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Articular ^{18}Fluorodeoxyglucose Uptake Is Associated With Clinically Assessed Swollen Joint Count in Patients With Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Examination and conventional radiography of joints are unable to precisely evaluate and measure disease activity in rheumatoid arthritis (RA). We quantified joint inflammation using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in people with RA to determine if PET-derived uptake variables were correlated with RA disease activity measures.

Methods. We cross-sectionally studied 34 patients with RA in a substudy of the Rheumatoid Arthritis Study of the Myocardium (RHYTHM). All patients underwent ^{18}F-FDG-PET scanning with CT for attenuation correction and anatomic co-registration. Linear regression was used to model the associations of disease activity scores with articular FDG uptake, calculated as standardized uptake values (SUVs). Weighted joint volume SUVs (wjSUV) representing 25%, 50%, 75%, and maximum (100%) uptake (wj25SUV, wj50SUV, wj75SUV, and wjMaxSUV, respectively) were calculated as global variables of the total volume of joint inflammation in each patient.

Results. Calculated wj25SUV (Spearman $\rho = 0.39$, $P = 0.04$), wj50SUV ($\rho = 0.39$, $P = 0.04$), and wj75SUV ($\rho = 0.37$, $P = 0.045$) measures were significantly correlated with the number of swollen joints. Similar significant correlations were found for the Simplified Disease Activity Index but not Clinical Disease Activity or Disease Activity Score in 28 joints. No associations were found between articular FDG uptake and non-articular RA-related variables (ie, disease duration, seropositivity, or RA treatments).

Conclusion. Articular FDG uptake in patients with RA was significantly correlated with the number of swollen joints but not with biochemical measures of inflammation.

Key Indexing Terms: diagnostic imaging, disease activity, rheumatoid arthritis

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Clinical indicators employed in the assessment of rheumatoid arthritis (RA) activity include individual variables such as physician-assessed swelling and tenderness in the joints, patient-reported pain, acute-phase reactant measurements, patient and evaluator global assessments of disease activity, and duration of morning stiffness or fatigue.[1] These variables may reflect different components of the disease, and may vary with time within individual patients. Composite indices in common use include, among others, the Disease Activity Score in 28 joints (DAS8),[2] Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI).[3] However, these composite scores have limited accuracy, reliability, or sensitivity to change.[3,4] For this reason, there is currently no ideal or gold standard measure of disease activity in RA. Thus, in recent years imaging modalities have been proposed as more accurate and/or objective measurements of disease activity in RA. In this sense, imaging techniques such as ultrasonography and magnetic resonance have been found to be more sensitive for the detection of synovitis than physical assessment[5] and are increasingly available to clinicians.[6]

Positron emission tomography (PET) is an imaging technique that uses metabolic compounds labeled with short-lived positron-emitting radionuclides (such as carbon-11, nitrogen-13,

oxygen-15 and fluorine-18) to measure cell metabolism. PET is now regularly used in the diagnosis and staging of cancer, and in assessing cardiovascular and brain diseases. However, the use of PET in RA to assess activity of articular disease or to study its role in other nonarticular characteristics of the disease has been scarce. In this report, our aim was to determine if articular FDG-PET–derived uptake variables were correlated with clinical and biologic measures of RA disease activity.

METHODS

Study participants. This was a cross-sectional study of 34 patients with RA, who were aged ≥ 18 years and fulfilled the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology diagnostic criteria for RA.[7] Patients were recruited as a substudy nested within the Rheumatoid Arthritis Study of the Myocardium (RHYTHM) cohort (n = 119), which has been described in detail elsewhere (ClinicalTrials.gov: NCT01548768).[8] The overall goal of RHYTHM was to evaluate the prevalence of myocardial inflammation and microvascular dysfunction in patients with RA without known cardiac disease, utilizing cardiac FDG-PET/CT. The main inclusion criteria were diagnosis of RA of any duration and severity, age > 18 years, and no prior clinical cardiovascular disease. In addition to the cardiac FDG-PET/CT scan, 34 random subjects of the 119 enrolled patients agreed to undergo a whole-body PET/CT scan to assess for articular FDG uptake. The study was approved by the Columbia University Institutional Review Board (approval n. AAAI1026). RA disease activity was measured using the Disease Activity Score in 28 joints with C-reactive protein (CRP)[2] and the CDAI.[3] Disability was determined using the Health Assessment Questionnaire (HAQ).

