An increased major vessel uptake by ^{18}F-FDG-PET/CT in NIH criteria inactive patients with Takayasu's arteritis

Q. Han[1,2,3], Q. Liang[2,3], F. Kang[4], J. Wang[4], Z. Wu[1,3], P. Zhu[1,2,3]

[1]Department of Clinical Immunology; [2]Department of Cell Biology, Fourth Military Medical University, Xi'an, Shaanxi Province; [3]National Translational Science Centre for Molecular Medicine, Xi'an, Shaanxi Province; [4]Department of Nuclear Medicine, Xi-jing Hospital, Fourth Military Medical University, Xi'an, Shaanxi Province, People's Republic of China.

Qing Han, MD*
Qiang Liang, MD*
Fei Kang, MD*
Jing Wang, MD, PhD
Zhenbiao Wu, MD, PhD
Ping Zhu, MD, PhD

**These authors contributed equally to this study.*

Please address correspondence to:
Dr Ping Zhu,
Department of Clinical Immunology, Xi-jing Hospital, The Fourth Military Medical University,
127 West Changle Road, Xi'an, Shaanxi Province, P.R. China.
E-mail: zhuping@fmmu.edu.cn
or
Dr Jing Wang,
Department of Nuclear Medicine, Xi-jing Hospital, The Fourth Military Medical University,
127 West Changle Road, Xi'an, Shaanxi Province, P.R. China.
E-mail: wangjing@fmmu.edu.cn

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ABSTRACT

Objective. *The commonly adopted method of defining active disease in Takayasu's arteritis (TAK) is the definition used by the US National Institutes of Health (NIH). A gold standard in imaging techniques for assessing disease activity in TAK has not been clearly established and the creation of practical and valid tools represents a challenge. To assess whether ^{18}F-FDG-PET/CT and NIH criteria show a good level of agreement in assessing disease activity of TAK patients.*

Methods. *^{18}F-FDG-PET/CT was performed in 17 patients with TAK. All 17 patients fulfilled the clinical criteria according to the American College of Rheumatology criteria. Two nuclear physicians visually assessed the degree of ^{18}F-FDG uptake in the inflammatory vascular lesion. ^{18}F-FDG-PET/CT and the inflammatory vascular lesion were evaluated by using the standardised uptake value (SUV) of ^{18}F-FDG accumulation were interpreted as active vasculitic lesions.*

Results. *Of the 17 patients, 6 were in the active stage and 11 were in the inactive stage according to the level of disease activity as clinically assessed by the NIH criteria. No significant ^{18}F-FDG accumulation was observed in the patients with inactive disease (SUV≤1.2). ^{18}F-FDG-PET/CT localised ^{18}F-FDG accumulation in the inflammatory lesion in the patients with TAK who had inactive disease (n=3) assessed by the NIH criteria. ^{18}F-FDG PET/CT revealed intense ^{18}F-FDG accumulation (SUV max 2.88) in the vasculature of 3 patients in the inactive stage of TAK. The other 8 patients in the active stage showed weak ^{18}F-FDG accumulation (SUV ≤1.2).*

Conclusion. *^{18}FDG-PET/CT appears to be a promising technique for the diagnosis and assessment of disease activity in patients of TAK, even those considered to be inactive by the NIH criteria. However, it needs to be validated in larger groups for cost-effectiveness and sensitivity to change.*

Introduction

Takayasu's arteritis (TAK) is an inflammatory disease, chronic large vessel arteritis that predominantly affects aorta, renal artery, their major branches and the pulmonary arteries. All large arteries can be affected, but the vessels most frequently involved are the aorta, subclavian, and carotid arteries (60–90%) (1). Although digital subtraction angiography (DSA) is a gold standard test for the diagnosis of TAK, DSA indicates only advanced structural changes and does not reflect early or active disease. The commonly adopted definition of active disease is the method used by the US National Institutes of Health (NIH) and the definition used in the present study (2).

However, the limit of a gold standard for assessing disease activity in TAK presents a challenge in creating practical and valid tools for disease estimation. Patients with a clinical suspicion of TAK may present with non-specifc signs and symptoms such as fatigue, malaise, weight loss, anorexia, subfebrile temperatures or night sweats, and increased C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) levels (3).

