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ORIGINAL RESEARCH

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/CT (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 patients with PsA in comparison with controls (mean target-to-background ratio for entire aorta, respectively, 1.63±0.17 vs 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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with psoriatic arthritis (PsA) are at increased risk of developing cardiovascular disease.

WHAT THIS STUDY ADDS

⇒ This is, to our knowledge, the first study to demonstrate increased vascular inflammation, assessed on 18-fluorodeoxyglucose positron emission tomography/CT, in PsA patients in comparison with controls.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The finding that PsA patients have increased vascular inflammation provides further insight into the pathophysiology of cardiovascular disease in PsA.

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 a 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 / computed 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.

PsA patients

Patients with PsA were included in the TOFA-PREDICT study, a multicentre 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[15] were aged 18–75 years, had a disease duration of at least 8 weeks and showed evidence of active peripheral arthritis (≥2 swollen joints and ≥2 tender joins). Detailed inclusion 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 1 hour later. A non-contrast-enhanced low-dose CT was performed for coregistration and attenuation correction. Due to the multicentre study design, kilovoltage peak, slice thickness and dosing of ^{18}F-FDG varied, depending on local protocols and devices (online supplemental table S1). PET/CT reconstructions were compliant to European Association of Nuclear Medicine Research (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 University Medical Center (UMC) Utrecht under supervision of professor de Jong. PET/CT scans without an EARL reconstruction and acquired with a prescan serum glucose of 10 mmol/L or higher were excluded from the analysis.

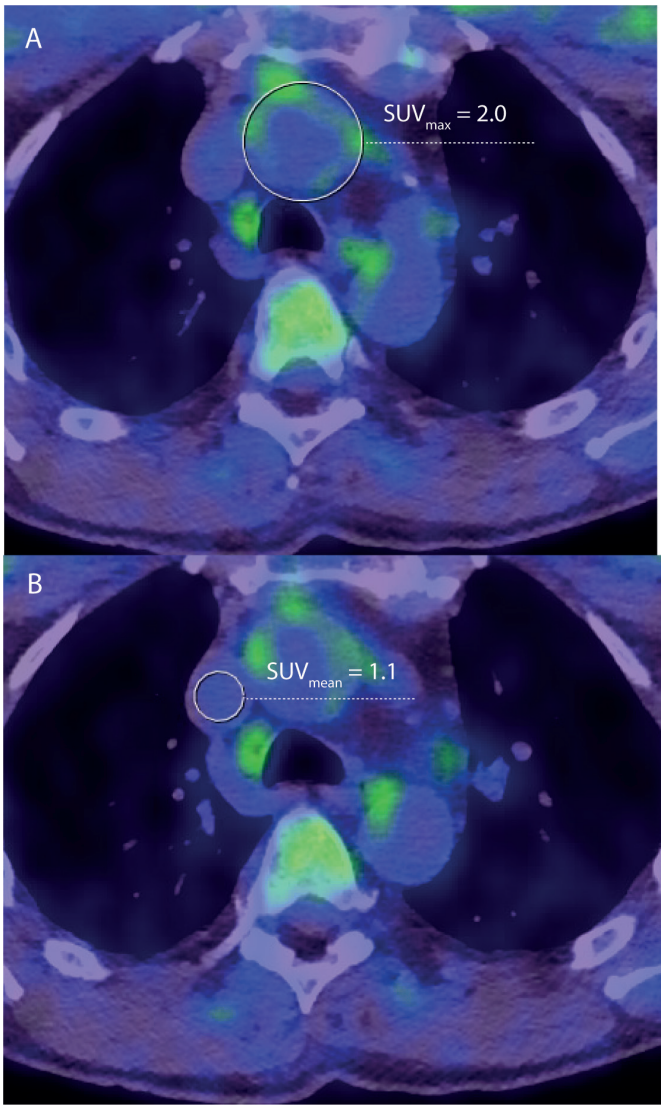

Figure 1 Figure showing fused PET/CT images in axial setting. (A) Placement of region of interest around the external aortic contour for measurement of the maximum standardised uptake value (SUVmax). This measurement is repeated along the entire vessel. (B) Placement of region of interest inside the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

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 standardised 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 SUV_{max} in the aorta was measured per slice and then averaged to produce the SUV_{max} for the entire aorta and per aortic segment (ascending aorta, aortic arch, descending aorta, suprarenal abdominal aorta and

infrarenal abdominal aorta). The SUV_{mean} for background measurement was derived by calculating the mean of 6–8 ROIs in the superior vena cava (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 SUV_{max} and SUV_{mean} 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 to 0.996).