FDG-PET/CT acquisition protocol. All patients were prescribed a no-carbohydrate diet the day before the scan, followed by a 12-hour fast. All patients had a blood sugar concentration of < 200 mg/dL at the time of imaging. The patients were injected with approximately 370 MBq of FDG intravenously, followed by a flush of 20 cc of normal saline, and residual activity was recorded. Next, they waited for approximately 90 minutes to allow for circulation and uptake and were allowed only minimal physical activity during that time. The patients were subsequently scanned on a Siemens MCT 64 PET/CT scanner (Siemens Medical Solutions) from the vertex of the skull through the feet, with the position of the arms by their sides for the emission scan. A transmission CT scan was done over the same region for attenuation correction and anatomic localization. Physical exam to assess joints count was performed on the visit day prior to the whole-body PET/CT scan.

A qualitative analysis based on visual identification of FDG uptake in the joints and measurements of standardized uptake values (SUVs) were obtained in bilateral shoulders, elbows, wrists, 2nd to 5th metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, hips, knees, and ankles. Because RHYTHM protocol established that disease activity and physical exam were performed in 28 joints, FDG uptake was assessed in the same 28 joints. Every joint was classified based on a 5-grade description as follows: grade 1, no FDG uptake in the joint; grade 2, FDG uptake in the joint equal to mediastinal uptake; grade 3, FDG uptake in the joint higher than mediastinal, but lower than liver, uptake; grade 4, FDG uptake in the joint equal to liver uptake; grade 5, FDG uptake in the joint higher than liver uptake. Only those joints with a grade > 3 were consequently analyzed. Correspondingly, the volume of the area with the highest activity with an SUV > grade 3, the best threshold for FDG visualization (thresholds remove variability introduced by differences in patient size and the amount of injected FDG), and an SUV average of the area with the highest activity were defined. The quantitative analysis was done using the Siemens TrueD analysis software on the Syngo platform. Volumes of interest (VOIs) were drawn around the joints using a 3D ellipsoid tool. The VOIs were placed so that they included the whole joint of interest, while trying to minimize regions beyond the joint as feasible. For the liver and inferior vena cava (IVC), a VOI was placed in a representative region in the target areas. We also calculated a weighted joint volume (wjSUV) as a measure of total metabolic volume. The wjSUV represents synovial volume multiplied by FDG uptake and represents the total volume of joint inflammation. This variable was calculated as follows:

$$wjSUV = \frac{\Sigma[SUV\text{joint (for 25\%, 50\%, 75\% and maximum SUV)} \times joint\ volume]}{\Sigma[SUV\text{ (for 25\%, 50\%, 75\% and maximum SUV) } all\ joints]}$$

SUVjoint (for 25%, 50%, 75%, and maximum SUV) was the mean SUV of a joint thresholded to the 25%, 50%, 75%, and 100% (maximum), respectively, of the maximum intensity voxel in the joint region of interest. The ∑ [SUV joint] was the sum of the SUV means of all joints at the same threshold.

Statistical analysis. Demographic and clinical characteristics of patients with RA are expressed as mean (SD). For nonnormally distributed continuous variables, data are expressed as median (IQR). Spearman correlation coefficients were calculated to assess the relation of FDG uptake to predefined disease activity variables (DAS28, SDAI, CDAI, HAQ, and CRP) and disease-related data that included duration of the disease; presence of rheumatoid factor (RF) and anticitrullinated protein antibody (ACPA); and the use of nonsteroidal antiinflammatory drugs, prednisone, methotrexate, and biologic therapies. Univariable regression analysis was performed to assess the association of RA disease characteristics with articular FDG uptake. These variables consisted of disease duration, seropositive status, individual and composite measures of disease activity, HAQ, CRP, and RA therapies.

RESULTS

Characteristics of the participants. A total of 34 participants with RA in the RHYTHM study, 27 females and 7 males, with a mean (SD) age of 54 (10) years, were recruited and included in the analyses. The demographic, disease-related characteristics, and comorbidities of the participants are shown in Table 1.

Correlation between FDG joint uptake and disease activity variables. Correlations of FDG joint uptake with disease activity variables are shown in Table 2. Calculated wj25SUV, wj50SUV, and wj75SUV FDG uptake measures were significantly correlated with the number of swollen joints and the SDAI score. In contrast, wjMaxSUV was not statistically significantly correlated with these variables. No correlation was found for any of the SUV measures with the number of tender joints, CRP levels, DAS28, CDAI, or HAQ scores.

