JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 9, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.09.027

FDG Uptake by Prosthetic Arterial Grafts in Large Vessel Vasculitis Is Not Specific for Active Disease

Taryn Youngstein, MD,[a] Enrico Tombetti, MD,[a,b] Jaita Mukherjee, MD,[a] Tara D. Barwick, MD,[c,d] Adil Al-Nahhas, MD,[c,d] Emyr Humphreys, MD,[e] Julian Nash, PhD,[f] Jacqueline Andrews, MD,[g] Elena Incerti, BSc, MSc,[h,i] Elisabetta Tombolini, MD,[b,j] Annalaura Salerno, MD,[j,k] Silvia Sartorelli, MD,[b,j] Giuseppe A. Ramirez, MD,[b,j] Maurizio Papa, MD,[l] Maria Grazia Sabbadini, MD,[b,j] Luigi Gianolli, MD,[h] Francesco De Cobelli, MD,[j,k] Federico Fallanca, MD,[h] Elena Baldissera, MD,[b] Angelo A. Manfredi, MD,[b,j] Maria Picchio, MD,[h] Justin C. Mason, PhD[a]

ABSTRACT

OBJECTIVES This study investigated the incidence and clinical significance of arterial graft-associated uptake of fluorodeoxyglucose in large-vessel vasculitis (LVV).

BACKGROUND The role of ^{18}F-labeled fluorodeoxyglucose-positron emission tomography/computed tomography ([^{18}F]FDG-PET/CT) in the management of LVV remains to be defined. Although [^{18}F]FDG uptake at arterial graft sites raises concerns regarding active arteritis or infection, its clinical significance in LVV has never been formally studied.

METHODS An observational prospective study sought to identify patients with Takayasu arteritis (TA) undergoing [^{18}F]FDG-PET/CT more than 6 months after graft surgery from a large cohort of patients from 2 tertiary referral centers. [^{18}F]FDG uptake by the graft and native arteries was scored on a scale of 0 to 3 relative to hepatic uptake, and periprosthetic maximum standardized uptake value (SUV_{max}) was calculated. Periprosthetic [^{18}F]FDG uptake in active disease was compared with that in inactive disease, and arterial progression was assessed by prospective magnetic resonance angiography (MRA).

RESULTS Twenty-six subjects with TA were enrolled. All were afebrile with negative blood culture. Periprosthetic uptake was significant in 23 of 26 patients, and the mean SUV_{max} was 4.21 $\pm$ 1.46. Median periprosthetic [^{18}F]FDG uptake score (3; interquartile range [IQR]: 3 to 3) was higher than in native aorta (1; IQR: 0 to 1; $p < 0.001$). Graft-specific [^{18}F]FDG uptake was unrelated to disease activity. Despite the high frequency of graft-associated [^{18}F]FDG uptake, sequential MRAs did not reveal arterial progression in 25 of 26 patients; the 1 remaining case showed minor progression limited to native arteries. Nine patients underwent repeated PET/CT scanning without showing changes in graft-specific uptake, despite increased treatment.

CONCLUSIONS Significant [^{18}F]FDG uptake that is confined to arterial graft sites in patients with LVV does not reflect clinically relevant disease activity or progression. To minimize exposure to immunosuppression and in the face of negative blood culture, clinically quiescent arteritis, normal or stably raised C-reactive protein levels, we elected not to escalate treatment and monitor progression with MRA. (J Am Coll Cardiol Img 2017;10:1042–52)

From the [a]Cardiovascular Sciences and Rheumatology Units, Imperial College Healthcare National Health Service Trust, London, United Kingdom; [b]Unit of Internal Medicine and Clinical Immunology, IRCCS San Raffaele Scientific Institute, Milan, Italy; [c]Imaging Department, Imperial College Healthcare National Health Service Trust, London, United Kingdom; [d]Division of Cancer and Surgery, Imperial College London, London, United Kingdom; [e]Prince Charles Hospital, Merthyr Tydfil, Wales; [f]Rheumatology Unit, University Hospital Wales, Cardiff, Wales; [g]Rheumatology Unit, Chapel Allerton Hospital, Leeds, United Kingdom; [h]Unit of Nuclear Medicine, IRCCS San Raffaele Scientific Institute, Milan, Italy; [i]University of Milan, Milan, Italy; [j]Vita-Salute San Raffaele University, Milan, Italy; [k]Unit of Radiology, IRCCS San Raffaele Scientific Institute, Milan, Italy; and the [l]Unit of Radiology-Ville Turro, IRCCS San Raffaele Scientific Institute, Milan, Italy. Supported by the Imperial College, National Institute for Health Research Biomedical Research Centre scheme. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Youngstein and Tombetti contributed equally this work and are to be considered first authors. Drs. Picchio and Mason contributed equally to this work and are to be considered senior authors.

Manuscript received July 19, 2016; revised manuscript received September 2, 2016, accepted September 15, 2016.

Positron emission tomography (PET) with ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG) is commonly used for investigation of large-vessel vasculitis (LVV) (1,2). [^{18}F]FDG uptake by metabolically active cells provides an estimate of the extent and intensity of arterial wall inflammation in active giant-cell arteritis (GCA) and Takayasu arteritis (TA) (3–6). Co-registration of images generated by [^{18}F]FDG-PET/computerized tomography (CT) allows precise anatomic location of metabolic activity and enhanced sensitivity for detection of arterial wall inflammation (7). In TA, the principle role for [^{18}F]FDG-PET/CT lies in the diagnosis of active disease (1). Likewise, [^{18}F]FDG-PET/CT can demonstrate LVV in patients with GCA and facilitates diagnosis in those presenting with prominent systemic symptoms but without characteristic features such as headache and jaw claudication (6).

SEE PAGE 1053

Assessment of LVV disease activity during follow-up is a major unmet need. Acute phase reactants and multi-item activity indices do not accurately reflect local pathogenic events or predict arterial disease progression. Likewise, in this regard, the role of [^{18}F]FDG-PET/CT remains unclear. First there is concern regarding cumulative radiation exposure. Second, although the sensitivity and specificity of [^{18}F]FDG-PET/CT may be high in active TA (3), opinion is divided concerning its sensitivity for detecting partially treated or relapsing disease (8). Relatively poor correlation between [^{18}F]FDG uptake and disease activity markers has been reported (9), although other studies suggest a closer relationship (10–12). Although the intense linear arterial wall [^{18}F]FDG uptake seen in active LVV may be reduced by immunosuppression (13), it is not uncommon to find low-grade uptake in those with clinically inactive disease and normal acute-phase reactants (9). Persistent [^{18}F]FDG uptake may reflect residual arterial wall inflammation, vascular remodeling, progressive fibrosis, or atherogenesis, and discriminating among these is complicated by the lack of available biopsy material.

