Short running head: Macrophage PET in early RA

Full title: Whole body macrophage PET imaging for disease activity assessment in early rheumatoid arthritis

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ABSTRACT

Objective

To investigate the potential of whole body positron emission tomography/computed tomography (PET/CT) with a macrophage tracer to image arthritis in patients with early rheumatoid arthritis (RA).

Methods

Thirty-five previously untreated, clinically active early RA patients underwent whole body PET/CT scanning with the macrophage tracer (*R*)-[^{11}C]PK11195 in addition to clinical assessment (Disease Activity Score of 44 joints [DAS44]). Tracer uptake was assessed quantitatively as standardized uptake values (SUV). In addition, two readers blinded to clinical assessment visually scored tracer uptake in joints. Clinical and PET variables were compared using Cohen's kappa, linear regression/correlation, and T-tests where appropriate.

Results

All but one patient showed enhanced tracer uptake in at least 1 joint. Twelve percent of all joints (171/1470) was visually PET positive, most frequently the small joints in feet (40%) and hands (37%), followed by wrists (15%). Correlations of visual scores with clinical findings both at patient and joint levels were absent or weak. In contrast, average SUV in hands, feet and whole body showed significant correlations with DAS-44 scores, with the best correlation seen in the feet ($R^2 = 0.29$, $p < 0.01$).

Conclusions

Clinically active, early RA patients had increased joint uptake of a macrophage PET tracer, especially in the feet. Quantitative, but not visual PET measures of whole body and joint groups, particularly the feet, showed moderate and statistically significant correlations with clinical outcome.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the synovial joints.[1] The disease is progressive by nature, causing permanent damage to bone and cartilage in the absence of timely treatment.[2] Clinical assessment of arthritis is the cornerstone in both diagnosis and treatment monitoring of RA, and the Disease Activity Score (DAS) is a valid tool to assess and monitor clinical disease activity.[3] Nevertheless, reliable clinical determination of (sub)clinical arthritis can be difficult.[4] More objective tools to facilitate early diagnosis and disease activity assessment of RA are needed.

Advanced imaging techniques may contribute to early diagnosis and therapy monitoring through sensitive detection of synovitis, and several techniques have been investigated. Although ultrasonography has shown promise for predicting development of clinical arthritis and therapy response through sensitive detection of inflammation and erosions,[5,6]. it is time-consuming and prone to inter-observer variability.[7] Magnetic resonance imaging (MRI) provides high sensitivity for detecting (changes in) RA disease activity and joint damage and is not operator-dependent. However, the field of view for scanning is limited and the specificity of MRI findings in joints is low in the early phase of RA.[8] Molecular imaging methods have shown promise as an alternative for early disease activity assessment and monitoring of RA.[9,10]

Positron emission tomography (PET) allows for highly sensitive depiction of targets at molecular level and can be used to specifically visualize (immune) cells of interest through the use of specific tracers.[11] Importantly, the whole body can be visualized in a single imaging session. The value of PET for imaging of inflammatory arthritis has previously been studied with the general tracer [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG), which proved to accurately and sensitively represent inflammatory activity in large joints in patients with RA.[12] Additionally, early changes in [^{18}F]FDG uptake proved to predict clinical outcome at a later stage of treatment.[9,13] However, even though [^{18}F]FDG is a sensitive tracer, it is not specific to arthritic activity. Tracers that bind specifically to activated macrophages have been very promising in this regard.[14]

(*R*)-[^{11}C]PK11195 (1-(2-chlorophenyl)-N-methyl-N(1-methyl-propyl)-3-isoquinoline carboxamide) is a PET macrophage tracer that allows for highly sensitive and specific imaging of disease activity in RA patients. Inflammatory activity was visualized in the hands and knees, providing predictive value for both early disease development and flares in patients that were clinically considered to be in remission.[10,15-17] Whole body macrophage PET imaging has not yet been evaluated for RA disease activity assessment. Including the feet during imaging provides special interest, as they are notoriously hard to assess clinically and are involved very early in the disease onset.[18]

In this proof of concept study, the potential of whole body (*R*)-[^{11}C]PK11195 PET-CT to image RA disease activity in clinically active, early RA patients was investigated. Three main aspects were assessed: 1. feasibility of whole body PET to image arthritis in multiple joints, 2. comparison of visual and quantitative PET variables and 3. relationship of PET assessments with clinical data.

