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Total-Body ^{18}F-FDG PET/CT in Autoimmune Inflammatory Arthritis at Ultra-Low Dose: Initial Observations

Running title:

Total-Body PET/CT in Arthritis

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ABSTRACT

Autoimmune inflammatory arthritides (AIA), such as psoriatic arthritis (PsA) and rheumatoid arthritis (RA), are chronic systemic conditions that affect multiple joints of the body. Recently, total-body (TB) PET/CT scanners have become available that exhibit superior technical characteristics (total-body coverage, geometric sensitivity) that could benefit AIA evaluation, compared to conventional PET/CT systems. The objectives of this work were to (1) assess the performance of an ultra-low-dose, ^{18}F-FDG TB-PET/CT acquisition protocol for evaluating systemic joint involvement in AIA; and (2) report the association of TB-PET/CT measures with joint-by-joint rheumatologic examination and standardized rheumatologic outcome measures.

Methods: Thirty participants (24 with AIA and 6 with osteoarthritis (OA)), were prospectively enrolled in this single-center, observational study. All participants underwent a TB-PET/CT scan for 20 min starting at 40 min after intravenous injection of 78.1±4.7 MBq of ^{18}F-FDG. Qualitative and quantitative evaluation of ^{18}F-FDG uptake and joint involvement were performed from the resulting images and compared with the rheumatologic assessments.

Results: TB-PET/CT enabled the visualization of ^{18}F-FDG uptake at joints of the entire body, including those of the hands and feet, in a single bed position, and in the same phase of radiotracer uptake. A range of pathologies consistent with AIA (and non-AIA in the OA group) were visualized, and the feasibility of extracting PET measures from joints examined by rheumatologic assessments was demonstrated. Out of 1997 evaluable joints, there was concordance between TB-PET qualitative assessments and joint-by-joint rheumatologic evaluation in the AIA and non-AIA cohorts for 69.9% and 91.1% joints,

respectively, while an additional 20.1% and 8.8% joints, respectively, deemed negative on rheumatologic examination showed PET-positivity. On the other hand, 10.0% and 0% joints in the AIA and non-AIA cohorts, respectively, were positive on rheumatologic evaluation but negative on TB-PET. Quantitative measures from TB-PET in the AIA cohort demonstrated a moderate to strong correlation (Spearman's ρ=0.53-0.70, $p<0.05$) with the rheumatologic outcome measures.

Conclusion: Systemic joint evaluation in AIA (and non-AIA) is feasible with a TB-PET/CT system and an ultra-low-dose protocol. Our results provide the foundation for future larger studies to evaluate the possible improvements in AIA joint assessment via the TB-PET/CT technology.

Key Words: Total-body PET/CT; autoimmune arthritis; rheumatoid arthritis; psoriatic arthritis; osteoarthritis

INTRODUCTION

Autoimmune inflammatory arthritides (AIA), such as psoriatic arthritis (PsA) and rheumatoid arthritis (RA), are chronic, systemic conditions with articular and extra-articular manifestation. Joint inflammation is regarded as the hallmark of AIA and is considered a bellwether for downstream joint destruction and pain (*1*). Consequently, disease activity and treatment response assessments in AIA have relied primarily on the physical evaluation of joints (e.g., tenderness and swelling) and composite scores from joint examination, joint pain and activity, and laboratory inflammatory markers. These assessments however are subjective (*2*) and lack the sensitivity required to detect early and/or subclinical disease (*3*).

To address this limitation, PET/CT scanning using the radiotracer ^{18}F-2-Deoxy-2-fluoro-D-glucose (^{18}F-FDG) has been proposed, with results demonstrating the ability to assess joint inflammation (*4-8*), considered a precursor to AIA-associated joint damage. Despite these advantages, concerns about using ^{18}F-FDG PET/CT on current systems in the AIA population have been expressed. These include the significant cumulative dose to the patient for chronic disease activity monitoring or measuring treatment response (*9,10*) and the assessment of only portions of the body (e.g., just large joints (*11*)), given the limited PET sensitivity and spatial resolution characteristics of systems used for quantifying radiotracer uptake in small joints of the hands and feet that are affected early in AIA (*7,12*).

Recently, long axial field-of-view PET/CT systems capable of imaging either the entire adult human body *(13)*, or large portions of the body *(14,15)* have become available. Their sensitivity characteristics are far superior to state-of-the-art conventional whole-body

PET/CT systems, and early studies have shown that dose reduction is possible (*16*). These systems have a spatial resolution comparable to or better than conventional whole-body PET/CT scanners (*13*). To date, however, these total-body (TB)-PET/CT systems have not been evaluated for assessing systemic autoimmune diseases, such as AIA.

In this paper we present the first-in-human evaluation of a TB-PET/CT scanner to document the head-to-toe articular manifestations of AIA. The objectives of this work were to (1) assess the performance of an ultra-low-dose ^{18}F-FDG TB-PET/CT acquisition protocol to assess joint involvement in AIA; and (2) report the association of rheumatologic measures of AIA joint and disease activity with those evaluated from TB-PET/CT.

MATERIALS AND METHODS

Study Participants

This prospective study was approved by Institutional Review Board of the University of California Davis and all participants provided written informed consent before study procedures began. The recruited participants had a confirmed diagnosis, according to established criteria, of one of two subtypes of AIA (PsA or RA) (*17,18*) or osteoarthritis (OA), a non-AIA (*19*).