Our use of [^{18}F]FDG-PET/CT in the management of LVV revealed an additional factor complicating its use, namely, the uptake of [^{18}F]FDG by arterial grafts in patients with clinically inactive disease and without evidence of progressive arterial involvement. This led us to review imaging studies of 220 cases. Twenty-six TA patients who had previously undergone open vascular graft insertion and subsequent [^{18}F]FDG-PET/CT scanning were identified and followed longitudinally. Arterial graft-specific [^{18}F]FDG uptake was sought, its cause investigated, and its clinical outcome determined. Data demonstrated that moderate graft-associated [^{18}F]FDG uptake in LVV, in the absence of other markers of disease activity, does not typically reflect clinically relevant arteritis or indicate graft complications such as progressive occlusion, perianastomotic aneurysms, or infection. [^{18}F]FDG uptake per se does not imply that further diagnostic work-up or therapy change is required.

ABBREVIATIONS AND ACRONYMS

CRP = C-reactive protein

[^{18}F]FDG-PET/CT = ^{18}F-labeled fluorodeoxyglucose-positron emission tomography/computed tomography

GCA = giant-cell arteritis

LVV = large-vessel vasculitis

MRA = magnetic resonance angiography

SUV = standardized uptake value

TA = Takayasu arteritis

METHODS

This cross-sectional and observational prospective study (April 2010 to December 2015) included 220 patients with TA followed at Hammersmith Hospital, London, or San Raffaele Scientific Institute, Milan. Inclusion criteria were presence of an arterial graft and [^{18}F]FDG-PET/CT and magnetic resonance angiography (MRA) scanning at least 6 months after graft surgery. Patients satisfying these criteria, whose baseline scanning was performed prior to 2010, were also included and followed prospectively. Online Figure 1 shows the study flowchart, which identified 26 TA cases satisfying these criteria. Demographic data including diagnosis, vascular surgical procedure, disease activity at the time of the PET/CT, and initial and current immunosuppressive therapy were collected (**Table 1**). Large-vessel vasculitis disease activity was assessed using C-reactive protein (CRP) level (normal: <10 mg/l) and the U.S. National Institutes of Health (NIH) index 4-point score (14). Additional assessment included baseline MRA, which was repeated during follow-up to assess lesion evolution and arterial progression. Nine patients underwent repeated [^{18}F]FDG-PET/CT scans which were included and compared with baseline studies. All [^{18}F]FDG-PET/CT and MRA images were reviewed by 2 independent physicians. In cases of discrepancy, the final interpretation was determined by consensus. Clinical assessments, imaging studies, and laboratory investigations were performed during routine clinical care for each patient.

[^{18}F]FDG-PET ACQUISITION. [^{18}F]FDG-PET was performed using a 64-slice PET/CT unit (either a Discovery model; General Electric, Milwaukee, Wisconsin; or a Biograph model; Siemens, Knoxville, Tennessee [U.S.] or Muenchen, Germany), following standard protocols (15,16). Patients fasted for >6 h, and the pre-scan blood glucose level was <12 mmol/l before the injection of 350 to 400 MBq of [^{18}F]FDG. An emission scan was obtained from midthigh to skull base, using the multiple-bed position technique (5 to 6 positions, 4 min per position) and following 60 to

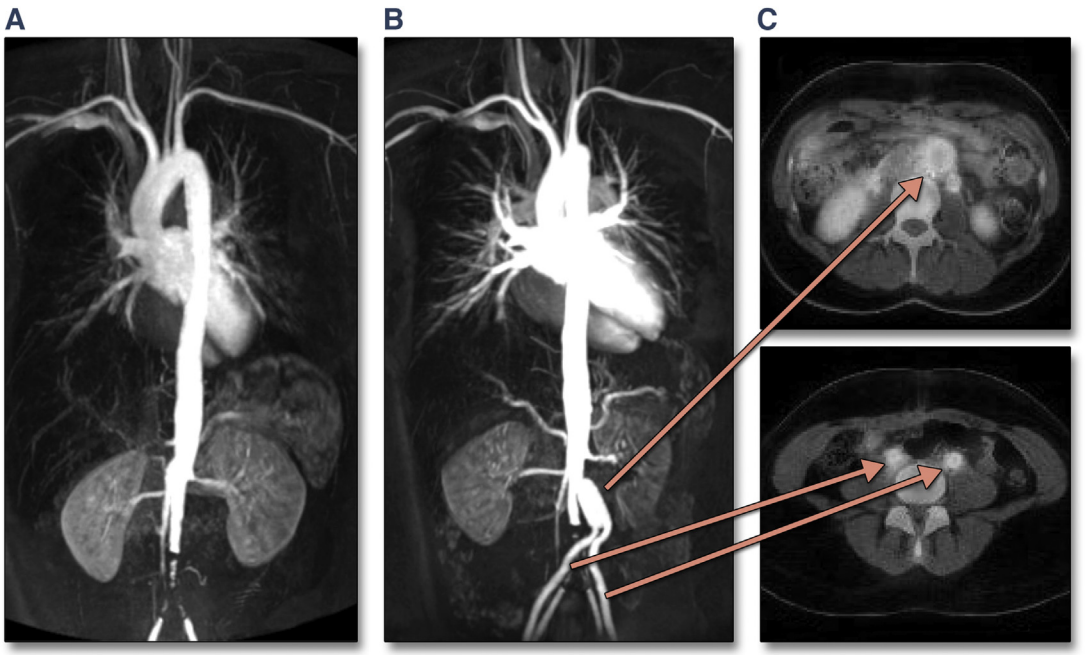
TABLE 1 Patient Demographics and Laboratory and Imaging Findings