Several reports have suggested the usefulness of F-18 fluoro-fluoro-deoxygulose positron emission tomography computed tomography (^{18}F-FDG-PET/CT) for the diagnosis and evaluation of disease activity in TAK (4, 5). ^{18}F-FDG-PET/CT has been recently reported to be useful in the diagnosis of vascular diseases such as atherosclerosis and large-vessel aortitis, as well as for the assessment of disease activity (6, 7). ^{18}F-FDG and the synergy of integrating functional and anatomical images with hybrid PET/CT may be of substantial

benefit in the diagnostic work-up of patients with a clinical suspicion of TAK (8, 9). ^{18}F-FDG-PET/CT may be an ideal technique for a metabolic assessment of inflammation (9, 10).

The purpose of this study was to assess whether ^{18}F-FDG-PET/CT can identify the distribution of inflammation in patients with inactive stage according to the NIH criteria (2) revealed increased accumulation in TAK by ^{18}F-FDG-PET/CT in clinical practice.

Material and methods

Patients and control subjects

The study included 17 patients (10 women, 7 man) with TAK according to the American College of Rheumatology criteria (11) and disease activity was clinically assessed by the NIH criteria, who underwent ^{18}F-FDG-PET/CT at the Xi-jing Hospital from April 2015 through July 2016. Median age at symptom onset was 8 (0.3-7ys) months; median age at diagnosis was 21 (12-35) years. The average delay to diagnosis was 1.1 (0.46-2.7) years. Of the 17 patients, 6 were in the active stage and 11 were in the inactive stage according to the NIH criteria. Exclusion criteria of the study were pregnancy, liver or renal function impairment, heart failure, respiratory failure, diabetes mellitus, psychological or neurological disorders and malignancy.

Table I. Characteristic of the patients with TAK.

Parameters	Active stage (n=6)	Inactive stage (n=11)	*p*-value
General state			
Age (y)	30 ± 9	31 ± 5	NA
Female/Male	4/2	6/5	NA
Time since diagnosis, years	1.2	1.6	NA
Symptoms			
Fatigue (n)	5	0	NA
Amaurosis (n)	5	0	NA
Dozziness (n)	4	0	NA
Chest distress (n)	1	0	NA
Laboratory tests			
CRP (mg/dl)	1.49 (0.20-3.23)	0.50 (0.10-1.25)	0.01*
ESR (mm/H)	52.7 (25-98)	9.7 (2-25)	0.01*
SUV			
<1.2	0	0	NA
1.2-2.0	2	8	NA
>2.0	4	3	NA

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. *p<0.05.

Table II. Characteristics of patients with TAK relative to the presence of active vasculitic lesions on ^{18}F- FDG-PET/CT.

	PET-positive (n=9)	PET-negative (n=8)	*p*-value
Age years (mean)	21	26	NA
Duration years (mean)	0.8	1.9	<0.01
ESR (mm/h)	40.6 (10-98)	7.1 (2-11)	<0.001
CRP (mg/dl)	1.23 (0.2-3.23)	0.53 (0.1-0.8)	<0.001
SUV mean			
Ascending aorta	1.59	1.49	<0.001
Arcus aorta	1.43	1.30	<0.001
Descending aorta	1.32	1.29	<0.01
Abdominal aorta	1.48	1.39	<0.01

^{18}F-FDG -PET/CT

Acquisition of image

^{18}F-FDG-PET/CT was performed using a PET-CT scanner (Biograph 40, SIEMENS) 60 minutes after intravenous injection of approximately 3.7 MBq (0.1 mCi)/kg of 18F-FDG FDG. The blood glucose levels that were checked before FDG administration were below 200 mg/dl. PET data were reconstructed iteratively with and without attenuation correction based on CT data and reoriented in axial, sagittal, and coronal slices.

Image analysis

Objective reference values were obtained for all patients by measuring mean standard uptake values (SUV mean) of mediastinal blood pool and liver. Vascular-wall FDG uptakes were quantified by drawing volume of interests (irregular and voxel) in the ascending aorta, arcus aorta, descending aorta, abdominal aorta, right brachiocephalic artery, right subclavian artery, left subclavian artery, right common carotid artery, left common carotid artery, and pulmonary arteries were not included due to their close relationship with histological intense cardiac FDG uptake. The quantified ^{18}F-FDG uptake using methods as standard uptake value (SUV). The mean SUV in the center of the inferior vena cava in all cases, and target/background ratio was calculated as max SUV in arterial wall/mean SUV in inferior vena cava in their study (12). A max SUV cut-off was set at 2.0 for detecting active inflammation of TAK in untreated cases and a cut-off for max SUV (strong accumulation, SUV>2.0; weak accumulation, SUV 1.2–2.0) (13).