METHODS

Patients

Thirty-five patients (age 54 ± 12 years, 51% male) of at least 18 years of age with de novo RA based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria of 2010[19] were included between April 2015 and December 2017. Patients were eligible if they had at least two swollen joints (as determined by a physician) in hands, wrists, feet and/or knees. Exclusion criteria were symptom duration exceeding two years, prior treatment with disease modifying anti-rheumatic drugs (with the exception of hydroxychloroquine), treatment with glucocorticoids at a dose exceeding 7.5 mg per day in the four weeks prior to inclusion, exposure to radioactivity for research purposes above 5 mSv in the last year, the use of experimental drugs in the previous three months, pregnancy, and breast-feeding. Patients were asked not to use benzodiazepines for at least 10 days prior to inclusion because of possible interaction with tracer binding to the translocator protein (TSPO) target on macrophages.

All patients gave written informed consent prior to inclusion. Ethical approval was obtained from the Medical Ethics Review Committee of the Amsterdam UMC location VUmc, under project number 2013.341.

Clinical assessment

Standard demographical and clinical data were collected by an experienced clinical investigator blinded to the imaging data. Disease activity was expressed as Disease Activity Score of 44 joints (DAS44) Blood withdrawal for the assessment of inflammation markers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), was performed.

PET/CT imaging

(*R*)-[^{11}C]PK11195 was synthesized according to Good Manufacturing Practice (GMP). The tracer is in routine use for clinical studies and was synthesized on site, as described previously.[15] PET/CT scanning was performed with either a Gemini TF scanner (Cleveland, Ohio, USA) or an Ingenuity TF scanner (Cleveland, Ohio, USA). Fasting or premedication were not required. Patients received one venous cannula for injection of 370 ± 10% MBq of (*R*)-[^{11}C]PK11195. Immediately after injection, the cannula was flushed with 20 mL NaCl 0.9.

Scanning was started 20 minutes after injection of (*R*)-[^{11}C]PK11195. Patients were scanned in supine position with the ventral side of the hands on the upper legs. Hands were placed in a special vacuum pouch for immobilization, knees were supported by a small cushion and feet were placed in a special fixation apparatus for immobilization. Three consecutive static emission scans of the upper body (shoulders to fingertips), knees and feet were obtained. Patients were scanned for 4 minutes per field of view (FOV). Each emission scan was preceded by a low dose CT scan, which was used for attenuation correction purposes and for anatomical localization. Patients were scanned for 45 to 60 minutes, depending on their height. All scan data were corrected for decay, scatter, random coincidences and photon attenuation through established procedures.[20] After reconstruction, images were transferred to off-line workstations for further analysis.

Image analysis

Two experienced readers (GZ and CvdL) blinded to the clinical data independently performed semi-quantitative visual scoring, using a dedicated workstation (Intellispace Portal 9.0, Koninklijke Philips NV, Amsterdam, Netherlands). A consensus round was used to resolve any differences in rating between the two readers. The 44 joints included in the DAS44 score were scored for visual tracer uptake on a scale from 0 to 3; with 0 for no increased uptake, 1 for low uptake, 2 for moderate uptake and 3 for high uptake, as compared to the surrounding background uptake.[10,16,17] Joints were scored positive on articular tracer uptake, with peri-articular and tendon uptake being disregarded.

Furthermore, tracer uptake in joints was quantified by drawing fixed size volumes of interest (VOIs) over 42 predefined joints (both on visual PET positive and negative joints): shoulders, elbows, wrists, metacarpophalangeal joints (MCPs), proximal interphalangeal joints (PIPs), hips, knees, ankles, and metatarsophalangeal joints (MTPs). The size and position of these VOIs were determined in consensus by two analysts (NV and JdJ) prior to analysis. VOIs were drawn with data analysis software developed in-house, using the low-dose CT as anatomical reference, and with exact positioning being dependent on the focus of tracer accumulation in the joint (in case of visual PET positive joints). Standardized Uptake Values (SUVs) were calculated by dividing the radioactive concentration in each VOI by the injected radioactivity normalized to body weight. The value used to represent tracer uptake was SUV_{peak}, defined as the highest average uptake within a sphere of 1.2 mL (hereafter named as SUV).

