



ORIGINAL RESEARCH ARTICLE

## Diagnostic agreement between clinical criteria and disease activity in Takayasu's arteritis by 2-<sup>18</sup>F]FDG PET-CT scan

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### ABSTRACT

**Introduction:** Large Vessel Vasculitis (LVV) is a chronic inflammatory process that affects the aorta and its main branches. LVV include Takayasu's Arteritis (TA) and Giant Cell Arteritis (GCA). The diagnosis of TA is made according to clinical criteria and based on the criteria of the American College of Rheumatology (ACR). Monitoring of disease progression and response to treatment is also done using the National Institutes of Health (NIH) criteria. Despite these criteria, diagnosing and evaluating TA activity is a challenging issue and usually occurs in the advanced stages of the disease. The lack of a comprehensive and non-invasive diagnostic method for diagnosing and monitoring the course of TA is obvious. The aim of this study was to evaluate the diagnostic agreement between 2-<sup>18</sup>F]FDG PET-CT scan and clinical criteria for assessing TA disease activity.

**Methods:** Twenty-four known cases of TA, who met the inclusion criteria, were enrolled in this study. The disease-related constitutional signs and symptoms, as well as laboratory and imaging findings were recorded. Patients underwent 2-<sup>18</sup>F]FDG PET-CT imaging with standard protocol. Fused PET-CT images were reviewed and, if necessary, images without attenuation correction were visualized as well. Also, 24 control patients of the same age and sex, among the patients who were referred to the imaging center for oncological indications were examined to compare the uptake of different vascular territories.

**Results:** Out of 15 active patients (according to the NIH criteria), 2-<sup>18</sup>F]FDG PET-CT scan was able to correctly identify 14 patients. Also, out of 9 inactive patients, PET scan was negative in eight patients showing that 2-<sup>18</sup>F]FDG PET-CT scan could well differentiate between active and inactive status of the disease (p-value < 0.0001). Sensitivity, specificity, positive predictive value and negative predictive value of scan in this study were 93.3%, 88.9%, 93.3% and 88.9%, respectively. The study also showed that the severity of vascular lesion uptake was not affected by immunosuppressive drugs, including corticosteroids and methotrexate. Scan findings were comparable with the results of anatomical imaging in terms of disease activity and the number of vascular lesions with p-value = 0.1 and 0.304, respectively.

**Conclusion:** In this study we showed that 2-<sup>18</sup>F]FDG PET-CT has comparable results with other imaging modalities and NIH criteria; therefore, it can play an important role in assessing the severity of TA, even when patients are on immunosuppressive drugs.

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## INTRODUCTION

After atherosclerosis, vasculitis is the most common vascular disease, causing a wide range of signs and symptoms depending on the size and type of involved arteries [1]. Large Vessel Vasculitis (LVV) is a chronic inflammation that affects the aorta and its main branches, including Takayasu's Arteritis (TA) and Giant Cell Arteritis (GCA). Although TA is rare, it causes significant morbidity in patients, particularly young people. It also sometimes causes premature death [1]. TA has a low prevalence; however, the disease distribution is different according to the geographical location and it is more prevalent in the Asian population than in other parts of the world [2]. The incidence of TA is estimated between 0.4 (in Europe) and 2.2 (in Kuwait) per million, and the prevalence is estimated between 0.9 (in the United States) and 40 (in Japan) per million based on various studies [2]. The diagnosis of this disease also seems to be growing in some communities [2]. Therefore, it is important to have an appropriate method to diagnose and monitor TA patients.

Diagnosis of TA is based on clinical criteria of the American College of Rheumatology (ACR) [3]. Monitoring of disease progression and response to treatment is also performed using the National Institutes of Health (NIH) criteria [4]. Despite these criteria, diagnosing and evaluating TA activity is a challenging issue and usually occurs in the advanced stages of the disease.

For example, one of the NIH criteria is the presence of systemic symptoms including fever, sweating, muscle aches, weakness and weight loss [3]; but in some studies researchers have shown that in pathological specimens of TA patients who were clinically inactive, 40 to 61% of active vasculitis lesions were observed [5, 6]. These symptoms are also subjectively reported, can be vary from patient to patient, and are non-specific, occurring in a wide range of diseases [7]. The other NIH criterion is increased ESR, which is a factor with both low specificity (56%) and low sensitivity (72%) [6]. It increases in a wide spectrum of diseases such as malignancy, infection and other rheumatic diseases [6]. In addition, ESR is affected by age and sex of patients, as well as the morphology of red blood cells and the presence of anemia [5]. Also, neither of these two mentioned NIH factors can provide information about the involved vascular territories. The third NIH criterion is evidence of vascular inflammation or ischemia (e.g. asymmetric blood pressure, pulse weakness, limb claudication, etc.). In this case, vascular territory is assessable; however, it is usually diagnosed in the late-stages of the disease, which may sometimes

be completely or somewhat irreversible. The last NIH criterion is the occurrence or worsening of angiographic criteria for which, invasive angiography, Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) or arterial Doppler ultrasound can be used [1, 8]. Using these imaging modalities, the risk of vascular territory can be well assessed, although usually the findings are related to the late-stage complications. Albeit, increasing the thickness, contrast enhancement and edema of the arterial wall are not limited to the late-stage disease and demonstrate disease activity, but sometimes the increase in wall thickness may remain constant even after response to treatment, which makes it unsuitable for response assessment in TA [9].

