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Arterial Inflammation Detected with ¹⁸F-Fluoro-Deoxyglucose Positron Emission Tomography in Rheumatoid Arthritis

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Abstract

Objectives—In addition to traditional risk factors, excess cardiovascular disease (CVD) in rheumatoid arthritis (RA) is attributed to enhanced vascular and/or systemic inflammation. In several small studies using ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) to directly assess vascular inflammation, FDG uptake was higher in RA patients than controls. Using a substantially larger RA sample, we sought to identify RA-disease characteristics independently associated with vascular FDG uptake.

Methods—RA patients underwent cardiac FDG-PET/CT, with aortic inflammation assessed by quantification of FDG uptake in the ascending aorta, calculated as the mean and maximum (max) standardized-uptake-value (SUV) of the entire ascending aorta, and of its most diseased segment (SUV MDS). Univariable and multivariable regression models were constructed to model the associations of patient characteristics with aortic FDG uptake.

Results—Ninety-one RA patients were scanned. In multivariable models, in addition to the independent associations of hypertension and body-mass-index with increased aortic FDG uptake, the prevalence of rheumatoid nodules correlated with the SUV-mean and SUV MDS-mean measurements, while anti-CCP antibodies inversely correlated with these measures and with the SUV-max and SUV MDS-max ($p < 0.05$). A significant association of RA disease activity with aortic FDG uptake was observed but restricted to anti-CCP seropositivity.

Conclusion—Traditional CV risk factors and RA-disease characteristics (rheumatoid nodules and DAS28-CRP in anti-CCP antibody positive individuals) were independently associated with ascending aortic FDG uptake in RA patients without clinical CVD.

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease primarily affecting the synovial joints but with important extra-articular features including significant effects on the cardiovascular system (1). Despite therapeutic advancements over the past decades, cardiovascular disease (CVD) continues to be the leading cause of excess deaths in RA with CVD mortality rates 1.5–3-fold higher than matched controls (2). Unfortunately, CV risk algorithms established for the general population generally underperform in RA (3), hence the development of strategies to better identify and manage the increased CV risk in RA has become a priority.

Chronic systemic and/or vascular inflammation are believed to contribute to the excess risk of atherosclerosis and CV events in RA. Atherosclerosis is an inflammatory process reflected in plaque by infiltrating macrophages and T cells, and systemically by mildly elevated levels of inflammatory cytokines such as tumor necrosis factor (TNF), interleukins-1 and -6 (IL-1, IL-6), and metalloproteases (MMPs) (4,5). Mild elevations of these cytokines and MMPs are potent predictors of future CV events in the general population, presumably through their promotion of plaque rupture (6–8). RA is characterized by much higher serum levels of the same molecules (5) which has led to the hypothesis that this amplified systemic inflammatory milieu accelerates atherosclerosis and plaque rupture in patients with RA. Indeed, a number of studies have shown circulating and articular measures of inflammation to be independent predictors of CV events in RA (9–11). However, an alternate or complementary hypothesis is that vascular inflammation is also enhanced in RA relative to non-RA controls but direct assessments of this hypothesis are few and consist of small sample sizes (12–14).

Most assessments of atherosclerosis in RA to date have utilized imaging techniques that identify the presence of atherosclerotic plaque and luminal stenosis, but not arterial wall inflammation. This is a crucial limitation as plaque inflammation is believed to represent one of the early and reversible steps of atherosclerosis (15,16). In addition, although assumed to be of rare occurrence, rheumatoid aortitis has been described in the spectrum of rheumatoid vasculitis independent of atherosclerotic plaque (17–19). The recent development of techniques that enable co-registration of PET with CT (or MRI) scans coupled with radioisotopes that are avidly taken up by macrophages (i.e., FDG) have enabled the direct identification of inflammation in vascular walls providing not only morphologic but physiologic information. Importantly, increased FDG uptake in the vessel wall suggests plaque instability, a risk factor for plaque rupture and CV events, but it may also represent vasculitis (20,21). Although identification of vascular inflammation in the coronaries is ultimately preferred, PET imaging of the coronary arteries remains challenging due to the small caliber of the coronary arteries as well as their motion during cardiac cycles (22). However, the known association of aortic atherosclerosis, as well as aortic FDG uptake, with CV events in the general population (20,21) makes the study of aortic inflammation of particular interest in RA.

Although vascular FDG-PET/CT studies in RA are few, Maki-Petaja et al reported a level of aortic FDG uptake in 17 RA patients with high disease activity equivalent to that of 34 non-RA subjects with stable CAD (12). A cross-sectional study of 10 psoriasis and 5 RA patients also demonstrated higher aortic FDG uptake compared with 10 healthy subjects after

adjusting for CV risk factors (13). However, the small RA sample sizes in these studies were inadequate to identify RA-specific factors associated with vascular inflammation. In this cross-sectional study, we hypothesized that RA-specific features would be associated with ascending aortic FDG uptake independent of conventional CV risk factors.

METHODS

Patients

The first 91 RA participants enrolled in the Rheumatoid arthritis study of The Myocardium (RHYTHM) between November 2011 and March 2015 constituted the study population. RHYTHM is an ongoing study to identify and evaluate factors associated with subclinical myocardial phenotypes in RA patients without clinical CVD. Eligibility for the RA patients required fulfillment of the 2010 (23) American College of Rheumatology criteria for RA and age \geq 18 years. Participants with a history of clinical CVD, defined as a self-reported physician diagnosed myocardial infarction, heart failure, coronary artery revascularization, angioplasty, peripheral arterial disease or procedures, pacemaker, or defibrillator devices, stroke and transient ischemic attack, were excluded from participation. Additional exclusion criteria included contraindications to receiving a vasodilator (adenosine or regadenoson) and an active history of cancer. Patients were consecutively recruited from the Columbia University Rheumatology Clinics and from local referring rheumatologists. All participants provided written consent prior to participation. The study was in compliance with the Helsinki Declaration and approved by the Columbia University Institutional Review Board. Enrollment for RHYTHM began in 2011 and is ongoing.