Statistical analysis

At joint level the agreement between visual PET assessment and clinical assessment values SJC and TJC was calculated using Cohen's kappa. First, the original ordinal visual score (0 to 3) was used, calculating weighted kappa's. Second, the ordinal score was dichotomized (a score of 0 remained 0, and any PET positivity was marked as 1, and joints were grouped, combining left and right, and grouping smaller joints (MCP2 to MCP5, all hand PIP joints and MTP2 to MTP5), resulting in the following groups: shoulders, elbows, wrists, MCP1 joints, MCP2-5 joints, hand PIP-joints, hips, knees, ankles, MTP1 joints and MTP2-5 joints. Two by two tables of the groups were generated with visual scores versus SJC and TJC, in order to compare visual positivity to clinical positivity. At the patient level, the number of visually PET positive joints in the hands (wrists, MCP and PIP joints) and feet (ankles and MTP joints) and whole body (hands ,feet, shoulders, elbows, hips and knees) were compared with the DAS-44 score, as well as with DAS components (ESR, SJC, TJC and pain score) and CRP with univariate linear regression.

The quantitative PET dataset was analysed with the same groups as mentioned above. SUV in the groups was compared with the clinical values SJC and TJC using independent T-tests. Boxplots were used to visualize differences in average SUV. At a patient level, quantitative tracer uptake was expressed as average SUV in hands group (wrists, MCP and PIP joints), feet group (ankles and MTP joints) and whole body (hands, feet, shoulders, elbows, hips and knees). Similar to the analysis of the visual data, the correlation between SUV in hands, feet and whole body and the previously mentioned clinical values was assessed through univariate linear regression. To assess the added value of both hands and feet to the whole body protocol, an analysis of the correlation of clinical values with the average SUV in the whole body minus hands and minus feet was performed through univariate linear regression.

Continuous variables with Gaussian distribution were summarized as mean ± standard deviation (SD) and 95% confidence interval (CI). Variables that were non-normally distributed were summarized as median and interquartile range (IQR). Visual interpretation of the PET/CT data was performed with descriptive statistics. The visual score was reported at an individual joint level or in groups (for MCP2-5 joints, PIP joints and MTP 2-5 joints). SPSS version 22.0 software (IBM SPSS, Armonk, N.Y, USA) was used to assess the distribution of both clinical and PET data. A P-value smaller than 0.05 was considered to be significant. As this is an explorative study, no corrections for multiple testing were applied. The analyses presented in this study incorrectly assume that all observations on joints are independent, where in fact they are 'nested' within patients and thus potentially correlated. However, given the exploratory nature of this study and the small sample size we decided against the use of more advanced (i.e. multilevel) modelling due to the burden of increased complexity of the model in analysis and interpretation.

RESULTS

Clinical data

PET/CT scans were obtained in 35 patients. Patients demonstrated moderate to high disease activity, with a mean (± SD) DAS44 score of 3.2 ± 1.0. Baseline characteristics of the 35 patients are shown in Table 1.

Visual PET data

Twelve percent of all joints (171/1470) in 35 patients were PET positive, with one patient showing no positive joints (only peri-articular joint uptake, which was not included in the PET assessment, see methods section), and the rest between 1 to 18 PET positive joints per patient. The inter-observer variability before consensus, as determined by a weighted Cohen's kappa calculation, was κ = 0,86. Over 90% of PET positive sites were located in either wrists (15%, example Figure 1), small hand joints (37%), or small feet joints (40%, example Figure 1). Uptake was rare in shoulders and knees, and absent in elbows and hips. Uptake was low in 102, moderate in 54 and high in 15 joints. Moderate or high scores were mainly seen in MTPs, PIPs and wrists (41%, 20% and 19% of total moderate or high scores, respectively). An image of whole body uptake is included in supplementary Figure 1.