All study participants underwent rheumatological evaluation by a fellowship-trained, board-certified rheumatologist and dermatologist with over 25 years of post-training experience in AIA within two weeks before the TB-PET/CT scan. The assessments included the evaluation of 68 joints based on the Disease Activity in Psoriatic Arthritis [DAPSA] outcome measure (*20*), and Disease Activity Score based on the assessment

of 28 joints [DAS-28] (*21*), which are subset of the 68 joints. Blood samples were drawn on the day of the scan for assessing serum C-reactive protein (CRP), used to calculate DAPSA score and DAS-28-CRP. The swollen and tender joint counts (SJC, TJC) were recorded. A joint was considered positive if it was tender, swollen, or both.

Total-Body ^{18}F-FDG PET/CT

All participants underwent scans on a TB-PET/CT scanner (uEXPLORER, United Imaging Healthcare) at a single time-point for 20 min starting at 40±1 min after an intravenous injection of 78.1±4.7 MBq of ^{18}F-FDG. Details of participant positioning, acquisition, reconstruction, and image assessment are provided in the *Supplementary File Sections S1 & S2*. TB-PET/CT image assessments were reported qualitatively for each of the 68 joints using a modified 4-point Likert scale *(5)*: 0, no uptake; 1, mild uptake comparable to the surrounding background; 2, moderate uptake higher than the surrounding background and comparable to blood pool (BP) at the ascending aorta; and 3, marked uptake higher than BP. For binary analyses, any uptake with a score ≥2 was considered positive. SUV_{max} was measured on 2.344 mm isotropic voxel reconstructions with no point-spread function modeling or post-processing smoothing. Measurements were performed only for joints that scored ≥1. Values were reported as a ratio ($rSUV_{max}$) between the joint SUV_{max} normalized by the BP SUV_{mean}. Positive joint count, summed qualitative scores, and summed $rSUV_{max}$ were derived for each scan. Further, a composite measure (PET_{comp}) was calculated analogous to the DAPSA score (*20*) as the sum of positive joints from PET, patient-reported outcomes of joint pain and activity (each between 1 to 10), and serum CRP level in mg/dL.

Statistical Analysis

Continuous variables were compared between two independent categorical groups using the Mann-Whitney U test. Association between categorical variables was assessed using Fisher's exact test. Correlation between two continuous measures was calculated using Spearman's ρ. All analyses were performed using SPSS version 21 (IBM Corp, Armonk, New York).

RESULTS

Participant Characteristics

Thirty participants (24 with established AIA [15 PsA and 9 RA], and 6 with non-AIA [OA], 7 females and 23 males), with median age 63.5 years, range: 28-77 years, were evaluated. Characteristics of the participants and outcomes of their rheumatologic assessments are presented in **Table 1**. As expected, participants with AIA had higher positive joint counts than those without AIA. There was no difference in participant characteristics or rheumatologic assessments between individuals with PsA and RA.

TB-PET/CT Systemic Joint Evaluation

All participants completed their TB-PET/CT scans. **Figure 1** shows PET maximum intensity projection (MIP) images for representative participants. Out of a total of 2040 joints (30 participants x 68 joints per participant), 43 (~2%) joints from 6 participants with AIA could not be adequately evaluated from the scans; due to prosthesis (8 joints), significant motion (30 joints), or being outside the PET and CT FOV (5 elbow joints). Thus, the analysis presented is for 1997 evaluable joints.

Most participants with AIA (23/24, 95.8%) presented with peripheral polyarthritis apparent on TB-PET/CT. **Figure 2** shows images through the hands and feet of representative study participants with AIA. **Table 2** provides details of joints with positive TB-PET/CT findings.

Comparison of TB-PET/CT Assessments with Rheumatologic Outcome Measures

Qualitative Evaluation

In the AIA cohort, out of 1589 joints evaluated, 69.9% showed concordance between the TB-PET and joint-by-joint rheumatologic evaluation (**Table 3**). An additional 20.1% were positive on TB-PET but negative on rheumatologic examination. Finally, 10.0% were negative on TB-PET but positive on rheumatologic evaluation. *Supplementary File, Table S1* summarizes the distribution of the 159 joints in the latter category. Of these joints, 148 (93.0%) were small joints of the hands or feet and 136 of the 148 joints (91.9%) were just tender on physical examination with no objective evidence of swelling or redness. In OA participants, concordance between TB-PET and joint-by-joint rheumatologic evaluation was 91.2%. An additional 8.8% of joints were positive on TB-PET but negative on rheumatologic examination, while no joints were negative on TB-PET and positive on rheumatologic examination (**Table 3**).

Quantitative Evaluation

Quantitative ^{18}F-FDG TB-PET/CT findings in joints are summarized in **Table 4**. Imaging metrics were higher in AIA participants compared to the non-AIA group. Systemic ^{18}F-FDG TB-PET metrics showed moderate to strong correlation with the DAPSA and DAS-

28 scores (**Table 5**). The correlation coefficient was higher with DAS-28 because the measure does not involve assessment of the hand DIP or any foot joints.

DISCUSSION

We report articular findings from first-in-human ^{18}F-FDG TB-PET/CT scans in an AIA and non-AIA (OA) population. The entire adult human body was imaged in a single bed position in the same phase of radiotracer uptake. An ultra-low dose protocol was implemented. The ability of assessing ^{18}F-FDG uptake for both large and small joints across the body was demonstrated.