Finally, the obvious lack of a comprehensive and non-invasive diagnostic method for the diagnosis and monitoring the course of TA prompted researchers for evaluating the role of 2-[<sup>18</sup>F]FDG PET-CT scan in the diagnosis and monitoring of the disease. For assessment of disease activity, some studies compared 2-[<sup>18</sup>F]FDG PET-CT scan with other available methods, providing different evaluation criteria based on 2-[<sup>18</sup>F]FDG PET-CT using qualitative and semi-quantitative methods, and finally defining the role of 2-[<sup>18</sup>F]FDG PET-CT scan in assessing the course of the disease have been conducted [9-12]. It should be noted that since the 2-[<sup>18</sup>F]FDG PET-CT scan is a whole-body imaging modality, it can provide a holistic view of vascular territories. The aim of this study was to evaluate the diagnostic agreement between 2-[<sup>18</sup>F]FDG PET-CT scan and clinical criteria for assessing TA disease activity, with the hope that by further studies in this field, the role of 2-[<sup>18</sup>F]FDG PET-CT scan, as a tool to assess disease severity and response to treatment, be well defined.

## METHODS

### *Study population*

In this cross-sectional study we enrolled 24 TA patients with a mean age of  $34.75 \pm 11.56$  years. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1397.498) and was conducted during the May 2018- September 2020. TA patients who were referred by a rheumatologist for 2-[<sup>18</sup>F]FDG PET-CT scan were included. Patients with a) active cancer, b) other concomitantly active rheumatic diseases, c) active infectious diseases, were excluded. Patients with high fasting blood sugar ( $> 180$  mg / dl) on the day of 2-[<sup>18</sup>F]FDG PET-CT scan were also excluded from the study. In patients who had a history of vascular surgery or STENT implantation in the

examined vessels, the relevant vessels were not included in the analysis.

We also considered 24 control patients, not known for TA, among cancer patients who had been referred to the nuclear medicine department by oncologists for evaluation of staging, restaging, response to treatment, etc. This group of exactly the same age and sex were evaluated by one-on-one matching as a control group. The control group also did not have any vascular lesions at the studied anatomical sites.

#### Data collection

All patients' characteristics including sex, age, height, weight, ESR and CRP level, constitutional symptoms, features of vascular ischemia/inflammation, results of imaging studies and the existence and type of simultaneous diseases and the medications were recorded in the data collection checklist. NIH criteria were used to estimate disease activity among the patients. NIH criteria define the development or worsening of at least 2 factors as active disease [13]. The details are shown in Table 1.

**Table 1.** NIH criteria for evaluation of TA disease activity

Constitutional symptoms (fever, musculoskeletal pain with no other cause identified)
Elevated ESR (>20 mm/h)
Features of vascular ischemia/inflammation (claudication, diminished or absent pulse, bruit, vascular pain, asymmetric blood pressure in the limbs)
Angiographic finding of new vascular lesions

#### 2-[<sup>18</sup>F]FDG PET-CT imaging and interpretation

2-[<sup>18</sup>F]FDG PET-CT scan was performed based on the standard method according to the protocol shown in Table 2. All scans were performed using Siemens Biograph T6 PET-CT scanner.

**Table 2.** Imaging protocol <sup>18</sup>F-FDG PET-CT

Low carbohydrate - high protein diet for 24 hours before the scan
Avoiding strenuous physical activity for 24 hours before the scan
6 hours fasting before the scan
No change in TA medication before the scan
Blood sugar level < 180 ml / dl at the time of <sup>18</sup> F-FDG injection
Imaging 60 minutes after <sup>18</sup> F-FDG injection
Skull-base to mid-thigh imaging with 3 minutes /bed position
Reconstruction with OSEM algorithm with post-reconstruction smoothing with Gaussian filter
Contrast-free low dose CT imaging

PET, CT and PET-CT images were evaluated in trans-axial, sagittal and coronal sections with special attention to 16 vascular territories (pulmonary artery, ascending and descending

aorta, aortic arch, bilateral carotid and subclavian arteries, innominate artery, abdominal aorta, celiac artery, superior mesenteric artery, as well as bilateral renal and common iliac arteries), by two nuclear medicine specialists who were unaware of the results of disease activity and treatment response of patients. Non-Attenuation Corrected (NAC) images were reviewed in areas containing vascular wall calcification to avoid attenuation correction artifact. The initial visual inspection was performed to see the areas with 2-[<sup>18</sup>F]FDG uptake using visual grading system [9], the details of which are shown in Table 3.

**Table 3.** Visual assessment criteria

<sup>18</sup> F-FDG uptake	Interpretation	Grade
No uptake	No uptake	0
Uptake more than mediastinum/ less than liver	Mild uptake	1
Uptake equal to liver	Moderate uptake (positive result)	2
Uptake more than liver	High uptake (positive result)	3

For quantification, the SUVmax of the lesions was measured using region of interest (ROI) plotting on the suspicious areas with high 2-[<sup>18</sup>F]FDG uptake. Also, liver and mediastinum uptake were measured using SUVmean. The background ROI in the mediastinum was plotted in the SVC and the background ROI in the liver was drawn in the right hepatic lobe. To measure SUVmax in the arteries, ROIs were drawn in non-calcified areas of the arterial walls. The ratio of maximum SUVmax to the liver SUVmean was estimated for evaluation of active vascular lesion. The total SUVmax and mean SUVmax of the lesions were used as a method for comprehensive patient evaluation.