Statistical analysis

Continuous variables were summarised as a mean depending on normality of distribution. Continuous variables were compared using Mann-Whitney U-test between groups. Categorical variables were compared using Fisher's exact test. Two-sided p<0.05 were considered statistically significant. All statistical analyses were performed using SPSS v. 18.0 software (SPSS, Chicago, IL).

Results

Characteristics of patients according to ^{18}F-FDG-PET/CT scan results

Of the 17 patients, 9 had active vasculitic lesions on ^{18}F-FDG-PET/CT scans. Mean disease duration of the patients

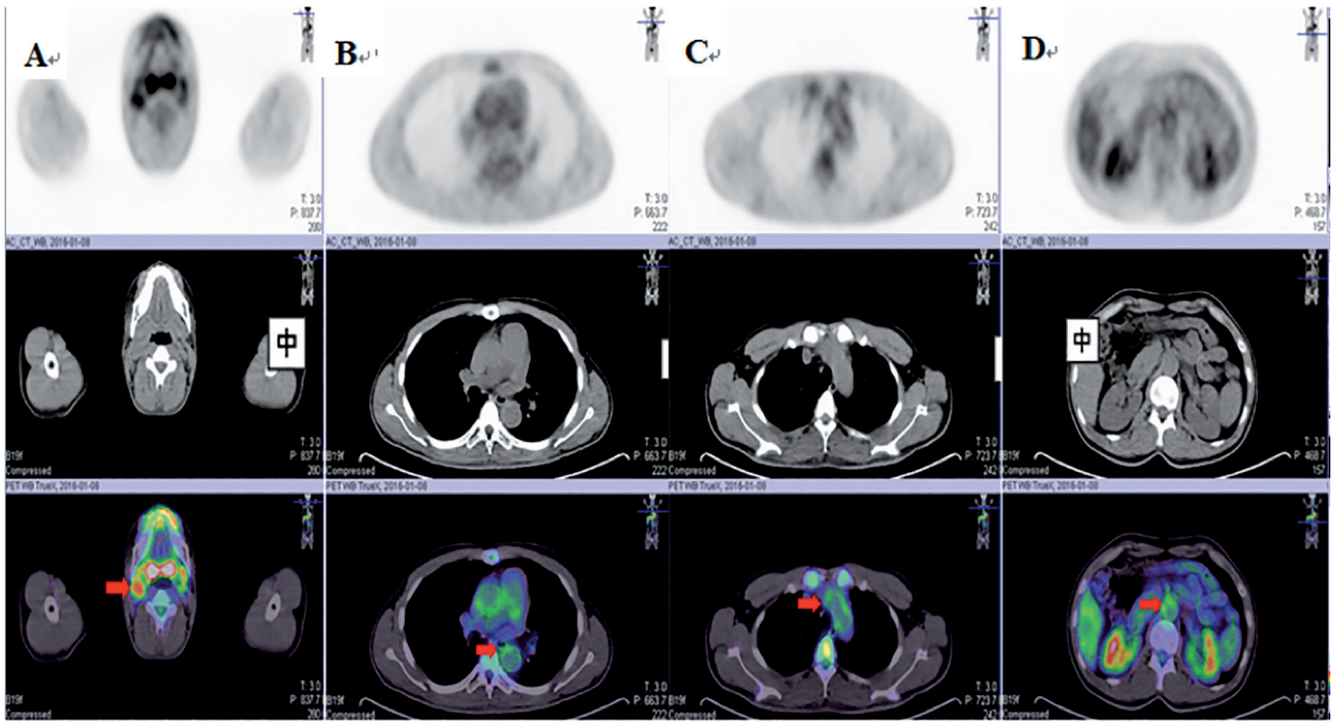

Fig. 1. 22-y-old man with active Takayasu arteritis. ^{18}F-FDG-PET coregistered with enhanced CT revealed that ^{18}F-FDG accumulations were localised in inflammatory vascular of right carotid arteries, arch of aorta, descending aorta and abdominal aorta. (**A**) Arrows show ^{18}F-FDG accumulation was observed in right carotid arteries. The standardised uptake value (SUV) of the ^{18}F-FDG uptake in the right carotid arteries was 2.88. (**B**) Arrows show ^{18}F-FDG accumulation was observed in arch of aorta. The standardised uptake value (SUV) of the 18F-FDG uptake in the arch of aorta was 2.03. (**C**) Arrows show ^{18}F-FDG accumulation was observed in descending aorta. The standardised uptake value (SUV) of the ^{18}F-FDG uptake in the arch of aorta was 2.12. (**D**) Arrows show ^{18}F-FDG accumulation was observed in abdominal aorta. The standardised uptake value (SUV) of the 18F-FDG uptake in the abdominal aorta was 2.26.