At the joint level, presence or absence of visual PET signal corresponded with presence or absence of tenderness or swelling in 74% and 75% of the joints respectively, with varying but generally low levels of agreement per joint (kappa <0.40; supplementary Table 1). At the patient level, the sum of the number of visually PET positive joints in hands, feet or whole body did, in general, not correlate with the DAS-44 score or its components. Only the sum of visual PET scores in the hands correlated with SJC (R^2 = 0.13, p = 0.03), and the sum of the whole body with ESR (R^2 = 0.11, p = 0.05). All calculated correlations are summarized in Supplementary Table 2.

Quantitative PET data

Quantitative data showed a large range in SUV values, from 0.07 to 4.97 (in a PIP5 and shoulder joint, respectively). With the exception of shoulders and knees, visually positive joints/joint groups had significantly higher SUV values than negative joints (Table 2).

At the joint level, all groups of the hand and feet joints (but not large joints outside these groups) showed significant SUV differences between clinically tender and non-tender, and between clinically swollen and non-swollen joints (as summarized in Table 3). The largest SUV differences were seen in ankles (0.7 vs 1.3, p = 0.04), MTP1 joints (0.7 vs 1.2, p < 0.001, and MTP2 – 5 joints (0.6 vs 0.8, p = 0.03) when comparing swollen with non-swollen joints, as depicted in Figure 2.

At the patient level, average SUV of the feet group had the highest correlation with the DAS44 score (R^2 = 0.29, p = 0.001) (Figure 3). The SUV of the hands group had a slight lower and SUV of the whole body showed the lowest, but still statistically significant, correlation with the DAS44 score (R^2 = 0.22, p = 0.005 and R^2 = 0.15, p = 0.02, respectively). Correlation of average whole body SUV with DAS44 decreased significantly from an R^2 of 0.15 to 0.03 and 0.04 without hands and feet, respectively. Apart from a correlation with DAS44, SUV hands also showed significant correlations with SJC and CRP (R^2 = 0.31, p < 0.001 and R^2 = 0.23, p = 0.004, respectively), and SUV feet with TJC and ESR (R^2 = 0.19, p = 0.009 and R^2 = 0.29, p = 0.001, respectively). The average whole body SUV also showed a weak correlation with ESR (R^2 = 0.14, p = 0.03). All calculated correlations are summarized in Supplementary Table 2.

DISCUSSION

This is the first whole body macrophage PET study of RA patients that specifically did include the feet. PET/CT with the macrophage targeting tracer (*R*)-[^{11}C]PK11195 proved feasible and provided clear visualization of inflammatory activity in multiple joints in this group of early RA patients. The high signal in the feet is clinically very relevant, as arthritis in the feet is often difficult to detect. Quantitative PET data allowed for more precise differentiation between clinically active and non-active joints than visual assessments. The combined PET outcome of the feet showed the best correspondence with disease activity at the patient level.

Several studies have shown the feasibility of whole body PET to assess disease activity in RA patients.[12,21-26] Most studies have used [^{18}F]FDG as tracer, which is sensitive but not specific for imaging arthritis. Some studies have only looked at visually enhanced uptake, while in other studies quantitative analyses were performed. The tracer used in this study targets macrophages and is thus more specific for arthritis.[15] In addition, both visual and quantitative analyses of an extensive number of joints, including all MTP joints, were explored.

Although some previous [^{18}F]FDG studies[23,25] have described a correlation between visual PET data and clinical disease activity measures at a patient level, poor correlations were described at a joint level.[25] In the present study, visual assessment of PET positivity and clinical findings in individual joints showed kappa values between visual PET and clinical data of <0.40, which correspond with those of Fosse et al.[25] The discordance between PET and clinical findings may appear disappointing at first sight, but could also indicate added value of PET. Previously it has been shown that (*R*)-[^{11}C]PK11195 uptake can precede clinical arthritis in patients at risk of RA or in remission.[17,27] Visual analysis depends on the expertise of the reader(s) and is limited by a relatively high intra-observer coefficient of variation in smaller joints.[23] In theory, quantitative PET data may provide more accurate measures of tracer uptake than visual analysis. By including both visual and quantitative analysis in this study, it was possible to demonstrate that quantitative PET assessments indeed outperformed visual PET assessments with respect to agreement and correlation with clinical findings. Quantitative assessment of 42 joints per patient is labour intensive. In the future, however, the development of artificial intelligence methods may automate this assessment and facilitate implementation of quantitative PET in clinical practice. Based on the results of this study, macrophage PET could have clinical value for early assessment of (changes in) disease activity to enable early diagnosis and early assessment of treatment outcome response. However, validation in additional (longitudinal) cohorts is necessary before this could be implemented in clinical practice.