#### Statistical analysis

Patients with TA were classified into active and inactive groups according to the NIH criteria; then the results of 2-[<sup>18</sup>F]FDG PET-CT scan were evaluated in these two groups. Also, in terms of drug administration, patients were divided into 2 other groups (medication-naïve and on-medication) and the severity of lesions uptake was compared in the two groups. Data with normal distribution were expressed as mean±standard deviation (SD). The appropriate tests were used to compare quantitative and qualitative data, as well as correlation coefficient. P-values <0.05 were defined as statistically significant.

## RESULTS

Twenty-four known cases of TA and 24 individuals of exactly the same age and sex (selected by one-

on-one matching as the control group) were evaluated. The patient group had a normal distribution in terms of age at the time of scan and age of disease onset. Among the TA group, 8 (33.3%) patients did not receive any immunosuppressive therapy at the time of

scanning and 16 (66.6%) patients were treated with steroid ± methotrexate. Details of demographic characteristics, drug dosage, duration of the treatment and number of patients underwent each anatomical imaging modalities are demonstrated in Table 4.

**Table 4.** Characteristics of studied patients (TA group)

Variable		Mean ± SD / n (%)
Age	Age at scanning time (years)	34.75 ± 11.56
	Age at disease onset (years)	27.33 ± 9.23
Gender	Female	18 (75.0%)
	Male	6 (25.0%)
Treatment	Immunosuppressive drug	16 (66.7%)
	Treatment duration (years)	4.59 ± 7.84
	Prednisolone (mg)	8.12 ± 11.89
	Methotrexate (mg)	5.06 ± 10.19
Anatomical Imaging (number of patients underwent each anatomical imaging modalities)	CTA	12 (50.0%)
	MRA	4 (16.7%)
	CDS	1 (4.2%)
	Invasive angiography	2 (8.3%)
	CTA + CDS	2 (8.3%)
	Without recent imaging	3 (12.5%)

CDS: color Doppler sonography; CTA: computed tomography angiography; MRA: magnetic resonance angiography

Details of frequency of constitutional symptoms and vascular symptom, signs, complications among

TA group are shown in Table 5.

**Table 5.** Symptoms, signs and complications secondary to TA in the study group

Signs and symptoms		N (%)
General symptoms	Weakness and lethargy	10 (41.7%)
	Significant weight loss	6 (25.0%)
	Fever	1 (4.2%)
	Sweating	1 (4.2%)
Hypertension	normal	13 (54.2%)
	Pre-hypertension	1 (4.2%)
	Stage 1 blood pressure	4 (16.7%)
	Stage 2 blood pressure	5 (20.8%)
	Renovascular hypertension	3 (12.50%)
Cardiovascular symptoms, signs, complications	Limb claudication	14 (58.3%)
	Unilateral pulse weakness	8 (33.3%)
	Bilateral pulse weakness	7 (29.2%)
	Head and neck pain	6 (25.0%)
	Stroke	1 (4.2%)
	Transient ischemic attack	1 (4.2%)
	Blurred vision	2 (8.3%)
	Acute coronary Syndrome	2 (8.3%)
	Valve replacement	2 (8.3%)
	Heart transplant	1 (4.2%)
	Aneurysm	1 (4.2%)
	Coarctation	1 (4.2%)
Embedded STENT	2 (8.3%)	
Deep vein thrombosis	1 (4.2%)	

In the control group, no active vascular lesions were seen according to the visual criteria and grade of uptake of all vascular territories was either 0 or 1. In patient assessment, visual criteria based on grading scale could differentiate active versus inactive TA patients (p-value < 0.0001) with sensitivity, specificity, positive predictive value and negative predictive value of 93.3%, 88.9%,

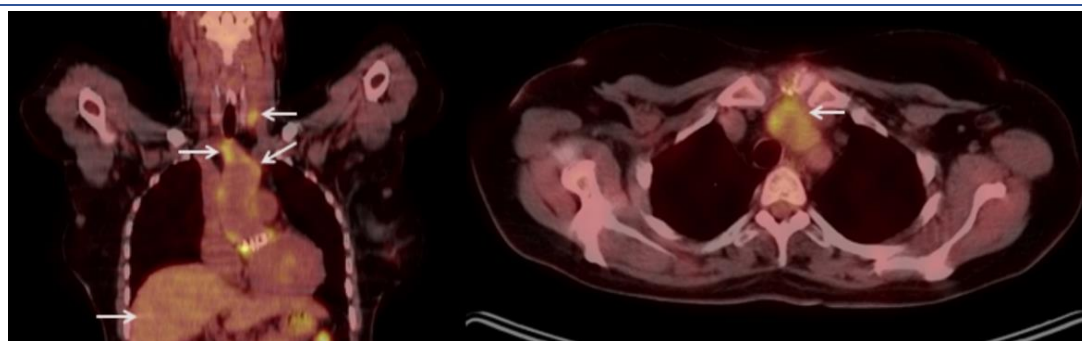
93.3% and 88.9%, respectively. Patients' age at the time of TA diagnosis and at the time of scanning were not statistically different between active and inactive groups according to the NIH criteria (p-value= 0.678 and 0.822, respectively). Also, the sex distribution of patients in the two groups was not statistically different (p-value = 0.812). There was no statistically significant

difference between active and inactive groups in terms of receiving or not receiving immunosuppressive therapies (p-value = 1.00). Details of the comparison of active and inactive

