	Subjects, no. [e)]	Psoriasis severity	FDG (activity)	Uptake time and protocol	VI outcome	TBR calculation	VI location
Goyal (2020) JACC Cardiovasc Imaging	Pso n=164 subgroup severe psoriasis (PASI>10)	Pso n=30; HC n=47 All psoriasis, subgroup severe	370 MBq	Mean 62 minutes ± 1. 8 hour fast, 1,5 mm axial slices.	TBR_{max}	Dividing SUV_{max} of each aortic slice by average of SUV_{mean} in SVC	Entire aortic vessel
Kaur (2018) Indian J Dermatol Venereol Leprol	Pso n=16, control n=NR	Moderate-severe (PASI≥5)	370 MBq	60 minutes	SUV_{max} (formula SUV_{max} not reported)	NA	Aortic segments
Youn (2015) J Dermatol	Pso n=10; HC n=10	Mild (BSA <5%, PASI<10)	5.18 MBq/kg	50 minutes. Overnight fast. 3.27 mm axial slices.	TBR_{max}	Dividing average SUVmax by mean SUV from three slices of the SVC	Aortic segments

*Table Legend: reported outcome variables are displayed as mean ± SD. * Statistically significant; a) In original study, p-value was presented as 'p=>0.0001', but we assume this should have been presented as indicated in our table 'p=<0.0001'; b) $TBR_{max- 10 pixels}$ is a method that reduces the risk of measurements based on single high pixel values; c) Exclusion criteria include, amongst others, tobacco use, hypertension, dyslipidemia, diabetes mellitus, history of cerebrovascular disease; d) Discrepancy between study results in Supplementary Table S3 and Figure 2 in original study. We assume that in the table, outcomes of psoriasis patients and healthy controls were reversed. Authors were contacted on 23-12-2020. e) Definition of healthy controls varied per study: Rose – "… participants without any diagnosis of illness by review of medical records, including LDL >190, fasting glucose >126 and BMI >30."; Hjuler – " … either patients with localized melanoma or patients with localized stage 1 penile cancer. Only patients who had not received any systemic chemotherapy and patients without metastatic disease on both initial and subsequent follow-up imaging were included."; Kim – (healthy controls not defined); Goyal – "…*

Result PsO vs HC	Adjustment results for cardiovascular risk factors	Summary of findings
- All Pso: 1.71 ± 0.26 vs 1.62 ± 0.20; p NR - Severe Pso: 1.78 ± 0.32 vs 1.62 ± 0.20; p=0.02	No	In severe Pso, significantly higher FDG uptake compared to healthy controls (p = 0.02)
- Ascending: 2.0 ± 0.5 vs 1.5 ± 0.4; p=0.03 * - Aortic arch: 2.0 ± 0.5 vs 2.0 ± 0.7; p=0.78 - Descending: 1.9 ± 0.8 vs 1.6 ± 0.5; p=0.66 - Suprarenal: 2.0 ± 0.7 vs 1.7 ± 0.6; p=0.71 - Infrarenal: 2.0 ± 0.5 vs 1.6 ± 0.5; p=0.35	No	In moderate-severe Pso, significantly more VI in ascending aorta.
- Ascending: 1.95 ± 0.21 vs 1.71 ± 0.14; p=0.0063 * - Arch: no significant difference (TBR NR) - Descending: no significant difference (TBR NR) - Suprarenal: 1.72 ± 0.23 vs 1.52 ± 0.13; p=0.0271 * - Infrarenal: 1.60 ± 0.17 vs 1.44 ± 0.11; p=0.0499 *	After adjusting for cardiovascular risk factors (age, sex, BMI, hypertension, cholesterol level and fasting glucose level): significant association remains	In mild Pso, significantly more VI in ascending, suprarenal and infrarenal aorta

a healthy comparator group without psoriasis"; Kaur – "… patients who underwent positron emission tomography/computed tomography imaging for suspected malignancy but were found to have no pathological anomaly."; Youn – "The control subjects underwent FDG-PET/CT for health screening purposes, ….". Abbreviations: FDG: F-18-fluorodeoxyglucose; BMI : body mass index; BSA: body surface area; HC: healthy control; LDL : low-density lipoprotein, n = number of subjects included in the study; NR: not reported; PASI: psoriasis area and severity index; PET/CT: positron emission tomography–computed tomography; PsA: psoriatic arthritis; Pso: psoriasis; RA = rheumatoid arthritis, SUVbw = the standardized uptake value based on body weight, SUV_{max}: maximal standardized uptake value; SVC: superior vena cava; TBR: target to background ratio; TBR_{max}: maximum target to background ratio; $TBR_{max\text{- }10\,pixels}$: maximum target to background ratio using a maximum SUV with a threshold of > 10 pixels for each slice.

Supplemental Table S4. The effects of systemic treatment on aortic vascular inflammation in patients with psoriatic disease.

Study	Subjects	Psoriasis severity	Design	Dosage ^{18}F-FDG	Uptake time and protocol	Treatment	Duration of treatment
Bissonnette (2013) Circ Cardiovasc Imaging	Pso n=30[a]	Moderate-severe Pso (BSA>5%)	RCT	370 MBq	2 hours. Overnight fast. Slice thickness 4.25 mm.	ADA n=20, control non-systemic treatment (topical, UVT, no treatment) n=10	15 weeks
Bissonnette (2017) J Invest Dermatol	Pso n=107[b]	Moderate-severe Pso (BSA>5%)	RCT	370 MBq	2 hours. Overnight fast. Slice thickness 3.2 mm.	ADA n=54 Placebo followed by ADA n=53	52 weeks (ADA) / 16+52 weeks (placebo+ADA)

VI outcome	TBR calculation	VI location	Results	Summary of findings
TBR_{max}, TBR_{mean}	TBR_{max} and TBR_{mean} = resp. arterial SUV_{max} or SUV_{mean} divided by SUV_{mean} SVC (ascending aorta TBR) or jugular veins (carotid arteries TBR)	Carotid arteries, ascending aorta	Vessel with highest baseline TBR_{max}: - Significant reduction TBR_{max} after ADA (-0.23 ± 0.07; p=0.004)* - No significant decrease TBR_{max} in control group (-0.10 ± 0.11; p=0.35) - No significant difference between study arms (least square means estimates ± SEM: -0.13 ± 0.13; p=0.32) Carotid arteries: - No significant reduction TBR_{max} after ADA (-0.08 ± 0.08; p=0.33) - Significant increase TBR_{max} in control group (0.24 ± 0.12; p=0.050) - Significant difference between study arms (least square means estimates ± SEM: -0.32 ± 0.15; p=0.037)* Ascending aorta: - Significant reduction TBR_{max} after ADA (-0.17 ± 0.06; p=0.011)* - No significant reduction TBR_{max} in control group (0.10 ± 0.09; p=0.28) - Significant difference (least square means estimates ± SEM: -0.26 ± 0.11; p=0.021)*	Vascular inflammation improved after 15 weeks adalimumab treatment in comparison with the control arm, both at the ascending aorta and at carotid arteries.
TBR_{max}	TBR_{max} = arterial SUV_{max} divided by SUV_{mean} SVC (ascending aorta TBR) or jugular veins (carotid arteries TBR)	Carotid arteries, ascending aorta	Results after 16 weeks (RCT): - Ascending aorta: no difference in change from baseline in TBR_{max} between study arms (adalimumab: 0.002 (95%CI = -0.048 – 0.053, calculated SD-value=0.18; placebo: -0.002 (95%CI = - 0.053 – 0.049, calculated SD-value=0.19; p=0.916) - Carotid arteries: no difference in change from baseline in TBR_{max} between study arms (adalimumab: 0.031 (95%CI = -0.005 – 0.066; placebo: 0.018 (95%CI -0.019 – 0.055); p=0.629) Results after 52 weeks adalimumab: - Ascending aorta: no significant change from baseline in TBR_{max} (-0.006, 95% CI = -0.049 to 0.038; p=0.796) - Carotid arteries: increase in TBR_{max} (0.027, 95% CI = 0.000 to 0.054; p=0.046)*	No significant difference in change in vascular inflammation (measured at the carotid arteries and ascending aorta), between arms treated with adalimumab or placebo for 16 weeks.

Supplemental Table S4. The effects of systemic treatment on aortic vascular inflammation in patients with psoriatic disease. (continued)

Study	Subjects	Psoriasis severity	Design	Dosage ^{18}F-FDG	Uptake time and protocol	Treatment	Duration of treatment
Mehta (2018) Circ Cardiovasc Imaging	Pso n=97	Moderate-severe (BSA≥10% and PASI>12)	RCT	555 MBq	Uptake time NR. Overnight fast. Slice thickness NR.	Completed 12 weeks: ADA n=32 UVT n= 30 Placebo n=30 Completed 52 weeks: n=61	52 weeks (ADA) / 12+52 weeks (UVT/ placebo+ADA)
Gelfand VIP-U (2020) J Invest Dermatol	Pso n=43	Moderate-severe (PASI≥12 and BSA ≥10%)	RCT	555 MBq	60 minutes. Overnight fast. 1.5-4 mm axial slices.	UST n=22 Placebo followed by UST n=19	52 weeks (UST) / 12+52 weeks (placebo+UST)
Gelfand VIP-S (2020) J Invest Dermatol	Pso n=91	Moderate-severe (PASI≥12, BSA≥10, IGA mod 2011 score≥3)	RCT	2.52 MBq/ kg body weight	60 minutes. Overnight fast. Slice thickness NR.	SEC n=37 Placebo followed by SEC n = 35§	52 weeks (SEC) / 12+40 weeks (placebo+SEC)

	VI outcome	TBR calculation	VI location	Results	Summary of findings
	TBR_{max}	TBR_{max} = SUV_{max} values from each aortic slice divided by the average SUV_{mean} SVC	Aorta	Results after 12 weeks (RCT): - No significant reduction in TBR_{max} in ADA-arm (-0.067, calculated SD-value = 0.298, p=0.213) - No significant reduction in in TBR_{max} in placebo arm (−0.052, calculated SD-value = 0.174, p=0.112) - Significant reduction in phototherapy group (-0.079, p=0.02)* - No significant change of 0.64% (95% CI -5.84% − 7.12%, p=0.844) between ADA and placebo Results after 52 weeks ADA: - Significant reduction in VI after 52 weeks ADA compared to baseline (-0.08 ± 0.002; p=0.005)*	No significant difference in change in vascular inflammation, between arms treated with ADA and placebo for 12 weeks.
	TBR_{max}	TBR_{max} = SUV_{max} values from each aortic slice divided by the average SUV_{mean} SVC	Whole aortic vessel	Results after 12 weeks (RCT): - Significant reduction in TBR_{max} after 12 weeks UST (mean difference =-0.102; p=0.041; SD calculated = 0.220). - Significant increase in TBR_{max} after 12 weeks placebo (mean difference = 0.144; p=0.014; SD calculated = 0.231) Results after 52 weeks UST: No significant reduction in TBR_{max} compared to baseline (-0.015; p=0.672)	Vascular inflammation improved after 12 weeks ustekinumab treatment in comparison with the control arm.
	TBR_{max}	TBR_{max}= SUV_{max} values from each aortic slice were divided by the average venous SUV_{mean}	Whole aortic vessel	Results after 12 weeks (RCT): - No significant reduction in TBR after 12 weeks SEC (-0.006 (95% CI, -0.081, 0.068) - No significant change after 12 weeks placebo (0.025 (-0.043 – 0.093) - No significant difference between study arms (SEC – placebo = -0.053; p=0.37) Results after 52 weeks SEC: No significant reduction in TBR for those initially assigned to SEC (n=37, -2.6%, 95% CI = -11.9% to 6.8%) and those initially assigned to placebo (n=35, 3.4%, 95% CI= -6.1% to 2.8%).	No significant difference in change in vascular inflammation, between arms treated with secukinumab or placebo for 12 weeks.