We quantified arterial calcifications of the aorta on consecutive axial slices of the 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 Pso 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 CVDs, BMI, glucose level and blood pressure.

Statistical analysis

Summary statistics are reported as mean±SD for normally distributed variables, median and 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, BMI, 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. The 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 disease-modifying antirheumatic drugs (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 V.26 (IBM SPSS Statistics, IBM).

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 (online supplemental 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, 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 Disease Activity index for Psoriatic Arthritis (DAPSA) scores (n=73), 90.3% had moderate to high disease activity. Skin disease was limited in 88% of patients, with less than 3% BSA involvement. A full overview of patients' characteristics is presented in table 1. Adverse events related to PET/CT imaging are reported in online 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).

Table 1 Patients' characteristics

Characteristic*	PsA (N=75)	Controls (N=40)	P value
Age, years, median (IQR)	53 (46–59)	52 (42–59)	0.353†
Male sex, n	43 (57.3)	23 (57.5)	1.000‡
BMI, kg/m^2, mean±SD	28.4±4.9	25.9±4.0	0.008§
MAP, mean±SD	102.8±11.6	98.5±13.9	0.090§
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‡
Hyperlipidaemia, n	1 (1.3)	2 (5.0)	0.277‡
Diabetes, n	2 (2.7)	0	0.542‡
Myocardial infarction, n	2 (2.7)	0	0.542‡
Cerebrovascular event, n	0	1 (2.5)	0.348‡
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‡

*Values are expressed as n (%) unless stated otherwise.
†Mann-Whitney U test.
‡Fisher's exact test.
§Independent samples t-test.
bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; BSA, body surface area; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; LDL, Low-Density Lipoprotein; LEI, Leeds Enthesitis Index; MAP, mean arterial pressure; NA, not available; PsA, psoriatic arthritis; SJC, swollen joint count; TJC, tender joint count.

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, CRP or 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).

DISCUSSION

This study confirmed our hypothesis that vascular inflammation quantified with PET/CT is increased in PsA compared with 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] While currently limited data are available on vascular inflammation in PsA, increased