Association of other RA disease characteristics with articular FDG uptake. No associations were found between FDG uptake variables and most of the nonarticular RA-related variables (Table 3). For example, FDG uptake variables were not related to disease duration, RF or ACPA status, or RA treatments including prednisone, methotrexate, or the use of biologic therapies. Similarly, clinically assessed swollen joint count (SJC) was also not significantly correlated with most of the nonarticular RA-related variables but, as expected, was correlated with disease activity scores (that use SJC in their formulas).

DISCUSSION

In the present study, we demonstrated that articular FDG uptake assessed by PET/CT scanning is significantly correlated with the number of swollen joints, but not tender joints, in RA.

Table 1. Baseline characteristics of 34 patients with RA.

	N = 34
Age, yrs	54 (10)
Female, n (%)	27 (79)
Waist circumference, cm	89 (16)
BMI, kg/m^2	29 (6)
Systolic BP, mmHg	114 (16)
Diastolic BP, mmHg	70 (9)
Current smoking, n (%)	7 (26)
Hypertension, n (%)	8 (24)
Diabetes, n (%)	3 (9)
Statin therapy, n (%)	2 (6)
CRP, mg/L, median (IQR)	2.98 (1.12-6.60)
RA-related characteristics	
Disease duration, yrs, median (IQR)	9 (3-14)
RF, n (%)	15 (44)
ACPA, n (%)	24 (71)
DAS28-CRP	3.72 (1.06)
CDAI, median (IQR)	17 (9-26)
Tender joint count, median (IQR)	6 (2-11)
Swollen joints, median (IQR)	7 (3-12)
HAQ, median (IQR)	1.11 (0.69-1.55)
NSAIDs, n (%)	7 (21)
Prednisone, n (%)	8 (24)
Methotrexate, n (%)	26 (76)
Sulfasalazine, n (%)	2 (6)
Hydroxychloroquine, n (%)	4 (12)
Leflunomide, n (%)	2 (6)
Biologic therapy, n (%)	12 (35)
Anti-TNF therapy, n (%)	7 (21)

Values are expressed as mean (SD) unless otherwise indicated. ACPA: anti-citrullinated protein antibody; BP: blood pressure; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis; RF: rheumatoid factor; TNF: tumor necrosis factor.

Clinical assessment of joint swelling is considered the gold standard for the detection of synovitis in clinical practice, research, and clinical trials in patients with RA or other inflammatory types of arthritis. However, the clinical joint count can vary widely among assessors. Tenderness in joints is highly variable from patient to patient, and can be confounded by comorbid musculoskeletal conditions such as osteoarthritis (OA) and fibromyalgia[9]; thus, the number of tender joints may skew composite scores of disease activity. The correlation of FDG uptake with joint swelling found in our study supports the notion that FDG uptake reflects the underlying RA articular inflammatory process leading to vascular damage, extravascular leakage, and synovial fluid accumulation.

Several studies using FDG-PET/CT to assess disease activity in RA have been reported previously. For example, in a report of 5 patients with RA and 3 patients with psoriatic arthritis, high-resolution FDG-PET/CT imaging of only the wrist and hand was feasible and capable of providing quantifiable measures of disease activity (synovitis, enthesitis, edema, and bone destruction).[10] In another report of 13 patients with RA and 17 controls, in which 12 joints of each patient were examined (shoulder, elbow, wrist, hip, knee, and ankle on both sides), quantitative variables such as maximum SUV, metabolic active volume, and total lesion glycolysis were assessed.[11] The authors concluded that quantitative PET variables could differentiate RA from non-RA through a visual score based on those quantitative variables. Similarly, FDG uptake has been proved to predict radiographic progression[12] and to be influenced by tocilizumab,[13] anti–tumor necrosis factor therapies,[14] and disease-modifying antirheumatic drugs.[15] However, extensive validation of this technique in RA has been reported only recently. In that study of 69 patients with active RA,[16] the number of PET-positive joints (out of a total of either 28 or 68 joints) was significantly correlated with the clinically assessed SJC and tender joint count (TJC), and with DAS28 using the erythrocyte sedimentation rate (ESR). Our study is in agreement with this report, although in ours, we have found a correlation only with swollen joints and not with the composite scores of disease activity.