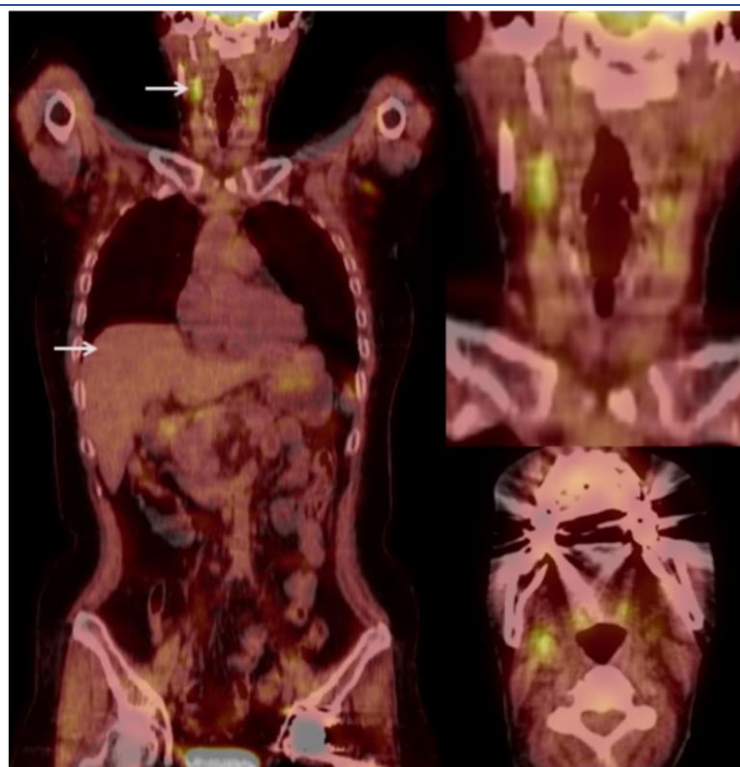
groups can be seen in Table 6. Some examples of 2-[<sup>18</sup>F]FDG PET-CT images in active and inactive TA patients are demonstrated in Figures 1-4.

**Table 6.** Comparison of active and inactive TA groups

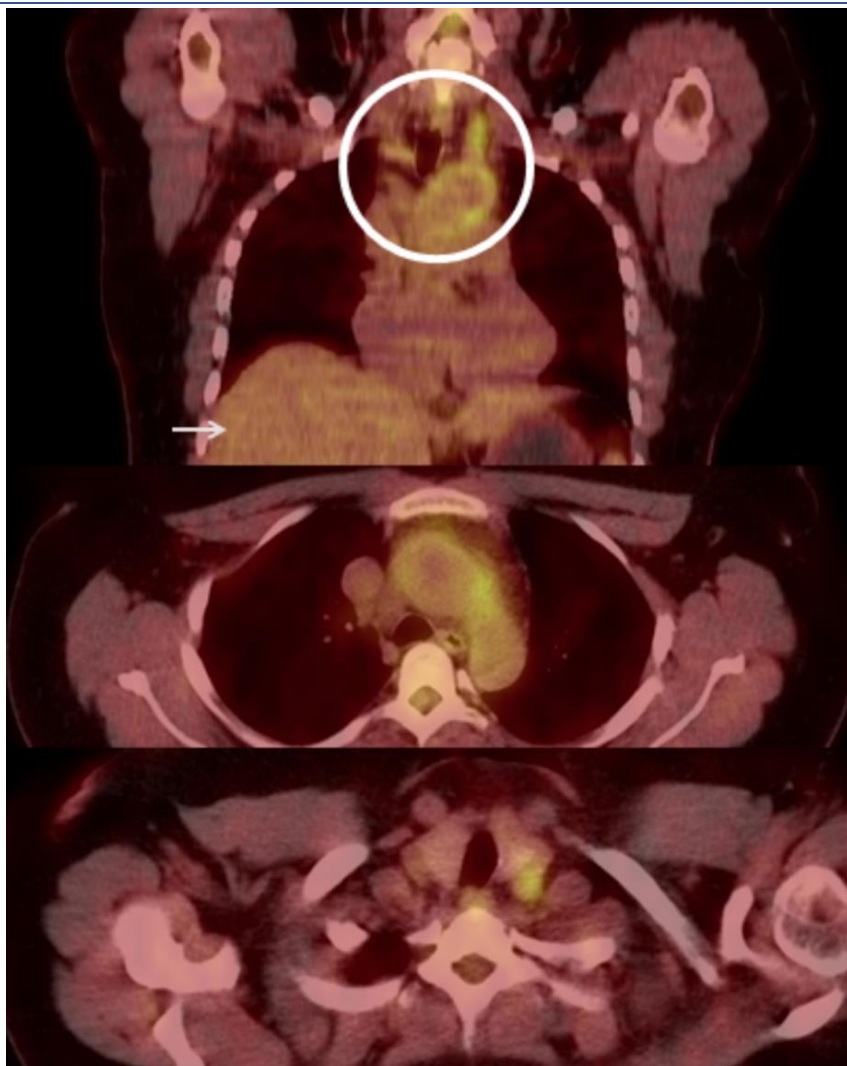
	Number (n)	Positive PET results (n)	Negative PET results (n)	Age at diagnosis (mean ± SD)	Age at scanning (mean ± SD)	Gender (n)	Immunosuppressive drug consumption (n)
Active disease	15	14	1	27.00 ± 9.42	33.93 ± 11.12	Female:11 Male: 4	10
Inactive disease	9	1	8	27.89 ± 9.16	36.11 ± 12.83	Female: 7 Male: 2	6
P-value	-	<0.0001		0.678	0.822	0.812	1.000