Patient # (Sex/Age)	Age at Diagnosis	Intervention for Arterial Grafting	Treatment	PET/CT (Months After Surgery)	Disease Activity (NIH Criteria)	PET Score Aorta*	PET Score Graft* (Uptake Pattern)	SUV Graft	CRP (mg/l)	MRA Progression (Months of FU)
1. F 24 yrs	20 yrs	Aorto-bifemoral bypass	Pred + MTX	14	No	0	3 (Diffuse)	8.0	1.3	None (57)
2. F 26 yrs	18 yrs	Mid-aortic graft	Pred + AZA	90	No	2	3 (Diffuse)	2.7	3.0	None (100)
3. F 59 yrs	39 yrs	AVR and ascending aortic graft	Pred + MTX	20	No	0	3 (Diffuse)	4.5	9.0	None (89)
4. F 60 yrs	18 yrs	Aortocarotid and aortoiliac bypass	None	68	No	0	3 (Diffuse)	4.9	2.6	None (23)
5. F 23 yrs	22 yrs	AVR and ascending aortic graft	Pred + MTX	6	No	0	3 (Diffuse)	6.2	16.0	None (69)
6. F 31 yrs	28 yrs	AVR and ascending aortic graft	None	35	No	0	2 (Diffuse)	2.5	1.0	None (150)
7. F 57 yrs	32 yrs	Aortocarotid bypass	Pred + MTX	44	No	1	3 (Focal)	5.1	5.0	None (67)
8. F 40 yrs	38 yrs	Aortocarotid bypass	Pred + AZA	6	No	0	3 (Diffuse)	4.7	3.0	None (180)
9. M 35 yrs	31 yrs	Aortocarotid bypass	Pred + Cyclo + MMF + tacrolimus	44	No	0	2 (Focal)	N/A	1.7	None (49)
10. F 42 yrs	42 yrs	Aortic arch graft	Pred + AZA	7	No	1	3 (Diffuse)	N/A	7.0	None (39)
11. F 41 yrs	41 yrs	AVR and ascending aortic graft	Pred + MTX	6	No	0	3 (Diffuse)	4.4	2.6	None (12)
12. F 43 yrs	35 yrs	Aorto-bifemoral bypass	Pred + MTX	93	Yes	1	3 (Diffuse)	4.3	18.8	46 (9)
13. F 48 yrs	34 yrs	AVR and ascending aortic graft	Pred + MTX + Infliximab	12	No	1	1 (Diffuse)	3.0	9.1	None (29)
14. M 62 yrs	18 yrs	AVR and ascending aortic graft	Pred + MMF	160	No	2	3 (Focal)	6.4	19.4	None (17)
15. F 45 yrs	31 yrs	Ascending aortic graft	Pred + MTX	35	Yes	2	3 (Focal)	3.9	7.0	None (20)
16. F 38 yrs	23 yrs	AVR and ascending aortic graft	Pred + MTX + Infliximab	38	No	1	3 (Focal)	2.8	1.0	None (29)
17. F 35 yrs	24 yrs	AVR and ascending aortic graft	Pred + sirolumus + Tocilizumab	30	Yes	0	0 (none)	1.2	0.2	None (10)
18. F 46 yrs	20 yrs	Ascending aortic graft	Pred + MTX + Tocilizumab	204	No	1	2 (Focal)	4.2	0.1	None (30)
19. F 46 yrs	30 yrs	AVR and ascending aortic graft	Pred + MTX + Infliximab	31	Yes	1	3 (Diffuse)	5.0	13.0	Mild (22)
20. F 38 yrs	24 yrs	Aortocarotid bypass	Pred + MTX	166	No	0	3 (Diffuse)	5.0	3.1	None (11)
21. F 53 yrs	45 yrs	AVR and ascending aortic graft	Pred + MTX + Infliximab	30	Yes	1	3 (Diffuse)	4.6	6.0	None (6)
22. F 46 yrs	32 yrs	AVR and ascending aortic graft, Aorto-bi-iliac L aortorenal bypass	MTX	42	No	3	3 (Focal)	3.9	1.7	None (21)
23. F 50 yrs	29 yrs	R subclavian-brachial bypass	AZA	240	Yes	1	0 (none)	2.2	4.0	None (2)
24. M 49 yrs	28 yrs	Abdominal Aortic aneurismectomy + aorto-bifemoral bypass	Pred	166	No	2	3 (Diffuse)	3.8	1.3	None (3)
25. F 42 yrs	39 yrs	Left common carotid patch	None	18	No	1	3 (Focal)	3.5	0.3	None (12)
26. F 44 yrs	22 yrs	Aorto-left carotid Aorto bifemoral Aorto-right humeral bypass	None	220	No	1	3 (Diffuse)	4.2	5.3	None (24)

*0 = no signal; 1 = less than liver; 2 = same as the liver; 3 = more than the liver.

AVR = aortic valve replacement; AZA = azathioprine; CRP = C-reactive protein; cyclo = cyclophosphamide; FU = follow-up; L = left; MMF = mycophenolate mofetil; MRA = magnetic resonance angiography; MTX = methotrexate; NIH = National Institutes of Health; PET/CT = positron emission tomography/computed tomography; Pred = prednisolone/prednisone; R = right; SUV = standardized uptake value.

FIGURE 1 Imaging Studies From a 24-Year-Old Woman With TA



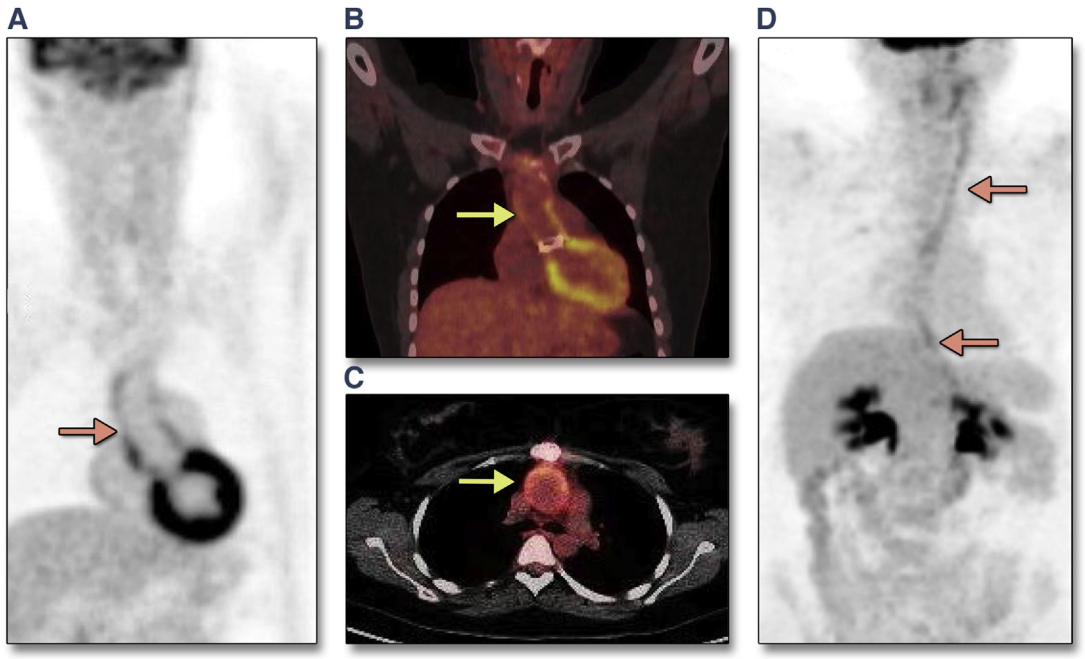
(A) MRA reveals a distal aortic occlusion, treated by **(B)** aortobifemoral grafting. **(C)** [^{18}F]FDG-PET 2 years later revealed diffuse tracer uptake confined to the aortic and femoral graft components. The **arrows** link MRA graft anatomy to relevant areas of the [^{18}F]FDG-PET scan. The patient remained well and no evidence for infection or disease activity was found. [^{18}F]FDG-PET = ^{18}F-labeled fluorodeoxyglucose-positron emission tomography; MRA = magnetic resonance angiography; TA = Takayasu arteritis.

90 min uptake. Computed tomography data were acquired without contrast and used for attenuation correction and image fusion. PET data were reconstructed using an ordered subset expectation maximization iterative reconstruction and attenuation and corrected using CT data. The radiation exposure from the [^{18}F]FDG-PET/CT was between 10.5 and 13.0 mSv.