In the present cohort, most PET positivity was seen in small hand and feet joints, with only low incidence in large joints as hips, shoulders, elbows and knees. Besides inclusion of MTP1 by Beckers et al, [23] no previous studies have included MTP joints. The pattern of inflammation found in the present study corresponds with the typical clinical presentation of early RA in small hand and feet joints, although large joints may also be involved, in particular in more severe RA.[28] Since quantitative PET outcome of the feet and hands groups each corresponded most with clinical disease activity at patient level, future studies should investigate whether PET imaging can be limited to a scanning protocol of feet or hands alone. A simplified scanning protocol of only feet or hands could allow for faster scanning and lower radiation dose for patients. Future studies should explore these findings.

There are some limitations to this study. Firstly, the limited involvement of large joints in this cohort of patients limits the assessment of the value of PET scanning of these joints. Secondly, the patients included had, on average, moderate disease activity, potentially impacting the correlation with imaging. Thirdly, although macrophage tracers are more specific for arthritis than FDG, (*R*)-[^{11}C]PK11195 still shows high peri-articular background uptake that negatively affects specificity.[15,16] This may be improved by using second generation macrophage tracers.[14,27] Fourthly, the measure for visual tracer uptake, assessed as 'none', 'low', 'moderate' or 'high' by the readers, is subjective in nature. Future studies should further focus on development of more objective classification of the intensity of the visual tracer uptake. Fifthly, in depth analysis of the best PET measure to assess disease activity was not included in the current study set-up. This analysis should be performed in future studies for further evaluation towards potential clinical application, but was outside the scope of this paper. In the current analysis 'average whole body SUV' was selected as measure for PET activity in the whole body because closest representation of visual PET positivity was found when using average whole body SUV as a summary measure, as compared to summation, median and maximum. Additionally, this measure showed the least outliers. Finally, positioning of the hand joints may need further improvement. To minimize discomfort, hands were positioned with fingers semi-flexed in a vacuum pouch on the abdomen, but this still allowed for small movements, and is therefore not optimal for accurate delineation of tracer uptake.

CONCLUSION

Whole body macrophage PET imaging in early RA patients showed clear uptake of (*R*)-[^{11}C]PK11195 in multiple joints, and specifically in the feet. Correlations with clinical arthritis were modest both at joint and whole body level, but with quantitative PET data outperforming visual scoring. These findings should stimulate future studies using second generation macrophage tracers.

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FIGURE LEGENDS

Figure 1: (R)-[^{11}C]PK11195 uptake in the left wrist (left) and the left MTP5 joint (right).

Figure 2: Boxplot figures of SUV values in ankles (left), MTP1 joints (middle) and MTP2 – 5 joints (left) that were clinically unaffected or swollen.

Figure 3: Correlation of the average SUV in the feet with the DAS44 score.

Supplementary figure 1: Whole body (R)-[^{11}C]PK11195 uptake in a patient.