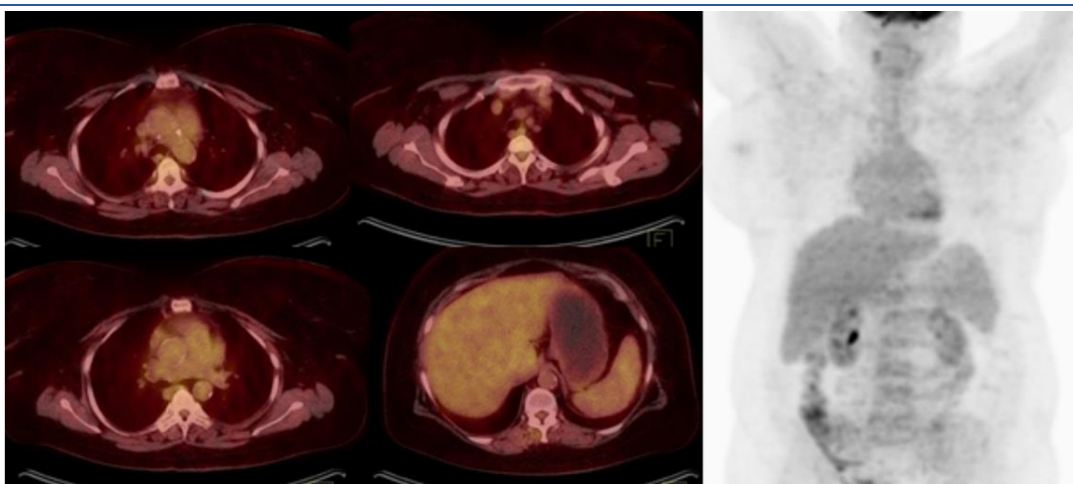
**Fig 1.** Positive scan result (grade 3 2-[<sup>18</sup>F]FDG uptake in the left carotid artery, innominate artery, and thoracic aorta (compared with liver background activity) in PET-CT fused images) in a person with active TA according to the NIH criteria treated with high-dose immunosuppressive drugs. A 40-year-old woman known case of TA from the age of 32 with a history of aortic valve replacement was treated with 50 mg of prednisolone daily and 30 mg of methotrexate weekly



**Fig 2.** Positive scan (grade 3 2-[<sup>18</sup>F]FDG uptake in the right carotid artery (compared with liver background activity) in PET-CT fused images) in a 37-year-old TA woman, known at the age of 28 with a history of suspected transient ischemic attack and headache treated primarily as a psychiatric disorder. At the time of study, the patient was treated with 5 mg of prednisolone daily and 7.5 mg of methotrexate weekly and had active TA according to NIH criteria



**Fig 3.** Positive scan (grade 3 2-[<sup>18</sup>F]FDG uptake in the thoracic aorta and left carotid artery (compared with liver background activity) in the PET-CT fused images) in a 27-year-old woman with known active TA according to the NIH criteria. The diagnosis was made when she was 25 years old based on the chief complaint of neck pain. She is being treated with 20 mg of prednisolone daily and 15 mg of methotrexate weekly



**Fig 4.** Negative scan (grade 0 and 1 2-[<sup>18</sup>F]FDG uptake in vascular territories in fused PET-CT images) in a patient with inactive disease based on NIH criteria. The patient was a 44-year-old woman with a history of several years of TA who was referred for a 2-[<sup>18</sup>F]FDG PET-CT scan due to generalized weakness

The pattern of 2-<sup>[18F]</sup>FDG uptake in the positive vascular domains (grades 2 and 3 in visual assessment) was diffuse heterogeneous uptake in the affected areas among all patients.

Maximum 2-<sup>[18F]</sup>FDG uptake in vascular territories of each patient (maximum SUVmax) and ESR levels both had normal distributions (p-value = 0.267, 0.149, respectively). Although a positive correlation was observed between these two variables ( $r = +0.123$ ), this correlation was not statistically significant (p-value = 0.586). The average of maximum SUVmax was higher in the vascular territories of patients with active TA ( $3.08 \pm 1.04$ ) compared with inactive patients ( $2.53 \pm 0.62$ ). Although the difference was not statistically significant (p-value = 0.119), it may become significant in the studies with larger sample sizes.