Supplemental Table S4. The effects of systemic treatment on aortic vascular inflammation in patients with psoriatic disease. (continued)

Study	Subjects	Psoriasis severity	Design	Dosage ^{18}F-FDG	Uptake time and protocol	Treatment	Duration of treatment
Dey (2017) JAMA Cardiol	Plaque psoriasis n=115[d] Severe psoriasis subgroup TNFi, n=17	Psoriasis, subgroup severe psoriasis (PASI range 6-15)	Cohort	370 MBq	60 minutes. Overnight fast. 1.5 mm axial slices.	Topical n=77 UVT n=21 Systemic or biologic n=45 TNFi n=17	52 weeks
Eder (2018) Arthritis Rheumatol	PsA n=34	Psoriatic arthritis	Case control	370 MBq	~60 minutes. Overnight fast. 1.5 mm axial slices.	TNFi n=21 Control (no treatment) n=13	52 weeks
Goyal (2020) JACC Cardiovasc Imaging	Severe Pso n=30[c]	All psoriasis, subgroup severe psoriasis (PASI>10)	Cohort	370 MBq	Approximately 60 minutes (mean 62minutes ± 1). Overnight fast. 1,5 mm slices.	'Intensive treatment' including: Topical n=20 UVT n=7 Systemic n=4 Biologic n=9 (TNFi n=3, IL-12/23i n=3, IL-17i n=3)	52 weeks

	VI outcome	TBR calculation	VI location	Results	Summary of findings
	TBR_{max}	TBR_{max} = aortic SUV_{max} divided by SUVmean SVC	Whole aortic vessel	- Significant reduction in TBR_{max} pooled treatment regimens compared to baseline (1.79 ± 0.22 vs 1.91 ± 0.29; p=<0.001)† - Subgroup TNFi: significant reduction in TBR_{max} compared to baseline (1.78 ± 0.22 vs 1.90 ± 0.35; p=0.04)*	In this cohort of psoriasis patients, a significant reduction in vascular inflammation was observed after 52 weeks follow-up.
	TBR_{max} = aortic SUV_{max}	divided by SUV_{mean} SVC[e]	Whole aortic vessel	- TNFi: significant reduction in TBR_{max} compared to baseline (1.76 ± 0.24 vs 1.90 ± 0.28; p=0.03)* - Control group: no significant reduction in TBR_{max} in control group compared to baseline (1.86 ± 0.21 vs 1.89 ± 0.26; p=0.32)	In this case-control study in patients with psoriatic arthritis, a significant reduction in vascular inflammation was observed after treatment with a TNF-inhibitor, In the control arm, no significant reduction in vascular inflammation was observed.
	TBR_{max}	TBR_{max}= SUV_{max} of each aortic slice divided by average of SUV_{mean} in SVC	Aorta	Significant reduction in TBR_{max} compared to baseline (1.67 ± 0.26 vs 1.78 ± 0.32; p=0.01)*	In this cohort of psoriasis patients, a significant reduction in vascular inflammation was observed after 52 weeks follow-up.

Supplemental Table S4. The effects of systemic treatment on aortic vascular inflammation in patients with psoriatic disease. (continued)

Study	Subjects	Psoriasis severity	Design	Dosage ^{18}F-FDG	Uptake time and protocol	Treatment	Duration of treatment
Kaur (2018) Indian J Dermatol Venereol Leprol	Pso n=16	Moderate-severe (PASI≥5)	RCT	370 MBq	60 minutes. 6 hour fast. Slice thickness not reported.	MTX+pioglitazone n=4 MTX+placebo n=4 Placebo+pioglitazone n=4 Placebo+placebo n=4	12 weeks
Kim (2018) J Am Acad Dermatol	Pso n=10[f,g]	Moderate-to-severe (PASI>10 or BSA>10%)	Cohort	5.18 MBq/kg	60 minutes. 5 mm axial slices.	Ustekinumab	Until PASI75 achieved
Rivers (2018) JACC Cardiovasc Imaging	Severe Pso n=13[g]	PASI>10	Cohort	370 Mbq	Approximately 60 minutes. Overnight fast. 1.5 mm axial slices.	Treatment varied, 6 (38%) systemic or biologic treatment	52 weeks

*Table Legend: reported outcome variables are displayed as mean ± SD, unless stated otherwise. *= Statistically significant; a) To be eligible, patients were required to have an history of coronary atherosclerosis, or a minimum of 3 risk factors for cardiovascular disease. TBR was required to be 1.6 or higher; b) TBR was required to be 1.6 or higher; c) relevant outcomes for meta-analysis were only reported in patients that finished the trial (52 weeks); d) patients with known cardiovascular disease and hypertension excluded; e) as described in methods by Nair et al (1); f) exclusion criteria include, amongst others, tobacco use, hypertension, dyslipidemia, diabetes mellitus, history of cerebrovascular disease; g) subgroup of patients from original trial. Reference: 1. Naik HB., Natarajan B., Stansky E., et al. Severity of Psoriasis Associates With Aortic Vascular Inflammation Detected by FDG PET/CT and Neutrophil Activation in a Prospective Observational*

	VI outcome	TBR calculation	VI location	Results	Summary of findings
	SUV_{max} (formula SUV_{max} not reported)	NA	Five aortic segments	No significant change in any of treatment arms study arms in any aortic segment. No composite score for aorta available.	No significant difference in composite SUV_{max} score (all aorta segments combined with liver, skin and joints) after 12 weeks of treatment in patients randomized to methotrexate or placebo.
	SUV_{max} (formula SUV not reported)	NA	Five aortic segments	Results after achievement of PASI75, compared to baseline: - Aortic arch: 1.50 ± 0.29 vs. 1.89 ± 0.52; p=0.0201* - Ascending aorta: 1.46 ± 0.36 vs. 1.95 ± 0.46; p=0.0071* - Descending aorta: 1.57 ± 0.25 vs. 1.92 ± 0.31; p=0.0121* - Suprarenal aorta: 1.53 ± 0.23 vs. 1.85 ± 0.41; p=0.0710 - Infrarenal abdominal aorta: 1.49 ± 0.33 vs. 1.89 ± 0.43; p=0.0040*	In this cohort of psoriasis patients, SUV_{max} values were reduced at the aortic arch, ascending aorta, descending aorta and infrarenal abdominal aorta after PASI75 was achieved with ustekinumab treatment.
	TBR_{max}	TBR_{max}= aortic SUV_{max} divided by SVC SUV_{mean} [e]	Aorta	Significant reduction of 9.6% in TBR_{max} after 52 weeks (1.79 ± 0.31 vs 1.98 ± 0.38; p= 0.02)*	In this cohort of psoriasis patients, a significant reduction in vascular inflammation was observed after 52 weeks follow-up.

Study. Arterioscler Thromb Vasc Biol 2015;35(12):2667–76. Doi: 10.1161/ATVBAHA.115.306460.
Abbreviations: ADA: adalimumab (TNFα inhibitor); FDG: F-18-fluorodeoxyglucose; MTX: methotrexate; n: number of subjects included in the study; NA: not applicable, NR: not reported; PASI75: 75% reduction in Psoriasis Area and Severity Index compared to baseline; PET/CT: positron emission tomography–computed tomography; PsA: psoriatic arthritis; Pso: psoriasis; RCT: randomized clinical trial; SEM: standard error of the mean, SEC: secukinumab (IL-17 inhibitor); SUV_{max}: maximal standardized uptake value; SVC = superior vena cava; TBR: target to background ratio; TBR_{max}: maximum target to background ratio; TBR_{mean}: mean target to background ratio; TNFi: tumor necrosis factor alpha inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab); UST: ustekinumab (IL-12/23 inhibitor); UVT: ultraviolet light therapy; VI: vascular inflammation.

Supplemental Table S5. Detailed PET/CT measurements of studies included in meta-analyses.