[^{18}F]FDG-PET/CT ANALYSIS. [^{18}F]FDG-PET/CT images were displayed and analyzed using a dedicated PET multiplanar workstation with coronal, transaxial, and sagittal planes, and rotating 3-dimensional (3D) maximum intensity projection images. All vascular lesions were evaluated using a qualitative (visual analysis) and a semi-quantitative PET parameter. Visual analysis was performed using a predetermined set of arteries and distinguished prosthetic grafts and native lesions. To assess whether the periprosthetic tissue demonstrated significant [^{18}F]FDG uptake, an uninvolved area of the native thoracoabdominal aorta was used as a reference. The aorta was chosen because: 1) its dimensions reduce underestimation of local activity due to geometric and partial volume effects; 2) the thoracoabdominal aorta represents the site most frequently involved in TA; and 3) it provides the most closely matched control for the grafted site, which included the aorta in 24 of 26 patients. Focal uptake in the arterial wall was compared to uptake in the liver, using a 4-point visual scale where grade 0 = no vascular uptake; grade 1 = uptake lower than that in the liver; grade 2 = uptake equal to the liver; and grade 3 = uptake greater than that in the liver (2). Grades 2 and 3 were considered significant vascular [^{18}F]FDG uptake. For semiquantitative analysis, a volumetric region of interest (ROI) was drawn manually around the vessel wall to exclude adjacent structures. Regions of interest were moved manually along the arterial walls in contiguous axial slices to locate the maximum standardized uptake value (SUV_{max}) within the arterial volume of interest.

MAGNETIC RESONANCE IMAGING. Magnetic resonance angiography was performed with 1.5-T MR whole-body scanners and dedicated coils (Philips Healthcare, Eindhoven, the Netherlands). Morphologic sequences were used (proton density black blood turbo spin echo: field of view 260 × 152; acquisition matrix = 260 × 264; reconstruction matrix = 528; acquisition voxel measurement, phase, and slice = 1.00/0.95/6.00 mm;

FIGURE 2 Nonphysiological [^{18}F]FDG Uptake Localized to Synthetic Aortic Grafts



(A to C) [^{18}F]FDG-PET/CT reveals increased [^{18}F]FDG uptake confined to the ascending aortic grafts **(arrows)** in 2 female TA patients. **(D)** [^{18}F]FDG uptake in another female patient with TA is confined to the aortocarotid and aorto-aorto graft **(arrows)** and not seen in the native aorta. Abbreviations as in Figure 1.

reconstruction voxel measurement, phase, and slice = 0.49/0.49/6.00 mm; repetition time/echo time (TR/TE) = 20/2; electrocardiography-triggered; in expiratory breath hold: 10 s). The high resolution sequences were performed before and after contrast administration (coronal high resolution 3D fast field echo: field of view 360 × 276; acquisition matrix = 684 × 521; reconstruction matrix 880; slice thickness = 0.8 mm; TR/TE/flip angle = 6.3 ms/2.1 ms/20°; acquisition time = 3 min 28 s). These sequences allowed evaluation of vessel wall thickness up to 1 mm. Progression was defined as the appearance of novel lesions or an increase in width and/or length and/or percentage of luminal stenosis in established lesions.

STATISTICS. Data were analyzed using Prism version 5 software (GraphPad, La Jolla, California). Numerical data are mean ± SD or median and interquartile range (IQR) as appropriate. Differences between groups were analyzed using the Mann-Whitney *U* test. Wilcoxon matched pairs signed-rank test was performed to compare periprosthetic [^{18}F]FDG uptake between baseline and repeated scans. Spearman's rank correlation coefficient was used for correlative analyses. Differences were considered significant at a p value of <0.05.

RESULTS

COHORT DEMOGRAPHIC DATA. Takayasu arteritis cohorts totaling 220 patients from 2 European tertiary referral centers were analyzed. Twenty-six patients (n = 23 women) who had undergone open surgery for synthetic graft insertion and/or mechanical valve replacement and who subsequently underwent [^{18}F]FDG-PET/CT scanning for investigation of suspected LVV disease activity were identified. They underwent clinical and laboratory follow-up including sequential MRA as part of standardized routine clinical care (Table 1, Figures 1 and 2). The mean age at diagnosis was 29 ± 8 years, with mean age at study baseline of 43 ± 10 years. Initial [^{18}F]FDG-PET/CT scanning was performed 70 ± 74 months after the last surgical intervention. The clinical indications for [^{18}F]FDG-PET/CT scanning included investigation of suspected disease relapse (n = 10) and monitoring response to changes in therapy (n = 16). C-reactive protein levels at baseline were low (median 3.0 mg/l; IQR: 1.3 to 7.5). Using the NIH disease activity score, we judged 20 TA patients to have inactive disease and 6 patients active disease at the time of the scan (Tables 1 and 2, Figure 3).

BASELINE ASSESSMENT: PERIPROSTHETIC [^{18}F]FDG UPTAKE IS FREQUENT IN LVV. Qualitative visual analysis was used to determine maximal [^{18}F]FDG uptake at graft sites and in the native aorta, relative to constitutive liver uptake. Significant (grade ≥2) periprosthetic uptake was seen in 23 of 26 cases (88%), with a mean SUV_{max} of 4.21 ± 1.46. The pattern of graft uptake was diffuse in 16 patients (62%) and focal in 8 (31%). In comparison, 16 patients (62%) had detectable [^{18}F]FDG uptake in the native aorta, and this was significant in only 5 patients (19%).

The median [^{18}F]FDG uptake score was higher in arterial grafts (3; IQR: 3 to 3) than in the native aorta (1; IQR: 0 to 1; $p < 0.001$) (Figure 4A). Analyzing individual patients, 22 of 26 (85%) exhibited higher [^{18}F]FDG uptake by the graft than the native aorta (Table 1). Another 3 patients had equivalent [^{18}F]FDG uptake scores at the 2 sites. In only 1 case (Table 1, Patient #23) did aortic uptake exceed that of the graft. However, in that case, the graft (a subclavian-humeral bypass) had a diameter at the limit of PET detection, and underestimation due to partial volume effect cannot be excluded.

PERIPROSTHETIC [^{18}F]FDG UPTAKE DOES NOT REFLECT LVV ACTIVITY STATUS. To investigate the influence of LVV activity on graft-associated [^{18}F]FDG uptake, patients were divided into active (NIH: ≥2; n = 6) or inactive (NIH: <2; n = 20) disease. Periprosthetic [^{18}F]FDG uptake scores did not reflect activity status (median scores in active vs. inactive patients: 3; IQR: 0 to 3 vs. 3; IQR: 1 to 3; $p = 0.494$). Likewise, the mean graft SUV_{max} in inactive disease did not differ significantly from that of active disease (4.4 ± 1.4 vs. 3.5 ± 1.5, respectively; $p = 0.343$). Despite inactive disease demonstrating higher [^{18}F]FDG arterial graft uptake scores than the native aorta (median: graft = 3; IQR: 3 to 3 vs. aorta = 1; IQR: 0 to 1; $p < 0.001$), this did not reach the threshold for significance in the active group (median: graft = 3; IQR: 1.5 to 3 vs. aorta = 1; IQR: 1 to 1; $p = 0.310$).