Also in the active and inactive groups, the ratio of maximum SUVmax to the liver SUVmean was estimated. This ratio had a normal distribution in patients and the mean ratio of maximum SUVmax to the liver SUVmean in the active TA group was higher compared to the inactive group ( $1.66 \pm 0.56$  and  $1.31 \pm 0.40$ , respectively). However, this difference was not statistically significant (p-value = 0.087), although it tends to be.

It is noteworthy that the average maximum SUVmax of the vascular lesions in the two groups treated with immunosuppressive drugs ( $2.93 \pm 0.99$ ) and the medication-naïve group ( $2.78 \pm 0.87$ ) were not statistically significant (p-value = 0.709). This also applies to the ratio of maximum SUVmax to the liver SUVmean that was not significantly different between the two groups treated with immunosuppressive drugs ( $1.47 \pm 0.46$ ) and the medication-naïve group ( $1.65 \pm 0.64$ ) (p-value = 0.489).

Total SUVmax was also compared between active and inactive TA groups ( $29.65 \pm 6.08$  and  $25.85 \pm 5.70$ , respectively, p-value = 0.141) showing no statistically significant difference.

Also, in comparing the results of 2-<sup>[18F]</sup>FDG PET-CT scan with other angiographic imaging modalities, no significant difference was observed (p-value = 0.1). Among them, in 13 patients, both imaging methods had positive results, in 3 patients, both modalities were negative, and in general, in 16 of 21 patients, a diagnostic agreement was observed between the two scans. There was no significant difference between the mean number of vascular lesions between 2-<sup>[18F]</sup>FDG PET-CT scan ( $4.86 \pm 4.40$ ) and angiographic images (invasive, CTA and MRA) ( $3.81 \pm 3.74$ ) (p-value = 0.304).

Finally, in 7 TA patients 2-<sup>[18F]</sup>FDG PET-CT scan demonstrated diffuse and homogenous increased 2-<sup>[18F]</sup>FDG uptake along the vertebrae and proximal parts of bilateral humeri and femora, in favor of bone marrow hyperplasia. All these 7 patients were anemic according to the laboratory data and it seems that the 2-<sup>[18F]</sup>FDG PET-CT finding was due to bone marrow hyperplasia in response to anemia of chronic disease.

## DISCUSSION

Evaluation of disease activity as well as response to treatment in TA patients is of great importance in order to prevent the consequences of inappropriate treatment. Therefore, various studies have been performed to evaluate the capability of different measurement tools, including clinical criteria of imaging modalities [10-12, 14].

The 2-<sup>[18F]</sup>FDG PET-CT scan is a functional imaging technique providing a good estimation of metabolic rate in TA patients [14]. For example, in a meta-analysis performed by Cheng et al., the pooled sensitivity and specificity of 2-<sup>[18F]</sup>FDG PET-CT compared with the NIH criteria for assessing disease activity in TA patients were 70 and 77%, respectively [15]. Also, according to another meta-analysis performed in 2015 on a total of 131 TA patients, the 2-<sup>[18F]</sup>FDG PET-CT scan had pooled sensitivity and specificity of 84% and 84%, respectively, in assessing disease activity compared to the NIH criteria [16]. These two meta-analyses were based on old articles done with older PET devices (some of the studies used PET-only imaging without CT). As we know, PET devices are becoming more and more sensitive in detecting lesion uptake. In a more recent 2020 study by Fan et al. on 22 patients with atypical Takayasu's disease, the diagnostic power of 2-<sup>[18F]</sup>FDG PET-CT compared with the NIH criteria showed sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 75%, 87.5% and 100%, respectively [17].

In our study, in addition to showing that 2-<sup>[18F]</sup>FDG PET-CT scan can differentiate active from inactive TA (p-value <0.0001), it was shown that this imaging modality has high diagnostic power (sensitivity, specificity, positive predictive value and negative predictive value of 93.3%, 88.9%, 93.3% and 88.9%, respectively). However, in the pathological studies, between 40-61% of cases in which patients diagnosed as inactive TA according to the NIH criteria, active inflammation was observed in pathological

specimens [5, 6]. Therefore, the NIH criteria may not seem to be a suitable method for evaluating the diagnostic power of other modalities in assessing disease activity; however, an acceptable diagnostic agreement with this criteria is the first step in assessing the diagnostic capability of other modalities.

In a study by Han et al. on 19 TA patients, an initial 2-[<sup>18</sup>F]FDG PET-CT scan performed to assess the disease status showed active vascular lesions in all participants. In the follow-up study of these patients after appropriate treatment, all of them had controlled disease according to the clinical criteria; however, 79% of these patients showed an increase in glucose metabolism in the vessel wall. This increase was not statistically significant though. This finding indicates the possibility of persistent active disease even with negative clinical criteria. These findings show the potential importance of 2-[<sup>18</sup>F]FDG PET-CT in TA patients, which of course requires further studies [18].