Study	How ROI regions were drawn	Slice thickness	2D (ROI) / 3D (VOI)	PET-scanner	Reconstruction
Hjuler (2017)	*Aorta*: Measurements made in axial planes by drawing a ROI containing the arterial wall and the lumen in each slice *Blood*: SUVmean measured by drawing small ROI in the SVC and then averaged to approach one single most accurate value for the circulating blood-pool signal in each individual	3 mm axial slices	2D	GE Discovery 690; GE Healthcare, Chicago, IL, U.S.A.	Reconstruction of attenuation-corrected images using an ordered subset expectation maximization algorithm with point-spread function and time-of-flight (three iterations, 24 subsets, matrix size 192 9 192, 4-mm Gaussian postprocessing filter)
Goyal (2020)	ROI placed on 1.5-mm-thick axial slices of the aorta from the aortic root through the bifurcation into the iliac arteries. ROI also placed on 10 continuous slices of the SVC to calculate and correct for background venous activity. Mean and maximum SUVs were generated using a dedicated PET/CT image analysis program, Extended Brilliance Workspace (Philips Electronics, Andover, Massachusetts)	1.5 mm axial slices	2D	Siemens Biograph mCT PET/CT 64-slice scanner (Siemens Medical Solutions USA, Malvern, Pennsylvania)	NR
Rose (2013)	Circular 2-dimensional ROI manually drawn around the external aortic contour of serial transverse sections extending from the aortic root to the iliac bifurcation. SUVmean and areas for each ROI in successive slices were auto-calculated using EBW software.	6 mm axial slices	2D	Gemini TF; Philips Medical Systems, Bothell, Washington	NR

Supplemental Table S5. Detailed PET/CT measurements of studies included in meta-analyses. (continued)

Study	How ROI regions were drawn	Slice thickness	2D (ROI) / 3D (VOI)	PET-scanner	Reconstruction
Kim (2019)	Uptake quantified by drawing a ROI around each part of the aorta on every slice of the coregistered PET/CT images.	5 mm axial slices	2D	Gemini TF, Philips, Milpitas	NR
Bissonnette (2013)	Arterial FDG uptake quantified by drawing a ROI around each artery on every slice of the coregistered PET/CT images.	Slice thickness 5 mm	2D	GE Healthcare (Milwaukee, WI) Discovery ST PET/CT scanner	Reconstructed using OSEM algorithm with corrections applied for normalization, dead time, random events, scatter, attenuation, and sensitivity
Bissonnette (2017)	Similar as Bissonette (2013)	Slice thickness 3.2 mm	2D	Similar as Bissonnette (2013)	Reconstructed using ordered subset expectation maximization algorithm with corrections applied for normalization, dead time, random events, scatter, attenuation, and sensitivity.
Mehta (2018)	FDG uptake within aorta directly measured by using a dedicated image analysis software (OsiriX MD, Pixmeo SARL, Bernex, Switzerland) to measure vascular inflammation calculated as TBR.	Slice thickness NR	2D	NR	NR

Supplemental Table S5. Detailed PET/CT measurements of studies included in meta-analyses. (continued)

Study	How ROI regions were drawn	Slice thickness	2D (ROI) / 3D (VOI)	PET-scanner	Reconstruction
Gelfand VIP-U (2020)	Extent of FDG uptake within the aorta measured using an image analysis software (OsiriX MD; Pixmeo SARL, Bernex, Switzerland) to measure vascular inflammation calculated as a TBR to blood pool activity. Each ROI produced the following two measures of metabolic activity: SUVmean and SUVmax; these were obtained in the entire aorta from the aortic outflow tract to the abdominal aorta. Moreover, ROI were placed on six contiguous slices over the SVC to obtain background activity of the FDG radiotracer.	1.5-4 mm axial slices	2D	Gemini TF and Ingenuity TF; Philips Medical Systems, Bothell, WA	NR
Gelfand VIP-S (2020)	Each ROI produced two measures of metabolic activity, SUVmean and SUV max, and these were obtained in the entire aorta. Moreover, ROI were placed on six contiguous slices over the superior vena cava to obtain background activity of the 18F-FDG tracer.	Slice thickness NR	2D	NR	NR

Table Legend. Abbreviations: 2D: two-dimensional; 3D: three-dimensional; FDG: F-18-fluorodeoxyglucose; NA: not applicable; NR: not reported; PET/CT: positron emission tomography–computed tomography; ROI: region of interest; SUV_{max}: maximal standardized uptake value; SUV_{mean}: mean standardized uptake value; SVC = superior vena cava; TBR: target to background ratio; TBR_{max}: maximum target to background ratio; TBR_{mean}: mean target to background ratio; VOI: volume of interest.

Chapter 7

Increased vascular inflammation on PET/CT in psoriatic arthritis patients in comparison with controls.

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Abstract

Background

Patients with psoriatic arthritis (PsA) have an increased risk of cardiovascular disease, possibly due to a chronic inflammatory state.

Objectives

The main objective of this study was to investigate the difference in vascular inflammation, measured with 18-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT), in PsA patients and controls. We conducted a secondary analysis to assess the association between clinical parameters of disease activity with vascular inflammation in PsA.

Methods

We included a total of 75 PsA patients with active peripheral arthritis (defined as ≥2 tender and swollen joints) from an ongoing clinical trial (EudraCT 2017-003900-28) and a retrospective group of 40 controls diagnosed with melanoma, without distant metastases and not receiving immunotherapy. The main outcome measure was aortic vascular inflammation which was measured on PET/CT-scans using target-to-background-ratios. Clinical disease activity in PsA was assessed with joint counts, body surface area and the Disease Activity index for PsA. Laboratory assessments included C-reactive protein and Erythrocyte Sedimentation Rate.

Results

Vascular inflammation was increased in patient with PsA in comparison with controls (mean TBR for entire aorta respectively 1.63±0.17 versus 1.49±0.16; p=<0.001). This association remained significant after correction for gender, age, body mass index, mean arterial pressure and aortic calcification (p=0.002). Vascular inflammation was not associated with disease-related parameters.

Conclusions

Aortic vascular inflammation was significantly increased in patients with active PsA compared with controls. This evidence supports the theory that inflammation in PsA is not limited to the skin and joints, but also involves the vascular system.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease, occurring in up to 30% of patients with psoriasis (Pso) and in 0.2% of the adult population.(1,2) PsA is an heterogeneous disease which can involve peripheral arthritis, spondylitis, and extra-articular features such as enthesitis and dactylitis.(3) PsA is associated with an increased risk of cardiovascular disease (CVD) compared with the general population.(4) Traditional cardiovascular risk factors can be increased in PsA, however, this does not fully explain the higher incidence of CVD in PsA.(5) It has been hypothesised that systemic inflammation could lead to endothelial dysfunction and accelerated atherosclerosis in psoriatic disease.(6)

With the use of 18-fluorodeoxyglucose (FDG) positron emission tomography (PET/CT), inflammatory activity at the arterial wall can be measured noninvasively. Vascular inflammation measured by FDG PET/CT is strongly correlated with atherosclerotic plaque inflammation and future cardiovascular events, but also a diagnostic marker of vasculitis.(7,8) In recent years there has been broad interest in studying the link between chronic inflammation and CVD with PET/CT. So far, investigations on vascular inflammation in psoriatic disease focused on Pso, rather than on PsA. Vascular inflammation measured with PET/CT is elevated in Pso compared with healthy controls, and skin severity is associated with aortic vascular inflammation.(9–14)

The aim of this study is to investigate whether vascular inflammation measured by FDG PET/CT is elevated in PsA in comparison with patients without PsA. As a secondary outcome measure, we assessed whether the extent of clinical disease activity in PsA was associated with vascular inflammation. This study may further advance our understanding of the pathophysiology of CVD in PsA.

Methods

Patients with PsA were included from the TOFA-PREDICT study, a multicenter trial predicting therapy response in PsA (EudraCT 2017-003900-28). This ongoing trial is conducted in the Netherlands and coordinated from the University Medical Center Utrecht. Participants met the ClASsification criteria for Psoriatic ARthritis (CASPAR) (15), were aged 18-75 years, had a disease duration of at least eight weeks, and showed evidence of active peripheral arthritis (≥2 swollen joints and ≥2 tender joins). Detailed in- and exclusion criteria have been reported in our previously published

design paper.(16) For the current analyses, we used the PET/CT-scans acquired at baseline in the first cohort of 80 patients included in the clinical trial.

Control patients

We included patients diagnosed with melanoma, aged 18-65 years, in whom whole body FDG PET/CT-scans were acquired for screening of distant metastases, as a retrospective control group. We excluded melanoma patients with distant metastases, patients receiving immunotherapy, and patients with a history of autoinflammatory or autoimmune disease.

PET/CT protocol

FDG was administered intravenously after an overnight fast. After administration of FDG, the FDG PET/CT was performed one hour later. A non-contrast-enhanced low-dose CT was performed for co-registration and attenuation correction. Due to the multicenter study design, kilovoltage peak (kvP), slice thickness and dosing of 18F-FDG varied, depending on local protocols and devices (Supplemental Table S1). PET/CT-reconstructions were compliant to European Association of Nuclear Medicine Research Ltd. (EARL) guidelines to achieve repeatability and reproducibility of quantitative PET/CT outcome measures.(17) PET/CT-scans were assessed for quality by local nuclear medicine technicians, under supervision of local radiologists or nuclear medicine physicians. Final judgement on scan quality was determined by the radiology team within the UMC Utrecht under supervision of professor de Jong. PET/CT-scans without an EARL reconstruction and acquired with a pre-scan serum glucose of 10 mmol/l or higher were excluded from the analysis.

Measurements of vascular inflammation and calcification on PET/CT

The primary outcome measure was vascular inflammation, which was assessed using a target-to-background ratio (TBR). Two dimensional regions of interests (ROIs) were manually placed on PET/CTs around the external aortic contour in axial setting, to provide a maximum standardized uptake value (SUV; Figure 1). ROIs were placed every 3, 4 or 5 mm, depending on slice thickness. This process was repeated along the whole length of the aorta. The SUVmax in the aorta was measured per slice and then averaged to produce the SUVmax for the entire aorta and per aortic segment (ascending aorta, aortic arch, descending aorta, suprarenal abdominal aorta and infrarenal abdominal aorta). The SUVmean for background measurement was derived by calculating the mean of six to eight ROIs in the superior vena cava (SVC; Figure

1), or, in one case at the inferior vena cava because of visual spill of activity of the myocardium. Subsequently, the maximum TBR was calculated by taking the ratio of SUVmax and SUVmean of the venous blood pool.(7,17) With the use of TBR, aortic vascular inflammation can be measured in a reliable and reproducible manner.(18) In addition, for assessment of the intraclass correlation coefficient (ICC), 12 aortic segments of randomly selected scans were scored by two observers, showing an excellent ICC (0.985, 95%-CI 0.949-0.996).

We quantified arterial calcifications of the aorta on consecutive axial slices of the computed tomography (CT)-scans. Arterial calcifications were defined as hyperdense lesions of ≥130 Hounsfield Units (HU). Calcification scores (Agatston scores) were calculated as the product of the area of calcification lesions and the weighted attenuation score, which is dependent on the maximal HU of the calcified region. (19) Measurement of aortic calcifications on CT has an excellent ICC.(20)

Clinical assessments

The following clinical parameters were assessed in PsA patients: disease duration, body mass index (BMI), blood pressure, tender joint count (68), swollen joint count (66), the Leeds Enthesitis Index (LEI), dactylitis count, and the body surface area (BSA) for assessment of psoriasis severity. Laboratory evaluation included serum lipid levels, glucose, C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR). From the retrospective cohort of control patients, we collected the following clinical variables from patient files: age, gender, history of cardiovascular diseases, BMI, glucose level and blood pressure.