Correlation analysis (Table 2) did not reveal a relationship between graft [^{18}F]FDG uptake and disease activity (number of NIH criteria: rho = −0.151; $p = 0.463$) or CRP levels (rho = 0.316; $p = 0.116$). Although periprosthetic SUV_{max} did not correlate with the number of NIH criteria (rho = −0.109; $p = 0.612$), a positive correlation with CRP was found (rho = 0.459; $p = 0.024$). However, CRP values in our sample of actively treated patients were predominantly in the normal range (Table 1) and were overlapping in active and inactive patients (median: 6.5; IQR: 3.0 to 14.4 vs. 2.8; IQR: 1.3 to 6.6 mg/l, respectively; $p = 0.196$). Therefore, these combined data suggest that periprosthetic [^{18}F]FDG uptake does not reflect LVV disease activity.

TABLE 2 Statistical Analysis

Qualitative Variable	
Sex (F:M ratio)	26:3
Specific therapy	
None	4 (15)
Steroids	20 (77)
Methotrexate	14 (54)
Azathioprine	4 (15)
Mycophenolate mofetil	2 (8)
Cyclophosphamide	1 (4)
Tacrolimus	1 (4)
Sirolimus	1 (4)
Infliximab	5 (19)
Tocilizumab	2 (8)
Active disease (NIH criteria)	6 (23)
Pattern of periprosthetic [^{18}F]FDG uptake	
Focal	5 (19)
Diffuse	16 (62)

Numerical Variables	
[^{18}F]FDG uptake score aorta	1 (0–1)
[^{18}F]FDG uptake score graft	3 (3–3)
Age at disease onset, yrs	29 ± 8
Age, yrs	43 ± 10
Months from vascular surgery	70 ± 74
CRP, mg/l	3 (1.3–7.5)
SUV_{max} graft	4.21 ± 1.46
Follow-up, months	24 (12–60)

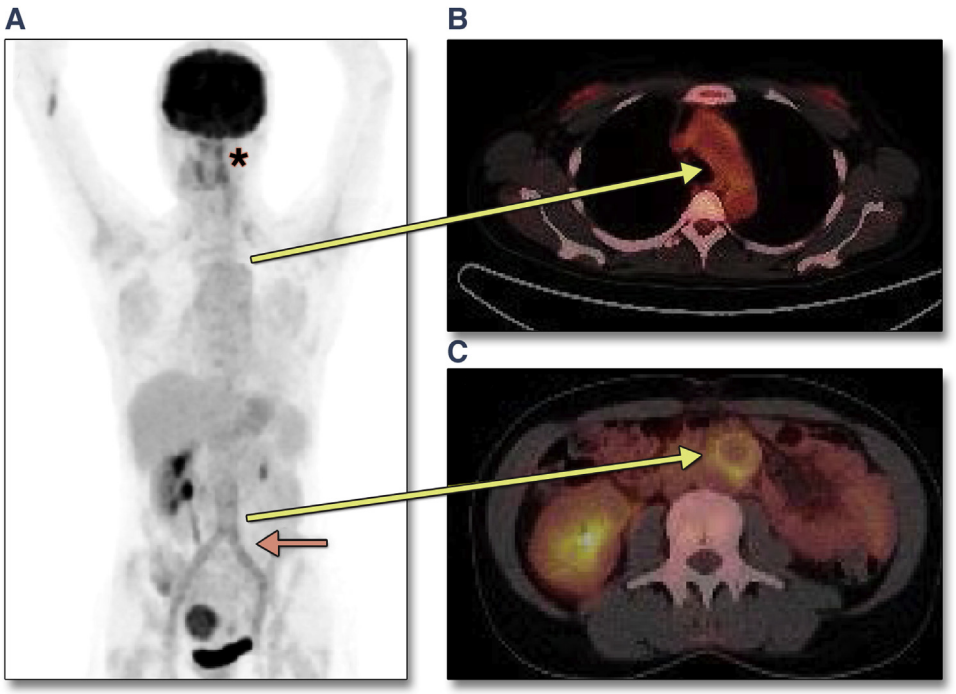
	Disease Activity		
Numerical Variables	Yes	No	p Value
[^{18}F]FDG uptake score graft	3 (0–3)	3 (3–3)	0.494
SUV_{max} graft	3.53 ± 1.50	4.44 ± 1.41	0.343

Spearman Correlation Analysis	Rho	p Value
N of NIH criteria and [^{18}F]FDG uptake score in the graft	−0.151	0.463
Plasma CRP levels and [^{18}F]FDG uptake score in the graft	0.316	0.116
N of NIH criteria and SUV_{max} in the graft	−0.109	0.612
Plasma CRP levels and SUV_{max} in the graft	0.459	0.024

Values are n (%), median (interquartile range), or mean ± SD.
Abbreviations as in Table 1.

LONGITUDINAL FOLLOW-UP: PERI-PROSTHETIC [^{18}F]FDG UPTAKE DOES NOT REFLECT ARTERIAL PROGRESSION OR GRAFT-ASSOCIATED COMPLICATIONS. During follow-up, MRA was used to exclude progressive arterial injury. The most recent MRA scans were analyzed and performed 24 (IQR: 12 to 60) months from baseline assessment. Despite the high frequency of periprosthetic [^{18}F]FDG uptake at baseline, 25 patients (96%) showed no sign of TA progression in native arteries or at arterial graft sites during longitudinal follow-up (Table 1). In 1 patient (Table 1, Patient #19), increased arterial wall thickening was

FIGURE 3 [^{18}F]FDG-PET/CT From a 43-Year-Old Woman With Active TA and Previous Aortobifemoral Graft Insertion



(A and B) [^{18}F]FDG uptake in the native aortic arch **(top arrow)** and vertebral arteries **(star)**. **(A and C)** Although no [^{18}F]FDG uptake was observed in the native abdominal aorta, enhanced uptake was seen confined to the aortobifemoral graft **(bottom arrows)**. Abbreviation as in Figure 1.

seen in the supra-aortic vessels and the thoracic aorta (separate from the arterial graft location). This was associated with mild loss of lumen diameter and necessitated a change from tocilizumab to infliximab. Importantly, radiographic follow-up did not demonstrate any complications at arterial graft sites, including restenosis/occlusion, perianastomotic dilation, or graft infection. Overall, these data show that periprosthetic [^{18}F]FDG uptake does not reflect either progressive arterial injury or the occurrence of local complications at the graft site.