Another issue in TA patients is the assessment of response to treatment. Glucocorticoids have been shown to reduce 2-[<sup>18</sup>F]FDG uptake, according to the available literature [19-21]. It remains unclear what effect the drug will have on 2-[<sup>18</sup>F]FDG uptake in TA patients. In a study by Santhosh et al., aimed at evaluating the role of 2-[<sup>18</sup>F]FDG PET-CT in the diagnosis and response assessment of 51 TA patients, the scan performed well in both new patients and patients with active disease during corticosteroid therapy [11]. In our study, we also showed that the use or non-use of immunosuppressive drugs, especially steroids, does not make a difference in the severity of vascular lesion uptake (defined as maximum SUVmax as well as the ratio of maximum SUVmax to the liver SUVmean). In another study by Karapolat et al., two clinical criteria (DEI-Tak along with NIH) were used to evaluate disease activity. They compare the two clinical criteria with 2-[<sup>18</sup>F]FDG PET-CT, showing comparable results even during the use of immunosuppressive drugs [10].

In our study, although the number of vascular lesions seen in the angiographic imaging techniques (CTA, MRA and invasive angiography) were not significantly different from 2-[<sup>18</sup>F]FDG PET-CT, the nature of the lesions were different. While the increase in vascular wall metabolism indicates the active phase of the disease, lesions in angiographic images were a combination of active and inactive lesions. Therefore, in order to evaluate the similarity / difference of imaging

modalities in evaluation of TA activity, it is necessary to design a detailed study to compare the absorption of 2-[<sup>18</sup>F]FDG in the vascular wall with edema, increase in thickness or contrast enhancement of the vascular wall in MRA, which indicates active disease. In this regard, in a study conducted by Parihar et al., it was shown that the results of 2-[<sup>18</sup>F]FDG PET-CT are well consistent with the NIH criteria in terms of disease activity, but given that conventional imaging methods show the more advanced stages of TA, the 2-[<sup>18</sup>F]FDG PET-CT appears to be more sensitive in assessing disease in the early stages [22].

In the study by Kang et al., which used the PETVAS visual criterion to evaluate the results of 2-[<sup>18</sup>F]FDG PET-CT, visual evaluation was superior to SUVmax evaluation alone in assessment of disease activity. In this study, ITAS-2010 criteria were used to assess disease activity in 54 TA patients and the final results showed the appropriate diagnostic power of 2-[<sup>18</sup>F]FDG PET-CT in assessing disease activity ( $p < 0.001$ ) [23]. This result was confirmed in our study using visual criteria in 16 vascular territories.

In a study by Janes et al., it was shown that 2-[<sup>18</sup>F]FDG PET-CT can predict disease progression and therefore the need for treatment change. In this study, in which 36 patients underwent baseline scans and followed for an average of 83.5 months,  $SUV_{max} \geq 1.3$  in the vascular wall was a predictor of disease recurrence; however, during this period, increased 2-[<sup>18</sup>F]FDG uptake in the vessel wall did not predict vascular damage. Eventually, it seems that early start of glucocorticoids or increasing the dose of the drug or changing to another medication (based on the result of the 2-[<sup>18</sup>F]FDG PET-CT scan) can serve as an interfering factor, preventing the occurrence of vascular anatomical lesions [24].

### **Limitation**

Considering the relative small patient population of our study (because of the rarity of Takayasu's Arteritis), multi-center studies with more sample sizes are required for more reliable statistical data.

### **CONCLUSION**

According to the results of our study, it seems that 2-[<sup>18</sup>F]FDG PET-CT scan differentiates active TA patients from inactive ones with good sensitivity and specificity in comparison with NIH criteria. The assessment of disease activity using



2-[<sup>18</sup>F]FDG PET-CT scan is not affected by the use of immunosuppressive drugs. Therefore, even patients taking high doses of steroids or methotrexate can be evaluated for disease activity using 2-[<sup>18</sup>F]FDG PET-CT scan. Quantitative evaluation of 2-[<sup>18</sup>F]FDG uptake in the lesions (maximum SUVmax and maximum SUVmax to the liver SUVmean ratio) may provide more reliable statistically significant data in studies with a larger population and may play a helpful role in the interpretation of the scans. 2-[<sup>18</sup>F]FDG PET-CT scan can play an important role in the patients' management: changing the dose of medications in order to avoid excessive or inadequate treatment.