In our study, joint FDG uptake was related to SDAI but not with other disease activity scores. We do not have an exact explanation for this; however, it should be noted that the majority of patients in our study were receiving RA disease-modifying therapies and many had low disease activity. DAS28 is known to be a good composite score for higher disease activity, but it is not sufficiently stringent nor reproducible across different agents when aiming at an outcome such as remission; this is perhaps due to the heavy weighting of tender joints in the DAS28 compared to other RA disease activity measures. The SDAI and CDAI, although more simplistic than the DAS28 due to their design for clinical practice, have more stringent cut-offs for remission and low disease activity than the DAS28; however, the CDAI

Table 2. Correlation between FDG joint uptake[a] and disease activity variables.

	TJC28		SJC28		DAS28		CDAI		SDAI		HAQ		CRP	
	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*	ρ	*P*
wj25SUV	0.20	0.31	**0.39**	**0.04**	0.32	0.09	0.32	0.09	**0.42**	**0.02**	0.11	0.55	−0.002	0.99
wj50SUV	0.17	0.37	**0.39**	**0.04**	0.30	0.12	0.30	0.11	**0.40**	**0.03**	0.09	0.64	−0.020	0.92
wj75SUV	0.16	0.42	**0.37**	**0.045**	0.28	0.14	0.29	0.13	**0.38**	**0.04**	0.07	0.71	−0.020	0.92
wjMaxSUV	0.14	0.47	0.36	0.05	0.27	0.16	0.27	0.15	0.37	0.05	0.07	0.71	−0.022	0.91

Values in bold are statistically significant. [a] Weighted joint volume SUVs (wjSUV) representing 25%, 50%, 75%, and maximum (100%) uptake (wj25SUV, wj50SUV, wj75SUV, and wjMaxSUV, respectively). CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; FDG: ^{18}F-fluorodeoxyglucose; ρ: Spearman rho; SDAI: Simple Disease Activity Index; SJC28: 28-joint swollen joint count; TJC28: 28-joint tender joint count.

Table 3. Association of disease characteristics with FDG uptake[a] in the 34 patients with RA.

	β (95% CI), *P*				
	wj25SUV	wj50SUV	wj75SUV	wjMaxSUV	SJC
Disease duration, yrs	0.44 (−0.02 to 0.89), 0.06	0.45 (−0.02 to 0.92), 0.06	0.46 (−0.01 to 0.93), 0.06	0.46 (−0.02 to 0.94), 0.06	0.05 (−0.09 to 0.18), 0.47
RF	5.3 (−3.2 to 13.7), 0.21	5.3 (−3.5 to 14.1), 0.23	5.3 (−3.6 to 14.2), 0.23	5.4 (−3.5 to 14.3), 0.23	0.92 (−2.52 to 4.35), 0.59
logCRP, mg/dL	−0.06 (−0.26 to 0.14), 0.54	−0.07 (−0.37 to 0.24), 0.65	−0.10 (−0.50 to 0.31), 0.63	−0.11 (−0.60 to 0.37), 0.63	−0.17 (−1.69 to 1.36), 0.83
ACPA	−1.1 (−10.8 to 8.7), 0.82	−1.5 (−11.6 to 8.6), 0.77	−1.6 (−11.7 to 8.6), 0.76	−1.5 (−11.8 to 8.7), 0.76	**−3.56 (−7.10 to −0.02), 0.049**
DAS28	2.6 (−1.2 to 6.4), 0.17	2.4 (−1.5 to 6.4), 0.21	2.4 (−1.5 to 6.4), 0.22	2.5 (−1.5 to 6.5), 0.21	**3.18 (2.08 to 4.27), < 0.001**
CDAI	0.32 (−0.02 to 0.66), 0.07	0.30 (−0.05 to 0.66), 0.09	0.30 (−0.05 to 0.67), 0.09	0.31 (−0.05 to 0.7), 0.09	**0.37 (0.31 to 0.43), < 0.001**
SDAI	**0.34 (0.03 to 0.65), 0.04**	0.32 (0.00 to 0.65), 0.05	0.33 (−0.01 to 0.66), 0.53	0.33 (0.00 to 0.66), 0.05	**0.31 (0.23 to 0.39), < 0.001**
TJC28	0.40 (−0.46 to 1.26), 0.35	0.36 (−0.54 to 1.25), 0.42	0.36 (−0.55 to 1.26), 0.42	0.37 (−0.54 to 1.28), 0.41	**0.66 (0.41 to 0.90), < 0.001**
SJC28	**0.94 (0.15 to 1.74), 0.02**	**0.93 (0.11 to 1.76), 0.03**	**0.95 (0.11 to 1.78), 0.03**	**0.96 (0.12 to 1.80), 0.03**	–
HAQ	0.25 (−6.75 to 7.25), 0.94	0.30 (−6.91 to 7.50), 0.93	0.28 (−7.02 to 7.57), 0.94	0.24 (−7.10 to 7.59), 0.95	0.43 (−2.11 to 2.96), 0.73
NSAIDs	−5.4 (−15.8 to 4.9), 0.29	−5.4 (−16.1 to 5.2), 0.30	−5.5 (−16.3 to 5.3), 0.30	−5.5 (−16.4 to 5.4), 0.30	−3.48 (−7.55 to 0.60), 0.09
Prednisone	2.0 (−8.6 to 12.6), 0.70	1.8 (−9.1 to 12.8), 0.73	1.8 (−9.2 to 12.9), 0.73	1.8 (−9.3 to 13.0), 0.74	1.25 (−2.85 to 5.35), 0.54
Methotrexate	−1.1 (−13.1 to 11.0), 0.86	−1.0 (−13.5 to 11.5), 0.87	−1.1 (−13.7 to 11.6), 0.86	−1.1 (−13.8 to 11.6), 0.86	−2.95 (−7.43 to 1.53), 0.19
Biologic therapy	6.1 (−2.5 to 14.7), 0.16	6.6 (−2.3 to 15.5), 0.14	6.8 (−2.3 to 15.8), 0.14	6.9 (−2.2 to 15.9), 0.13	0.25 (−3.34 to 3.84), 0.89
Anti-TNF therapy	8.8 (−1.3 to 19.0), 0.09	9.1 (−1.4 to 19.7), 0.09	9.3 (−1.4 to 19.9), 0.09	9.4 (−1.2 to 20.1), 0.08	−1.19 (−5.41 to 3.03), 0.57