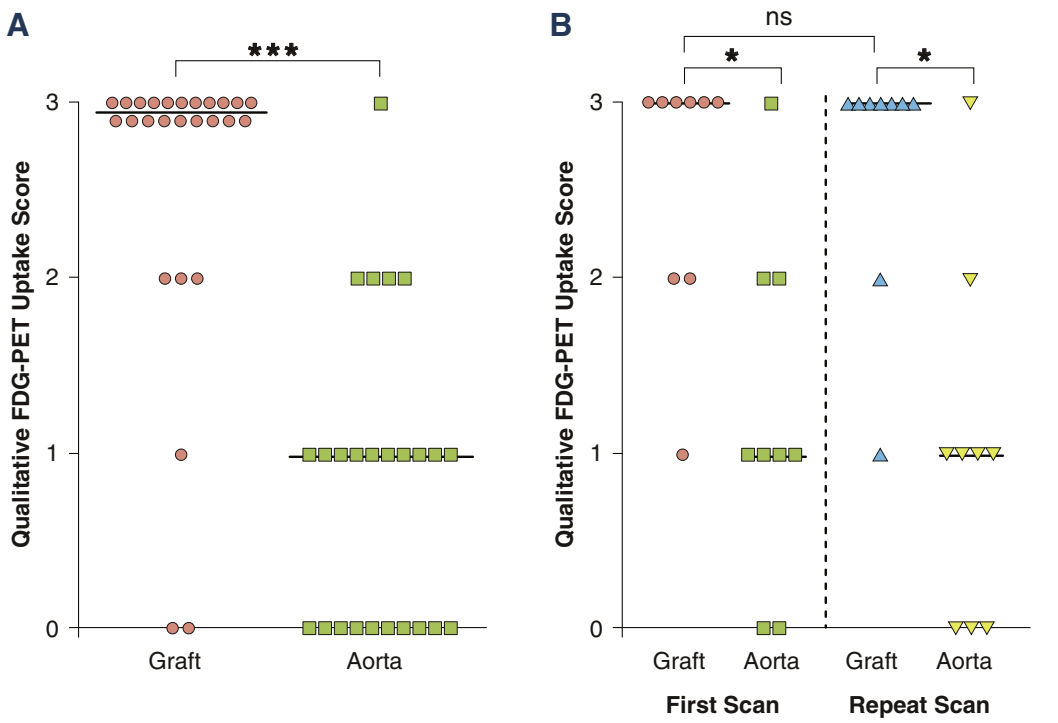
During longitudinal follow-up, 9 TA patients underwent repeated ^{18}FDG-PET/CT at 15 (IQR: 11 to 49) months after the first scan. Despite 7 patients who received immunosuppressive therapy during this time, the increased periprosthetic [^{18}F]FDG uptake scores recorded at the first scan were not significantly changed in the follow-up scans (Figure 4B).

DISCUSSION

[^{18}F]FDG-PET/CT IN LVV MANAGEMENT. [^{18}F]FDG-PET/CT is a sensitive, noninvasive technique for the early diagnosis of active LVV (1,5,6). However, its precise role in disease follow-up remains to be established (2). Determining whether low-grade [^{18}F]FDG uptake represents active arteritis requiring treatment escalation, noninflammatory remodeling, or local glucose analog uptake without major clinical relevance is challenging. Clinical studies offer contrasting conclusions concerning the relationship between [^{18}F]FDG uptake and disease activity biomarkers (9–12). Adding to this complexity, our study of [^{18}F]FDG-PET/CT scans performed in 26 patients more than 6 months after arterial graft surgery demonstrates that [^{18}F]FDG avidity for the prosthetic graft exceeds that for the native aorta. Importantly, uptake did not reflect disease activity or progression and was not indicative of clinically relevant events at arterial graft sites. As far as we are aware, the current report is the first [^{18}F]FDG-PET/CT study of LVV patients with synthetic arterial grafts.

The graft-specific [^{18}F]FDG uptake observed led to clinical concerns regarding disease reactivation, complications, or the presence of an infected graft.

FIGURE 4 **[^{18}F]FDG Uptake by Both the Native Aorta and That Associated With Prosthetic Grafts Was Scored Relative to Constitutive Uptake in the Liver, Using 4-Point Visual Scale**



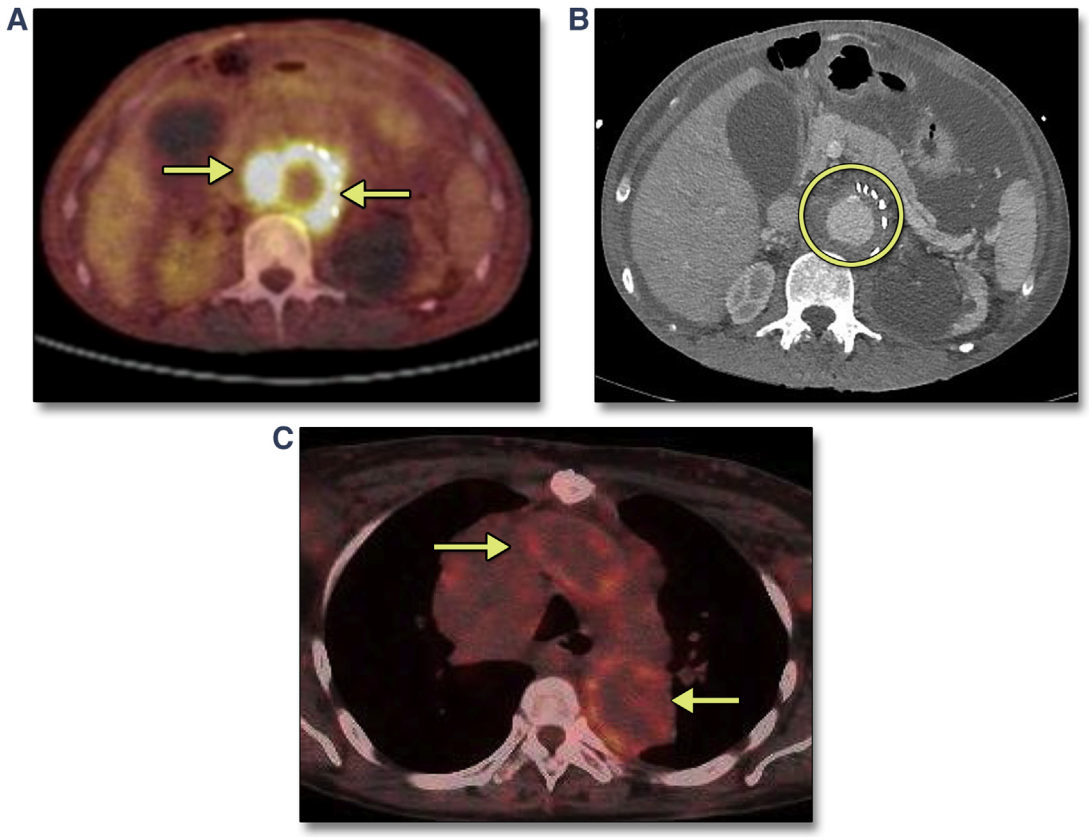
(A) Comparative [^{18}F]FDG uptake in all patients is shown. **(B)** Shows [^{18}F]FDG uptake in those patients who underwent repeat [^{18}F]FDG-PET/CT scanning, comparing native and prosthetic graft uptake in the first and most recent scans. Data are individual patient scores with the medians indicated **(solid horizontal lines)**. Data were analyzed using the Wilcoxon signed-rank test. ***p $<$ 0.001, *p $<$ 0.05; ns = not significant; other abbreviation as in **Figure 1**.