Outcome Measures

Ascending Aortic ^{18}F FDG-PET/CT uptake—FDG-PET/CT imaging of the ascending aorta was performed using reproducible, validated methods (24,25). Specifically, FDG was administered intravenously (10 mCi) after 18-hours of a carbohydrate-free diet (in order to suppress myocardial FDG uptake) and overnight fast. All patients had a blood sugar concentration of $<$ 200 mg/dl at the time of imaging. Imaging was performed 90 mins after FDG injection. A CT scan was obtained for attenuation correction and anatomical co-registration, using a voltage of 120 kVp and MAS of 25. Thereafter, PET imaging of the chest was performed, with 10 min per bed position. The pitch was 2.8 and slice thickness was 3.27 mm. Reconstruction of attenuation-corrected images was done using the OSEM algorithm with corrections for normalization, dead time, random events, scatter, attenuation and sensitivity. Analyses were restricted to the ascending aorta, since the CT scan performed for co-registration was a cardiac CT which did not include the upper chest or neck. The area of interest was defined as the region of the aorta beginning 1 cm above the origin of the left main coronary artery and ending at the aortic arch in transaxial view. Ascending aortic inflammation was determined by ^{18}F FDG PET uptake in the arterial wall calculated as the standardized uptake value (SUV): $\text{SUV} = r / (a' / w)$, where r is the radioactivity activity concentration [kBq/ml] measured by the PET scanner within a region of interest (ROI), a' is the decay-corrected amount of injected radiolabeled FDG [kBq], and w is the weight of the patient [g], which is used as a surrogate for a distribution volume of tracer. ROIs were drawn around the artery in transaxial orientation to measure the SUV for each region of interest.

We used several metrics to report the measured SUV. The SUV mean was defined as the average SUV of the entire ascending aorta (as defined above). Since each slice has a mean and a maximal value, we calculated the average of the mean values (SUV mean) and of the maximal values (SUV max) for all slices. The SUV of the most diseased segment (SUV MDS) was also assessed, defined as the average SUV-max (SUV MDS max) or the average MDS mean (SUV MDS mean) for three consecutive slices centered on the aortic slice with the highest SUV and the adjacent slice superior and inferior to it, providing ~1 cm of the most inflamed section of the aortic wall. Each study was read by two experienced readers using the Medview display integrated into the Corridor 4DM v. 7.0 software (Invia Medical Imaging Solutions, Ann Arbor, MI) (26). Inter-reader correlation for the SUV measurements was 0.997.

Coronary artery calcification (CAC)—CAC was ascertained with cardiac CT using a multi-detector row computed tomography system, and quantified by the Agatston method (27).

Clinical Covariates

Information on demographics and smoking was collected by standardized health questionnaires. Resting blood pressure (BP) was measured three times, and the mean value of the last two measurements was used in the analyses. Hypertension was defined as a systolic BP of ≥ 140 mm Hg, diastolic BP of ≥ 90 mm Hg, or use of antihypertensive medications. Diabetes was defined as a fasting serum glucose level of ≥ 126 mg/dl or use of antidiabetic medications. Body mass index (BMI) was calculated as the weight (in kg) divided by the height (in m²). Prescription and over-the-counter medications taken within the preceding 2 weeks were documented from containers supplied by the participants. RA disease duration was calculated from the date of physician diagnosis. RA activity was calculated using the Disease Activity Score in 28 joints (DAS28) with CRP level (28). Current and past use of glucocorticoids and of biologic and non-biologic DMARDs was ascertained by patient interview and medical records. Non-biologic DMARDs included methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Biologic DMARDs included adalimumab, etanercept, infliximab, certolizumab, golimumab, tocilizumab, abatacept, tofacitinib, anakinra, and rituximab.

Laboratory Covariates

Phlebotomy was performed after an overnight fast at the same visit as the FDG PET/CT. Serum and plasma were separated by centrifugation and stored at -80°C . All analytes were measured in the Biomarkers Core Laboratory of the Columbia University Irving Institute for Clinical and Translation Research. Anti-CCP antibodies were assessed by enzyme-linked immunosorbent assay (ELISA) using the CCP3 kit with positivity defined as ≥ 60 units. Total cholesterol, high-density lipoprotein-cholesterol, and triglycerides were measured in plasma by colorimetric assay using Cobas Intergra 400 Plus kits (Roche Diagnostics, Indianapolis, IN) and LDL was calculated using the Friedewald formula. IL-6 was assayed by ELISA test kits from R&D Systems (Minneapolis, MN). High-sensitivity CRP was measured by turbidimetric immunoassay from Cobas Intergra 400 Plus kits from Roche

Diagnostics. Rheumatoid factor (RF) IgM antibodies were assessed by ELISA with RF defined as positive at a concentration of ≥ 40 units.