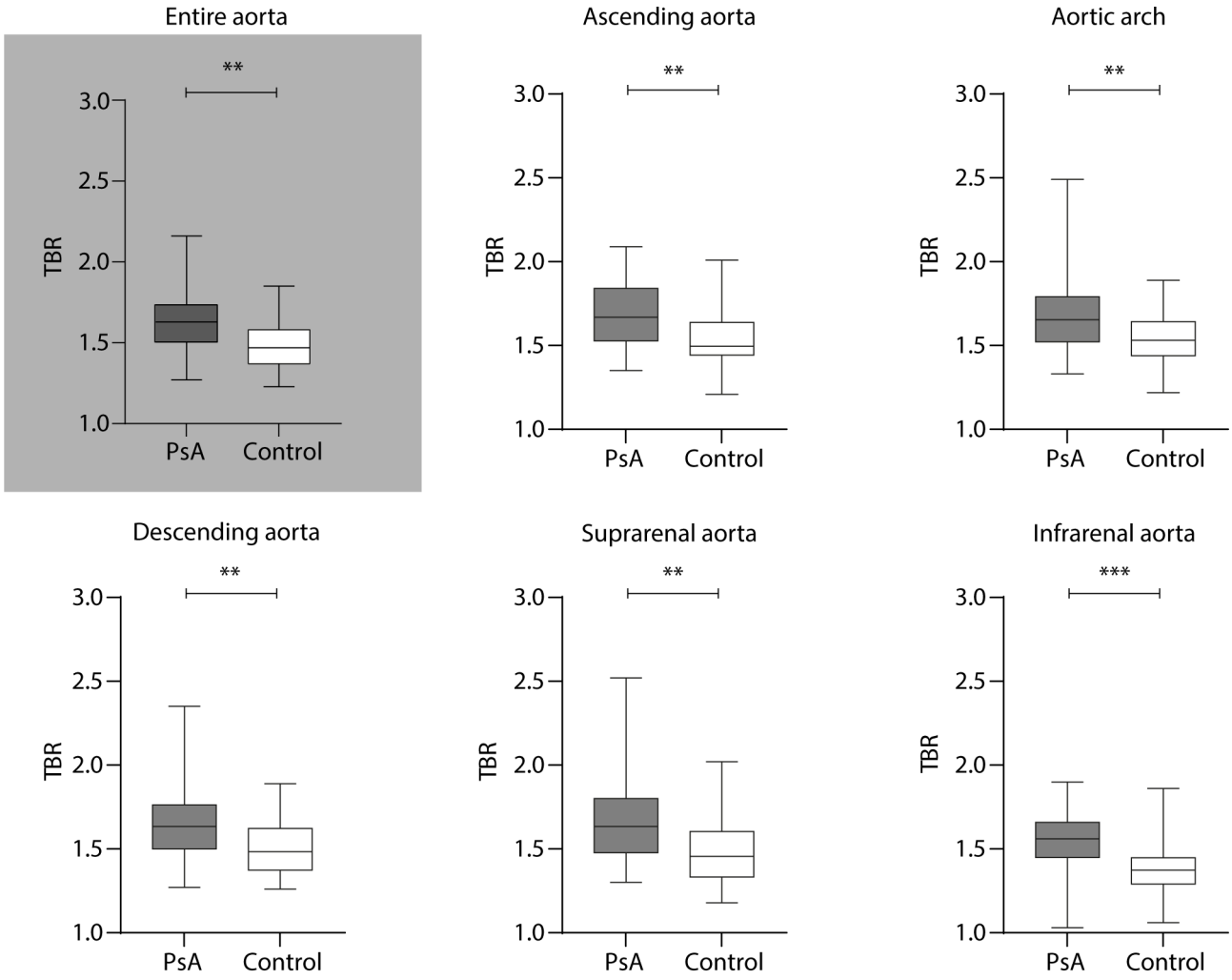

Figure 2 Increased vascular inflammation in the entire aorta and all separate aortic segments, assessed with the TBR, in psoriatic arthritis in comparison with controls. PsA, n=75 (total aortic segments measured=366), controls, n=40 (total aortic segments measured=198). Lower and upper fences are the 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<0.01, ***p<0.001. PsA, psoriatic arthritis; TBR, target-to-background ratio.

atherosclerosis and CVD 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 this 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 MRI), could be of added value, since CT does not capture non-calcified plaques.[22 29]

Table 2 Vascular inflammation (TBR) in PsA and controls

Aortic segment	PsA (N=75)	Controls (N=40)	Unadjusted analysis (p value)*	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)

Values are expressed as mean±SD unless stated otherwise.

*Independent samples t-test.
BMI, body mass index; MAP, mean arterial pressure; PsA, psoriatic arthritis; TBR, target-to-background ratio.

Study limitations

There are certain limitations to the current study. Since the data for controls were 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. Second, due to the multicentre study setting and the use of retrospective controls, PET/CT acquisition protocols varied across sites, and between PsA patients and controls (online supplemental table 1). We, however, performed measurements on EARL reconstructions to harmonise 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, except the infrarenal aorta, which could be considered as active inflammation according to previously proposed criteria, 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 CVD in PsA and confirms that PsA should be regarded as a systemic inflammatory disease.

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Contributors Methodology: NJK, PAdJ and WF; formal analysis, NJK; investigation, NJK, NS, HEV and AH; data curation, NJK and NS; writing—original draft preparation, NJK; writing—review and editing, NJK, JS, HEV, KPMS, AH, MH,

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Competing interests KPMS: consulting/advisory relationship: Bristol-Myers Squibb, Merck Sharp and Dome, Abbvie, Pierre Fabre, Novartis, Sairopa. Honoraria received: Novartis, Roche, Merck Sharp and Dome. Research funding: TigaTx, Bristol Myers Squibb, Philips. All paid to the institution and outside the submitted work. PAdJ has a research collaboration with Vifor Pharma and Philips Healthcare. WF received research grants unrelated to the topic of the present study from Novo Nordisk and Pfizer, which were paid to the institution. HEV reports having received grants, consulting fees or honorarium from AbbVie, Boehringer Ingelheim, Novartis, Pfizer, UCB, Janssen and Galapagos; all outside the submitted work.

Patient consent for publication Not applicable.

Ethics 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.

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

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