was 0.3±2.5years. Mean ESR was 50.8±13.2 mm/hour and mean CRP level was 28.5±22.1mg/L. Active vasculitic lesions were observed by ^{18}F-FDG-PET/CT in 9 of 17 (52.9%) patients, but clinically silent disease. PET/CT showed increased FDG uptake suggestive of active disease in 7 of 17 in arch of aorta and its branches in 9 patients, while two patients showed increased uptake in abdominal aorta. In the four patients, although clinical and laboratory parameters indicated active disease, however, PET scan did not show any increased FDG uptake. Study protocol was approved by Local Ethics Committee, and a written informed consent was obtained from each patient. Details of the patients are summarised in Table I.

^{18}F-FDG-PET/CT uptake in the arcus aorta was involved in 23.5%, ascending aorta in 29.4%, descending aorta in 35.2%, abdominal aorta in 11.8%, right subclavian arteryin 17.6%, left subclavian artery in 17.6%, right common carotid artery in 35.2%, and left common carotid artery was involved in 41.2% of the investigated vessels. When we compared the SUV mean value of the involved vessels between PET-positive and-negative patients, we did not find any difference. But there was a significant difference between PET-positive and -negative patients regarding ESR (p<0.001) and CRP level (p<0.001) (Table II).

Distribution of ^{18}F-FDG uptake

Patients with positive scans showed high-SUV, linear ^{18}F-FDG uptake along the active artery. Among the 9 patients with positive ^{18}F-FDG-PET/CT scans, 7 patients had their maximal ^{18}F-FDG uptake in the thoracic aorta, 4 in the abdominal aorta (Fig. 1), and 5 in the carotid artery (Fig. 2). Kobayashi *et al*. was the first to establish a cutoff for SUV max (strong accumulation, SUV≥2.1). Then, Tezuka *et al*. suggested a SUV max cut-off of 2.1 for detecting active inflammation of TAK in untreated and relapsing cases (14).

Discussion

The diagnosis of TAK is made from image analysis and clinical symptoms (12). The key finding for the diagnosis of TAK is the image analysis of angiograms, enhanced CT, and MRI showing the stenosis, occlusion, or aneurysm formation in large- and medium-sized vessels (14). It is difficult to diagnose TAK in its early stage in suspected cases that do not have any vascular deformity. Therefore, direct identification of the inflammation in the vasculature of TAK facilitates the diagnosis in the early stage. DSA is the "gold standard" for precisely delineating the stenosis, occlusions, and aneurysms that characterise the latter stages of TAK, but it is difficult to detect inflammation of the arterial wall in the early phases of disease before irreversible structural changes. Diagnosis of TAK by CTA is based on narrowing, stenosis, or aneurysm of large vessels. Several reports show the value of ^{18}F-FDG-PET/CT in the diagnosis of large-vessel arteritis (13) and show strong ^{18}F-FDG signals in the vascular lesions that could be detected in several patients.

The most commonly adopted approach for disease assessment in TAK is the

simple definition of "active disease" originally used in a study from NIH as the presence of constitutional symptoms, new-bruits, elevated APRs or new angiographic features (2). A literature search performed for TAK have shown that items in NIH series were preferred by most studies to define "active" disease (15). Computerised tomography (CT) provides excellent anatomical characterisation of structural aortic changes, but is limited in its assessment of early disease activity (16). MR angiography can show vessel wall thickening and oedema, however, this correlates poorly with clinical activity or APR and is shown to have a limited role for long-term follow-up (17-19).

However, we found that ^{18}F-FDG-PET analyses give the strong signals in that patients with inactive TAK according to NIH definition (n=3). ^{18}F-FDG-PET positive group duration years of patients were shorter than negative group. The earliest detectable inflammation in TAK is difficult in the early acute stage. The assessment of disease activity of TAK is very important. Although the ACR criteria were reported to have a sensitivity of 90.5% and a specificity of 97.8% (14), in the study by Kerr *et al*., 44% specimens that were obtained from patients who were clinically inactive had histological evidence of active disease (2). In this study, ^{18}F-FDG positive rate was 52.94% (9/17). So, while a practical method remains to be discovered, the ^{18}F-FDG-PET/CT might to be better tool to estimate disease activity.