Statistical Analysis

The analyses in this report were not conceived in the original design of the RHYTHM Study, which focused on myocardial FDG uptake; rather they were performed as post-hoc analyses, hence with no a priori hypothesis or power calculation to test the aortic FDG uptake. However, the question of interest was whether RA-specific characteristics would identify patients with higher aortic FDG uptake, independent of conventional CV risk factors. Because uptake could conceivably represent discrete (or diffuse) atherosclerotic plaque or diffuse vasculitic involvement, we explored as our primary outcome several measurements of FDG uptake (SUV-mean, SUV-max, SUV MDS-mean, and SUV MDS-max). The normality of the variables of interest was determined by graphical assessment and the Kolmogorov-Smirnov test. Summary statistics for outcomes and predictor variables were examined, with comparisons made using student t-test and Wilcoxon rank-sum test for normally and non-normally distributed continuous variables, respectively. Counts and percentages were calculated for categorical variables and compared using the chi-square or Fisher's exact test, as appropriate. Linear regression models were constructed to explore the association of RA-disease characteristics and traditional CV risk factors with ascending aortic ^{18}F FDG uptake quantified as the log transformed SUV-mean, SUV-max, SUV MDS-mean, and the SUV MDS-max. Tolerance was calculated to ensure that variables with excessive collinearity were not co-modeled; none of the variables had a tolerance <0.1 . To isolate the association between CV risk factors and RA-disease characteristics with the measures of ascending aortic FDG uptake, confounders were defined as those variables associated with both the outcome (ascending aortic FDG uptake) and the independent variables (CV risk factors and RA-disease characteristics). All statistical calculations were performed using Stata 12 and SAS 9.4. In all tests, a 2-tailed α of 0.05 was defined as the level of statistical significance.

RESULTS

Patient Characteristics

The characteristics of the study participants are summarized in Table 1. Most patients (80%) were female with established disease (median RA duration=7.2 years); however, 25% had disease duration less than 1.6 years. The majority (65%) were seropositive for RF and/or anti-CCP, and 8% had rheumatoid nodules. Seventy-seven percent were treated with a non-biologic DMARD, 40% with a biologic, and one third was currently receiving prednisone at a median daily dose of 5 mg. Forty-two percent had hypertension and 43% were current or ever smokers; only 9% had diabetes, 18% were taking statins, a third had a CAC score > 0 , and the median of those with a CAC > 0 was 130 (28–573). Figure 1 shows an example of a patient with high SUV uptake compared to a patient with low uptake. For the total group of RA patients, the median ascending aortic SUV-mean, SUV-max, SUV MDS-mean and SUV MDS-max were 1.83, 2.43, 1.91, and 2.59, respectively (Table 1).

Univariate analysis of the association of patient characteristics with ascending aortic ¹⁸F-FDG uptake

In univariate analysis (Table 2), age, BMI, hypertension, and CAC score were positively associated with the four study measures of ascending aortic FDG uptake (SUV-mean, SUV-max, SUV MDS-mean, and the SUV MDS-max), while HDL levels were negatively associated with these outcomes. Among RA characteristics, RA nodules were positively associated with SUV-mean and SUV-MDS mean.

Multivariable analysis of the association of patient characteristics with ascending aortic ¹⁸F-FDG uptake

In multivariable analyses (Table 3), BMI remained significantly associated with all 4 measures of ascending aortic FDG uptake. In addition, the association between hypertension and SUV-mean and SUV MDS-mean persisted, as well as the association of age and SUV MDS-max (Table 3). Although in univariate analysis the association of anti-CCP antibody titer > 60 units with SUV ascending aortic measures did not reach statistical significance, in adjusted models the association of anti-CCP antibody titer > 60 units and all 4 measures of ascending aortic FDG uptake was statistically significant (Figure 2A). Interestingly, the association between RA-disease activity (measured by DAS28-CRP) and ascending aortic FDG uptake varied depending on anti-CCP antibody status (*p* interaction term= 0.047): in those with anti-CCP > 60 units, the higher the DAS28-CRP, the higher the SUV-mean and SUV MDS-mean (Figure 2B). In addition, the association of rheumatoid nodules with SUV-mean and SUV MDS-mean observed in univariate analysis remained significant in the adjusted analyses (Figure 3). No association was identified between the shared epitope and ascending aortic FDG uptake measures.

DISCUSSION

The key finding in this study is that several RA-specific features (anti-CCP seropositivity and rheumatoid nodules) are associated with ascending aortic inflammation, as measured by ¹⁸F-FDG PET/CT, independent of conventional cardiovascular risk factors. Additionally, we have shown that the association between RA disease activity and ascending aortic inflammation was restricted to patients with anti-CCP seropositivity. Finally, this study supports the ability of PET imaging as a tool to detect aortic vessel wall inflammation in RA patients without clinical CVD; our study serving as the largest study to date to investigate this vascular outcome in RA using this imaging modality.

Cardiovascular disease continues to be the leading cause of death in RA patients. The excess risk compared with controls is only partially explained by traditional cardiovascular risk factors, with RA itself being independently associated with CVD (29). Inflammation is known to play an important role in all phases of atherosclerosis, from initiation to atherothrombosis (15,16). Chronically higher levels of circulating inflammatory cytokines in RA, relative to non-RA patients with atherosclerosis, may fuel plaque inflammation and rupture leading to increased risk of CV events; however infiltration of plaque itself with increased numbers of inflammatory cells is hypothesized to play a key role in this increased risk.