Values in bold are statistically significant. [a] Weighted joint volume SUVs (wjSUV) representing 25%, 50%, 75%, and maximum (100%) uptake (wj25SUV, wj50SUV, wj75SUV, and wjMaxSUV, respectively). ACPA: anticitrullinated protein antibody; DAS28: Disease Activity Score in 28 joints; CDAI: Clinical Disease Activity Index; NSAID: nonsteroidal antiinflammatory drug; HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; SJC28: 28-joint swollen joint count; TJC28: 28-joint tender joint count; TNF: tumor necrosis factor.

does not incorporate levels of acute-phase reactants such as ESR and CRP, whereas the SDAI does.[4] These factors may influence the association of FDG joint uptake with SDAI but not to other scores in our study where there was a mix of patients with active and inactive disease.

In our study, with the exception of the clinical SJC, FDG uptake was not associated with other disease-related features, such as RF or ACPA status, or disease treatments. This was also found in relation to clinical SJC with the same disease-related variables. This may be due to the small size and cross-sectional nature of our study. Nonetheless, the association of articular FDG uptake with joint swelling, the sine qua non of RA disease activity, provides strong confirmation that articular FDG uptake truly reflects joint inflammation.

We acknowledge some limitations in our study. First, we did not recruit controls as we were not focused on FDG uptake as a diagnostic measure. Second, intra- or interreader reliability was not assessed in our work. However, 1 reader (IFA) performed all the VOIs. We understand that FDG uptake could be considered a subjective method and dependent on the observer who performs the analysis since the capture/analysis of the images is made manually. Future studies will need to address not only this aspect but others like sensitivity to change in repeated assessments. Automated software or machine learning algorithms may be needed to decrease the variability of this technique. Third, TJC and SJC can be confounded due to comorbid musculoskeletal conditions such as OA. Moreover, FDG-PET can detect inflammation in OA joints. For this reason, we cannot rule out the possibility of comorbid OA in some joints.

FDG-PET/CT is a new imaging technique that generates fast and quantitative results. In this preliminary study, FDG uptake performed moderately in the detection of joint inflammation in patients with RA. Larger studies that incorporate a broad range of disease activity are needed to determine the diagnostic performance and therapeutic responsiveness of this novel method for assessing joint inflammation in RA, as well as to inform its appropriate use in routine clinical care.

In conclusion, our findings indicate that articular FDG-PET–derived uptake variables are moderately correlated to joint inflammation in patients with RA.

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