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

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Running Title: FDG uptake in RA.

Funding: Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases under Award Number AR-050026 (JMB), and by the National Institutes of Health National Center for Translational Science Clinical and Translational Science Award (CTSA) grant UL1 TR000040, of the National Institutes of Health, and by the Rheumatology Research Foundation Award Number RHEUMARF CU12-3892. The content is solely the responsibility of the authors and does not necessarily represent the official views of The National Institutes of Health.

Declaration of Conflicting Interests: Dr Polack is currently Head of Medical Information, Global Medical Affairs, Advanced Accelerator Applications, a Novartis Company. Her contribution to this

work was performed while a Visiting Professor in Radiology at Columbia University. The other authors report no conflicts.

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 FDG PET-CT (^{18}F-Fluorodeoxyglucose positron emission computed tomography) in people with RA to determine if PET-derived uptake parameters were correlated with RA disease activity measures.

Methods. We cross-sectionally studied 34 RA patients in a sub-study of the Rheumatoid Arthritis Study of the Myocardium (RHYTHM). All patients underwent ^{18}F-FDG-PET scanning with computed tomography 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 (SUV). Weighted joint volume SUVs (wjSUV) representing 25%, 50%, 75% and maximal (100%) uptake (wj25SUV, wj50SUV, wj75SUV, and wjMAX SUV) were calculated as global parameters of the total volume of joint inflammation in each patient.

Results. Calculated wj25SUV (Spearman rho =0.390, p=0.037), wj50SUV (rho=0.385, p=0.039), and wj75SUV (rho=0.374, p=0.045) measures were significantly correlated with the number of swollen joints. Similar significant correlations were found for the SDAI score but not CDAI or DAS28. No associations were found between articular FDG uptake and non-articular RA-related variables (i.e. disease duration, seropositivity, or RA treatments).

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

Introduction

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 report of 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 (DAS)(2), the Simplified Disease Activity Index (SDAI), and the 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. For this reason, 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 labelled 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 non-articular characteristics of the disease has been scarce. In this report, our aim was to determine if articular FDG-PET-derived uptake parameters 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. All RA patients were 18 years old or older and fulfilled the 2010 ACR/EULAR diagnostic criteria for RA. Patients were recruited as a sub-study nested within the RHeumatoid arthritis studY of THe Myocardium (RHYTHM) cohort (n=119), which has been described in detail elsewhere (ClinicalTrials.gov Identifier: NCT015487689) (7). The overall goal of RHYTHM was to evaluate the prevalence of myocardial inflammation and microvascular dysfunction in RA patients without known cardiac disease, utilizing cardiac FDG-PET/CT. The main inclusion criteria were diagnosis of RA of any duration

and severity, age greater than 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 Boards (approval n. AAAI1026). RA disease activity was measured using the Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP) (2) and the Clinical Disease Activity Index (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 joint with a grade ≥ 3 were consequently analyzed. Correspondingly, volume of the area with the highest activity with an SUV $\geq$ grade 3, the best threshold for FDG visualization (thresholds remove variability introduced by differences in patient size and the amount of injected FDG), and a SUV average of the area with the highest activity were defined. The quantitative analysis was done using the Siemens True D program 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 definitely 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, respectively. 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 parameter was calculated as:

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

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 ± standard deviation. For non-normally distributed continuous variables, data are expressed as median and interquartile range (IQR). Spearman's correlation coefficients were calculated to assess the relation of FDG uptake to pre-defined disease activity parameters (DAS28, SDAI, CDAI, HAQ and CRP) and disease related data that included duration of the disease, the presence of rheumatoid factor and ACPA, and the use of NSAIDS, prednisone, methotrexate and biological 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 RA participants 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 parameters

Correlations of FDG joint uptake with disease activity parameters 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 parameters. No correlation was found for any of the SUV measures with the number of tender joints, CRP levels, DAS28 or HAQ scores.

Association of other RA disease characteristics with articular FDG uptake

No associations were found between FDG uptake parameters and most of the non-articular RA-related variables (Table 3). For example, FDG uptake parameters were not related to disease duration, rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA) status, RA treatments including prednisone, methotrexate, or the use of biological therapies. Similarly, clinically assessed swollen joint count was also not significantly correlated with most of the non-articular RA-related variables but, as expected, was correlated with disease activity scores (that use swollen joints count in their formulae).

Discussion

In the present study, we have 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.