A novel imaging modality, the ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET), has emerged in the last decade as a marker of atherosclerosis in the general population as it allows the quantification of ^{18}F -2-deoxy-D-glucose uptake (vascular inflammation) within the atheroma and overall in the arterial wall (24,30). Standardized uptake values (SUVs), the outcome variables in our study, are a measure of radiotracer uptake normalized for injected dose and patient weight. SUVs are most commonly used in the assessment of ^{18}F -FDG PET/CT oncology studies for the diagnosis and staging of cancer. In addition to the anatomical imaging that CT and MRI offer, multimodal imaging with FDG-PET/CT provides molecular and functional data allowing the detection of signature pathological mechanisms. More recently, FDG PET/CT has been used in cardiac imaging for the diagnosis and follow-up of patients with inflammatory conditions of the heart including sarcoidosis, endocarditis and pacemaker infections. In vivo measures of FDG PET uptake are reproducible, positively correlate with metabolically active macrophages and macrophage infiltration into the vessel wall, and are modifiable by different pharmacological interventions targeted at reducing atherosclerotic inflammation, such as statins (31–34). More importantly, increased arterial FDG uptake is known to predict plaque expansion and rupture, leading to CV events including myocardial infarction and strokes (20,21). FDG-PET/CT is increasingly used as a primary outcome in randomized controlled trials of anti-atherogenic drugs because arterial inflammation is believed to represent one of the early and reversible steps of atherosclerosis (35,36). Several studies have also shown an association between FDG signal and CV risk factors or risk scores (21,37–40). Moreover, vascular FDG PET imaging has proven to improve the prediction of CVD beyond the traditionally used Framingham risk stratification score (41). All of these features make the use of FDG PET vascular imaging compelling in the study of CVD in RA, an illness in which systemic and articular inflammation are the sine qua non.

Aortic FDG PET imaging in two prior small studies of RA patients without clinical CVD revealed significantly increased subclinical aortic FDG uptake when compared with controls (12,13). Rose et al reported an SUV-mean of 1.49 in RA patients; similarly, we identified an ascending aortic SUV-mean of 1.83 in our RA cohort. In the general population it is documented that vessel wall inflammation leads to endothelial dysfunction, aortic stiffening, accelerated atherosclerosis, plaque destabilization, and adverse CV events (20,21,37). Indeed, Maki-Petaja et al (12) showed in a study of 17 RA patients that a decrease in aortic stiffness in response to anti-TNF treatment was paralleled by a decrease in aortic FDG uptake. Additionally, in a study of 23 RA subjects Bernelot Moens et al showed that RA patients in long-term clinical remission did not have increased arterial wall inflammation compared to controls. However, those on TNF-inhibitors had increased aortic uptake compared to subjects on non-biologic DMARDs, an association explained by longer RA disease duration (42). Hence, identification of vessel wall inflammation in RA may detect those patients at highest risk for plaque instability/rupture and CV events. It is also possible in RA that aortic wall inflammation could represent rheumatoid vasculitis (aortitis), which the FDG PET/CT technology would not be able to differentiate from plaque inflammation. The prevalence of aortitis in RA had been considered low based on autopsy studies from the 1970s and 1980s (17,18) but the challenges in diagnosing it preclude establishing its true prevalence. Thus, while most studies of vascular FDG uptake utilize maximal SUV uptake

values (32,33) as the primary outcome because of their focus on atherosclerotic plaque, we also explored mean SUV values for both the MDS and the whole ascending aorta as potential outcomes that might be more reflective of diffuse homogenous inflammation as might be envisioned with vasculitis. We speculated that conventional CV risk factors might be related to the four measures of FDG uptake differently from RA-specific characteristics. However, this did not appear to be the case, as a conventional CV risk factor (BMI) and an RA-specific characteristic (anti-CCP titer > 60) were both independently associated with all four measures of aortic FDG uptake. Likewise, another CV risk factor (hypertension) and another RA-specific characteristic (nodules) were both independently associated with SUV mean and SUV-MDS mean but not with SUV-max or SUV-MDS max. It should be noted, however, that SUV-max has been reported to have significantly improved reproducibility as compared to SUV-mean since the SUV-max value within a region of interest (ROI) is typically invariant with respect to small spatial shifts of the ROI, while the SUV-mean is only accurate if the lesion of interest has a uniform true SUV value (43).

That a component of ascending aortic FDG uptake in our RA patients is due to plaque is suggested by the independent association of BMI and hypertension with aortic FDG uptake; moreover, this association is consistent with reports in the general population in which arterial FDG uptake correlated with burden of CV risk factors (40). In non-RA patients, aortic FDG uptake has also been associated with baseline CAC as well as its progression (44, 45); however, in our RA patients, the association of CAC with ascending aortic FDG uptake lost statistical significance in the adjusted analysis, which could have been due to the exclusion of patients with clinical CVD in our studies in which the median overall CAC score was zero.

Interestingly, among the RA-specific characteristics examined, we found a positive correlation between rheumatoid nodules and FDG uptake even after adjustment for CV risk factors. Surprisingly, in univariate analyses we observed a negative correlation between anti-CCP antibody status and ascending aortic FDG PET uptake. This apparent counterintuitive association was explained, at least in part, in the multivariable analyses by an interaction with disease activity. Thus, in patients with active disease, CCP seropositivity was positively associated with SUV uptake. Interestingly, citrullinated proteins have been demonstrated within aortic atherosclerotic plaque of autopsied non-RA patients, and anti-citrullinated protein antibodies (ACPAs) in RA subjects have been associated with an increase in aortic plaque burden (46), suggesting a role for ACPAs in the acceleration of atherosclerosis in RA.

In non-RA patients, several groups have shown that statin therapy results in a significant reduction in arterial FDG PET uptake after 3 months (31–33). In ankylosing spondylitis, similar results were seen in a small study evaluating the change in aortic FDG uptake following treatment with atorvastatin (34). However, we did not find an association between the use of statins and aortic FDG uptake in our cross-sectional study possibly due to the fact that only 16 of the patients in our cohort were on statins. Additionally, a reduction in aortic FDG uptake has been described in a small study of 17 RA patients following 8-week treatment with anti-tumor necrosis factor- α (12). Although in another study, the use of TNF blockers in 13 RA subjects was associated with increased arterial uptake compared to 10 RA

patients on non-biologics DMARDs, the association was confounded by RA disease duration (42). However we did not see an association between the use of TNF-inhibitors and the extent of ascending aortic FDG uptake in our cross-sectional study. An interesting question is whether any RA therapy that can induce disease remission will also reduce vascular inflammation. To address this question, the Treatments Against RA and Effect on FDG PET/CT (TARGET) Trial (NCT0237402) will evaluate the effect of two different DMARD regimens (anti-TNF plus methotrexate vs triple therapy with methotrexate, sulfasalazine and hydroxychloroquine) on aortic and carotid inflammation and will correlate these findings with changes in RA disease activity (<https://clinicaltrials.gov/ct2/show/NCT02374021?term=TARGET+RA&rank=1>).