Ethical committee approval

All PsA patients included in the study provided written consent and the study was approved by the Medical Research Ethics Committee in Utrecht, Netherlands (reference number NL63439.041.17). Given the retrospective use of PET/CTs in the control group and limited clinical data used, no formal approval of this study was required, and a waiver of informed consent was in place as stated by the Medical Ethics Committee of the UMC Utrecht.

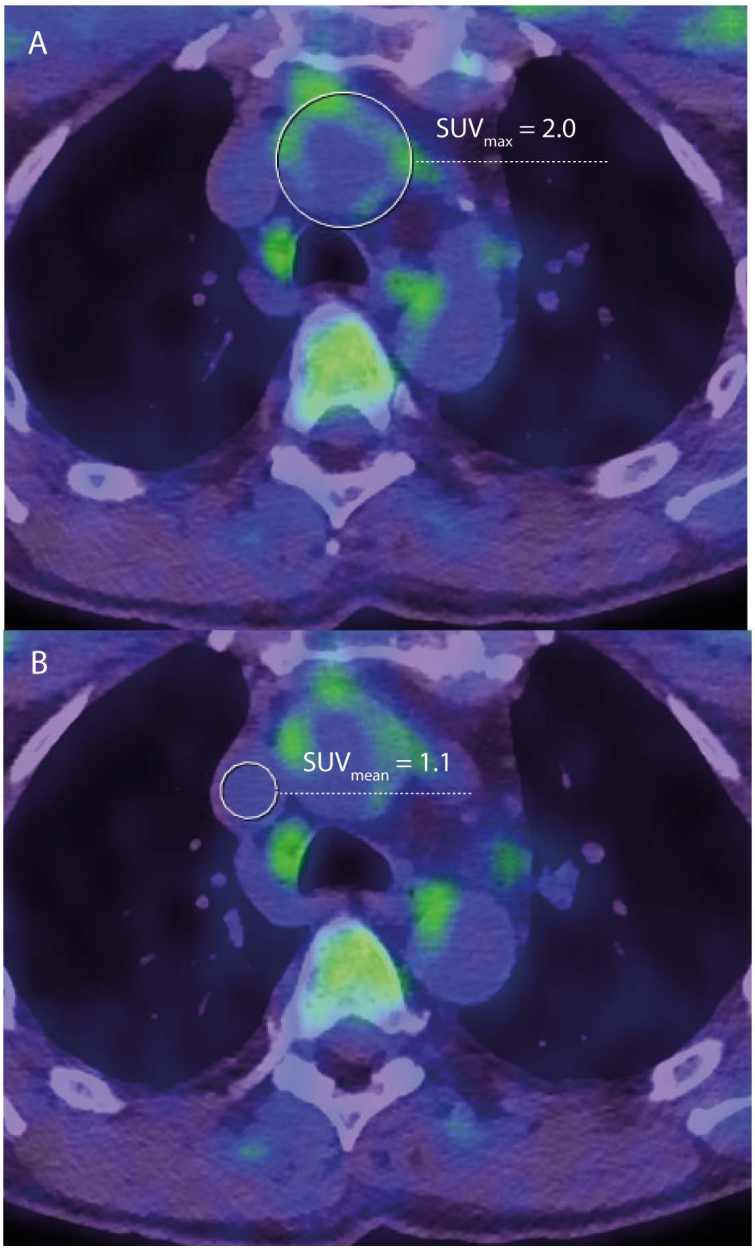

Figure 1.
Figure showing fused PET/CT images in axial setting. A) Placement of region of interest around the external aortic contour for measurement of the maximum standardized uptake value (SUVmax). This measurement is repeated along the entire vessel. B) Placement of region of interest inside the superior vena cava for calculation of the mean standardized uptake value, as a measure for background activity. PET/CT=positron emission tomography / computed tomography

Statistical analysis

Summary statistics are reported as mean ± standard deviation (SD) for normally distributed variables, median and interquartile range (IQR) for non-normally distributed variables and absolute or relative frequencies for categorical variables. Between-group differences were assessed using the unpaired t-test with equal variances for normally distributed variables and the Mann Whitney U test for non-normally distributed continuous variables. Differences in categorical variables were assessed using Fisher's exact test.

The primary outcome measure was the difference in vascular inflammation (assessed using the TBR) between PsA patients and controls and was assessed using the unpaired t-test with equal variances. Subsequently, to correct for traditional cardiovascular risk factors, a multiple linear regression analysis was performed with vascular inflammation as the dependent variable and disease category (PsA in comparison with controls), age, gender, body mass index, mean arterial pressure (MAP) and aortic calcification as independent variables. To test the assumption of normal distribution of the residuals, we used normal probability plots. Homogeneity of variances was evaluated with error plots. We assessed the association of vascular inflammation with clinical parameters of disease activity in PsA visually with scatter plots, and with Spearman's rank correlation coefficient. Differences in vascular inflammation between PsA patients with and without DMARD use, and between PsA patients included in the UMC Utrecht in comparison with other hospitals, were assessed using the unpaired t-test with equal variances. The predetermined significance level was set at $p < 0.05$. Statistical analysis was performed using SPSS version 26 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).

Results

Patients' characteristics

A total of 80 PsA patients, and 41 controls were included in the study. In four PsA participants, no PET/CT-scan was available. One PsA patient was excluded because the PET/CT was of insufficient quality, and one PET/CT of the control group because the patient had a serum glucose level of > 10 mmol/l. The final study population consisted of 75 PsA patients and 40 controls. Although local PET/CT-protocols in different hospitals varied (Supplementary Table 1), no differences were observed in vascular inflammation on PET/CT-scans performed in PsA patients in the UMC Utrecht (n=50), in comparison with patients included in other sites (n=25); ($p>0.05$).

Overall, study participants were middle-aged, with a slight male preponderance in both patients and controls. There were no significant differences between PsA patients and controls regarding age, mean arterial pressure (MAP) and history of CVD. PsA patients had a higher BMI in comparison with controls (Table 1).

The median time from PsA diagnosis was 10 months. DMARD-treatment had been prescribed in 49% of PsA patients. Of PsA patients with available DAPSA scores (n=73), 90.3% had moderate to high disease activity. Skin disease was limited in 88% of patients, with less than three percent body surface area involvement. A full overview of patients' characteristics is presented in Table 1. Adverse events related to PET/CT imaging are reported in Supplemental Table S2.

Vascular inflammation

Vascular inflammation in the whole aorta and all aortic segments, assessed with TBR, was significantly greater in patients with PsA in comparison to controls, in unadjusted analyses (Figure 2; Table 2). 13.3% of PsA patients had a TBR of the whole aorta >90th percentile, in comparison with 5.0% of controls (p=0.21).

In multivariable regression analyses, PsA remained significantly associated with vascular inflammation after correction for age, gender, BMI, MAP and overall aortic calcification (Table 2).

Association between clinical characteristics and vascular inflammation in PsA

We assessed whether disease activity in PsA was associated with vascular inflammation on PET/CT in the entire aorta, but found no significant associations for the tender or swollen joint count (of 68 and 66 joints respectively), the BSA, the LEI, disease duration, or CRP and ESR (p>0.05). There were no differences in vascular inflammation outcomes in the entire aorta and separate aortic segments, in PsA patients with and without current DMARD treatment (p>0.05).

Table 1. Patients' characteristics.

Characteristic[a]	PsA (N=75)	Controls (N=40)	p-value
Age, years, median (IQR)	53 (46-59)	52 (42-59)	0.353[b]
Male sex, n	43 (57.3)	23 (57.5)	1.000[c]
BMI, kg/m^2, mean±SD	28.4±4.9	25.9±4.0	0.008[d]
MAP, mean±SD	102.8±11.6	98.5±13.9	0.090[d]
Missing, n	0	5 (12.5)	
Current smoking, n	10 (13.3)	NA	
History of cardiovascular disease:			
Hypertension, n	12 (16.0)	6 (15.0)	1.000[c]
Hyperlipidemia, n	1 (1.3)	2 (5.0)	0.277[c]
Diabetes , n	2 (2.7)	0	0.542[c]
Myocardial infarction, n	2 (2.7)	0	0.542[c]
Cerebrovascular event, n	0	1 (2.5)	0.348[c]
PsA disease duration,months, median (IQR)	10.0 (1.0-123)	NA	
Current csDMARD use, n	37 (49.3)	NA	
Prior bDMARD use, n	3 (4.0)	NA	
Nail psoriasis, n	49 (65.3)	NA	
Dactylitis, n	19 (25.3)	NA	
TJC (of 68 joints), median (IQR)	4.0 (6.5-10.0)	NA	
SJC (of 66 joints), median (IQR)	3.0 (5.0-9.0)	NA	
LEI count (1-6), median (IQR)	0 (0.0-1.0)	NA	
BSA, median (IQR)	1.0 (1.0-3.0)	NA	
BSA ≥ 3, n	9 (12.0)	NA	
CRP, median (IQR)	1.0 (4.0-10.3)	NA	
ESR, median (IQR)	9.0 (5.0-22.3)	NA	
LDL-cholesterol, mean±SD	3.0±0.9	NA	
Aortic calcification (Agatston), median (IQR)	11.4 (0.0 – 252.3)	0.0 (0.0 - 595.1)	0.086[c]

Table Legend
[a]Values are expressed as n (%) unless stated otherwise.
[b]Mann-Whitney test
[c]Fisher's exact test
[d]Independent Samples t-test
Abbreviations. BMI = body mass index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, DMARD = Disease Modifying Anti-Rheumatic Drugs, LEI = Leeds Enthesitis Index, NA= not available, MAP = Mean Arterial Pressure, PASI = Psoriasis Area Activity Index, SD = standard deviation, SJC = swollen joint count, TJC = tender joint count

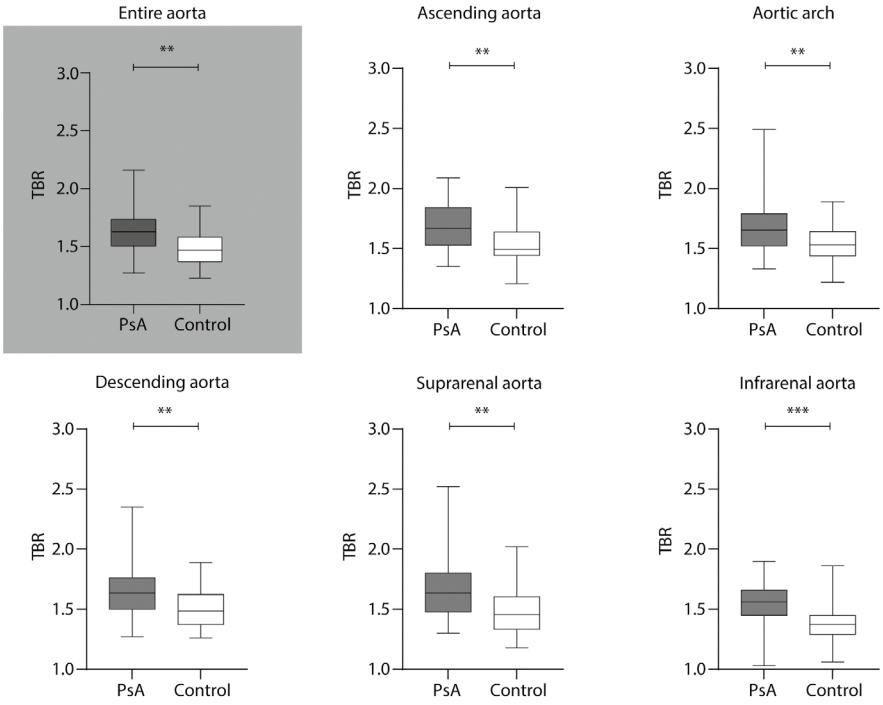

Figure 2.