Early diagnosis of AIA and initiation of treatment at its onset is essential to achieve clinical remission or at least low or minimal disease activity (*22,23*). There is currently no validated diagnostic test for PsA (*24*) while clinical assessments for AIA are suboptimal (*2*). Therefore, the ability to perform a systemic evaluation of AIA-associated joint inflammatory activity in a quantitative manner on a per patient basis via TB-PET/CT, as demonstrated by our study, could offer an important tool to the rheumatology community. Furthermore, TB-PET/CT could be useful to monitor response to therapies on a personalized basis and justify cessation, reduction and/or switching to another line of treatment (*24-26*). Beyond joints, TB-PET/CT provides the visualization of other tissues that AIA may impact, such as the axial skeleton, entheses, digits (dactylitis), and nail and skin, as well as organs such as heart, brain, liver, kidneys, and skeletal muscle (*27,28*). Future investigations in assessing the impact of AIA on these tissues could further expand our understanding of the disease process.

Our findings indicate that 20.1% of AIA joints deemed negative on rheumatologic examination were PET-positive. This mismatch has also been reported by other PET

studies (*8,29,30*). It is plausible to hypothesize that ^{18}F-FDG PET, due to its ability to detect cellular metabolic activity, is sensitive to sub-clinical AIA inflammation that may be occult on rheumatologic evaluation but may play a role in joint damage (*31*). Future studies with short- and long-term follow-up will be needed to test this hypothesis. On the other hand, 10.0% joints that were positive on rheumatologic evaluation were PET-negative. There could be three possible reasons for this discrepancy. First, 93.6% of these joints were assessed as being tender on rheumatologic evaluation. Tenderness alone in established AIA may not reflect active inflammation (*32-34*). Furthermore, inclusion of the TJC in rheumatologic assessment may confound evaluation of AIA inflammatory activity (*35*). Our results support this premise and could help better establish the clinical value of tenderness in AIA evaluation, with or without synovitis or swelling. The second reason could be the limited TB-PET spatial resolution (~3 mm (*13*)) for the small joints of the hand and feet. The reconstructed radiotracer uptake was likely underestimated for the small joints; data suggest that the contrast recovery coefficient for a 10-mm sphere with 4-to-1 source-to-background ratio and employing the same reconstruction method used here is ~50% (*13*). The quantification of small lesion activity could likely be improved with the implementation of advanced image reconstruction methods developed specifically for TB-PET/CT (*36*). Spatial resolution is particularly important in AIA imaging, as AIA may coexist with OA or another musculoskeletal condition in the same anatomical region (for example, small joints of the hand (*7*)), and defining the pattern may be critical for differential diagnosis (*22*). Finally, despite the use of positioning aids, intrascan motion likely confounded the evaluation of the small joints of the hand and feet. Impact of motion could be mitigated by shortening image acquisition

time or retrospective temporal binning of the data into shorter frames and either software-driven motion correction or choosing frames with the least intrascan motion (*37*). For shortening the image acquisition time while maintaining the signal to noise ratio, an increase in the injected dose may be necessary. On the other hand, advanced low-count image reconstruction methods (*36*) will be essential when using short frames.

Owing to the high sensitivity of the TB-PET/CT system (*13*), an ultra-low-dose protocol was implemented. Our findings are overall consistent with documented patterns of joint involvement in AIA, and with the findings of previous studies (*5,6,8,29,38,39*), though those studies utilized 3-5 times higher injected dose than that utilized in our study. Dose is a significant limitation for the broader adoption of PET/CT technology in AIA (*9,10*), given its chronic nature and the potential need for monitoring disease activity in both treatment responders and non-responders. Low-dose approaches such as those utilized in our work could therefore provide means for the rheumatology community to capitalize on the benefits offered by TB-PET/CT.

A 40-min ^{18}F-FDG uptake time was utilized based on the tracer's arterial blood clearance characteristics (*40,41*), with a 20-min scan time, and data were reconstructed into a single frame matching our current clinical protocols (*42*). Our pilot data recently showed that shorter scans may provide reasonable image quality (*43*). These shorter scans need further validation; however, they could motivate the creation of more practical scanning protocols suitable for the AIA population that experiences significant difficulty in tolerating long scan times. The shorter frames could also enable future classification of ^{18}F-FDG kinetics in lesions over the 20-min window and provide additional biomarkers, such as

those from relative Patlak plots (*44*). Furthermore, the 40-60 min scanning window used will allow future exploration of optimizing the scan start time within that window.

Our study has limitations. First, this was a feasibility study with a modest sample size. Second, this was a cross-sectional study with participants enrolled with different levels of AIA disease activity, and the treatments they were receiving could have affected the PET findings. Follow-up TB-PET imaging will be essential to establish the test-retest reliability in this patient population. Third, semiquantitative SUV_{max}-based measures were employed and other measures, such as metabolically active volume, can be considered in the future. Fourth, our ultra-low-dose CT protocol, while supporting PET attenuation correction and anatomical localization, resulted in an overall low CT image quality. An increase in dose and deployment of recently developed machine-learning-based methods for low-dose CT reconstruction (*45*) could be helpful to address this limitation and to assess the added value of CT-based joint findings. Fifth, the transaxial FOV was not sufficient to capture the elbows consistently. Positioning schemes that would enable the capture of all joints of the body will be helpful to implement in the future. Sixth, the study was not powered to assess differences in PET uptake patterns between the AIA subtypes. Finally, we did not compare our findings with those from other imaging modalities like ultrasound or MRI. These studies could help define the future role of TB-PET/CT for AIA assessment compared to other imaging modalities.