Strengths of our study include the comprehensive phenotyping of the RA cohort for cardiovascular and RA characteristics, including both structural and physiological measures of atherosclerosis. This, coupled with our large sample size, allowed us to evaluate for the first time the independent contribution of conventional CV risk factors and disease-specific characteristics with increased ascending aortic FDG uptake in patients with RA.

Limitations of our study include its cross-sectional nature, which precludes establishment of causation for our findings, and the evaluation of whether changes in the ascending aortic FDG uptake might parallel changes in RA-disease features (i.e. disease activity, inflammatory markers, treatment modifications). Also, while the consistency in the covariates retained in our final models across the different SUV measures make our findings less likely to be due to chance, results should be interpreted with caution.

In conclusion, in addition to conventional CV risk factors, ascending aortic FDG uptake in RA was associated with the presence of rheumatoid nodules and disease activity in those with anti-CCP antibody seropositivity. Our study results suggest that both traditional CV risk factors and RA-disease characteristics are independently associated with ascending aortic wall inflammation and likely the development of atherosclerosis in RA. These findings support the use of FDG PET imaging as an additional research modality for assessing CV risk in RA patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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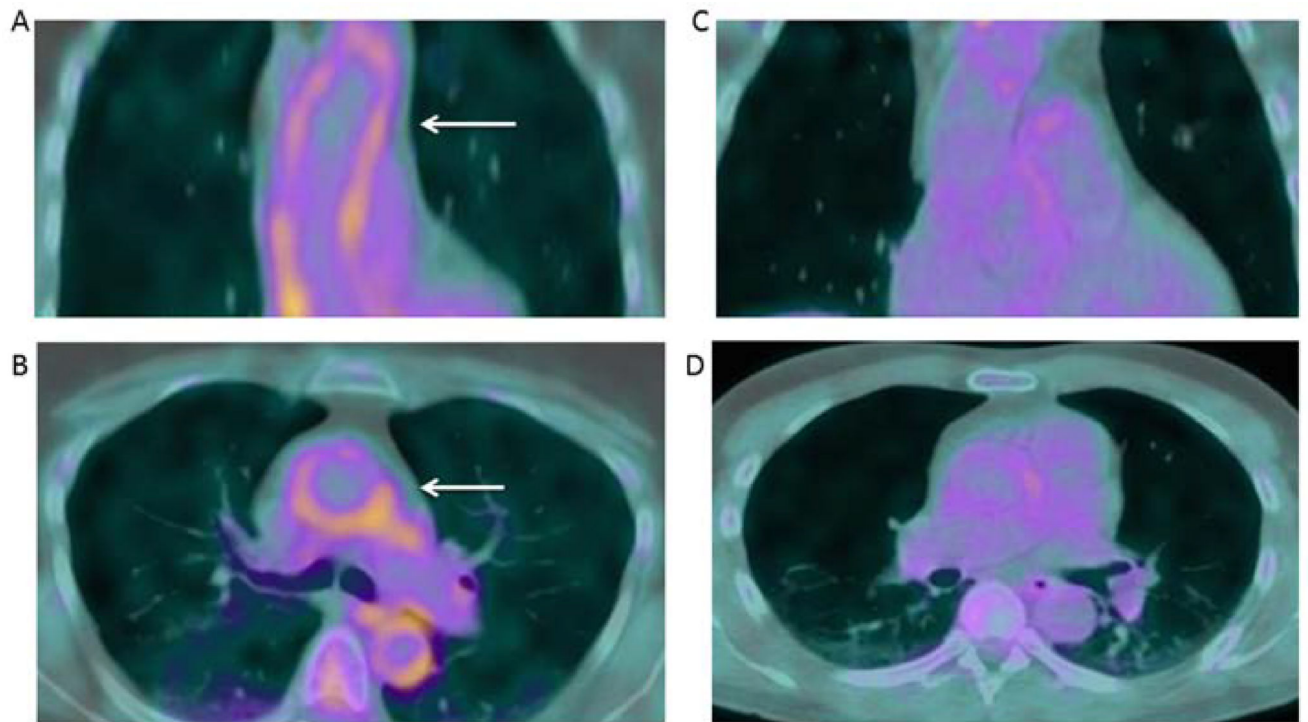


Figure 1.

Aortic FDG Uptake in RA.

Representative FDG PET/CT imaging of patients with RA with high vs low FDG uptake are shown. Radiotracer uptake in the aorta is diffuse (arrow) with an SUV-max of 2.81 and an SUV-MDS max of 2.91(A: coronal view. B: axial view) vs low 18 F-FDG uptake with an SUV-max of 1.11 and an SUV-MDS max of 1.16 (C: coronal view. D: axial view).