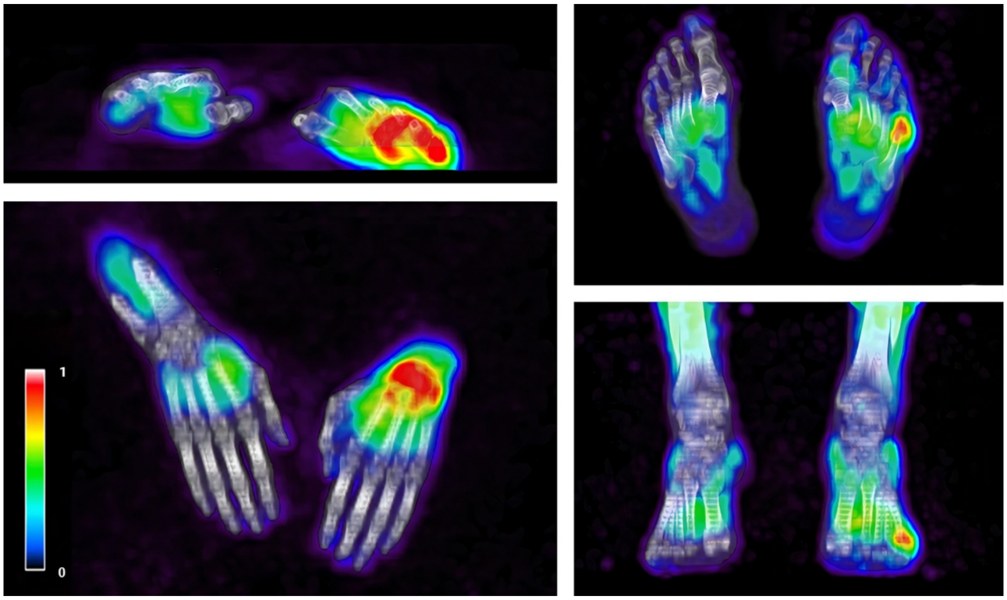

Figure 1: (*R*)-[^{11}C]PK11195 uptake in the left wrist (left) and the left MTP5 joint (right).

170x100mm (300 x 300 DPI)

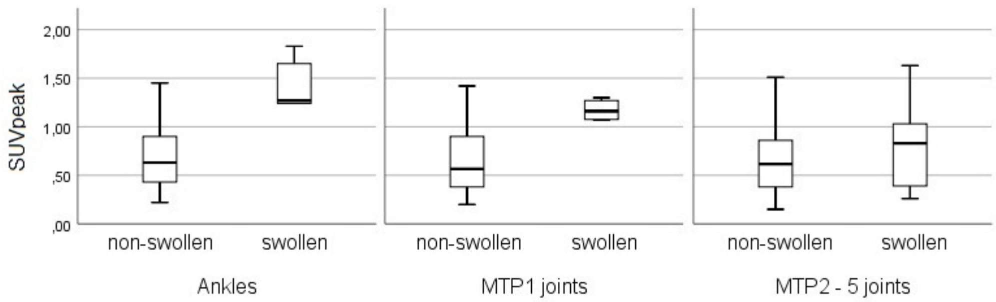

Figure 2: Boxplot figures of SUV values in ankles (left), MTP1 joints (middle) and MTP2 – 5 joints (left) that were clinically unaffected or swollen.

64x19mm (300 x 300 DPI)

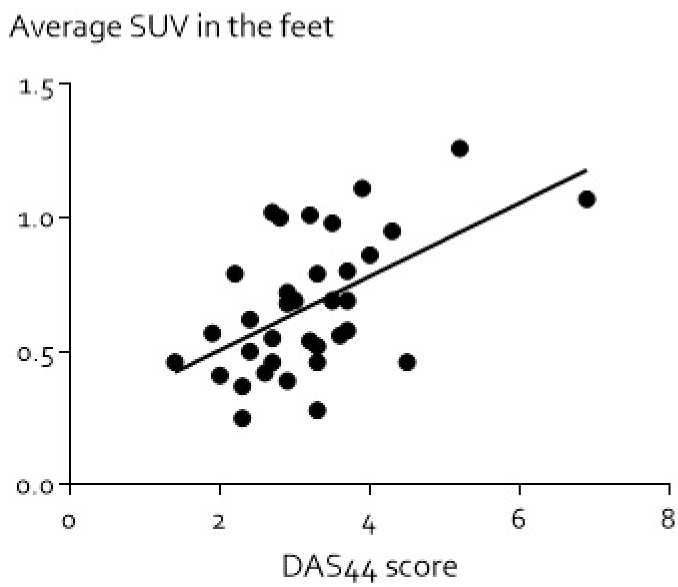

Figure 3: Correlation of the average SUV in the feet with the DAS44 score.