*Increased vascular inflammation in the entire aorta and all separate aortic segments, assessed with the TBR, in psoriatic arthritis in comparison with controls. PsA, n=75 (total aortic segments measured = 366), controls, n=40 (total aortic segments measured =198). Lower and upper fences are the 25th and 75th percentile, the middle line represents the median value. Statistical analysis by multiple linear regression analysis (independent variable: TBR; dependent variables: disease category, age, gender, body mass index, mean arterial pressure, aortic calcification). ***=P < 0.001, **=P < 0.01. Abbreviations: PsA = psoriatic arthritis, TBR = target-to-background ratio.*

Table 2. Vascular inflammation (TBR) in PsA and controls.

Aortic segment	PsA (N=75)	Controls (N=40)	Unadjusted analysis (p-value)[a]	Beta coefficient for effect PsA on TBR (p-value) in model adjusted for age, sex, BMI, MAP and aortic calcification (Agatston score)
Entire aorta	1.63±0.17	1.49±0.16	<0.001	β 0.297 (0.002)
Ascending aorta	1.69±0.19	1.55±0.18	<0.001	β 0.289 (0.002)
Aortic arch	1.67±0.19	1.55±0.17	0.002	β 0.259 (0.009)
Descending aorta	1.66±0.20	1.52±0.17	<0.001	β 0.257 (0.009)
Suprarenal aorta	1.65±0.22	1.50±0.19	<0.001	β 0.271 (0.005)
Infrarenal aorta	1.54±0.16	1.40±0.18	<0.001	β 0.351 (<0.001)

Table legend: Values are expressed as mean±SD unless stated otherwise.
[a]= independent samples T-test

Discussion

This study confirmed our hypothesis that vascular inflammation quantified with PET/CT is increased in PsA compared to controls. The results remained significant after adjusting for age, gender, BMI, blood pressure and aortic calcifications. Our second hypothesis was that vascular inflammation was associated with disease activity in PsA, but this was not observed.

To our knowledge, this is the first study that describes vascular inflammation, measured with PET/CT, in PsA in comparison with controls. Our observations are in line with previous work that has consistently showed increased vascular inflammation in Pso in comparison with the general population. (9–14) Whilst currently limited data is available on vascular inflammation in PsA, increased atherosclerosis and cardiovascular disease have been reported in this population. Specifically, previous imaging studies have demonstrated increased coronary calcifications on CT, significantly higher common carotid artery intima-media thickness, and a higher prevalence of carotid atherosclerosis, assessed on ultrasound.(21–23) In contrast to studies in Pso, we did not identify an association between skin severity and vascular inflammation.(13,24) Furthermore, no associations between factors relating to PsA severity (joint count, enthesitis count, disease duration, inflammatory markers CRP and ESR and the composite score DAPSA), and vascular inflammation emerged from our analysis. The limited variability in disease activity, and low disease activity of

the skin, in PsA patients in the present study may explain why we did not observe any correlations between vascular inflammation and the above mentioned factors relating to PsA severity.

Different hypotheses could account for the finding that vascular inflammation is elevated in PsA. First, PsA patients exhibit an increased frequency of classical CVD risk factors, which could lead to increased vascular inflammation and (subclinical) atherosclerosis.(25) However, after correction for some classical risk factors, the association between psoriatic disease and vascular inflammation remained significant in the current study in PsA, and in past studies in Pso.(9–11,26) Since classical risk factors do not entirely explain the process of atherosclerosis in PsA, it has been proposed that PsA-related inflammatory mechanisms could contribute to the risk of CVD in PsA .(27)(28) This theory is supported by our findings. Further research is needed to understand the relational interplay between PsA and vascular inflammation in more detail. Additional imaging techniques, such as ultrasound of the carotid arteries or contrast angiography (combined with CT, or magnetic resonance imaging (MRI)), to assess the presence of subclinical atherosclerosis (22), could be of added value, since CT does not capture non-calcified plaques.(22,29)

Study limitations

There are certain limitations to the current study. Since the data for controls was collected retrospectively, it was not possible to retrieve information on all relevant confounders, such as smoking and lipid spectrum. While our observation was that vascular inflammation in the PsA group remained higher after correction for aortic calcifications, we cannot exclude soft plaques as a reason for increased PET/CT tracer uptake. Secondly, due to the multi-center study setting and the use of retrospective controls, PET/CT acquisition protocols varied across sites, and between PsA patients and controls (Supplemental Table 1). We, however, performed measurements on EARL reconstructions to harmonize quantitative PET/CT outcomes.(30) Furthermore, there were no differences observed in vascular inflammation on PET/CT in PsA patients included in the UMCU or other hospitals. Another limitation is that there is no 'true' cut-off value for increased vascular inflammation. Several authors have proposed that vessels or segments with a (mean) TBR of ≥1.6 should be considered as 'active'. (31,32) The mean TBR value in PsA patients in the current study was higher than 1.6 in all aortic segments which could be considered as active inflammation according to previously proposed criteria, except the infrarenal aorta, where mean aortic TBR values of the control group were all below 1.55 (Table 2).

Lastly, the current cross-sectional study only provides indirect evidence for the hypothesis that due to vascular inflammation there is an increased risk of CVD in PsA. Large longitudinal studies with hard cardiovascular outcomes are required to accurately determine the pathophysiological processes leading to CVD in PsA, but also the impact of PET/CT findings as an independent risk factor for major cardiovascular events in PsA patients.

Clinical perspectives

Our work indicates that vascular inflammation measured with PET/CT is increased in PsA, in comparison with controls. PET/CT-quantified vascular inflammation is an imaging biomarker strongly associated with future cardiovascular events.(8) It is currently unclear whether treatment with disease-modifying drugs will temper vascular inflammation in PsA, and this will be further evaluated by longitudinal follow-up with PET/CT. Currently, there is no indication for clinical follow-up with PET/CT.

Conclusion

This is the first study to demonstrate increased vascular inflammation in PsA patients. This finding could contribute to insights to the pathophysiology of cardiovascular disease in PsA, and confirms that PsA should be regarded as a systemic inflammatory disease.

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Author Contributions

All authors listed have made substantial contributions to the study design, or the acquisition, analysis or interpretation of data, and approved the final version for publication.

Ethical approval

The TOFA-PREDICT study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the University Medical Center Utrecht (protocol code 15-429, 17-11-2015). Given the retrospective use of PET/CTs in the control group, no formal approval of this study was required as stated by the Medical Ethics Committee of the UMC Utrecht.

Informed Consent Statement

All PsA study subjects included in the TOFA-PREDICT study provided written informed consent. Given the retrospective use of PET/CTs in the control group a waiver of informed consent was in place as stated by the Medical Ethics Committee of the UMC Utrecht.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplemental information. Data are available upon reasonable request. Please contact corresponding author

Conflicts of Interest

Financial support for the PsA patients included in the TOFA-PREDICT study was provided by Pfizer. The collaboration project is co-funded by the PPP Allowance made available by Health Holland, Top Sector Life Sciences & Health, to stimulate public–private partnerships. The sponsors had no role in the design, execution, interpretation, or writing of the study.

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Supplemental material

Supplemental Table S1. Different PET/CT protocols specified per study site.

Study site	Scanner type	Radio-active tracer	kvP	Dosage radio-active tracer	Slice thickness	Reconstruction method
UMC Utrecht	Siemens Biograph mCT 40 or Siemens Biograph Vision	18F-FDG	100-120	3.0 MBq/kg (PsA) or 2.0 MBq/kg (controls)	1.5 – 3.0 mm axial slices	EARL-1
Gelre ziekenhuis	Siemens Biograph mCT 40	18F-FDG	120	1.8 MBq/kg	3.0 mm axial slices	EARL-1
Medisch Spectrum Twente	Siemens Biograph mCT 40	18F-FDG	120	Weight ≤ 90 kg 2.0 MBq/kg, with an upper limit of 75MBq Weight > 90 kg 2.5 MBq/kg	3.0 mm axial slices	EARL-1
Maastricht UMC+	GE Discovery	18F-FDG	140	3.0 MBq/kg	2.5 mm axial slices	EARL-1
VieCuri	Siemens Biograph mCT 40	18F-FDG	100	3.0 MBq/kg	5.0 mm axial slices	EARL-1

Table legend. Abbreviations: 18F-FDG = [18F]Fluorodeoxyglucose, kvP = kilovoltage peak, MBq = megabecquerel, EARL = the European Association of Nuclear Medicine Research Ltd, PsA = psoriatic arthritis

Supplemental Table S2. (Serious) Adverse Events related to PET/CT in the PsA population. PET/CT-scans acquired in the control group were part of standard clinical care.

Description of (Serious) Adverse Event	Outcome
Renal Cell Carcinoma detected with PET/CT	Resection required. DMARD-treatment was terminated.
Abdominal pseudocyst detected with PET/CT, requiring resection	Pathology showed no signs of malignancy. The surgery was complicated by a post-operative pneumonia, requiring admission to the Intensive Care Unit and non-invasive ventilation. Patient has recovered.
Pulmonary sarcoidosis detected with PET/CT	Referral to pulmonologist. Since patient had no pulmonary complaints, no further treatment was initiated.
Thyroid nodus detected with PET/CT	Referral to internal medicine specialist.