These findings suggest that ^{18}F-FDG-PET may be a potential tool for estimating the disease activity of TAK. However, more cases must be studied to confirm these findings. But the following limitations should be noted when using ^{18}F-FDG-PET/CT in assessing disease activity of TAK. ^{18}F-FDG uptake not only in inflammation of the vessel wall, but also in vasculitic conditions such as atherosclerosis (20). The thickness of vessel >5 mm usually made a ^{18}F-FDG uptake in the inflammatory lesion, and it also influences the result of ^{18}F-FDG-PET after immunotherapy. To avoid such limitations of SUV, we used the semi-quantitative visual assessment of FDG uptake in the vascular wall using liver uptake as an internal reference of uptake in cases without liver disease. As glucose uptake in ^{18}-FDG-PET is not limited to inflammatory cells in vascular wall, hot ^{18}-FDG-PET scans may also be observed in patients in clinical remission (21).

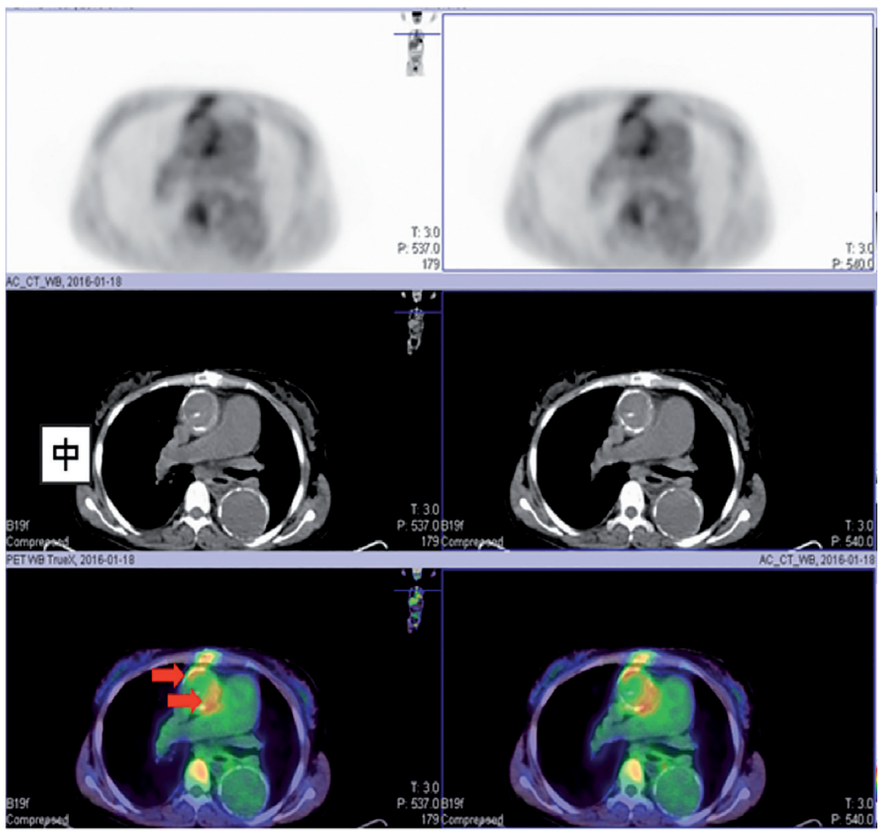

Fig. 2. 32-y-old woman showing ^{18}F-FDG uptake (indicated by arrows) in the ascending aorta was noted (arrow). The standardised uptake value (SUV) of the ^{18}F-FDG uptake in the abdominal aorta was 2.78. This case were assessed as active disease by the NIH criteria.

These findings intend to highlight the promising results found by the use of PET in large-vessel vasculitis and also the often conflicting results at the time of supporting disease activity by the use of this technique, particularly in patients with Takayasu. FDG-PET/CT scan appears to be useful for the diagnosis and management of patients with large-vessel vasculitis by showing a metabolic functional image of the vessel wall inflammation before structural changes can be seen (9, 10). In this regard, previous studies have confirmed good results by the use of this tool in the evaluation of the aortic involvement in patients with large-vessel vasculitis (22, 23). A study also showed a decrease of FDG uptake following anti-IL6 tocilizumab therapy in some patients with Takayasu (24). Unfortunately, an increase in FDG uptake may also be a feature of tissue vessel wall hypertrophy, repair and regeneration and not specifically of active disease. Therefore, the validity of an increased FDG uptake equating to active disease in Takayasu arteritis needs to be clarified. The present study aims to provide new information on this issue.

It suggests that 18F-FDG accumulation observed in TAK directly indicates vascular inflammation. 18F-FDG/PET used together with enhanced CT should be useful in the diagnosis and management of Takayasu arteritis. Additional useful tool to diagnosis methods were edded, for the limited of sensitivity of current TAK criteria in detected disease activity, more studies are needed.

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