31x26mm (300 x 300 DPI)

Male, count (%)	18 (51)
Age, years (mean ± SD)	54 ± 12
Height, cm (mean ± SD)	173 ± 9
Weight, kg (mean ± SD)	80 ± 15
BMI, kg/m^2 (mean ± SD)	27 ± 4
IgM RF positivity, number (%)	24 (69)
Anti-CCP positivity, number (%)	27 (77)
DAS 44 score (mean ± SD)	3.2 ± 1.0
44-swollen joint count (median (IQR))	5 (7)
44-tender joint count (median (IQR))	6 (5)
CRP, mg/L (median (IQR))	14 (20)
ESR, mm/h (median (IQR))	22 (28)

Table 1: Baseline patient demographics together with clinical and functional characteristics.

Joint	Average SUV (mean ± SD) for visually PET negative joints	Number of visually PET negative joints	Average SUV (mean ± SD) for visually PET positive joints	Number of visually PET positive joints	*P* – value
Shoulders	2.1 ± 0.9	67	2.4 ± 0.3	3	0.67
Elbows	1.1 ± 0.3	70	n.a.	0	n.a.
Wrists	0.8 ± 0.3	44	1.0 ± 0.3	26	< 0.01
MCP1 joints	0.6 ± 0.2	64	0.9 ± 0.2	6	< 0.01
MCP2 – 5 joints	0.5 ± 0.2	264	0.8 ± 0.2	16	< 0.01
PIP joints	0.4 ± 0.2	309	0.7 ± 0.2	41	< 0.01
Hips	2.5 ± 0.8	70	n.a.	0	n.a.
Knees	1.1 ± 0.6	66	1.4 ± 0.4	4	0.48
Ankles	0.7 ± 0.3	63	1.4 ± 0.3	7	< 0.01
MTP1 joints	0.6 ± 0.3	52	1.1 ± 0.3	18	< 0.01
MTP2 – 5 joints	0.6 ± 0.3	230	1.0 ± 0.3	50	< 0.01

Table 2: Average SUV (mean ± SD) in individual and groups of joints, divided in visually PET negative (left) and PET positive joints (right).

Joint	Average SUV (mean ± SD) for non-swollen joints	Average SUV (mean ± SD) for swollen joints	*P* – value	Average SUV (mean ± SD) for non-tender joints	Average SUV (mean ± SD) for tender joints	*P* – value
Shoulders	2.1 ± 0.9	1.6 ± 0.3	0.23	2.1 ± 0.9	2.4 ± 1.3	0.65
Elbows	1.1 ± 0.3	1.0 ± 0.3	0.32	1.1 ± 0.4	1.0 ± 0.2	0.09
Wrists	0.8 ± 0.3	1.0 ± 0.3	0.08	0.9 ± 0.3	0.9 ± 0.3	0.40
MCP1 joints	0.5 ± 0.2	0.7 ± 0.2	< 0.01	0.6 ± 0.2	0.8 ± 0.2	< 0.01
MCP2 – 5 joints	0.4 ± 0.2	0.6 ± 0.2	< 0.01	0.4 ± 0.2	0.6 ± 0.2	< 0.01
PIP joints	0.4 ± 0.2	0.6 ± 0.2	< 0.01	0.4 ± 0.2	0.5 ± 0.2	0.04
Hips	2.5 ± 0.8	n.a.	n.a.	2.5 ± 0.8	2.5	n.a.
Knees	1.1 ± 0.6	1.3 ± 0.7	0.41	1.1 ± 0.6	1.3 ± 0.6	0.42
Ankles	0.7 ± 0.3	1.3 ± 0.5	0.04	0.7 ± 0.3	1.2 ± 0.6	0.09
MTP1 joints	0.7 ± 0.3	1.3 ± 0.5	< 0.01	0.6 ± 0.3	0.8 ± 0.4	0.11
MTP2 – 5 joints	0.6 ± 0.3	0.8 ± 0.4	0.03	0.6 ± 0.3	0.8 ± 0.4	< 0.01

Table 3: Average SUV (mean ± SD) in groups of joints, divided in swollen and non-swollen (left) and tender and non-tender (right).