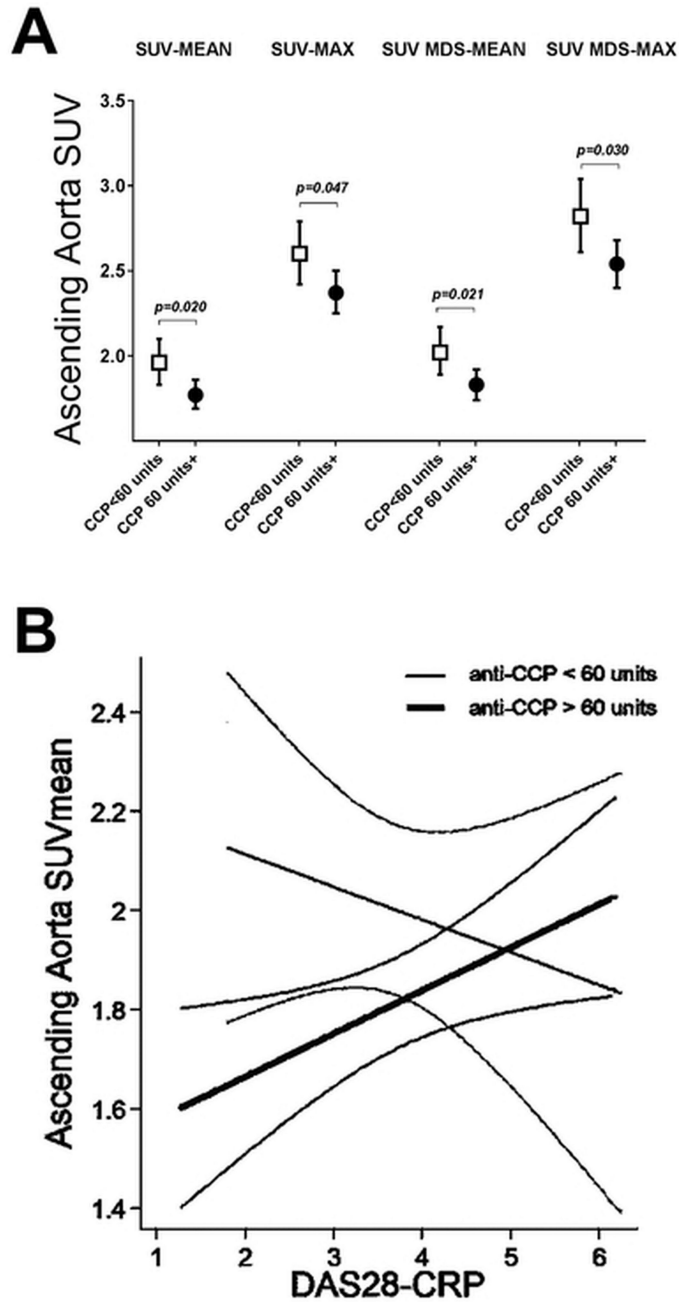


Figure 2. Adjusted Associations of anti-CCP level with Measures of FDG Uptake in the Ascending Aorta. **A.** Means and 95% confidence intervals depicted. Adjusted for age, BMI, hypertension, and the presence of rheumatoid nodules. **B.** Interaction plot depicting the association between RA-disease activity (measured by DAS28-CRP) and aortic SUV uptake vary by anti-CCP antibody level (interaction term $p=0.047$).