CONCLUSION

The feasibility of acquiring total-body ^{18}F-FDG PET/CT scans in participants with AIA, and a non-AIA comparator group, at an ultra-low dose was demonstrated. TB-PET/CT enabled the acquisition of joints of the entire body, including hands and feet, in a single

bed position, and in the same phase of radiotracer uptake. A range of pathologies consistent with AIA (and non-AIA) were visualized, and the feasibility of extracting PET measures from anatomical sites commonly examined clinically (68 and 28 joints) was demonstrated. Quantitative measures from TB-PET/CT demonstrated a moderate to strong correlation with outcomes of AIA rheumatologic assessments. These results provide the foundation for future studies to substantiate these findings and quantitatively evaluate the improvements possible in AIA assessment via the TB-PET/CT technology.

DISCLOSURE

University of California Davis has a research and a revenue-sharing agreement with United Imaging Healthcare. RDB, SRC, and LN are investigators on a research grant funded by United Imaging Healthcare, the manufacturer of the scanner used in this article.

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KEY POINTS

QUESTION:

Is it feasible to assess joint involvement in autoimmune arthritis using ^{18}F-FDG and an ultra-low-dose protocol on a total-body PET/CT scanner?

PERTINENT FINDINGS:

In this prospective study systemic joint involvement in participants with autoimmune arthritis was successfully visualized and ^{18}F-FDG uptake per joint was quantified. Results showed a high concordance of total-body PET/CT measures with joint-by-joint rheumatologic evaluation and moderate to strong correlation with rheumatologic outcome measures. Total-body ^{18}F-FDG PET/CT was positive for 20% of joints deemed negative on rheumatologic examination, suggestive of its ability to potentially detect subclinical disease activity.

IMPLICATIONS FOR PATIENT CARE:

Evaluation of autoimmune arthritis is feasible using ultra-low-dose, total-body ^{18}F-FDG PET/CT scans.