Table legend. Abbreviations: DMARD = Disease Modifying Anti-Rheumatic Drug, PET/CT = 18-fluorodeoxyglucose positron emission tomography/computed tomography, PsA = psoriatic arthritis

Chapter 8

Summary and general discussion

Key findings in this thesis

Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS)

- In clinically unaffected plantar fascia and Achilles tendon entheses of psoriasis and spondyloarthropathy patients, HEMRIS abnormalities are highly prevalent.
- In Achilles tendons of spondyloarthropathy patients with clinical enthesitis, the HEMRIS structural damage score was significantly increased.
- There was a weak association between total and structural damage HEMRIS scores and local metabolic activity on PET/CT at the Achilles tendon, in psoriasis and spondyloarthropathy patients.
- During 1-year follow up, only minimal changes in the HEMRIS were observed in psoriasis and spondyloarthropathy patients. Changes in the HEMRIS were not associated with changes in clinical disease activity.

Vascular inflammation in psoriatic disease

- Both psoriasis and psoriatic arthritis are associated with increased vascular inflammation on PET/CT.
- There is insufficient evidence for a beneficial effect of biologic treatment on vascular inflammation in psoriasis.

Summary

Part 1

The Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS) was previously developed by the Outcome Measures in Rheumatology (OMERACT) group to evaluate disease activity at the Achilles tendon and plantar fascia enthesis. In **chapter two** the results of a prospective study, evaluating the HEMRIS in a total of 38 patients diagnosed with psoriasis (Pso), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), are described. Patients were included regardless of presence or absence of clinical heel enthesitis. The HEMRIS structural damage score was significantly higher in Achilles tendons with clinical enthesitis, in comparison to Achilles tendons without clinical enthesitis (respective median scores 1.0 and 0.5; p=0.04). Also in clinically

unaffected entheses, HEMRIS abnormalities were highly prevalent, occurring in 63% of Achilles tendons and 33% of plantar fascia. There was a weak association between local inflammation at the Achilles tendon enthesis measured with positron emission tomography/computed tomography (PET/CT), and the total and structural damage HEMRIS. Overall, this study revealed a disagreement between clinical, MRI, and PET/CT findings in regards to assessment of enthesitis.

In **chapter three** the changes in HEMRIS over time in the same population of Pso, PsA, and AS patients in an observational setting were assessed. An increase in the inflammatory and structural HEMRIS was observed in respectively 17.9% and 6.0% of patients in one-year intervals. Changes in HEMRIS over time were infrequent and the change was non-significant, and not associated with clinical disease activity.

Part 2

In **chapter four** we describe the study protocol of the TOFA-PREDICT study. Because early treatment essential to prevent clinical and radiographic irreversible joint damage in PsA(1), there is an urgent clinical need to predict treatment response. In this clinical trial we aim to predict treatment response to tofacitinib, a Janus kinase (JAK) inhibitor, in patients with active PsA (defined as ≥2 swollen and ≥2 tender joints). Secondary outcome measures include treatment efficacy of different DMARDs and structural response to treatment using different imaging techniques and molecular mechanisms associated with clinical response to tofacitinib, in comparison with methotrexate and etanercept.

PsA patients who are treatment naive are randomized to tofacitinib or methotrexate. PsA patients who are resistant to treatment with disease-modifying antirheumatic drugs (DMARDs) are randomized to tofacitinib or etanercept. The study has a multi-omics systems medicine approach, integrating clinical, molecular, and imaging data to define pretreatment profiles (imaging parameters included) associated with treatment response. Imaging techniques applied in the TOFA-PREDICT study are MRI-scans of both ankles, whole body FDG PET/CT and conventional radiographs of the hands and feet. We use a two-step data analysis approach to both discover and validate pretreatment models.

Chapter five addresses differences in ankle MRI outcomes (HEMRIS(2)), PET/CT outcomes (vascular inflammation and synovitis), and radiographies of hands and feet (assessed using the Sharp van der Heijde score, adjusted for PsA(3)) in active PsA patients included in the TOFA-PREDICT study who are either DMARD-naïve of DMARD-resistant. There was a minimal difference (approximately 0.5 on a scale of

0-9, p=0.04) in HEMRIS structural damage at the Achilles tendon in DMARD-resistant PsA patients, in comparison with the DMARD-naïve group. The minimal clinically important difference in HEMRIS is currently unknown. After correction for clinical parameters (age, BMI, current smoking status, gender, times since first diagnosis of PsA, times since first diagnosis of psoriasis), this difference was no longer observed. PET/CT and radiography imaging outcomes were equal between DMARD-naïve and DMARD-resistant patients.

Part 3

In **chapter six** a systematic review and two meta-analyses were performed to assess whether patients with psoriasis had increased vascular inflammation in comparison with the general population, and if treatment with systemic medication reduced vascular inflammation. Studies were included with patients with moderate to severe psoriasis, since systemic treatment is mainly indicated for this patient category. Pooled results demonstrated significantly increased vascular inflammation in psoriasis patient at the entire aorta, and thoracic and suprarenal aortic segments, but not for the infrarenal aorta (p=0.06). We found insufficient evidence for a beneficial effect of adalimumab (a tumor necrosis factor alpha (TNF-α) inhibitor), and secukinumab (an interleukin(IL)-17A inhibitor) on PET/CT measured aortic inflammation. One study, by Gelfand and colleagues, reported a reduction in vascular inflammation in psoriasis patient after treatment with ustekinumab (an IL-12 and IL-23 inhibitor).(4)

Thus far, research on vascular inflammation was focused on psoriasis, rather than PsA specifically. In **chapter seven** we demonstrated that aortic inflammation on PET/CT was elevated in a population with active PsA, in comparison with a control group. This finding remained significant after correction for gender, age, body mass index, mean arterial pressure, and aortic calcification. We did not find any association between aortic inflammation, and clinical measures for activity (tender and swollen joint counts, psoriasis body surface area, Leeds Enthesitis Index (LEI), disease duration), or laboratory parameters (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)).

General discussion

Pathophysiology of enthesitis in spondylarthritis

Inflammation at the enthesis (enthesitis) is common in spondylarthritis (SpA), leads to functioning impairment and can be difficult to control.(5,6) Unfortunately, it is not yet fully understood why SpA patients are more likely to develop enthesitis.

The concept of an enthesis organ is important to understand the pathophysiology and imaging features of enthesopathies.(5–8) The enthesis is the anatomical location were tendons and ligaments insert the bone surface, linking connective tissue with the skeleton. Entheses provide stability (in case of ligaments) or transduce mechanical forces (in case of tendons). It has been proposed that the enthesis is part of a larger anatomical group referred to as the 'enthesis organ', consisting of the enthesis and its adjacent structures (fibrocartilages, bone, bursa, fat pad). The rationale of the enthesis organ is that both the enthesis and its adjacent structures aid in the transduction of mechanical stress at the interface of soft- and hard-tissue. (5–8)

Inflammation at the enthesis, or enthesitis, can occur in healthy individuals as a result of mechanical overload. Enthesitis is also a key clinical feature in PsA and AS.(5,6). It is thought that individuals with SpA have a lower threshold for mechanical stress at the enthesis, which triggers an inflammatory cascade. A similar process, also known as the Koebner phenomenon, is observed in psoriasis, where mechanical irritation causes local skin disease.(9,10) Potential explanations for the apparent low threshold for enthesitis development in SpA include genetic, immunological, and microbial factors. The relative contribution of each component (genetic, immunological, or microbial) may differ per individual patient. In some patients, genetic factors may be the dominant trigger, and in other patients environmental factors.(11) Genetic susceptibility in SpA is predominantly MHC-region-based (specifically HLA-B27 for AS), but there is also an association with genes involved in the generation of cytokines.(12) The critical role of the microbiome for onset of enthesitis in SpA is suggested in murine models, that demonstrated that enthesopathy does not develop in germfree mice(13,14).

It has been proposed that enthesitis could trigger synovitis, in which enthesitis is considered an important factor in overall disease pathogenesis in PsA and AS.(15) This hypothesis is supported by several murine studies, where either TNFα- in combination with mechanical stress - or IL-23/17 dysregulation, lead to entheseal inflammation, followed by synovitis.(16,17) Research on imaging the enthesis will be helpful to understand preclinical phases of PsA and other forms of SpA in humans. Therefore,

in this thesis imaging methods were used aiming to get more grip on early enthesitis and its pathophysiology in (patients at risk for) spondylarthritis.

In **chapter two**, we identified that changes at the enthesis, detected by magnetic resonance imaging (MRI), occurred already frequently in psoriasis patients: the Heel Enthesitis MRI Scoring System (HEMRIS) structural or inflammatory abnormalities (cut-off value ≥1) were observed in 65% of Achilles tendons and 35% of plantar fascia. An important limitation of this study is that we did not have data on the occurrence of MRI findings at the enthesis in healthy subjects. Thus far, there are no publications about the occurrence of HEMRIS findings in asymptomatic, healthy subjects. This remains to be evaluated in future studies in order to evaluate the specificity of findings. In support of our finding is that an ultrasound study reported higher power doppler signal grades at the entheses located at the hands, knees, and ankles in psoriasis patients suggesting more disease activity at the entheses in comparison with healthy controls aged <60 years.(18) The main hypothesis for the study was that subclinical enthesopathy – detected by MRI - could predict PsA in psoriasis patients, or predict disease activity in SpA patients. In **chapter three,** we found no differences in HEMRIS results at time of inclusion in the 2 psoriasis patient that developed PsA during two years longitudinal follow-up, in comparison with the 9 psoriasis patients that did not develop PsA. A possible explanation for our negative study is obviously the low number of patients included and the relatively short follow-up duration. In a larger ultrasound study in 118 patients with psoriasis, it was demonstrated that subclinical ultrasound-defined active enthesitis was associated with clinical PsA development during longitudinal follow-up.(19) The role of HEMRIS in possible detection of subclinical enthesitis remains to be determined, for example using data from the prospective TOFA-PREDICT study (see chapter four).

In **chapter three** we observed that changes in the HEMRIS were not associated with changes in general disease activity in PsA (assessed using Minimal Disease Activity), or AS (assessed using the Bath Ankylosing Spondylitis Disease Activity Index). This finding could potentially be explained by the relatively low clinical disease activity and mild HEMRIS abnormalities at baseline and during longitudinal follow-up. Furthermore, we imaged only the Achilles tendon and plantar fascia insertions, while throughout the body over 100 entheses can be identified. In future studies whole-body MRI may provide an overview of global entheseal inflammation, provided sufficient resolution can be obtained. An important limitation of whole-body MRI is the limited details on the small entheses within a feasible scanning time.(20) Therefore, choices on sites of interest need to be made in order to perform the optimal imaging strategy

to diagnose (subclinical) enthesitis. In addition to whole-body MRI, PET/CT may be a promising alternative for detection of whole-body enthesitis in patients with SpA. However, the clinical relevance of PET/CT-detected enthesitis remains unclear. In **chapter two**, we found no differences between Achilles tendon and plantar fascia entheses with and without clinical enthesitis with regard to local 2deoxy218Ffluoro-dglucose (18F-FDG)-uptake. Other studies on PET/CT-assessment of enthesitis in SpA are scarce. A study, using PET/CT with the radiotracer 18F-sodium fluoride (18F-NaF), found that 70.5% of the PET-positive entheses in a population of 16 PsA patients were clinically negative.(21) In future research, it would be interesting to further evaluate the clinical relevance of (subclinical) enthesitis on PET/CT, by determining if it is predictive of onset of clinical enthesitis and/or general SpA disease activity.