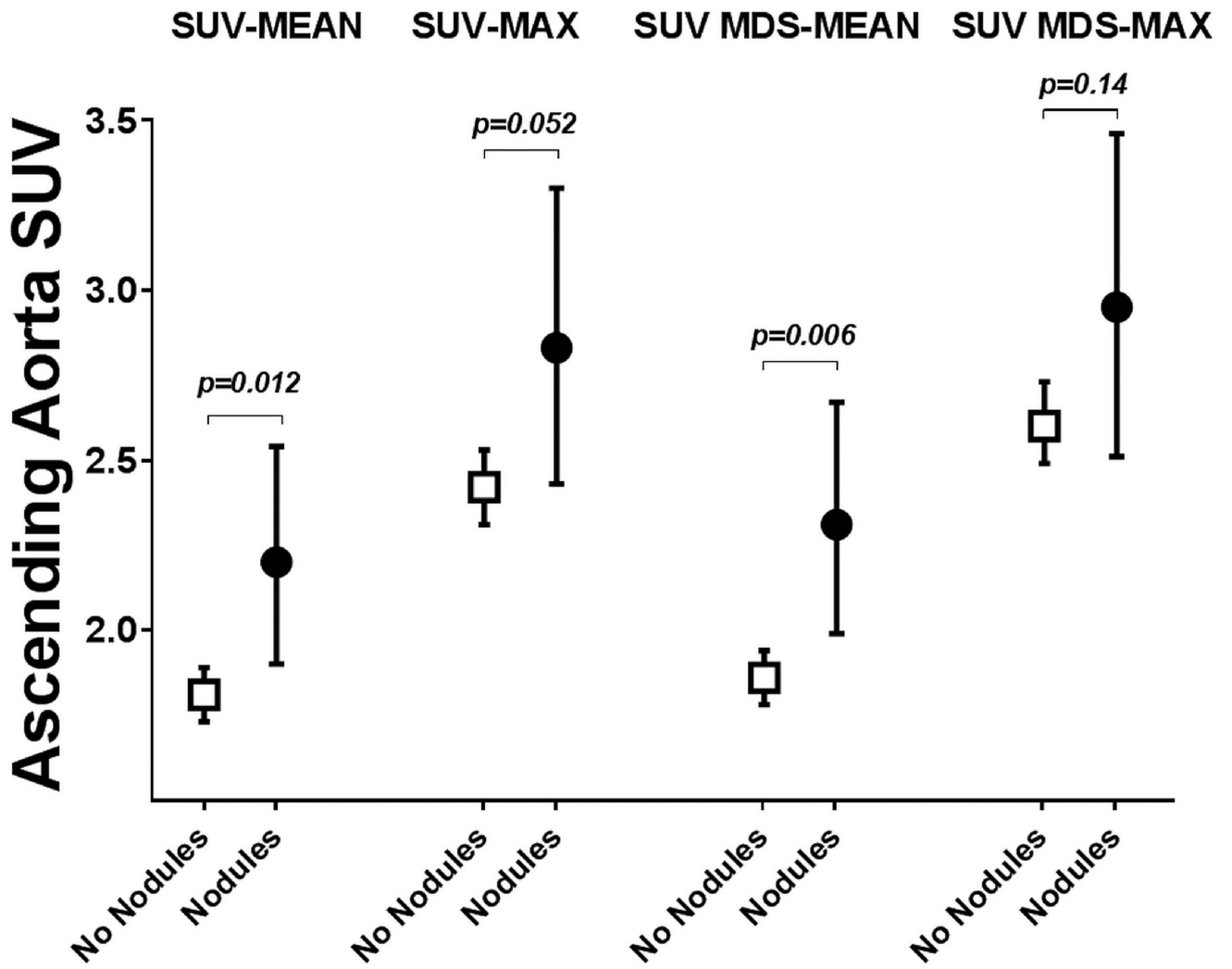


Figure 3. Adjusted Associations of Rheumatoid Nodules with Measures of FDG Uptake in the Ascending Aorta. Means and 95% confidence intervals depicted. Adjusted for age, BMI, hypertension, and anti-CCP.

Table 1

Patient Characteristics.

	RA (n=91)
Demographics	
Age, years	55 ± 13
Female, n (%)	73 (80)
Race/Ethnicity	
Non-Hispanic White, n (%)	36 (40)
Non-Hispanic Black, n (%)	12 (13)
Hispanic, n (%)	40 (44)
Other, n (%)	3 (3)
RA Characteristics	
RA duration, years	7.2 (1.6–14.4)
RF > 40 units, n (%)	49 (54)
CCP > 60 units, n (%)	58 (64)
Shared Epitope, n (%)	53 (58)
DAS28-CRP	3.7 ± 1.2
Nodules, n (%)	7 (8)
CRP, mg/L	2.2 (1.0–6.7)
IL-6, pg/mL	2.3 (1.3–7.0)
HAQ	1.0 (0.5–1.75)
Any non-biologic DMARD, n (%)	69 (76)
Any biologic DMARD, n (%)	36 (40)
Current prednisone, n (%)	30 (33)
Conventional CV Risk Factors	
BMI	28 ± 6
Ever smoking, n (%)	39 (43)
Current smoking, n (%)	9 (10)
Hypertension, n (%)	38 (42)
Diabetes, n (%)	8 (9)
Total Cholesterol	192 ± 35
LDL	110 ± 31
HDL	60 ± 19
Triglycerides	93 (77–132)
Statin use, n (%)	16 (18)
CAC > zero, n (%), [median] (IQR)	32 (35), [130] (28–573)
CAC score	0 (0–45)
Median SUV-Mean	1.83 (1.58–2.11)
Median SUV-Max	2.43 (2.14–2.79)
Median SUV MDS-Mean	1.91 (1.64–2.19)
Median SUV MDS-Max	2.59 (2.30–3.11)

Characteristics are expressed as n (%), as the mean ± standard deviation (SD), or as the median (interquartile range). RF, rheumatoid factor; anti-CCP, anti-citrullinated cyclic peptide; DAS28-CRP, disease activity score with C-RP; C-RP, C-reactive protein; HAQ, health assessment

questionnaire; DMARD, disease modifying antirheumatic drug; BMI, body mass index; LDL, low-density lipoprotein-cholesterol; HDL, high-density lipoprotein-cholesterol; CAC, coronary artery calcium; SUV, standardized uptake value; MDS, most diseased segment.

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Table 2

Univariate association of patient characteristics with ¹⁸F-FDG PET aortic uptake.

	Log SUV-mean		Log SUV-max		Log SUV-MDS Mean		Log SUV-MDS max	
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
Demographics								
Age, years	0.0037	0.033	0.0045	0.012	0.0036	0.038	0.0051	0.005
Male	-0.027	0.64	0.029	0.63	-0.028	0.64	0.062	0.32
NH-White	-0.014	0.77	-0.015	0.76	-0.012	0.80	-0.012	0.82
NH-Black	-0.029	0.68	-0.032	0.66	-0.024	0.74	-0.058	0.43
Hispanic	0.028	0.56	0.030	0.53	0.028	0.56	0.034	0.50
RA Characteristics								
RA duration, year	0.00087	0.68	0.00044	0.84	0.0013	0.53	0.00083	0.71
RF>40 units	-0.072	0.12	-0.058	0.22	-0.063	0.18	-0.055	0.27
CCP>60 units	-0.090	0.061	-0.086	0.083	-0.090	0.064	-0.100	0.053
Shared Epitope	-0.045	0.41	-0.046	0.41	-0.060	0.28	-0.050	0.39
DAS28-CRP	0.024	0.22	0.023	0.25	0.025	0.20	0.016	0.44
Nodules	0.178	0.039	0.136	0.13	0.198	0.023	0.102	0.28
log CRP, per mg/L	0.022	0.23	0.027	0.15	0.020	0.28	0.020	0.30
log IL-6, per pg/mL	0.0035	0.87	0.0017	0.94	0.011	0.62	-0.0062	0.78
HAQ, per unit	0.017	0.58	0.024	0.45	0.022	0.47	0.031	0.34
Non-biologic DMARDs	0.012	0.83	0.023	0.69	0.017	0.77	0.051	0.40
Biologic DMARDs	-0.0015	0.98	0.016	0.75	0.010	0.83	0.034	0.51
Current prednisone	-0.014	0.77	-0.018	0.72	-0.010	0.84	-0.018	0.74
Conventional CV Risk Factors								
BMI, per unit	0.012	0.004	0.013	0.002	0.011	0.007	0.012	0.005
Ever smoking	0.077	0.099	0.065	0.18	0.090	0.057	0.063	0.21
Current smoking	0.041	0.60	0.018	0.82	0.057	0.47	-0.010	0.90
Hypertension	0.130	0.005	0.107	0.027	0.129	0.006	0.105	0.036
Diabetes	0.091	0.26	0.059	0.48	0.111	0.17	0.037	0.67
Total cholesterol, per mg/dL	-0.0002	0.79	-0.00058	0.40	-0.00022	0.75	-0.0010	0.14