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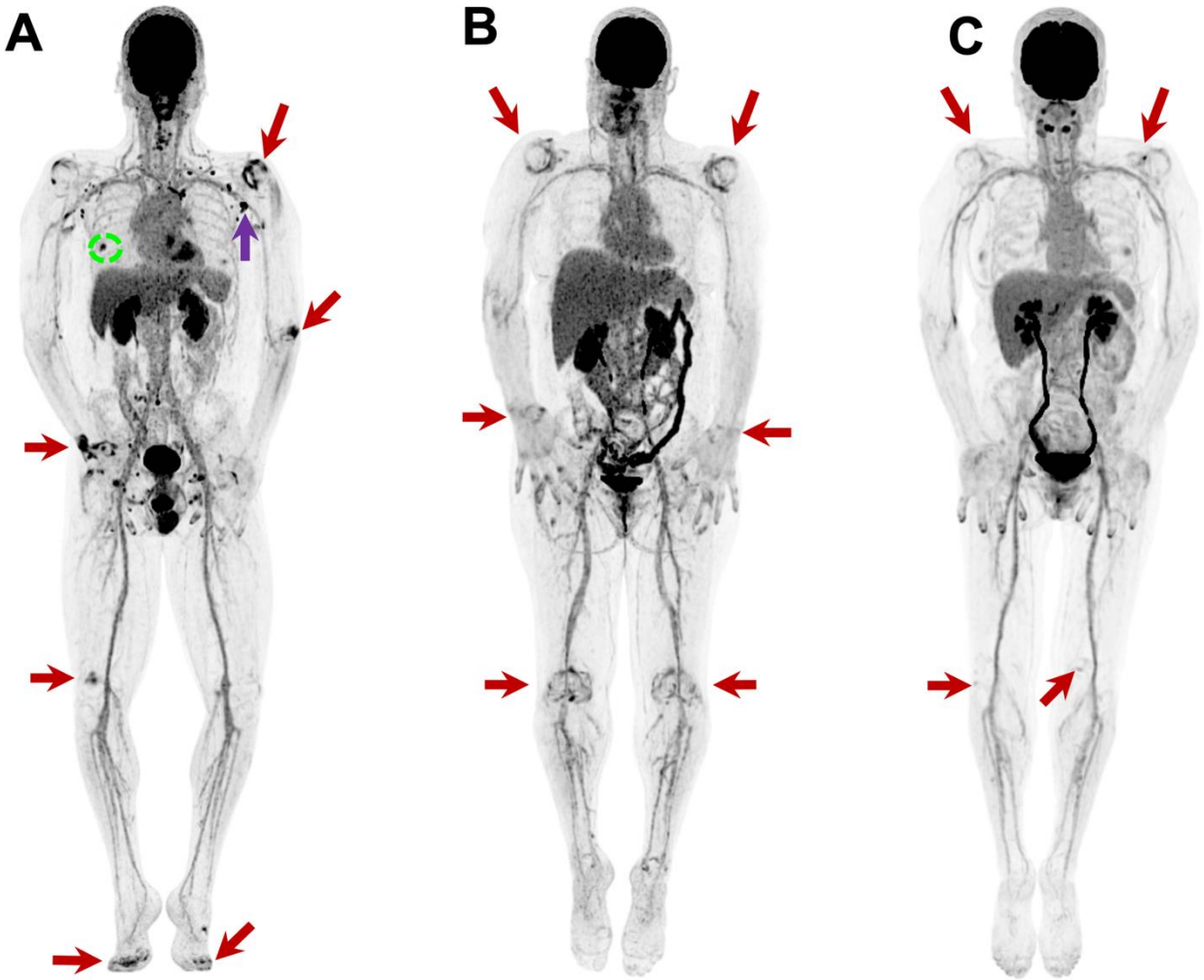
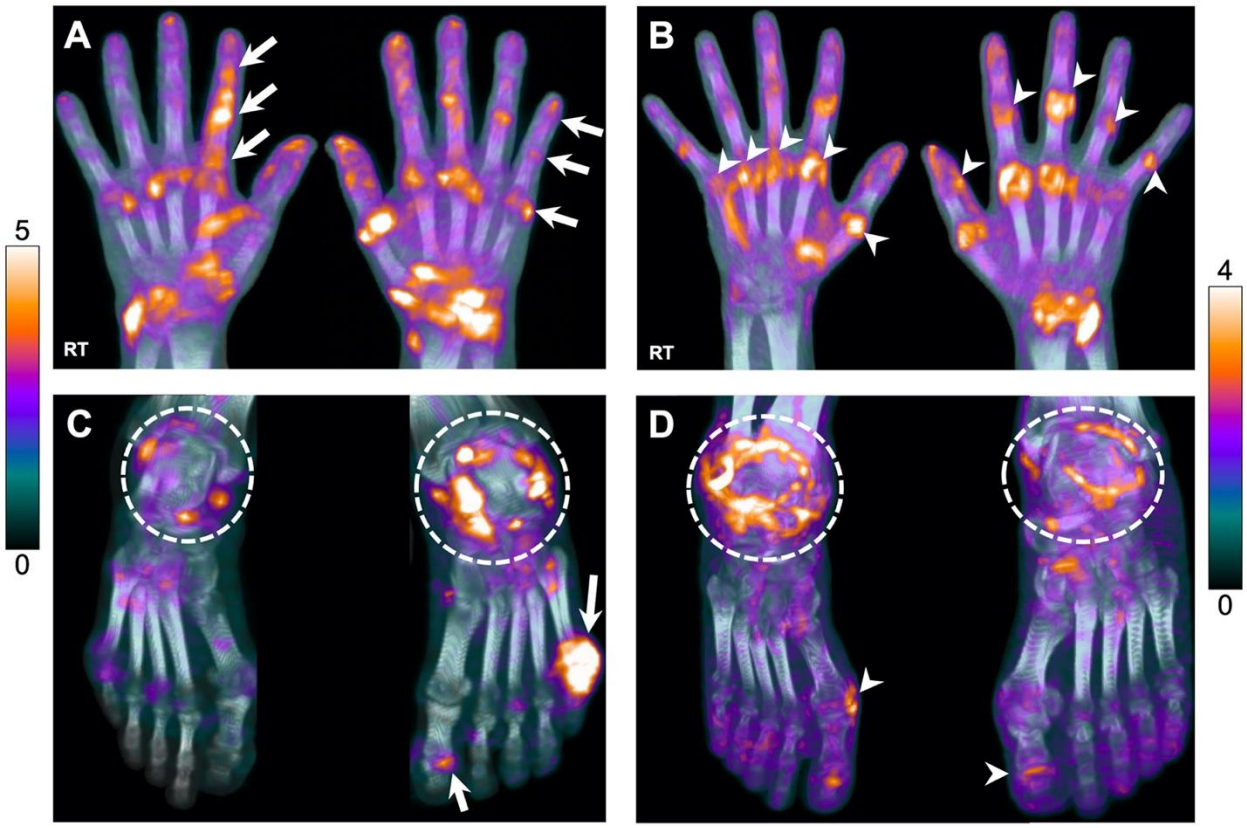
FIGURE 1:



Total-body ^{18}F-FDG PET uptake in participants with AIA compared to those with OA, shown as maximum intensity projections (MIPs); (A) 33-year-old man with PsA, showing asymmetric polyarthritis involving left shoulder, left elbow, right wrist, right knee, and small joints of the hands and feet (arrows); (B) 59-year-old woman with RA, showing mostly bilateral symmetric joint involvement of the shoulders and knees, and to lesser extent the wrist joints; and (C) 64-year-old woman with OA, presenting primarily mild-to-moderate uptake at fewer joints (shoulders and knees) commonly involved in this condition. Several extra-articular findings are noted in (A) including ^{18}F-FDG-avid bilateral axillary and left

supraclavicular lymph nodes. The left side uptake is secondary to COVID vaccination (purple arrow), and the active spot (dashed circle) seen opposite the inferior angle of the scapula corresponds to inflamed scapulothoracic bursa.

FIGURE 2:



^{18}F-FDG uptake in the hands and feet of participants with AIA; (A) 54-year-old man with PsA showing elevated uptake at multiple hand joints. Ray-like distribution, as indicated by arrows, in MCP, PIP, and DIP joints in sequence, attributed to the involvement of the flexor and/or extensor tendons; (B) 47-year-old woman with RA, showing involvement of the entire row of MCP (arrowheads, right hand) and PIP/IP joints (arrowheads, left hand); (C) feet images of the same PsA participant in (A) demonstrating increased uptake at the ankle joints (dashed circles), more intense on the left side, and left 1st IP and 5th MTP joints (arrows); and (D) feet images of a 71-year-old man with RA, demonstrating bilateral, rather symmetric, uptake around the ankles, as well as the right 1st MTP and left 1st IP joints, suggestive of synovitis (arrowheads).