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 co-morbid musculoskeletal conditions such as osteoarthritis and fibromyalgia (8); 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 recent report of 5 RA and 3 psoriatic arthritis patients, high-resolution 18F-FDG PET/CT imaging of only the wrist and hand was feasible and capable of providing

quantifiable measures of disease activity (synovitis, enthesitis, oedema and bone destruction) (9). In another report of 13 RA patients and 17 controls, in which twelve joints of each patient were examined (shoulder, elbow, wrist, hip, knee, and ankle on both sides), quantitative parameters such as SUVmax, metabolic active volume, and total lesion glycolysis were assessed (10). The authors concluded that quantitative PET parameters could differentiate RA from non-RA through a visual score based on those quantitative parameters. Similarly, FDG uptake has been proved to predict radiographic progression (11) and to be influenced by tocilizumab (12), anti-TNF therapies (13), and DMARDs (14). However, extensive validation of this technique in RA has only been reported recently. In that study of 69 patients with active RA (15), the number of PET-positive joints (out of a total of either 28 or 68 joints) was significantly correlated with the clinically assessed swollen joint count and tender joint count, and with the DAS in 28 joints using the erythrocyte sedimentation rate. Our study is in agreement with this report, although in ours we have found a correlation only with swollen joints but not with the composite scores of disease activity.

Joint FDG uptake was related, in our study, 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 were non-active. It is known that DAS28 is a good score for higher disease activity, but not sufficiently stringent nor reproducible across different agents when aiming at an outcome such as remission, perhaps due to the heavy weighting of tender joints in the DAS28 compared to other RA disease activity measures. The SDAI and CDAI, while more simplistic than the DAS due to their design for clinical practice, have more stringent cut-offs for remission and low disease activity than the DAS28, but the CDAI does not incorporate levels of acute phase reactants such as ESR and C-reactive protein while 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 swollen joint count, FDG uptake was not associated with other disease related features such as RF or ACPA status or disease treatments. This was also found in the relation of clinical swollen joints count with the same disease related parameters. 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 inter-reader reliability was not assessed in our work. However one reader (IFA) performed all of 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 essentially made manually. Future studies will need to address not only this aspect but others like sensitivity to change in repeated assessments. Automatic software or machine learning algorithms may be needed to decrease the variability of this technique. Third, tender and swollen joint count can be confounded due to comorbid musculoskeletal conditions such as osteoarthritis. Moreover, FDG PET can detect inflammation in osteoarthritis joints. For this reason, we cannot rule out the possibility of co-morbid osteoarthritis 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 and to inform its appropriate use in routine clinical care.

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

Acknowledgments: The authors thank the RHYTHM study staff (Afshin Zartoshti, Christopher Depender, Rachel Broderick, Janine Rose, and Rachelle Morgenstern) for their hard work and dedication, and the participants in the RHYTHM study who graciously agreed to participate in this research. We also thank Drs. Alice Chu, Anna Broder, Teja Kapoor, Edward Dwyer, Jane Kang, Laura Geraldino, Katherine Nickerson, Elizabeth Mayer, Amanda Sammut, Neil Gonter, Alexandru Kimel, and others for generously recommending their patients for this study.

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Table 1. Baseline characteristics of 34 RA patients

Age, years	54 ± 10
Female, n (%)	27 (79)
Waist circumference, cm	89 ± 16
BMI, kg/m2	29 ± 6
Systolic blood pressure, mmHg	114 ± 16
Diastolic blood pressure, mmHg	70 ± 9
Current smoking, n (%)	7 (26)
Hypertension, n (%)	8 (24)
Diabetes, n (%)	3 (9)
Statin therapy, n (%)	2 (6)
C reactive protein, mg/l	2.98 (1.12-6.60)
Rheumatoid arthritis related data	
Disease duration, years	9 (3-14)
Rheumatoid factor, n (%)	15 (44)
ACPA, n (%)	24 (71)
DAS28-CRP	3.72 ± 1.06
CDAI	17 (9-26)
Tender joints, n	6 (2-11)
Swollen joints, n	7 (3-12)
HAQ	1.113 (0.688-1.550)
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)

Data represent means SD or median (interquartile range) when data were not normally distributed.
DAS: disease activity score; CDAI: Clinical Disease Activity Index
TNF: tumor necrosis factor; ACPA: Anti-citrullinated protein antibody
NSAIDs: nonsteroidal anti-inflammatory drugs; HAQ: Health Assessment Questionnaire

Table2. Correlation between FDG joints uptake and disease activity parameters

	rho Spearman's correlation, p													
	Tender joints count	p	Swollen joints count	p	DAS28	p	CDAI	p	SDAI	p	HAQ	p	CRP	p
wj25SUV	0.196	0.31	**0.390**	**0.037**	0.323	0.087	0.322	0.088	**0.424**	**0.022**	0.114	0.55	-0.002	0.99
wj50SUV	0.171	0.37	**0.385**	**0.039**	0.297	0.12	0.300	0.11	**0.396**	**0.034**	0.090	0.64	-0.020	0.92
wj75SUV	0.156	0.42	**0.374**	**0.045**	0.282	0.14	0.286	0.13	**0.379**	**0.043**	0.073	0.71	-0.020	0.92
wjMaxSUV	0.141	0.47	0.363	0.053	0.268	0.16	0.271	0.15	0.365	0.052	0.072	0.71	-0.022	0.91

CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; DAS28: disease activity score; CRP: C-reactive protein
SDAI: Simple Disease Activity Index

Table 3. Association of disease characteristics with joints FDG in the 34 RA patients

	beta coef. (95% CI), p				
	wj25SUV	wj50SUV	wj75SUV	wjMaxSUV	Swollen joints count
Disease duration, years	0.44 (-0.02-0.89), 0.059	0.45 (-0.02-0.92), 0.060	0.46 (-0.01-0.93), 0.059	0.46 (-0.02-0.94), 0.058	0.05 (-0.09-0.18), 0.47
Rheumatoid factor	5.3 (-3.2-13.7), 0.21	5.3 (-3.5-14.1), 0.23	5.3 (-3.6-14.2), 0.23	5.4 (-3.5-14.3), 0.23	0.92 (-2.52-4.35), 0.59
log C Reactive Protein, mg/dl	-0.06 (-0.26-0.14), 0.54	-0.07 (-0.37-0.24), 0.65	-0.10 (-0.50-0.31), 0.63	-0.11 (-0.60-0.37), 0.63	-0.17 (-1.69-1.36), 0.83
ACPA	-1.1 (-10.8-8.7), 0.82	-1.5 (-11.6-8.6), 0.77	-1.6 (-11.7-8.6), 0.76	-1.5 (-11.8-8.7), 0.76	**-3.56 (-7.10--0.02), 0.049**
DAS28	2.6 (-1.2-6.4), 0.17	2.4 (-1.5-6.4), 0.21	2.4 (-1.5-6.4), 0.22	2.5 (-1.5-6.5), 0.21	**3.18 (2.08-4.27), <0.001**
CDAI	0.32 (-0.02-0.66), 0.067	0.30 (-0.05-0.66), 0.092	0.30 (-0.05-0.67), 0.092	0.31 (-0.05-0.7), 0.085	**0.37 (0.31-0.43), <0.001**
SDAI	**0.34 (-0.03-0.65), 0.035**	0.32 (-0.00-0.65), 0.053	0.33 (-0.01-0.66), 0.53	0.33 (0.00-0.66), 0.050	**0.31 (0.23-0.39), <0.001**
Tender joints 28, n	0.40 (-0.46-1.26), 0.35	0.36 (-0.54-1.25), 0.42	0.36 (-0.55-1.26), 0.42	0.37 (-0.54-1.28), 0.41	**0.66 (0.41-0.90), <0.001**
Swollen joints 28, n	**0.94 (0.15-1.74), 0.021**	**0.93 (0.11-1.76), 0.029**	**0.95 (0.11-1.78), 0.028**	**0.96 (0.12-1.80), 0.026**	-
HAQ	0.25 (-6.75-7.25), 0.94	0.30 (-6.91-7.50), 0.93	0.28 (-7.02-7.57), 0.94	0.24 (-7.10-7.59), 0.95	0.43 (-2.11-2.96), 0.73
NSAIDs	-5.4 (-15.8-4.9), 0.29	-5.4 (-16.1-5.2), 0.30	-5.5 (-16.3-5.3), 0.30	-5.5 (-16.4-5.4), 0.30	-3.48 (-7.55-0.60), 0.095
Prednisone	2.0 (-8.6-12.6), 0.70	1.8 (-9.1-12.8), 0.73	1.8 (-9.2-12.9), 0.73	1.8 (-9.3-13.0), 0.74	1.25 (-2.85-5.35), 0.54
Methotrexate	-1.1 (-13.1-11.0), 0.86	-1.0 (-13.5-11.5), 0.87	-1.1 (13.7-11.6), 0.86	-1.1 (-13.8-11.6), 0.86	-2.95 (-7.43-1.53), 0.19
Biologic therapy	6.1 (-2.5-14.7), 0.16	6.6 (-2.3-15.5), 0.14	6.8 (-2.3-15.8), 0.14	6.9 (-2.2-15.9), 0.13	0.25 (-3.34-3.84), 0.89
Anti TNF alpha therapy	8.8 (-1.3-19.0), 0.086	9.1 (-1.4-19.7), 0.087	9.3 (-1.4-19.9), 0.086	9.4 (-1.2-20.1), 0.081	-1.19 (-5.41-3.03), 0.57

DAS28: disease activity score; CDAI: Clinical Disease Activity Index; NSAIDs: nonsteroidal anti-inflammatory drugs
TNF: tumor necrosis factor; ACPA: Anti-citrullinated protein antibody
HAQ: Health Assessment Questionnaire