Imaging the enthesis in patient care and clinical studies

Identification of enthesitis is important for diagnosing PsA and monitoring of treatment response. (22-25) Clinical assessment of enthesitis is performed by evaluation of local tenderness after applying pressure. Clinical assessment of enthesitis has both limited sensitivity and specificity.(23,26) In **chapter two** we compared the MRI scoring model HEMRIS with clinical assessment of enthesitis and local inflammation detected by PET/CT. We found a large discrepancy between MRI compared to clinical examination and PET/CT. Plantar fascia with and without clinical enthesitis did not differ in HEMRIS scores. Achilles tendons with clinical enthesitis had higher HEMRIS structural damage scores, in comparison with Achilles tendons without clinical enthesitis, but no difference was observed in HEMRIS inflammation and total scores. Although we found that subclinical HEMRIS findings are frequently observed, we noted in **chapter three** that HEMRIS abnormalities were not associated with the occurrence of future clinical enthesitis or bone erosions at one-year intervals. At the moment, there is insufficient evidence to recommend the HEMRIS for diagnosis of enthesitis in psoriasis or SpA patients. In the future, a threshold value of the HEMRIS for clinical relevance would be of added value. When we compared the HEMRIS with PET/CT in **chapter two**, we found weak correlations between the structural and total HEMRIS at the Achilles tendon and local metabolic uptake (resp. rs=0.25, p=0.03, and rs=0.26, p=0.03). Possible explanations are that PET/CT is not sensitive enough to detect (small) metabolic changes at the enthesis, or that HEMRIS findings are not metabolically active.

In **chapter five** we evaluated whether failure of previous treatment with a DMARD influenced HEMRIS outcomes, at baseline in PsA patients included in the

TOFA-PREDICT study. We hypothesized that patients that had previously failed a DMARD would have higher HEMRIS outcomes, in comparison with patients that had not. However, we did not identify baseline differences in the HEMRIS in PsA patient with or without previous DMARD treatment, after correction for clinical patients' characteristics (age, BMI, current smoking status, gender, times since first diagnosis of PsA, times since first diagnosis of psoriasis). This finding may indicate that failure of a DMARD is not independently associated with increased inflammation or structural damage observed with HEMRIS. It also learned us that combining DMARD-naïve and DMARD-resistant patients (after correction of demographics) is a valid approach in further analyses.

Sensitivity to change is an important aspect of outcome measures. The sensitivity of HEMRIS to change was partly evaluated only for its inflammatory features.(27) In **chapter three** we reported only little HEMRIS inflammatory and structural changes after one-year-intervals in an observational cohort of psoriasis and SpA patients. One previous clinical trial in PsA and axial SpA patients with MRI abnormalities at baseline found a higher reduction in the HEMRIS total entheseal inflammation score in patients treated secukinumab compared to placebo, but this finding was not significant. Noteworthy, the mean changes in structural damage score were minimal in both groups.(28) In the TOFA-PREDICT clinical trial, as described in **chapter four**, changes in the HEMRIS in active PsA patients, that are either DMARD-naïve or cs-DMARD resistant, will be evaluated. DMARD-naïve patients will be randomized to treatment with tofacitinib or methotrexate. Cs-DMARD resistant patients will be randomized to treatment with tofacitinib or etanercept. Ankle MRIs will be acquired at baseline, after 16 weeks and after one year of longitudinal follow-up. At this moment, the role of ankle MRI and PET/CT in assessment of enthesitis clinical trials in PsA is unresolved.

Pathophysiology of cardiovascular disease and imaging of vascular inflammation in psoriatic disease

Psoriasis and PsA are associated with an increased risk of cardiovascular disease (CVD) in comparison with the general population.(29,30) This increased risk is attributed to the presence of chronic systemic inflammation in psoriatic disease.(31) The idea that inflammation in psoriatic disease is not 'skin-deep' or 'joint-deep' but systemic, represents a paradigm shift, and is supported by increased levels of inflammatory cytokines, such as interferon (IFN)-α, IL-22, the IL-23/IL-17 axis, and TNF-α. Furthermore, in psoriatic disease patients elevated levels of acute phase reactants such as C-reactive protein (CRP) may be observed. Excessive inflammatory

stimuli, like the systemic inflammation observed in psoriatic disease, can affect the vascular endothelium and promote endothelial dysfunction.(32,33) Endothelial dysfunction is considered the first step in the initiation of atherosclerosis, resulting in impaired vascular relaxation, increased endothelial permeability, increased leukocyte adhesion, and the development of a prothrombotic state.(34) Elevated endothelial dysfunction has been observed in ultrasound studies performed in psoriasis and PsA patients.(35,36) Finally, it is possible that systemic inflammation and traditional risk factors, that are elevated in the psoriasis and PsA population (28,29), act synergistically in accelerating atherosclerosis. To investigate the occurrence of vascular inflammation in psoriatic disease we performed a meta-analysis of PET/CT studies performed in psoriasis patients in comparison with controls (**chapter six**), and an original study comparing vascular inflammation in PsA patients specifically in comparison with controls (**chapter seven**).

In **chapter six** we performed a meta-analysis, and demonstrated increased aortic inflammation on PET/CT in patients with moderate-severe psoriasis, in comparison with controls. In **chapter seven** we demonstrate that aortic inflammation is increased in patients with active PsA (defined as ≥2 swollen and tender joints), in comparison with controls. This finding remained significant after correction or traditional CVD risk factors (age, gender, body mass index, and mean arterial pressure), and aortic calcification as a measure of atherosclerosis burden. In contrast to the clinical aortitis that is observed in SpA, vascular inflammation in psoriatic disease is low-grade, but apparently also not the mild inflammation that is seen in atherosclerotic lesions, although we did not correct for non-calcified lesions. A limitation of the study conducted in chapter seven was that data on the control group were collected retrospectively, and not all possible confounders, such as smoking and lipid spectrum, could be identified. However, our observation was that the inflammation remained higher after correction for calcifications. Overall, these findings further support the concept of involvement of the arterial wall in psoriatic disease. In addition to aggressive cardiovascular risk factor management, anti-inflammatory therapy may be needed. In atherosclerosis there is currently great interest in colchicine, but whether this would resolve the excessive inflammation in psoriatic disease remains to be determined.

When reviewing the literature on the effects of biologic treatment on vascular inflammation in psoriasis patients in **chapter six**, we found conflicting results. A small randomized controlled trial (RCT; n=30) reported a greater reduction in ascending aortic inflammation in psoriasis patients treated with the TNF-inhibitor adalimumab

compared to patients receiving non-systemic treatment, in whom no reduction in aortic inflammation was observed.(38) This finding was not repeated in two larger RCTs examining vascular inflammation of the ascending aorta and the entire aorta, respectively.(39,40) However, patients included in the study that reported a positive effect of adalimumab were required to have a positive history CVD, or at least three risk factors for CVD.(41) This could have confounded results since PET/CT detected vascular inflammation is associated with cardiovascular events.(42) Two other studies have assessed the impact of biologic treatment, intervening at the IL-23/IL-17 axis, on vascular inflammation in psoriasis. One reported a greater reduction in aortic inflammation after 12 weeks of treatment with ustekinumab, an IL-12 and IL-23-inhibitor, in comparison with patients treated with placebo, in whom an increase in vascular inflammation was observed. Nevertheless, after 52 weeks the effect of ustekinumab on aortic inflammation was diminished.(4) Another study found no beneficial effect of secukinumab, an IL-17A-inhibitor, on aortic inflammation in psoriasis patients.(43)

The finding that various targeted biologic therapies, with proven efficacy in treatment of psoriasis, do not reduce vascular inflammation is unexpected. Treatment with adalimumab does reduce blood-based biomarkers CRP and IL-6, that may be elevated in psoriasis, but are also markers of cardiovascular risk.(44) Furthermore, prior observational research indicates that TNF-inhibitors may reduce the risk of cardiovascular disease in psoriasis patients. However, these studies have limitations, such as selection bias and information bias, inherent to the observational study design.(45,46) Vascular inflammation detected by PET/CT can improve rapidly, within 3 months after initiation of treatment with statins.(47,48) Based on the currently available evidence it is not recommended to initiate biologic treatment for psoriasis to reduce cardiovascular risk.

Taken together, aortic vascular inflammation detected by PET/CT is elevated in psoriatic disease. This finding is supportive of the hypothesis that inflammation in psoriatic disease is not limited to skin and joints, but also affects the cardiovascular system. This could eventually lead to accelerated atherosclerosis. Systemic treatment has not been proven effective in reducing vascular inflammation in psoriasis and precise molecular mechanisms causing vascular inflammation in psoriatic disease remain unknown. Larger randomized-controlled trials with longer follow-up duration would be required to accurately determine the effect of different systemic treatments on cardiovascular risk in psoriatic disease. The TOFA-PREDICT study (study protocol described in **chapter four**) is, to our knowledge, the first study to assess the effect

of systemic treatment (with methotrexate, the TNF-α-inhibitor etanercept, and the Janus kinase (JAK) inhibitor tofacitinib) on vascular inflammation PsA.

Conclusion

In conclusion, although many further steps are needed, the works presented in this thesis show that subclinical disease is common at enthesis of Pso and SpA patients and that the inflammatory reaction may also involve non-musculoskeletal organs such as the arterial wall. With the TOFA predict study we aim to deliver evidence-based imaging predictors of treatment response and learn more on the relevance of subclinical findings on MRI and PET/CT.