TABLE 1:

Characteristics of the Study Participants and a Summary of their Rheumatologic Assessments

Characteristic	Non-AIA (N=6)	AIA (N=24)	*P*	AIA		*P*
				PsA (N=15)	*RA (N=9)*	
Age (yrs)	54.5±14.5 (36-72)	58.5±13.9 (28-77)	0.63	56.8±16.3 (28-77)	61.4±8.3 (47-71)	0.79
BMI (kg/m^2)	28.6±8.4 (19.8-40)	31.3±6.3 (20-46.6)	0.49	32.3±7.1 (20-46.6)	29.6±4.5 (23.1-36.4)	0.36
TJC (68 joints)	0.5±0.8 (0-2)	12.5±14 (0-55)	<0.001	10.5±13.7 (0-55)	16±14.4 (4-45)	0.22
SJC (68 joints)	0	1.6±2.4 (0-9)	-	1.9±2.7 (0-9)	1.2±2.0 (0-6)	0.67
TJC (28 joints)	0	8.7±7.1 (0-25)	-	7±6.8 (0-25)	11.6±7.1 (4-23)	0.13
SJC (28 joints)	0	1.2±1.7 (0-6)	-	1.1±1.6 (0-5)	1.2±2.0 (0-6)	0.92
DAS-28-CRP*	-	3.7±1.1 (2.1-5.4)	-	3.7±1.1 (2.1-5.4)	3.7±1.0 (2.4-5.1)	0.93

Values reported as mean ± standard deviation (minimum-maximum). AIA=autoimmune arthritis; PsA=psoriatic arthritis; RA=rheumatoid arthritis; BMI=body mass index; TJC=Tender Joint Count; SJC=Swollen Joint Count; CRP= C-reactive protein.

** DAS-28-CRP is not a validated outcome measure for non-AIA (OA) so was not calculated.*

TABLE 2:

Frequency and Distribution of Positive Joints on ^{18}F-FDG TB-PET/CT

Joint or joint group		**Positive joint count/ number of participants (average)**	
		Non-AIA	**AIA**
Hand joints	1st IP & 2-5th PIP	6/2 (3.0)	82/17 (4.8)
	1-5th MCP	1/1 (1.0)	71/15 (4.7)
	2-5th DIP	0/0 (0)	38/10 (3.8)
	Sum	**7/2 (3.5)**	**191/20 (9.6)**
Feet joints	1st IP, 2-5th PIP & DIP	0/0 (0)	15/5 (3.0)
	1-5th MTP	4/3 (1.3)	41/10 (4.1)
	Sum	**4/3 (1.3)**	**56/11 (5.1)**
Upper limb joint	Gleno-humeral	6/4 (1.5)	37/21 (1.8)
	Acromio-clavicular	3/2 (1.5)	23/13 (1.8)
	Sterno-clavicular	3/3 (1.0)	26/17 (1.5)
	Elbows	3/2 (1.5)	11/8 (1.4)
	Wrists	4/2 (2.0)	31/19 (1.6)
	Sum	**19/5 (3.8)**	**128/22 (5.8)**
Lower limb	Hips	5/3 (1.7)	22/13 (1.7)
	Knees	1/1 (1.0)	20/14 (1.4)
	Talo-tibial	3/2 (1.5)	20/12 (1.7)
	Mid-tarsal & sub-talar	0/0 (0)	17/12 (1.4)
	Sum	**9/4 (2.3)**	**79/21 (3.8)**
Temporomandibular joints		0/0 (0)	9/6 (1.5)
Sum of all positive joints/participants (average)		39/6 (6.5)	463/23 (20.1)

AIA=autoimmune arthritis; OA=osteoarthritis; IP=interphalangeal; PIP=proximal interphalangeal; MCP=metacarpophalangeal; DIP=distal interphalangeal.

TABLE 3:

Qualitative ^{18}F-FDG TB-PET/CT Findings in Joints in Comparison with Rheumatologic Examination

^{18}F-FDG TB-PET evaluation	**Rheumatologic examination**			
	AIA		***Non-AIA***	
	Negative	***Positive (T/S/TS)***	***Negative***	***Positive (T/S/TS)***
Negative	*967*	*159 (146/4/9)*	*369*	*0*
Positive	*320*	*143 (117/3/23)*	*36*	*3 (3/0/0)*
Total (N=1997)*	***1287***	***302***	***405***	***3***

T/S/TS = tender/swollen/tender & swollen
**A total of 43 joints in AIA participants were unevaluable on PET, 6 of them were tender on rheumatologic examination*

TABLE 4:

Quantitative Findings from ^{18}F-FDG TB-PET/CT Positive Joints

^{18}F-FDG PET metrics derived from:		**Non-AIA (N=6)**	**AIA (N=24)**	***P***
68 Joints	Positive count	6.5±4.9 (2-14)	19.3±12.6 (0-49)	0.01
	Summed scores	14.2±10.7 (4-30)	44.5±30.2 (0-124)	0.01
	Summed $rSUV_{max}$	10.7±8.7 (2.9-25.2)	28.6±19.3 (1.5-90.2)	0.001
28 Joints	Positive count	3.5±2.7 (0-7)	10.7±7.6 (0-26)	0.02
	Summed scores	7.7±5.9 (0-14)	24.1±17.1 (0-64)	0.02
	Summed $rSUV_{max}$	6.7±4.1 (1.8-12.5)	16.3±11.1 (4.2-50.3)	0.001