However, careful analysis and prospective follow-up largely refuted these hypotheses, suggesting that graft-associated [^{18}F]FDG-uptake reflects a nonspecific foreign body reaction not requiring treatment change. Uptake of [^{18}F]FDG was more intense in the arterial graft sites than in the native aorta in all but 4 patients. Only in a single case did activity in the native aorta exceed that of the graft. However, the diameter of the vessels affected (4 to 5 mm) was at the limit of PET/CT resolution, and graft-associated activity might have been underestimated due to a partial volume effect.

Our contention that [^{18}F]FDG avidity for synthetic grafts does not reflect LVV activity was further supported by the 9 cases in which a repeat scan was performed. Six of these cases had their immunosuppressive treatment increased, and 1 patient received intravenous antibiotics. Despite continuous or enhanced immunosuppression and the typical relapsing course of TA, periprosthetic [^{18}F]FDG uptake remained unchanged for up to 116 months after the first scan, an observation compatible with findings in patients without LVV (17). Progressive arterial injury or graft failure may occur as a consequence of low-grade clinically undetectable disease activity or noninflammatory remodeling. Thus, it remains possible that PET/CT reveals such events at graft sites without reflecting systemic or local disease activity. In GCA, the baseline intensity of aortic [^{18}F]FDG uptake correlates with subsequent risk of thoracic artery aneurysms (18). However, this proved not to be the case in our TA cohort, despite the high incidence of graft-specific FDG uptake.

Synthetic graft material is avid for [^{18}F]FDG in up to 92% of noninfected patients, following surgery for repair of noninflammatory aneurysm or bypass of obstructive arterial atherosclerosis (17,19,20). These data are comparable to our findings in 26 TA patients. Of note, 3 additional patients with suspected LVV and previous arterial grafting were referred during the study period. Extensive work-up excluded LVV, so they were not enrolled. One patient had an infected

FIGURE 5 [^{18}F]FDG-PET/CT From a Man With an Infected Aortic Graft



(A) Axial-fused PET/CT and axial contrast-enhanced CT at the same level reveal intense circumferential [^{18}F]FDG uptake around the aortic graft (SUV_{max}: 17.1) **(arrows)**. **(B)** The associated contrast-enhanced CT reveals local abscess formation at the site of [^{18}F]FDG uptake **(circle)**, consistent with bacterial infection of the graft. **(C)** [^{18}F]FDG-PET/CT from a 56-year-old woman with noninflammatory aneurysms, ascending and descending aortic grafts. [^{18}F]FDG uptake is confined to parts of the aorta replaced by prosthetic grafts **(arrows)**. CT = computed tomography; PET = positron emission tomography; SUVmax = maximum standard uptake value; other abbreviations as in Figure 1.

graft (Figures 5A and 5B), while the other 2 had noninflammatory diseases. Periprosthetic [^{18}F]FDG uptake in the noninflammatory cases was comparable to that seen in LVV in terms of pattern and intensity (Online Table 1, Figure 5C), supporting our contention that vasculitis is not the major determinant of periprosthetic [^{18}F]FDG uptake in LVV.

FDG UPTAKE AND GRAFT INFECTION. Graft infection, especially if unrecognized, has a mortality rate of >50%. It has been proposed that the pattern and intensity of [^{18}F]FDG uptake associated with prosthetic grafts may distinguish nonspecific graft uptake from infection. An [^{18}F]FDG-PET study of 33 patients who had undergone aneurysm repair identified 11 with infected grafts. Uptake of [^{18}F]FDG was intense, focal, and predominantly at sites identified as abnormal by CT scanning. In contrast, the pattern of [^{18}F]FDG uptake in uninfected grafts was diffuse and circumferential (21). Comparable findings have been reported elsewhere (17,22,23), and it has been suggested that the SUV_{max} is particularly high in infected grafts, with a cutoff value of 8.0 (24). This is supported by a study in which 10 of 12 synthetic grafts had increased [^{18}F]FDG uptake. The SUV_{max} of the one graft that was confirmed infected was 8.0, whereas SUVs of the noninfected grafts were 1.7 to 6.5 (20). Our findings in TA were similar, with a mean graft SUV_{max} of 4.21 ± 1.46 (range 1.2 to 8.0), normal graft anatomy and negative blood cultures. Meanwhile, the patient with an infected graft had a periprosthetic SUV_{max} of 17.1, and he eventually succumbed to sepsis. However, the accuracy of individual ^{18}FDG-PET/CT parameters including SUV_{max}

for separating infected from noninfected grafts has been questioned (19). It is possible that ongoing antibiotic therapy may impair discrimination of graft infection from nonspecific uptake at PET/CT, and further prospective analysis is required. Notwithstanding, in our unselected LVV patients with moderate FDG uptake (SUV_{max}: <8) and no other clinical, laboratory, or imaging signs of active disease, we did not observe any graft infections. These data suggest that moderate periprosthetic FDG uptake p*er se* does not imply the presence of graft infection.

MECHANISM OF FDG UPTAKE. We propose that periprosthetic [^{18}F]FDG uptake reflects a low-grade foreign body inflammatory reaction to graft material. Immunohistology reveals a chronic inflammatory response to the graft, with macrophage recruitment and subsequent formation of multinucleate giant cells. This is followed by neovascularization and fibrosis (25–27). Activated macrophages/giant cells, proliferating endothelial cells, and myofibroblasts are all sufficiently metabolically active to demonstrate enhanced uptake of [^{18}F]FDG and to generate the positive PET signal (28,29).

STUDY LIMITATIONS. The limitations of our study include the relatively small number of LVV cases with prosthetic grafts. This in turn reflects the rarity of LVV, falling rates of surgical intervention, and increasing use of endovascular aneurysm repair. In the last, the stent grafts used are less likely to demonstrate [^{18}F]FDG-PET/CT avidity (20). We tried to minimize these limitations by using a multicenter study design incorporating 2 of the largest TA patient cohorts in Europe.

CONCLUSIONS

The findings herein demonstrate that [^{18}F]FDG uptake confined to prosthetic graft sites in LVV does not necessarily equate to active vasculitis, and nor does it imply the presence of graft infection, restenosis, or perianastomotic dilation. Most commonly, periprosthetic [^{18}F]FDG uptake reflects a low-grade foreign body reaction to the graft material. In patients with clinically quiescent disease, no signs of infection, normal CRP, and negative blood cultures, we elect to monitor with serial annual MRA and do not escalate treatment. Active disease elsewhere in the aorta can be identified and treated in the conventional way. We suggest that these findings will help to minimize exposure of patients to unnecessary immunosuppression or antibiotic therapy.