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### REFERENCES

- Mason JC. Takayasu arteritis--advances in diagnosis and management. *Nat Rev Rheumatol*. 2010 Jul;6(7):406-15.
- Onen F, Akkoc N. Epidemiology of Takayasu arteritis. *Presse Med*. 2017 Jul-Aug;46(7-8 Pt 2):e197-e203.
- de Souza AW, de Carvalho JF. Diagnostic and classification criteria of Takayasu arteritis. *J Autoimmun*. 2014 Feb-Mar;48-49:79-83.
- Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, Hoffman GS. Takayasu arteritis. *Ann Intern Med*. 1994 Jun 1;120(11):919-29.
- Salvarani C, Cantini F, Boiardi L, Hunder GG. Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis. *Clin Exp Rheumatol*. 2003 Nov-Dec;21(6 Suppl 32):S23-8.
- O'Connor TE, Carpenter HE, Bidari S, Waters MF, Hedna VS. Role of inflammatory markers in Takayasu arteritis disease monitoring. *BMC Neurol*. 2014 Mar 28;14:62.
- Shek Y, Song SS. Takayasu's arteritis. In: Park MS, Kalani SMY, de Havenon A, McNally JS, editors. *Carotid Artery Disease*. 1<sup>st</sup> ed. Switzerland: Springer Cham; 2020. p. 233-45.
- Yamada I, Nakagawa T, Himeno Y, Kobayashi Y, Numano F, Shibuya H. Takayasu arteritis: diagnosis with breath-hold contrast-enhanced three-dimensional MR angiography. *J Magn Reson Imaging*. 2000 May;11(5):481-7.
- Slart RHJA; Writing group; Reviewer group; Members of EANM Cardiovascular; Members of EANM Infection & Inflammation; Members of Committees, SNMMI Cardiovascular; Members of Council, PET Interest Group; Members of ASNC; EANM Committee Coordinator. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET Interest Group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging*. 2018 Jul;45(7):1250-1269.
- Karapolat I, Kalfa M, Keser G, Yalçın M, Inal V, Kumanlioğlu K, Pirildar T, Aksu K. Comparison of F18-FDG PET/CT findings with current clinical disease status in patients with Takayasu's arteritis. *Clin Exp Rheumatol*. 2013 Jan-Feb;31(1 Suppl 75):S15-21.
- Santhosh S, Mittal BR, Gayana S, Bhattacharya A, Sharma A, Jain S. F-18 FDG PET/CT in the evaluation of Takayasu arteritis: an experience from the tropics. *J Nucl Cardiol*. 2014 Oct;21(5):993-1000.
- Serra R, Butrico L, Fugetto F, Chibireva MD, Malva A, De Caridi G, Massara M, Barbetta A, Cannistrà M, de Franciscis S. Updates in pathophysiology, diagnosis and management of Takayasu arteritis. *Ann Vasc Surg*. 2016 Aug;35:210-25.
- Russo RAG, Katsicas MM. Takayasu arteritis. *Front Pediatr*. 2018 Sep 24;6:265.
- Tezuka D, Haraguchi G, Ishihara T, Ohigashi H, Inagaki H, Suzuki J, Hirao K, Isobe M. Role of FDG PET-CT in Takayasu arteritis: sensitive detection of recurrences. *JACC Cardiovasc Imaging*. 2012 Apr;5(4):422-9.
- Cheng Y, Lv N, Wang Z, Chen B, Dang A. 18-FDG-PET in assessing disease activity in Takayasu arteritis: a meta-analysis. *Clin Exp Rheumatol*. 2013 Jan-Feb;31(1 Suppl 75):S22-7.
- Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, Mekinian A. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. *Medicine (Baltimore)*. 2015 Apr;94(14):e622.
- Fan J, Wei D, Zhang H, Sun X, Cai J, Fan L, Yu J, Ma W, Song L, Zhou X. <sup>18</sup>F-FDG PET/CT plays a unique role in the management of Takayasu arteritis patients with atypical manifestations. *Clin Rheumatol*. 2021 Feb;40(2):625-633.
- Han Q, Zhou X, Ding J, Zheng Z, Kang F, Zhang K, Yang F, Miao J, Wang J, Zhu P. 18F-FDG-PET/CT plays a key role in formulating treatment strategies for Takayasu arteritis. *Res Sq*. 2020; in press.
- Taimen K, Salomäki SP, Hohenthal U, Mali M, Kajander S, Seppänen M, Nuutila P, Palomäki A, Roivainen A, Piriälä L, Kemppainen J. The clinical impact of using <sup>18</sup>F-FDG-PET/CT in the diagnosis of suspected vasculitis: the effect of dose and timing of glucocorticoid treatment. *Contrast Media Mol Imaging*. 2019 Aug 29;2019:9157637.
- Milman N, Mortensen J, Sloth C. Fluorodeoxyglucose PET scan in pulmonary sarcoidosis during treatment with inhaled and oral corticosteroids. *Respiration*. 2003 Jul-Aug;70(4):408-13.
- Ahmadian A, Pawar S, Govender P, Berman J, Ruberg FL, Miller EJ. The response of FDG uptake to immunosuppressive treatment on FDG PET/CT imaging for cardiac sarcoidosis. *J Nucl Cardiol*. 2017 Apr;24(2):413-424.
- Parihar A, Kumar R, Singh H, Mittal B. 18F-FDG PET/CT in Takayasu arteritis-Active or Inactive? *J Nucl Med*. 2020 May 1; 61(supplement 1): 643-643.
- Kang F, Han Q, Zhou X, Zheng Z, Wang S, Ma W, Zhang K, Quan Z, Yang W, Wang J, Zhu P. Performance of the PET vascular activity score (PETVAS) for qualitative and quantitative assessment of inflammatory activity in Takayasu's arteritis patients. *Eur J Nucl Med Mol Imaging*. 2020 Dec;47(13):3107-3117.
- Janes ALF, Castro MF, Arraes AED, Savioli B, Sato EI, de Souza AWS. A retrospective cohort study to assess PET-CT findings and clinical outcomes in Takayasu arteritis: does 18F-fluorodeoxyglucose uptake in arteries predict relapses? *Rheumatol Int*. 2020 Jul;40(7):1123-1131.