Values are given as mean±SD (minimum-maximum). AIA=autoimmune arthritis

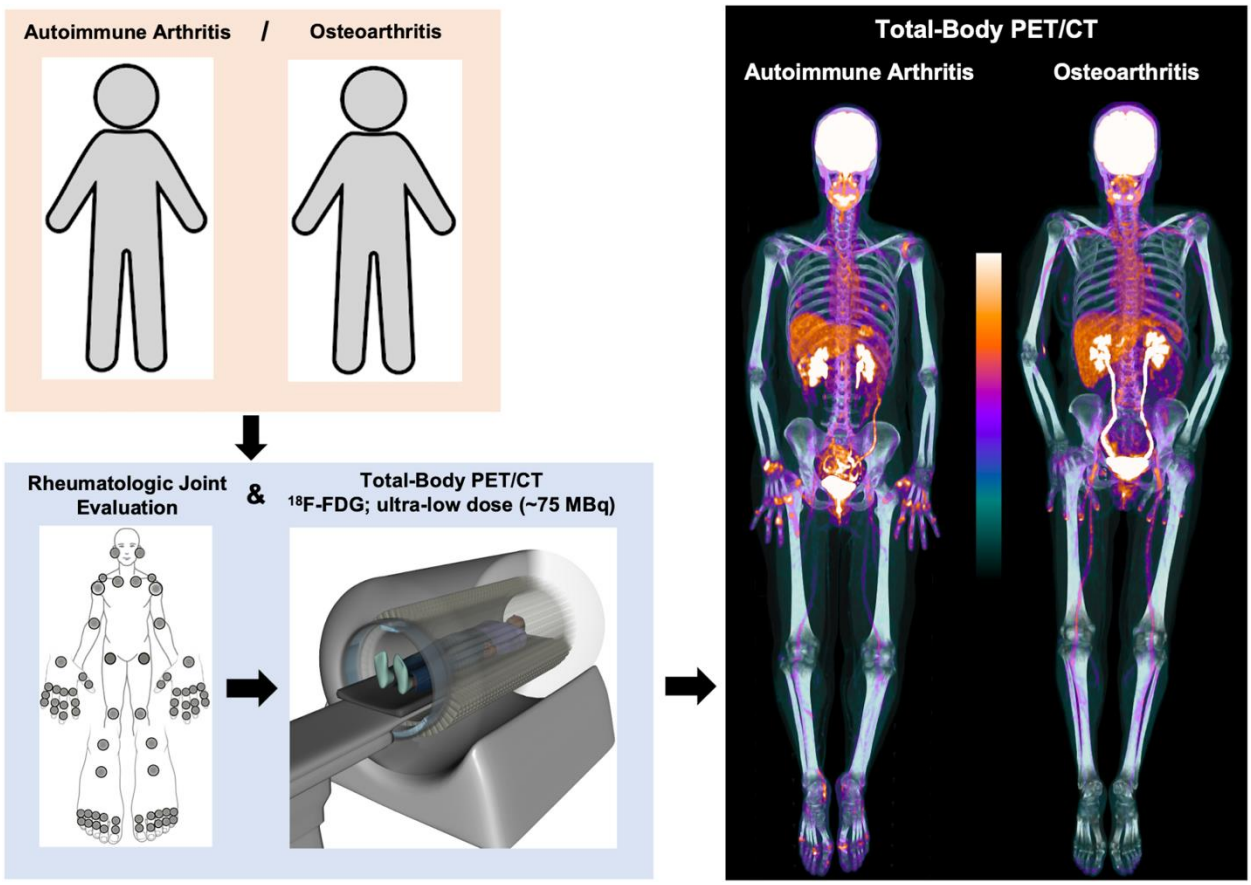
TABLE 5:

Spearman's Correlation (ρ) between Systemic Joint Measures from ^{18}F-FDG TB-PET/CT and Rheumatologic Assessments

^{18}F-FDG PET metrics		**Rheumatologic assessments**	
		DAPSA score (N=15 with PsA)	**DAS-28-CRP (N=24 with AIA)**
68 Joints	Positive count	0.61* (0.10-0.88)	0.62** (0.30-0.82)
	Summed scores	0.61* (0.08-0.89)	0.61** (0.27-0.83)
	Summed $rSUV_{max}$	0.56* (0.03-0.86)	0.53** (0.18-0.77)
	PET_{comp}†	0.63* (0.17-0.87)	0.70* (0.40-0.86)
28 Joints	Positive count	0.55* (0.06-0.89)	0.68** (0.40-0.86)
	Summed scores	0.57* (0.09-0.89)	0.68** (0.39-0.87)
	Summed $rSUV_{max}$	0.53* (0.01-0.87)	0.60** (0.29-0.84)

Values are given as Spearman's rho (ρ) coefficient (95% confidence interval).
Since DAPSA score is not validated for evaluating RA, data under the DAPSA column is extracted from participants with PsA, while data under DAS-28-CRP are extracted from all the 24 participants with AIA.
** = P < 0.05, ** = P < 0.01,*
†PET_{comp} = positive joint count + patient-reported joint activity + patient-reported joint pain + CRP