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Appendices

Nederlandse samenvatting, list of publications,
dankwoord, Curiculum Vitae

Nederlandse samenvatting

Artritis psoriatica is een heterogeen ziektebeeld, dat gekenmerkt wordt door psoriasis van huid en/of nagels, in combinatie met gewrichtsontstekingen (van perifere gewrichten, bekken, of wervelkolom), dactylitis (zwelling van een hele teen of teen) en/of enthesitis (ontsteking op de plaats waar pezen/ligamenten aanhechten aan het botoppervlak). Artritis psoriatica behoort tot de groep reumatische aandoeningen die we aanduiden als 'spondylartritis', waartoe ook onder andere ankyloserende spondylitis, reactieve artritis en artritis in het kader van inflammatoire darmziekten behoren. De 'spondylartritiden' hebben een gedeeltelijk overeenkomende genetische achtergrond en een overlap in klinische symptomen.

De hiel is vanwege de hoge mechanische druk een veelvoorkomende lokalisatie van enthesitis bij mensen met artritis psoriatica of andere vormen van spondylartritis. Om enthesitis van de hiel beter in beeld te brengen ontwikkelde de Outcome Measures in Rheumatology (OMERACT) groep het Heel Enthesitis Magnetic Resonance Imaging Scoring System (HEMRIS). In **hoofdstuk twee** beschrijven we de resultaten van een prospectieve studie, uitgevoerd bij in totaal 38 patiënten met de diagnose psoriasis (Pso), psoriatische artritis (PsA) en ankyloserende spondylitis (AS). De patiënten werden geïncludeerd ongeacht de aan- of afwezigheid van klinische enthesitis van de plantaire fascie ('hielspoor') of de Achillespees. De HEMRIS structurele schade score was significant hoger in Achillespezen met klinische enthesitis, in vergelijking met Achillespezen zonder klinische enthesitis (respectievelijke mediaan scores 1,0 en 0,5; p=0,04). Maar ook in klinisch niet-aangedane entheses kwamen HEMRIS-afwijkingen veel voor, namelijk in 63% van de Achillespezen en 33% van de fascia plantaris. Er was een zwakke associatie tussen lokale ontsteking aan de Achillespees enthese, gemeten met positron emissie tomografie/computed tomografie (PET/CT), en de totale en structurele schade HEMRIS scores. Over het geheel genomen toonde dit onderzoek een discrepantie aan tussen de MRI bevindingen ter plaatse van de entheses van de hiel, en bevindingen bij lichamelijk onderzoek en met PET/CT.

In **hoofdstuk drie** evalueerden we de veranderingen in de HEMRIS na verloop van tijd in dezelfde populatie van Pso-, PsA- en AS-patiënten als geïncludeerd in hoofdstuk twee, in een observationele setting. Een toename in de inflammatoire en structurele HEMRIS werd waargenomen in respectievelijk 17,9% en 6,0% van de patiënten, gemeten in intervallen van één jaar. Veranderingen in HEMRIS in de loop van de tijd kwamen niet vaak voor, de veranderingen in scores waren daarnaast niet statistisch significant, noch geassocieerd met klinische ziekteactiviteit van Pso, PsA of AS. De

klinische betekenis van de frequente HEMRIS afwijkingen die waargenomen worden is daarom nog onduidelijk, en zal verder bepaald moeten worden met prospectieve studies, bijvoorbeeld in de TOFA-PREDICT studie.

In **hoofdstuk vier** beschrijven we het studieprotocol van de TOFA-PREDICT studie. Omdat tijdige effectieve behandeling essentieel is om onomkeerbare gewrichtsschade bij patiënten met PsA te voorkomen, zou het nuttig zijn om de individuele respons op verschillende behandelingen te kunnen voorspellen. In deze klinische studie willen we onder andere de respons op behandeling met de Janus kinase (JAK)-remmer tofacitinib voorspellen bij patiënten met actieve PsA (gedefinieerd als tenminste 2 gezwollen en tenminste 2 gevoelige gewrichten). Daarnaast kijken we naar de effectiviteit van verschillende behandelingen voor PsA, zowel wat betreft klinische symptomen als met geavanceerde beeldvormende technieken, en proberen we moleculaire mechanismen die ten grondslag liggen aan behandeleffecten te ontrafelen.

De TOFA-PREDICT studie kent vier verschillende behandelarmen. PsA-patiënten die nooit eerder behandeld zijn met zogenaamde 'disease-modifying antirheumatic drugs' (DMARDs) worden gerandomiseerd naar behandeling met de medicijnen tofacitinib of methotrexaat. PsA-patiënten die actieve ziekte hebben ondanks eerdere behandeling met een DMARD worden gerandomiseerd naar behandeling met tofacitinib of etanercept. Daarnaast continueren zij hun behandeling met een conventionele DMARD (methotrexaat, sulfasalazine of leflunomide).

Het TOFA-PREDICT onderzoek maakt gebruik van een 'systems medicine' aanpak, waarbij klinische, moleculaire en beeldvormingsgegevens worden geïntegreerd om profielen te definiëren die verband houden met de respons op behandeling. Beeldvormende technieken die worden toegepast in de TOFA-PREDICT-studie zijn MRI-scans van beide enkels, PET/CT van het hele lichaam en röntgenfoto's van de handen en voeten. We analyseren de data van de studie in twee delen, waarbij we bij het eerste cohort modellen ontwikkelen om behandeleffecten te voorspellen, en bij het tweede gedeelte van het cohort deze modellen valideren.

Hoofdstuk vijf behandelt verschillen in MRI-scores (o.a. de HEMRIS), PET/CT-uitkomsten (vasculaire ontsteking en gewrichtsontstekingen) en röntgenfoto's van handen en voeten tussen patiënten met actieve PsA die ofwel DMARD-naïef ofwel DMARD-resistent zijn. Alle patiënten zijn geïncludeerd in de TOFA-PREDICT studie, deze analyse betreft de baseline-gegevens.

Er werd een minimaal verschil (ongeveer 0,5 op een schaal van 0-9, p=0,04) in structurele schade waargenomen met HEMRIS, tussen DMARD-resistente PsA-

patiënten, in vergelijking met de DMARD-naïeve groep. Het minimaal klinisch relevante verschil in HEMRIS is momenteel onbekend. Na correctie voor klinische parameters (leeftijd, BMI, huidige rookstatus, geslacht, tijd sinds eerste diagnose van PsA, en tijd sinds eerste diagnose van psoriasis) werd dit verschil niet langer gezien. De uitkomsten van PET/CT en radiografie waren gelijk tussen DMARD-naïeve en DMARD-resistente patiënten. De data van deze studie suggereert dat het falen van behandeling met één DMARD geen verhoogde kans geeft op structurele of inflammatoire veranderingen, beoordeeld met verschillende beeldvormingstechnieken.

Patiënten met psoriasis en artritis psoriatica hebben een verhoogd cardiovasculair risico. Mogelijk is dit het gevolg van systemische inflammatie. In **hoofdstuk zes** hebben we een systematische review en twee meta-analyses uitgevoerd om na te gaan of patiënten met psoriasis meer vasculaire inflammatie hadden in vergelijking met de algemene bevolking, en of behandeling met systemische medicatie de vasculaire inflammatie verminderde. We includeerden studies verricht in patiënten met matige tot ernstige psoriasis, omdat systemische behandeling voornamelijk is geïndiceerd voor deze patiëntencategorie. Gepoolde resultaten toonden significant verhoogde vasculaire inflammatie aan bij psoriasispatiënten ter plaatse van de gehele aorta, en thoracale en suprarenale aortasegmenten, maar niet van de infrarenale aorta (p=0,06). We vonden onvoldoende bewijs voor een gunstig effect van adalimumab (een tumornecrosefactor alfa (TNF-α) remmer) en secukinumab op vasculaire inflammatie. Eén onderzoek, door Gelfand en collega's, rapporteerde een vermindering van vasculaire ontsteking bij psoriasispatiënten na behandeling met ustekinumab.(4)

Tot nu toe was het onderzoek naar vasculaire inflammatie gericht op psoriasis en niet specifiek op PsA. In hoofdstuk zeven toonden we aan dat inflammatie van de aorta op PET/CT verhoogd is in een populatie met actieve PsA, in vergelijking met een controlegroep. Deze bevinding bleef significant na correctie voor geslacht, leeftijd, body mass index, bloeddruk en aortaverkalking. We vonden geen verband tussen vasculaire inflammatie en klinische uitingen van ziekte-activiteit van PsA (aantal pijnlijke en gezwollen gewrichten, psoriasis lichaamsoppervlak, Leeds Enthesitis Index, ziekteduur), of laboratoriumparameters (bezinkingssnelheid en C-reactief proteïne).

Concluderend kunnen we stellen dat, hoewel er nog veel stappen nodig zijn, het in dit proefschrift gepresenteerde werk heeft aangetoond dat subklinische ziekte veel voorkomt bij de enthesis van Pso- en SpA-patiënten en dat de ontstekingsreactie ook niet-musculoskeletale organen zoals de vaatwand van de slagaders kan betreffen. Met

de TOFA-PREDICT studie willen we de behandelrespons op medicatie voorspellen, o.a. met beeldvormende technieken, en meer te weten komen over de relevantie van subklinische bevindingen op MRI en PET/CT.

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List of publications

List of publications:

van Campen, J. S., Jansen, F. E., Kleinrensink, N. J., Joëls, M., Braun, K. P. J., & Bruining, H. (2015). Sensory modulation disorders in childhood epilepsy. *Journal of Neurodevelopmental Disorders*, *7*(1). https://doi.org/10.1186/s11689-015-9130-9

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Curriculum Vitae

Nienke Josephine Kleinrensink (Hamburg, 1989) grew up in Voorburg and later in Breda, and finished her secondary school at the Stedelijk Gymnasium in Breda in 2007. After a year of Spanish courses in Salamanca, Spain, and traveling in South America, she studied Medicine at the University of Utrecht from 2008-2015. Highlights of her study Medicine included an internship Gynaecology in Buenos Aires, at Hospital de Clínicas José de San Martín, and an elective internship at the Rheumatology department of the UMC Utrecht. After finishing her studies in 2015, she enrolled in training to become a rheumatologist. She started as a resident Internal Medicine at the St. Antonius Ziekenhuis in Nieuwegein and Utrecht. From 2018 until 2023, Nienke interrupted her residency to work as a PhD-candidate at the UMC Utrecht under supervision of professor de Jong and professor Lafeber, with co-guidance of Wouter Foppen and Julia Spierings. During her PhD-trajectory, Nienke coordinated the imaging logistics of the clinical multicenter study 'TOFA-PREDICT'. Some of the work of this thesis was selected for presentation at the conferences of the European League Against Rheumatism (EULAR). Nienke currently works as a resident Rheumatology at the Sint Antonius Ziekenhuis and the UMC Utrecht. She lives in Utrecht with her partner Michiel and their son Samuel (2021).