	Log SUV-mean		Log SUV-max		Log SUV-MDS Mean		Log SUV-MDS max	
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
LDL, per mg/dL	0.00026	0.72	0.000071	0.93	0.00028	0.71	-0.00032	0.69
HDL, per mg/dL	-0.0023	0.052	-0.0030	0.012	-0.0025	0.034	-0.0034	0.007
log Triglycerides, per mg/dL	0.083	0.13	0.080	0.16	0.087	0.12	0.073	0.22
Statin use	0.036	0.56	0.058	0.36	0.049	0.43	0.065	0.32
Any CAC	0.088	0.069	0.079	0.12	0.080	0.10	0.082	0.11
log CAC +1	0.020	0.023	0.019	0.040	0.019	0.034	0.020	0.034

Univariable linear regression coefficients and p values of the association of each patient and RA-specific characteristic with FDG aortic uptake measured as the log-transformed aortic FDG-PET SUV-mean, SUV-max, SUV MDS-mean, and the SUV MDS-max. SUV, standardized uptake value; MDS, most diseased segment; NH, non-Hispanic; RF, rheumatoid factor; anti-CCP, anti-citrullinated cyclic peptide; DAS28-CRP, disease activity score with C-RP; HAQ, health assessment questionnaire; DMARD, disease modifying antirheumatic drug; BMI, body mass index; LDL, low-density lipoprotein-cholesterol; HDL, high-density lipoprotein-cholesterol; CAC, coronary artery calcium.

Table 3

Multivariable associations of patient characteristics with FDG uptake in the Ascending Aorta.

	Extended MV Model		Reduced MV Model	
	Coefficient	p value	Coefficient	p value
<i>log SUV-mean</i>				
Age, year	0.00092	0.62		
BMI, kg/m ²	0.0089	0.045	0.01	0.006
Hypertension	0.095	0.048	0.097	0.025
Ever smoking	0.037	0.41		
HDL, mg/dL	-0.0014	0.27		
log Triglycerides	-0.031	0.63		
RF>40 units	-0.08	0.11		
CCP>60 units	-0.06	0.24	-0.101	0.02
DAS28-CRP	-0.0016	0.93		
Nodules	0.195	0.016	0.195	0.012
R ²	0.194	0.0022*	0.211	0.0001*¹
<i>log SUV- max</i>				
Age, year	0.0022	0.28	0.0031	0.073
BMI, kg/m ²	0.0103	0.035	0.012	0.002
Hypertension	0.056	0.26		
Ever smoking	0.029	0.55		
HDL, mg/dL	-0.0022	0.13		
log Triglycerides	-0.057	0.4		
RF>40 units	-0.07	0.18		
CCP>60 units	-0.058	0.28	-0.091	0.047
logCRP	-0.002	0.92		
Nodules	0.149	0.074	0.158	0.052
R ²	0.161	0.0069*	0.177	0.0004*²
<i>log SUV MDS-mean</i>				
Age, year	0.0006	0.75		
BMI, kg/m ²	0.0077	0.091	0.0098	0.011
Hypertension	0.1	0.05	0.097	0.028
Ever smoking	0.055	0.24		
Diabetes	-0.028	0.75		
HDL, mg/dL	-0.0019	0.17		
log Triglycerides	-0.028	0.67		
RF>40 units	-0.071	0.16		
CCP>60 units	-0.064	0.22	-0.102	0.021
DAS28-CRP	0.00086	0.96		
Nodules	0.212	0.012	0.215	0.006
R ²	0.185	0.0039*	0.207	0.0001*³

	Extended MV Model		Reduced MV Model	
	Coefficient	p value	Coefficient	p value
<i>log SUV MDS-max</i>				
Age, year	0.0027	0.19	0.0038	0.038
BMI, kg/m ²	0.0089	0.074	0.011	0.009
Hypertension	0.066	0.23		
Ever smoking	0.034	0.5		
Diabetes	-0.068	0.46		
HDL, mg/dL	-0.0029	0.057		
log Triglycerides	-0.067	0.34		
RF>40 units	-0.06	0.27		
CCP>60 units	-0.0057	0.18	-0.105	0.03
DAS28-CRP	-0.0057	0.79		
Nodules	0.128	0.15	0.125	0.14
R ²	0.142	0.016*	0.158	0.0010*⁴

Multivariable linear regression coefficients and p values of the association of patient and RA-specific characteristic with FDG aortic uptake measured as the log-transformed aortic FDG-PET SUV-mean, SUV-max, SUV-MDS mean, and the SUV-MDS max.

¹Root Mean Square Error (RMSE) of 0.19;

²RMSE of 0.20;

³RMSE of 0.19;

⁴RMSE of 0.21.

SUV, standardized uptake value; MDS, most diseased segment; SUV, standardized uptake value; MDS, most diseased segment; BMI, body mass index; HDL, high-density lipoprotein-cholesterol; RF, rheumatoid factor; anti-CCP, anti-citrullinated cyclic peptide; DAS28-CRP, disease activity score with C-RP.