ADDRESS FOR CORRESPONDENCE: Dr. Justin C. Mason, Vascular Sciences, Imperial Centre for Translational and Experimental Medicine, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0NN, United Kingdom. E-mail: justin.mason@imperial.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: [^{18}F]FDG-PET/CT is an important tool in the management of LVV. However, interpretation is complicated in those with arterial grafts. [^{18}F]FDG uptake confined to the graft site, and in the absence of other markers of disease activity, does not typically reflect active arteritis or infection, is not associated with disease progression and rarely requires a change in treatment.

TRANSLATIONAL OUTLOOK: Periprosthetic localization of [^{18}F]FDG likely reflects a chronic inflammatory response to the graft material. Metabolically active macrophages, giant cells, endothelial cells, and fibroblasts will take up FDG. Further investigative studies and improved PET ligands for the assessment of LVV activity are now required.

REFERENCES

1. Mason JC. Takayasu arteritis—advances in diagnosis and management. Nat Rev Rheumatol 2010; 6:406–15.

2. Fuchs M, Briel M, Daikeler T, et al. The impact of (18)F-FDG PET on the management of patients with suspected large vessel vasculitis. Eur J Nucl Med Mol Imaging 2012;39:344–53.

3. Webb M, Chambers A, AL-Nahhas A, et al. The role of ^{18}F-FDG PET in characterising disease activity in Takayasu arteritis. Eur J Nucl Med Mol Imaging 2004;31:627–34.

4. Andrews J, Mason JC. Takayasu's arteritis—recent advances in imaging offer promise. Rheumatology (Oxford) 2007;46:6–15.

5. Walter MA. [(18)F]fluorodeoxyglucose PET in large vessel vasculitis. Radiol Clin North Am 2007; 45:735–44.

6. Blockmans D, Bley T, Schmidt W. Imaging for large-vessel vasculitis. Curr Opin Rheumatol 2009;21:19–28.

7. Kobayashi Y, Ishii K, Oda K, et al. Aortic wall inflammation due to Takayasu arteritis imaged with 18F-FDG PET coregistered with enhanced CT. J Nucl Med 2005;46:917–22.

8. Alibaz-Oner F, Aydin SZ, Direskeneli H. Advances in the diagnosis, assessment and outcome of Takayasu's arteritis. Clin Rheumatol 2013;32: 541–6.

9. Arnaud L, Haroche J, Malek Z, et al. Is (18) F-fluorodeoxyglucose positron emission tomography scanning a reliable way to assess disease activity in Takayasu arteritis? Arthritis Rheum 2009;60:1193–200.

10. Lee KH, Cho A, Choi YJ, et al. The role of ^{18}F-fluorodeoxyglucose-positron emission tomography in the assessment of disease activity in patients with Takayasu arteritis. Arthritis Rheum 2012;64:866–75.

11. Tezuka D, Haraguchi G, Ishihara T, et al. Role of FDG PET-CT in Takayasu arteritis: sensitive detection of recurrences. J Am Coll Cardiol Img 2012;5:422–9.

12. Alibaz-Oner F, Dede F, Ones T, Turoglu HT, Direskeneli H. Patients with Takayasu's arteritis having persistent acute-phase response usually have an increased major vessel uptake by 18F-FDG-PET/CT. Mod Rheumatol 2015;25:752–5.

13. Andrews J, Al-Nahhas A, Pennell DJ, et al. Non-invasive imaging in the diagnosis and management of Takayasu's arteritis. Ann Rheum Dis 2004;63:995–1000.

14. Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med 1994;120:919–29.

15. Barwick TD, Lyons OT, Mikhaeel NG, Waltham M, O'Doherty MJ. 18F-FDG PET-CT uptake is a feature of both normal diameter and aneurysmal aortic wall and is not related to aneurysm size. Eur J Nucl Med Mol Imaging 2014;41:2310–8.

16. Bettinardi V, Presotto L, Rapisarda E, Picchio M, Gianolli L, Gilardi MC. Physical performance of the new hybrid PETCT Discovery-690. Med Phys 2011;38:5394–411.

17. Keidar Z, Pirmisashvili N, Leiderman M, Nitecki S, Israel O. 18F-FDG uptake in noninfected prosthetic vascular grafts: incidence, patterns, and changes over time. J Nucl Med 2014;55:392–5.

18. Blockmans D, Coudyzer W, Vanderschueren S, et al. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. Rheumatology (Oxford) 2008;47:1179–84.

19. Berger P, Vaartjes I, Scholtens A, et al. Differential FDG-PET uptake patterns in uninfected and infected central prosthetic vascular grafts. Eur J Vasc Endovasc Surg 2015;50:376–83.

20. Wasselius J, Malmstedt J, Kalin B, et al. High 18F-FDG uptake in synthetic aortic vascular grafts on PET/CT in symptomatic and asymptomatic patients. J Nucl Med 2008;49:1601–5.

21. Fukuchi K, Ishida Y, Higashi M, et al. Detection of aortic graft infection by fluorodeoxyglucose positron emission tomography: comparison with computed tomographic findings. J Vasc Surg 2005;42:919–25.

22. Keidar Z, Engel A, Hoffman A, Israel O, Nitecki S. Prosthetic vascular graft infection: the role of 18F-FDG PET/CT. J Nucl Med 2007;48:1230–6.

23. Spacek M, Belohlavek O, Votrubova J, Sebesta P, Stadler P. Diagnostics of "non-acute" vascular prosthesis infection using ^{18}F-FDG PET/CT: our experience with 96 prostheses. Eur J Nucl Med Mol Imaging 2009;36:850–8.

24. Tokuda Y, Oshima H, Araki Y, et al. Detection of thoracic aortic prosthetic graft infection with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. Eur J Cardiothorac Surg 2013;43:1183–7.

25. Hagerty RD, Salzmann DL, Kleinert LB, Williams SK. Cellular proliferation and macrophage populations associated with implanted expanded polytetrafluoroethylene and polyethyleneterephthalate. J Biomed Mater Res 2000;49:489–97.

26. Salzmann DL, Kleinert LB, Berman SS, Williams SK. Inflammation and neovascularization associated with clinically used vascular prosthetic materials. Cardiovasc Pathol 1999;8:63–71.

27. van Bilsen PH, Popa ER, Brouwer LA, et al. Ongoing foreign body reaction to subcutaneous implanted (heparin) modified Dacron in rats. J Biomed Mater Res A 2004;68:423–7.

28. Maschauer S, Prante O, Hoffmann M, Deichen JT, Kuwert T. Characterization of 18F-FDG uptake in human endothelial cells in vitro. J Nucl Med 2004;45:455–60.

29. Vucic E, Dickson SD, Calcagno C, et al. Pioglitazone modulates vascular inflammation in atherosclerotic rabbits noninvasive assessment with FDG-PET-CT and dynamic contrast-enhanced MR imaging. J Am Coll Cardiol Img 2011;4:1100–9.

KEY WORDS arterial graft, large-vessel vasculitis, MR angiography, positron emission tomography, Takayasu arteritis

APPENDIX For a supplemental table and figure, please see the online version of this article.