Graphical Abstract



Supplementary File

MATERIALS AND METHODS

S.1. Total-Body ^{18}F-FDG PET/CT Protocol

The standard scan preparation instructions included fasting for at least 4 hours, and avoiding exercise, strenuous activity, and excessive hand usage over at least one day prior to the scan. The participants received an injection of 78.1±4.7 MBq of ^{18}F-FDG via a peripheral venous line inserted in the antecubital region. Per SNMMI/EANM guidelines, the effective dose is 0.019 mSv per MBq, i.e., 1.5±0.09 mSv. For comparison, a standard 370 MBq injection of ^{18}F-FDG used in routine clinical practice corresponds to approximately five times higher effective dose. Blood glucose was measured before ^{18}F-FDG injection, and all the measurements were <160 mg/dL. After radiotracer injection, participants rested in the uptake rooms for approximately 30 min, and then were instructed to void their urinary bladder. They were then asked to lay supine on the bed of the TB-PET/CT scanner (uEXPLORER, United Imaging Healthcare). Hands were positioned over the thighs, or, if not possible for the participant, over the chest. This position of the arms and hands, rather than arms stretched above the head, was used to exploit the sensitive, central region of the scanner field of view (FOV). Hand and foot immobilization aids were employed to limit subject movement. Image acquisition was started at 40±1 min post-injection and was carried out for a total of 20 min in a single bed position covering the entire body (field-of-view = 60 x 60 x 194 cm in X, Y, Z directions, respectively). A whole-body, ultra-low-dose CT scan was acquired before the PET

acquisition for attenuation correction. The CT scan parameters were: 5 mAs tube current, 140 kV tube voltage, and pitch of 1.4 (effective dose ~ 1 mSv).

The 20-min PET data were reconstructed using the manufacturer-provided software employing the 3D ordered subset expectation maximization (OSEM) algorithm with 4 iterations and 20 subsets into a 256 x 256 matrix, at an isotropic voxel size of 2.344 mm. All the standard corrections were applied. No point-spread function (PSF) information or post-processing smoothing was employed. CT images were reconstructed using the manufacturer-provided software with a slice thickness of 2.344 mm to match those of PET and an in-plane voxel size of ~0.49x0.49 mm.

The PET/CT scanning sessions were scheduled for late morning to afternoon to minimize the variability resulting from AIA-associated morning stiffness and other circadian rhythm-associated confounders.

S.2. ^{18}F-FDG PET/CT Image Analysis

Scans were evaluated by a fellowship-trained nuclear medicine physician with over 10 years of post-training experience. DICOM images were transferred to a viewing workstation running OsiriX MD (Pixmeo SARL, Bernex, Switzerland). The image series was displayed as 2D orthogonal views, including CT only, PET only, and fusion images. Oblique multi-planar reformats were generated for the hands and feet, as appropriate. Image assessment included both visual and quantitative evaluation of the 68 joints assessed in the DAPSA score, and the 28 joints assessed in DAS-28.

Qualitative/visual reading was reported on a 4-point Likert-like scale, as detailed in the main manuscript. For binary analyses, any uptake with score 2 or more was considered positive. We opted to this modification since the blood pool (BP) activity was still high closer to 40 min post-injection on the PET images.

Quantitative evaluation involved placing volumes of interest (VOIs) covering each of the evaluated joints in the DAPSA and DAS-28 outcome measures and recording the maximum standardized uptake value (SUV_{max}) when the evaluated site was visually scored 1 or more. Quantification was performed in the same session with the qualitative assessment. Unless otherwise specified, all SUV measurements were reported as a ratio ($rSUV_{max}$) of the joint SUV_{max} normalized to the ascending aorta BP activity, measured as SUV_{mean} of a 3.7 ml VOI placed on the ascending aorta.

Analogous to the DAPSA joint evaluation, the number of joints that were interpreted as positive from ^{18}F-FDG TB-PET/CT from these 68 joints, their ^{18}F-FDG visual scores (0-3), and their $rSUV_{max}$ were independently summed per participant to obtain the DAPSA-equivalent ^{18}F-FDG joint count, summed ^{18}F-FDG visual score, and summed $rSUV_{max}$, respectively. The same was done for the 28 joints covered by the DAS-28.

SUPPLEMENTARY TABLE

TABLE S1: Analysis of the 159 Joints Positive on Rheumatologic Examination but Negative on ^{18}F-FDG TB-PET/CT

Negative ^{18}F-FDG TB-PET (Score 0, Score 1)	*Positive rheumatologic examination*		
	Tender only	*Swollen only*	*Tender and swollen*
Hands	***95 (71,24)***	***0***	***7 (5,2)***
DIPs	*17 (12,5)*	*0*	*0*
IPs and PIPs	*37 (25,12)*	*0*	*2 (2,0)*
MCPs	*41 (34,7)*	*0*	*5 (3,2)*
Feet	***41 (33,8)***	***4 (3,1)***	***1 (1,0)***
IPs, PIPs & DIPs	*14 (11,3)*	*3 (3,0)*	*0*
MTPs	*27 (22,5)*	*1 (1,0)*	*1 (1.0)*
Other joints	***10**** *(7,3)*	***0***	***1***† *(1,0)*

The numbers in parenthesis detail the qualitative negative ^{18}F-FDG TB-PET scores (i.e., frequency of Score 0, frequency of Score 1, respectively).
**3 wrist, 1 shoulder, 2 hip, 2 knee, 2 ankle, and 1 subtalar joint(s). †ankle joint*